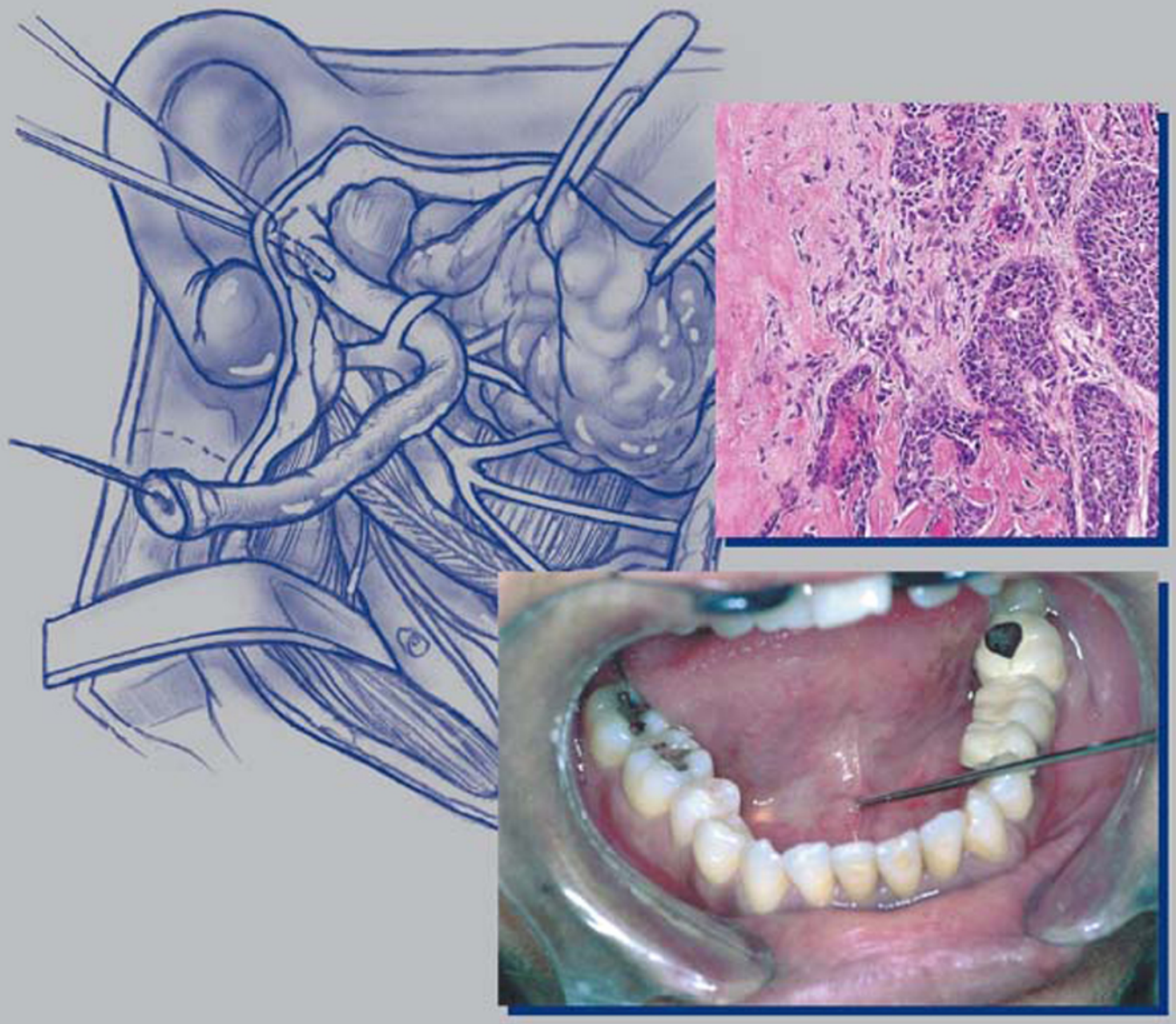
Salivary Gland Diseases

Surgical and Medical Management

Robert L. Witt



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Robert L. Witt, M.D.
Chief, Section of Otolaryngology–Head and Neck Surgery
Christiana Care Health Systems (CCHS)
Wilmington, Delaware

Chief, Head and Neck Oncology
Helen F. Graham Cancer Center (CCHS)
Newark, Delaware

Assistant Professor
Jefferson Medical College
Philadelphia, Pennsylvania

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Dedicated, in fond memory, to the two most influential teachers of my career, Harold F. Schuknecht, M.D., and William W. Montgomery, M.D.

Contents

Foreword

Salivary gland disorders are composed of a wide spectrum of clinicopathologic conditions including developmental, reactive, and inflammatory conditions as well as tumors. Acute and chronic sialadenitis, sialolithiasis, and chronic granulomatous inflammations represent the common reactive and inflammatory conditions. Salivary gland neoplasias encompass diverse and overlapping phenotypic and biological entities ranging from the common benign tumors such as pleomorphic adenoma to the highly aggressive and frequently lethal salivary duct and high-grade mucoepidermoid carcinomas. The management of salivary gland disorders has improved significantly with refinement in imaging techniques and histomorphologic classification, and a more widely accepted and standardized taxonomy of salivary gland neoplasia. Recently, advances in molecular characterization of tumors have been applied to salivary gland neoplasms and are providing insight into mechanisms responsible for tumor progression. Characterization of molecular pathways that promote tumor progression is providing insight that will permit application of biologic therapy as an adjunct to our standard approach of surgery with or without adjuvant radiotherapy.

Robert L. Witt, M.D., editor of *Salivary Gland Diseases*, has assembled an outstanding group of contributors who through their experience, expertise, and in-depth review of the pertinent literature provide the clinician with insight into the pathogenesis, diagnosis, and treatment for patients with salivary gland disease. This work is unique in that few published texts address the spectrum of salivary gland disorders in a comprehensive manner. *Salivary Gland Diseases* will provide the physician in training with a knowledge base upon which to build. It will serve the practicing clinician as a resource for managing patients with pediatric and adult, inflammatory or neoplastic disorders.

Randal S. Weber, M.D., F.A.C.S.
Hubert L. and Olive Stringer Distinguished Professor and Chairman
Department of Head and Neck Surgery
University of Texas M. D. Anderson Cancer Center

Preface

This is a comprehensive clinical text on the medical and surgical management of salivary gland disease and has been meticulously edited to minimize overlap between chapters and to read seamlessly. It includes complete coverage of current didactic information in the field, surgical treatment chapters with illustrations of basic and advanced surgical procedures and extensive color histologic, pathologic, and cytologic photomicrographs.

The chapter authors come from otolaryngology, head and neck surgery, pediatric otolaryngology, plastic and reconstructive surgery, oral and maxillofacial surgery, oral medicine, head and neck pathology, oral pathology, radiation oncology, medical oncology, head and neck radiology, and medical law and are members of thirteen leading academic institutions in four countries.

The intended readers are practicing otolaryngologists, head and neck surgeons, oral surgeons, plastic surgeons, general surgeons, radiation oncologists, and pathologists. The resident and medical student will also find the classic material that forms the foundation of treatment of salivary gland diseases and the detail to feel comfortable understanding and treating the exotic cases in this text.

Salivary gland pathology is felt by many to be the most complex in all of medicine. This book will demonstrate the common and unusual pathological entities in this exciting, expanding field. It will show how studiously considering the underlying anatomy, physiology, histology, pathology, and imaging leads to the appropriate decision for surgical or medical management of a case. Step by step illustrations are demonstrated of the surgical treatment of diseases that are congential, inflammatory, neoplastic and reconstructive. Dramatic advances in sialendoscopy, radiotherapy (adaptive IMRT), and xerostomia (de novo tissue engineering of functioning salivary gland tissue) are examples of new horizons in the field. A unique final chapter focuses on medicolegal issues in salivary gland diseases and a cross-comparison of tort systems in the United States and Germany.

I sincerely wish to instill in the reader a passion for this extraordinary field of medicine, and, in so doing, further advance the treatment of patients suffering from salivary gland diseases.

Acknowledgments

I would like to thank my wife, Carol Landefeld, V.M.D., for her insightful comments, and my children, Alex and Cara, for their inspiration. Thanks also to Pat Wilson, M.D., who tirelessly educates me on pathology; Ellen Justice, who always meets me with a smile on yet another literature search; and Douglas Bugel, who provided significant help with the photography.

Contributors

Gregory J. Artz, M.D.
Department of Otolaryngology
Thomas Jefferson University Hospital
Philadelphia, Pennsylvania

Madhavi L. Battineni, D.O.
University of Pennsylvania Medical Center
Philadelphia, Pennsylvania

Ara A. Chalian, M.D.
Associate Professor
Department of Otorhinolaryngology
University of Pennsylvania Medical Center
Philadelphia, Pennsylvania

Steven P. Cook, M.D.
Clinical Assistant Professor Pediatrics
Clinical Assistant Professor Otolaryngology
Department of Otolaryngology
and Pediatrics
Thomas Jefferson University Hospital
Philadelphia, Pennsylvania

Mary F. Cunnane, M.D.
Clinical Associate Professor
Department of Pathology, Anatomy, and Cell Biology
Thomas Jefferson University Hospital
Philadelphia, Pennsylvania

Daniel G. Deschler, M.D., F.A.C.S.
Associate Professor
Department of Otology and Laryngology
Massachusetts Eye and Ear Infirmary
Harvard Medical School
Boston, Massachusetts

Adel K. El-Naggar, M.D., Ph.D.
Professor of Pathology and Head
and Neck Surgery
University of Texas M. D. Anderson
Cancer Center
Houston, Texas

John D. Harrison, Ph.D., F.D.S.R.C.S.Eng., F.R.C.Path.
Reader and Consultant of Oral Pathology
Department of Oral Pathology
King's College London
Guy's Hospital
London, England

F. Christopher Holsinger, M.D.
Assistant Professor
Attending Surgeon
Department of Head and Neck Surgery
University of Texas M. D. Anderson
Cancer Center
Houston, Texas

Sarah H. Kagan, Ph.D., R.N.
Associate Professor
Gerontological Nursing
University of Pennsylvania
Philadelphia, Pennsylvania

Axel Koch
Dr. Kaul & Partner
Stuttgart, Germany

Laurie A. Loevner, M.D.
Professor
Department of Radiology
Neuroradiology Division
University of Pennsylvania
Philadelphia, Pennsylvania

Kelly M. Malloy, M.D.
Department of Otolaryngology–Head and Neck Surgery
Thomas Jefferson University
Philadelphia, Pennsylvania

Susan J. Maygarden, M.D.
Professor
Department of Pathology
University of North Carolina–Chapel Hill
Chapel Hill, North Carolina

Sherry C. McReynolds, J.D.
Wilmington, Delaware

Oded Nahlieli, D.M.D.
Associative Professor of Oral and Maxillofacial Surgery
Faculty of Dental Medicine
Hebrew University

Chairman
Department of Oral and Maxillofacial Surgery
Barzilai Medical Center
Ashkelon, Israel

Adjunct Associate Professor
New York University College of Dentistry
New York, New York

Kenneth R. Nissim, M.D.
Voluntary Associate Professor
Department of Otolaryngology
University of Miami
Miller School of Medicine
Miami, Florida

Snehal G. Patel, M.D., M.S., F.R.C.S.
Attending Surgeon
Assistant Professor of Surgery
Head and Neck Service, Department of Surgery
Memorial Sloan-Kettering Cancer Center
Weill Medical College of Cornell University
New York, New York

Adam Raben, M.D.
Helen F. Graham Cancer Center
Department of Radiation Oncology
Newark, Delaware

James S. Reilly, M.D., M.S.
Professor of Otolaryngology
Department of Otolaryngology–Head and Neck Surgery
Jefferson Medical College
A.I. duPont Hospital for Children
Wilmington, Delaware

Michael B. Rho, M.D.
Clinical Instructor
Department of Otology and Laryngology
Massachusetts Eye and Ear Infirmary
Harvard Medical School
Boston, Massachusetts

David Rosen, M.D.
Assistant Professor
Department of Otolaryngology–Head and Neck Surgery
Thomas Jefferson University Hospital
Philadelphia, Pennsylvania

Marc R. Rosen, M.D.
Assistant Professor
Department of Otolaryngology–Head and Neck Surgery
Thomas Jefferson University Hospital
Philadelphia, Pennsylvania

David I. Rosenthal, M.D.
Associate Professor of Radiation Oncology
Director, Head and Neck Translational Research
University of Texas M. D. Anderson Cancer Center
Houston, Texas

Paul Sabini, M.D.
Christiana Care Health Systems
Newark, Delaware

Richard J. Schmidt, M.D.
Clinical Instructor
Department of Otolaryngology
Thomas Jefferson University

Staff Physician
Division of Pediatric Otolaryngology
A.I. duPont Hospital for Children
Wilmington, Delaware

Charles J. Schneider, M.D., F.A.C.P.
Clinical Assistant Professor of Medicine
Attending Physician, Oncology Division
Department of Internal Medicine
Division of Medical Oncology
Helen F. Graham Cancer Center
Christiana Care Health Systems
Thomas Jefferson Medical College
Newark, Delaware

Jonathan A. Ship, D.M.D.
Professor of Oral Medicine
New York University
New York, New York

Christopher A. Sullivan, M.D.
Assistant Professor
Wake Forest University
Baptist Medical Center
Winston Salem, North Carolina

Leonardo Torres, M.D.
University of Texas M.D. Anderson Cancer Center
Houston, Texas

Randal S. Weber, M.D.
Chairman
Department of Head and Neck Surgery
Professor of Surgery
University of Texas M.D. Anderson Cancer Center
Houston, Texas

Robert L. Witt, M.D.
Chief, Section of Otolaryngology–Head and Neck Surgery
Christiana Care Health Systems (CCHS)
Wilmington, Delaware

Chief, Head and Neck Oncology
Helen F. Graham Cancer Center, CCHS
Newark, Delaware

Assistant Professor
Jefferson Medical College
Philadelphia, Pennsylvania

1

Salivary Gland Anatomy

MICHAEL B. RHO AND DANIEL G. DESCHLER

The salivary gland system of the upper aerodigestive tract plays a critical role in the functions of digestion, respiration, communication, and overall homeostasis. Two distinct types of glands compose this system. The major salivary glands are the paired parotid, submandibular, and sublingual glands. The remaining glands are the thousands of small minor salivary glands that line the oral cavity and can be found in the pharynx, supraglottis, nasal cavity, and paranasal sinuses. These glands produce saliva, which functions in digestion, immunity, dental hygiene, lubrication, and hydration. This chapter will review the anatomical relationships of the salivary glands relevant for surgical management of neoplastic and non-neoplastic salivary gland disorders, as well as other processes that may involve the glands secondarily. The histology of salivary glands will be discussed in detail in Chapter 4.

■ Parotid Gland

The parotid gland, weighing 15 to 30 g, is the largest of the salivary glands and is a slender, lobulated gland. The parotid glands are positioned on the lateral aspect of the face overlying the posterior surface of the mandible and anteroinferiorly to the auricle (**Fig. 1–1**). The lateral surface of the gland consists of fascia that forms a dense capsule. This fascia also covers the masseter muscle and is referred to as the parotidomasseteric fascia. John Conley[1] describes four ''dorsal investments of fascia'' at the posterior border of the gland: (1) The fascia superior to the tragus is thick and partially attaches to the root of the zygoma. The temporal artery and vein and auriculotemporal nerve can be found there. (2) There is a thin fascia along the tragal and conchal cartilage that separates easily with blunt dissection. (3) The fascia is thick again as it attaches to the mastoid process. (4) There is a confluent thickening of the fascia at the inferior tip of the parotid gland separating it from the submandibular gland.

The gland has a small superior surface and larger anteromedial, posteromedial, and superficial surfaces. The superior border is the zygomatic arch. The anterior border is the masseter muscle. The posterior border is the tragal cartilage and the anterior border of the sternocleidomastoid muscle. The gland has a so-called tail, which is located posteriorly between the ramus of the mandible and the sternocleidomastoid muscle. This region overlies the digastric muscle. The inferior border of the parotid gland is variable and extends along the anterior border of the sternocleidomastoid muscle and the carotid sheath. Anteromedially, the gland is attached to the masseter muscle, the posterior border of the mandibular ramus, and the medial pterygoid muscle. Posteromedially, the gland is adjacent to the posterior belly of the digastric muscle, the styloid process, and its associated muscles and ligaments. Deeply, portions of the parotid gland rest in the prestyloid compartment of the parapharygeal space.

There has been much debate as to whether or not the parotid gland truly has a superficial and deep lobe. A traditional approach is to divide the gland into a superficial and deep lobe based on the course of the facial nerve as it travels through the gland (**Fig. 1–2**). This approach is particularly useful in defining the type

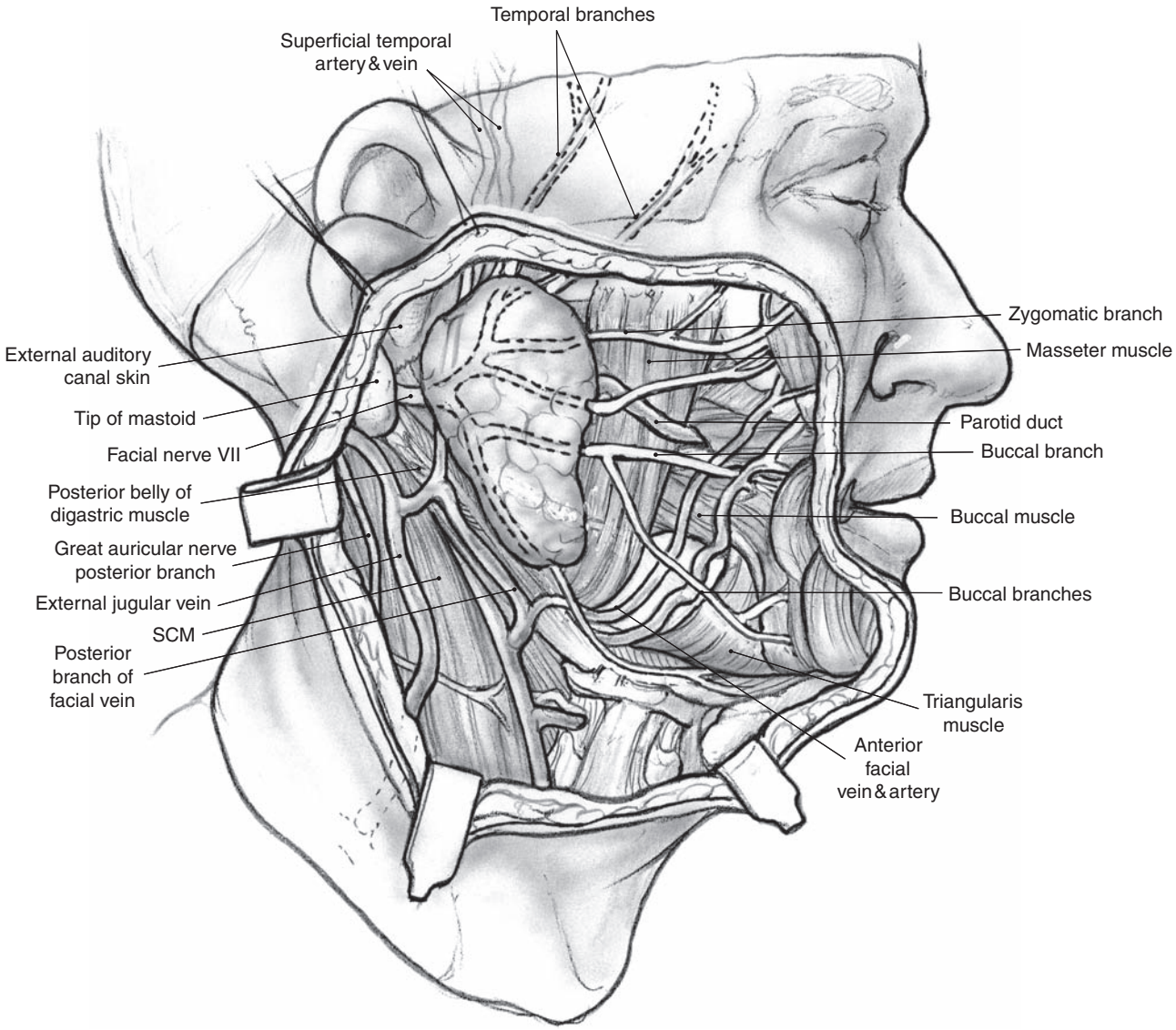

FIGURE 1–1 Lateral view of the face showing the parotid gland. SCM, sternocleidomastoid muscle.

of surgical resection that is undertaken. The superficial lobe is defined as parotid tissue located lateral to the facial nerve. The deep lobe is the remaining gland located medial to the facial nerve. Most benign tumors of the parotid gland are located in the superficial lobe and can be resected with a superficial parotidectomy. However, it is not uncommon to discover that masses that were initially diagnosed as superficial based on physical examination are actually located in the deep lobe.

With this prominent position in the head and neck, the parotid gland has an intimate relationship with numerous critical structures in the head and neck. Similarly, important arterial, venous, and neural structures traverse these glands.

Arterial Anatomy

The external carotid artery divides from the carotid bifurcation and travels below the posterior belly of the digastric muscle (**Fig. 1–3**, p. 4). Here the facial artery branches off and travels deep to the posterior belly of the digastric muscle to enter the submandibular triangle. The external carotid artery then courses medial to the parotid gland to divide into the maxillary artery and the superficial temporal artery. The maxillary artery exits the medial surface of the gland and divides to supply the infratemporal fossa and the pterygopalatine fossa. The superficial temporal artery gives off the transverse facial artery and exits from the superior pole of the gland. The superficial temporal artery then

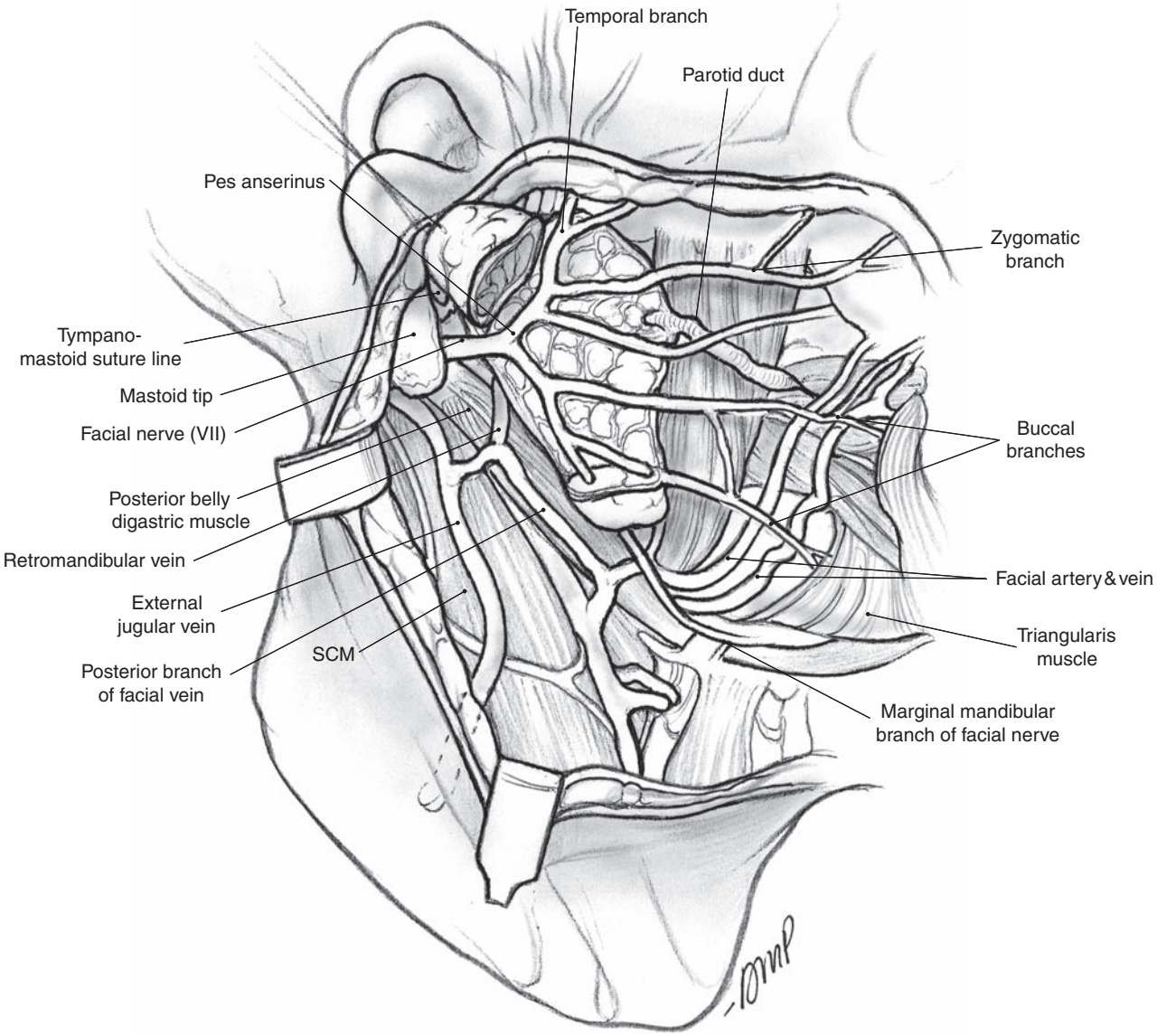

FIGURE 1–2 Superficial lobe is removed. SCM, sternocleidomastoid muscle.

runs superior in the superior pretragal region toward the scalp.

Of note, a prominent branch of the posterior auricular artery is located within 2 mm of the main trunk of the facial nerve. This branch can be an inadvertent source of bleeding during dissection, leading to difficulty when identifying the main trunk of the facial nerve. Similarly, care should be taken not to confuse this structure with the facial nerve proper.

Venous Anatomy

The venous system within the parotid gland parallels the arteries. The maxillary and superficial temporal veins join to form the retromandibular vein, which exits the gland inferiorly and then joins the external jugular vein. The retromandibular vein may also give off a posterior facial vein that joins the anterior facial vein, forming the common facial vein, draining into the internal jugular vein. This will often be the prominent draining pattern in situations where the external jugular system is small or nonexistent. The posterior facial vein is a reliable landmark for identifying the marginal mandibular branch of the facial nerve, as this vein lies immediately deep to the marginal mandibular branch. A mass that imaging studies demonstrate to be superficial to the retromandibular vein will usually be superficial to the nerve. Yet reports do exist of the nerve running deep to the vein.[2,3]

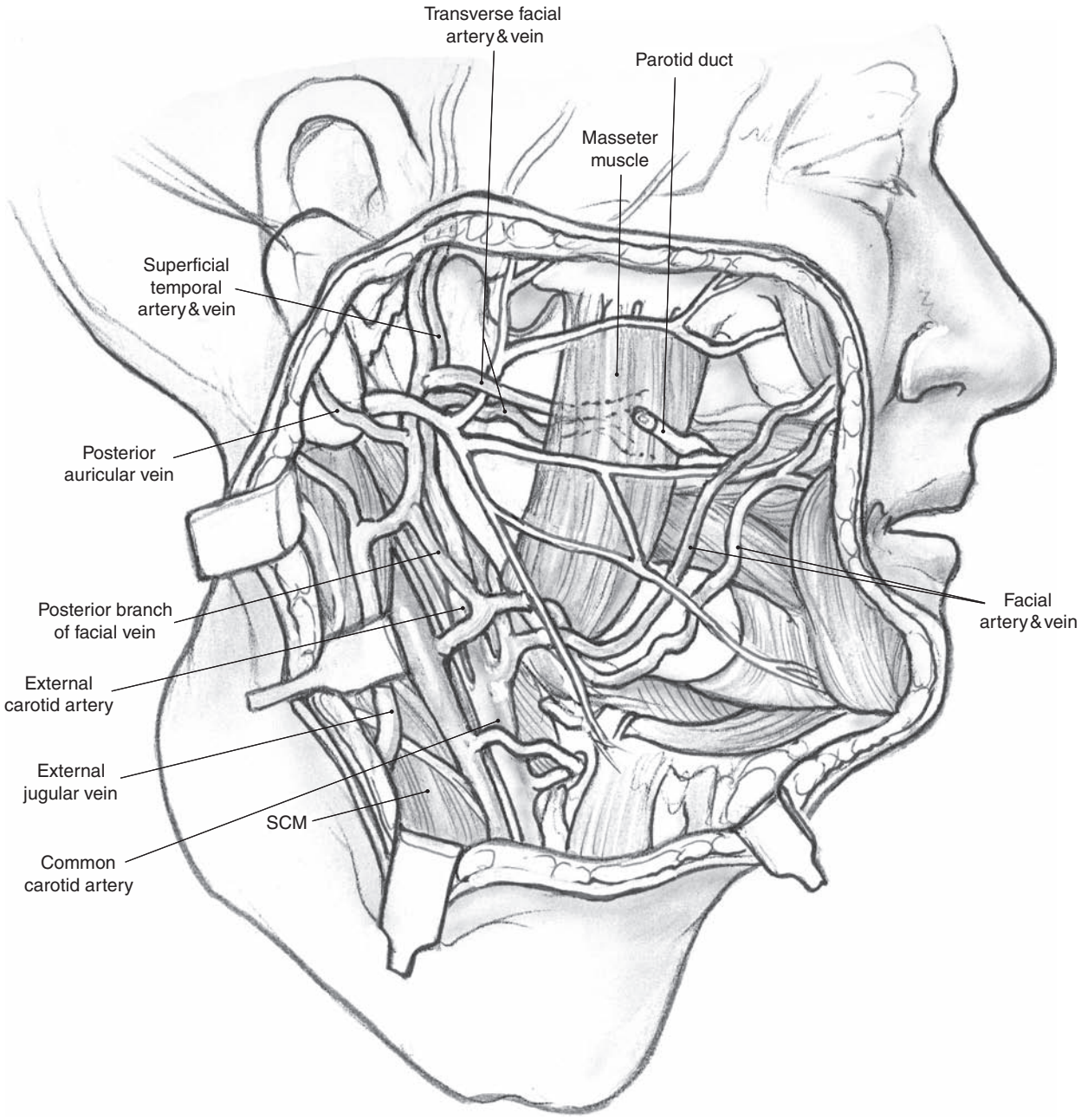

FIGURE 1–3 Arterial and venous anatomy. SCM, sternocleidomastoid muscle.

Stensen's Duct

The parotid duct, or Stensen's duct, forms from ductules that arise from the superficial lobe, deep lobe, or both. They join near the anterior border of the gland and traverse forward over the lateral surface of the masseter approximately a finger breadth below the zygomatic arch. The duct can be found along this imaginary line between the oral commissure and the attachment of the ear lobule, measuring 4 to 7 cm. The duct courses anteriorly and then makes a sharp turn and pierces the buccinator muscle and buccal fat pad. The duct opens into the oral cavity at the parotid papilla at the level of the upper second molar. A small accessory parotid gland can be found in 21 to 56% of patients.[4,5] It can be found along the parotid duct between the buccal and zygomatic branches of the facial nerve and can be a source of parotid tumors. Accessory glands are distinct from the main body of the parotid but drain into Stensen's duct via one or more small tributaries.

Neural Anatomy

Great Auricular Nerve

The great auricular nerve is a sensory nerve that arises from the cervical plexus, specifically rootlets of C2 and C3. The nerve is located approximately 1 cm cephalad to the external jugular vein along the lateral surface of the sternocleidomastoid muscle in a subplatysmal plane. As the nerve approaches and enters the tail of the parotid gland, it divides into anterior and posterior branches. The anterior branch supplies the facial skin overlying the parotid gland. The posterior branch supplies the ear lobule. The great auricular nerve is commonly sacrificed during parotid surgery, with resultant long-term postoperative numbness of the ear lobule. Efforts to save the posterior branch of the great auricular nerve during parotidectomy are favored by some surgeons with varying degrees of success. Up to 50% of patients who have preservation of the posterior branch of the facial nerve will have reduced hyposthesia.[6] In such dissections, the nerve must be dissected through the lateral surface of the gland. Specific care must be taken during the elevation of the lobule not to sever the distal branches of the nerve as they enter the lobule.

Facial Nerve

Thorough familiarity with the anatomy of the facial nerve is critical to any successful surgical procedure involving the parotid gland. The facial nerve has five segments before exiting the temporal bone: intracranial (pontine) segment, internal auditory canal (meatal) segment, labyrinthine segment, tympanic segment, and mastoid segment (**Fig. 1–4**). The pontine segment measures 23 to 24 mm long and extends from the pons up to the internal auditory canal. The meatal segment measures 7 to 8 mm and is contained within the internal auditory canal. The labyrinthine segment measures 3 to 4 mm long and extends from the fundus of the

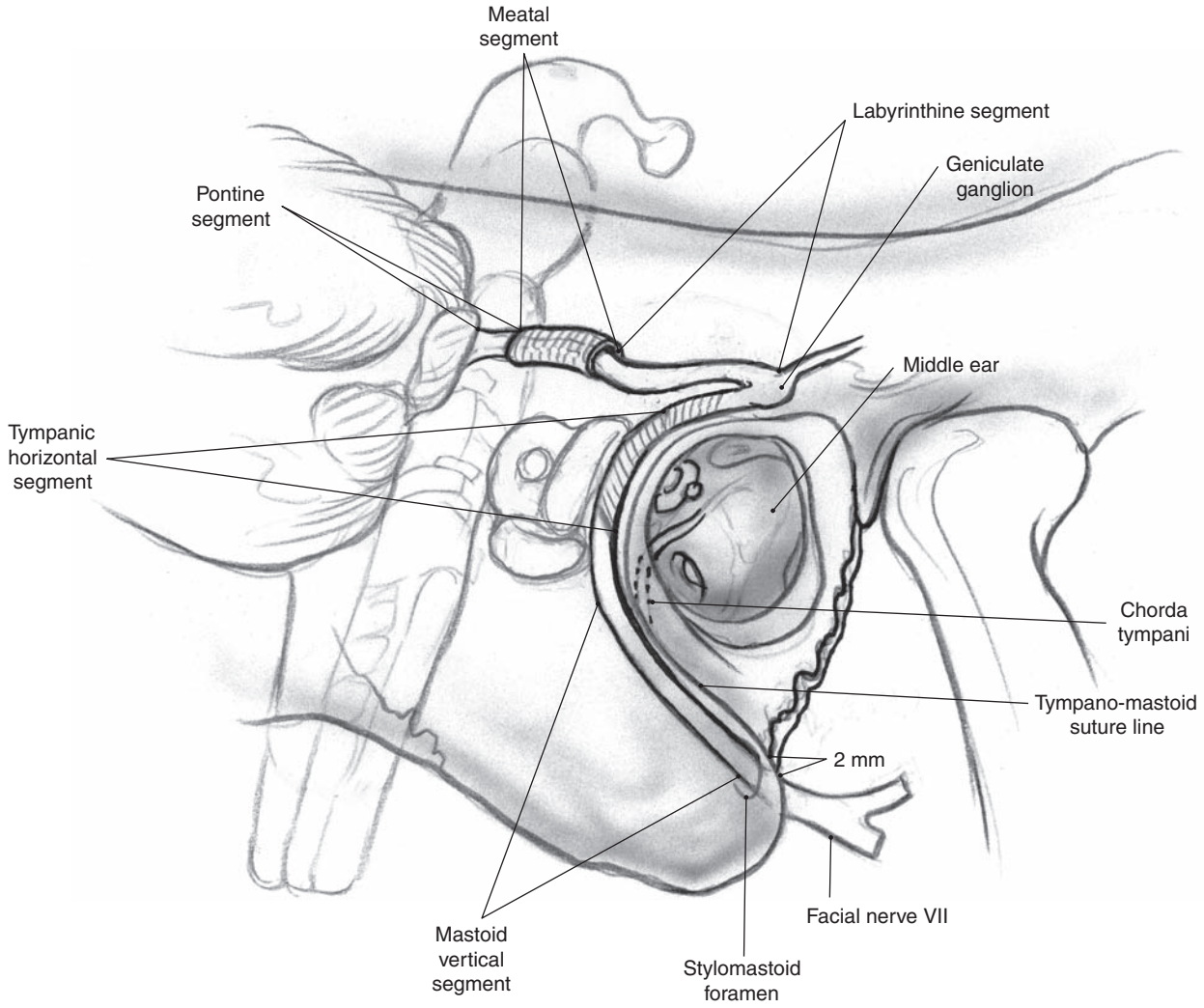

FIGURE 1–4 Facial nerve from brainstem to stylomastoid foramen.

internal auditory canal to the geniculate ganglion. The tympanic segment (or horizontal segment) measures 12 to 13 mm long and extends from the geniculate ganglion to the pyramidal turn. The mastoid segment (or vertical segment) measures 15 to 20 mm long and extends from the pyramidal turn to the stylomastoid foramen.

The extratemporal segment of the facial nerve exits the skull base at the stylomastoid foramen. It is located slightly posterolateral to the styloid process and anteromedial to the mastoid process and digastric groove. In rare occasions, the nerve may follow an aberrant course and exit from the anterior surface of the mastoid process. Before the main trunk of the facial nerve enters the parotid gland, it usually gives off branches to the posterior belly of the digastric muscle, the stylohyoid muscle, and the auricular muscles. The facial nerve divides within the parotid gland, and as it courses through the gland, it becomes more superficial. As the facial nerve enters the parotid gland, it forms the pes anserinus (the characteristic multiple branching pattern that resembles a goose foot), which gives off the two main divisions of the facial nerve. The upper division (temporofacial) branches into the temporal, zygomatic, and buccal branches. The lower division (cervicofacial) gives off the marginal mandibular and cervical branches. Buccal branches may arise from the upper division or the lower division.

There have been many variations of facial nerve branching patterns described. Davis et al[7] described six types of branching patterns. The type I pattern, seen in 13% of cases, has no anastomosis between the five branches. The other five types have varying patterns of anastomosis between the five branches. Miehlke et al[8] described eight branching patterns where no anastomoses between the branches were seen in 48% of patients. This group also found that the buccal branches can arise from either the temporofacial division (21%) or the cervicofacial division (35%). The temporal branches innervate the anterior auricular muscle, superior auricular muscle, frontalis muscle, and orbicularis oculi muscle. The zygomatic branches innervate the orbicularis oculi muscle, nasal aperture muscles, and elevators of the upper lip. The buccal branches innervate the muscles of the upper and lower lip. The marginal mandibular branch innervates the muscles of the lower lip. The cervical branch innervates the platysma muscle (**Table 1–1**).

TABLE 1–1 Facial Nerve Branches and the Muscles They Innervate

Facial nerve branch	Facial muscle
Temporal branch	Frontalis muscle
Temporal branch	Anterior and superior auricular muscle
Posterior auricular branch	Posterior auricular muscle
Temporal and zygomatic branch	Orbicularis oculi muscle
Buccal branch	Levators of lip/mouth (zygomaticus major and minor, levator anguli oris, levator labii superioris)
Buccal branch	Orbicularis oris muscle
Buccal branch	Buccinator muscle
Mandibular branch	Depressors of lip/mouth (depressor angularis oris, depressor labii inferioris)
Cervical branch	Platysma muscle

Locating the main trunk of the facial nerve can be facilitated by the following landmarks (**Fig. 1–5**): (1) The tympanomastoid (TM) suture line is the most constant landmark for finding the main trunk. The facial

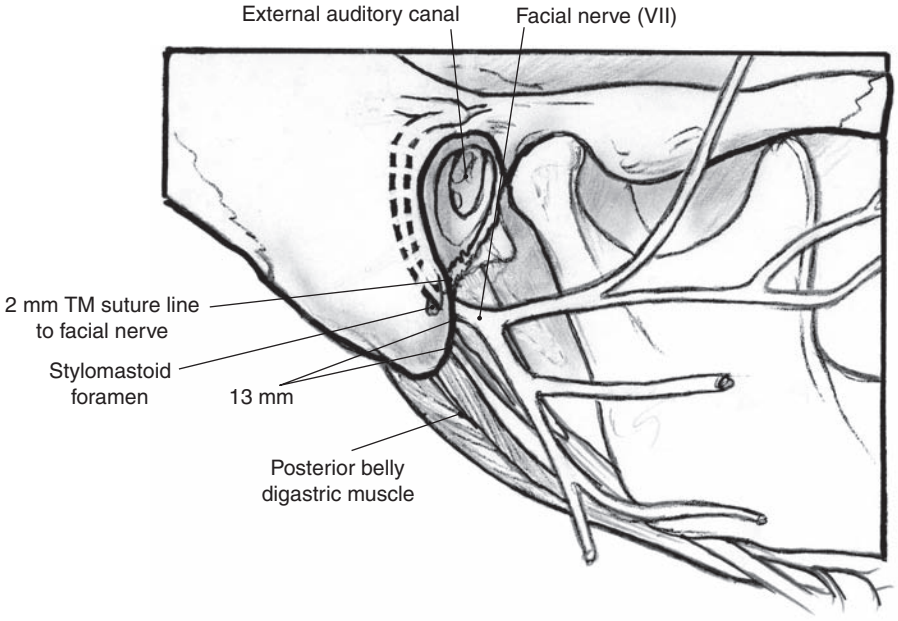

FIGURE 1–5 Surgical landmarks to identify cranial nerve (CN) VII. TM, tympanomastoid.

nerve is usually located ~2 to 4 mm deep to the inferior end of the tympanomastoid suture line. (2) The posterior belly of the digastric muscle is a good landmark for the approximate depth of the main trunk. (3) The tragal pointer is the medial end of the tragal cartilage in the tympanomastoid notch. The facial nerve is located ~1 cm deep and slightly anteroinferior to the tragal pointer. (4) The styloid process can be identified during dissection, and the nerve will be in the soft tissue inferior and superficial to this structure.

The two most important competing landmarks, the tympanomastoid suture and posterior belly of the digastric muscle, have been compared.[9] The mean closest distances from the tympanomastoid suture and posterior belly of the digastric muscle to the facial nerve are 1.8 mm (range 0–4 mm) and 12.4 mm (range 7–17 mm), respectively ($p < .05$), for cadavers. The mean closest distances in live patients from the tympanomastoid suture and posterior belly of the digastric muscle to the facial nerve are 2.0 mm (range 0–4 mm) and 10.7 mm (range 5–14 mm), respectively ($p < .05$). The tympanomastoid suture is a significantly closer and less variable anatomical landmark compared with the posterior belly of the digastric muscle both in cadaver dissection and in live patients (**Fig. 1–6**).

Should the main trunk not be identifiable at the stylomastoid foramen, alternative means of identification can be undertaken. One approach is to locate the distal branches and trace them centrally toward the main trunk. The marginal mandibular nerve can be identified as it passes over the submandibular gland fascia and dissected retrograde. The marginal mandibular nerve will usually pass superficial to the posterior facial vein. Similarly, the buccal branch can be identified anteriorly at the middle portion of the gland. This branch will lie in close approximation to Stensen's duct as it courses toward the mouth. The zygomatic branches can likewise be identified as they cross the zygomatic arch. Should this approach fail or if transtemporal identification is preferable, as is seen during reoperation with extensive scarring, a mastoid approach can be used. This is achieved by detaching the sternocleidomastoid muscle from the mastoid tip, which can be opened with a drill to expose the main trunk of the facial nerve. Simple mastoidectomy can also assist with this approach.

The Autonomic Nerve Supply

The glossopharyngeal nerve (ninth cranial nerve, CN IX) supplies the secretomotor fibers to the parotid gland (**Fig. 1–7**). The parasympathetic preganglionic fibers arise from the inferior salivatory nucleus and travel via CN IX through the jugular foramen. The tympanic branch (Jacobson's nerve) turns back into the skull via the inferior tympanic canaliculus and enters the middle ear inferiorly over the promontory proceeding anterosuperiorly. It then courses along the roof of the middle ear to the petrous ridge in the subdural space of the middle cranial fossa as the lesser petrosal nerve. The lesser petrosal nerve then exits the skull through the foramen ovale, and the fibers synapse within the otic ganglion. The otic ganglion is found on the undersurface of the mandibular division (V_3) of the trigeminal nerve. The postganglionic parasympathetic fibers exit the ganglion and join the auriculotemporal branch of the mandibular division of the trigeminal nerve in the infratemporal fossa. The auriculotemporal nerve travels parallel to the superficial temporal vein

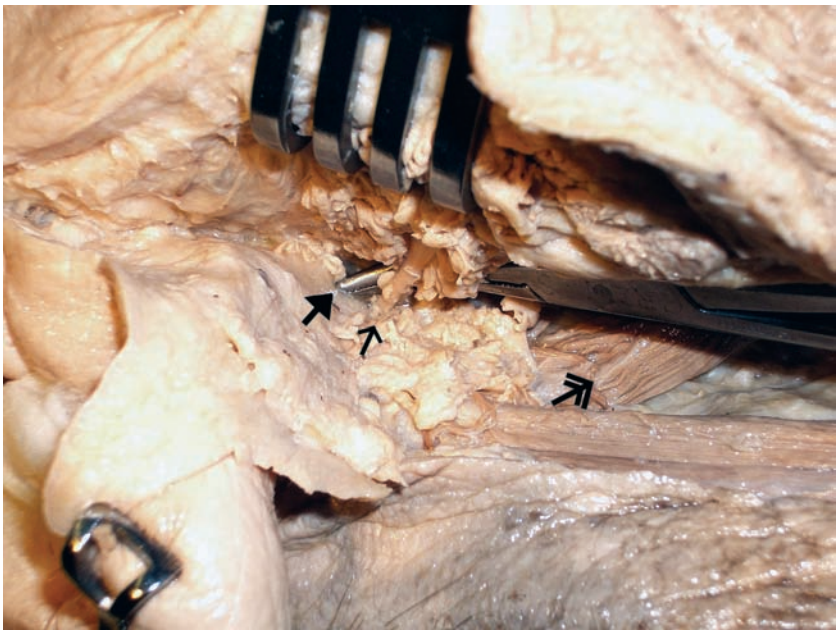

FIGURE 1–6 Cadaver dissection. Single arrow: facial nerve; arrowhead: tympanomastoid suture; double arrow: posterior belly of digastric muscle.

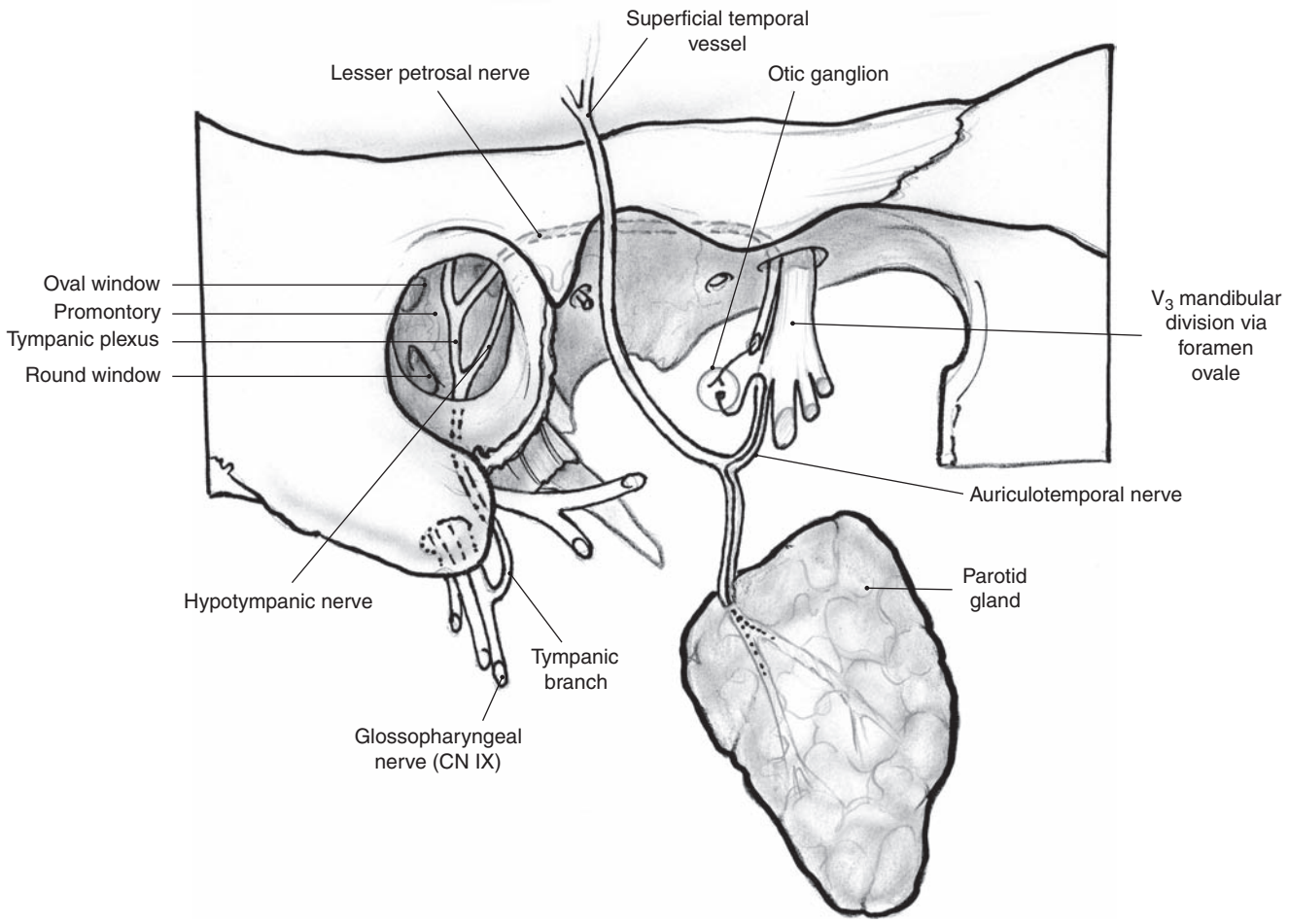

FIGURE 1–7 Autonomic nerve supply to the parotid gland.

and artery, supplying parasympathetic innervation to the parotid gland for salivary production.

The sympathetic supply reaches the gland from the superior cervical ganglion via the external carotid plexus. Injury to the cervical sympathetic chain leads to anhydrosis as part of Horner's syndrome. Loss of sympathetic input to the parotid is the explanation for first bite syndrome in patients who have had carotid body tumors (paragangliomas) resected. Cramping in the parotid area is described with the first bite of food of the day or with strong sialagogues such as tart food. With gustatory stimulation, parasympathetic neurotransmitters are released, and concomitant cross-stimulation of sympathetic receptors causes a supramaximal response or denervation supersensitivity of myoepithelial cells.[10]

Lymph Nodes

The parotid gland is seeded with lymph nodes, unlike other salivary glands. These lymph nodes are within and around the parotid parenchymal tissue. About 90% are located in the superficial lobe.

Parapharyngeal Space

Deep lobe parotid tumors can extend into the parapharyngeal space. The parapharyngeal space is described as an inverted pyramid with its base at the petrous bone of the skull base and apex at the hyoid bone. The medial boundary is the lateral pharyngeal wall, consisting of the buccopharyngeal fascia, tensor veli palatini, and superior constrictor muscles of the pharynx and nasopharynx. The lateral boundary is the medial pterygoid muscles and its fascia and the ramus of the mandible. The posterior boundary is the carotid sheath, prevertebral fascia, and paravertebral muscles. The anterior boundary extends along the medial pterygoid muscle and the pterygomandibular raphe. The parapharyngeal space lies posterior to the infratemporal fossa.

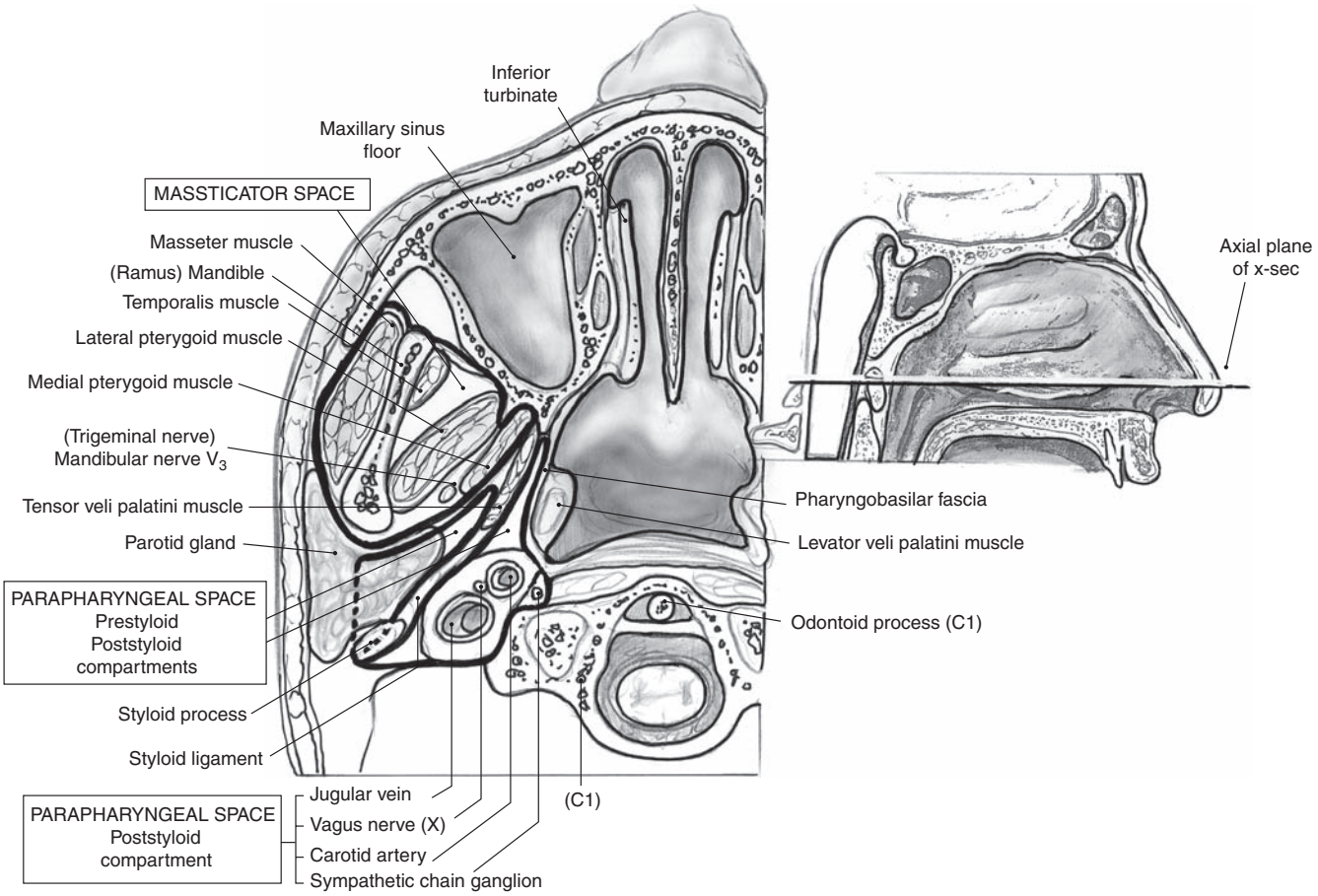

FIGURE 1–8 Deep parotid anatomy.

The parapharyngeal space is divided into a prestyloid and poststyloid compartment by the fascia of the tensor veli palatini muscle (**Fig. 1–8**). The prestyloid compartment normally contains only lymphatics, adipose tissue, and small blood vessels. The poststyloid compartment contains the carotid sheath, with the internal jugular vein, carotid artery, and vagus nerve. This compartment is also traversed by the cervical sympathetics, the glossopharyngeal nerve, and the hypoglossal nerve. On computed tomography (CT) imaging, one can see this fascia extending obliquely from the pterygoid plates anteromedially to the styloid process posterolaterally. Masses that are located anterior and lateral to the fascia are in the prestyloid compartment. Conversely, masses that are posterior and medial to the fascia are in the poststyloid compartment. Deep lobe tumors of the parotid gland are the most common masses of the prestyloid compartment of the parapharyngeal space. Neurogenic tumors such as paragangliomas are the most common tumors of the poststyloid compartment. Schwannomas of the cervical sympathetics and of cranial nerves IX, X, XI, and XII also may be present here.

Parotid gland masses can extend medially into the parapharyngeal space in two ways: (1) the mass can pass posteroinferior to the stylomandibular ligament, or (2) the tumor can pass through the stylomandibular tunnel into the parapharyngeal space, forming a dumbbell-shaped mass. Patients typically present with a mass either in the neck or in the lateral pharyngeal wall (**Fig. 1–9**). Examination of the oropharynx can reveal medial displacement of the soft palate, tonsil, and lateral pharyngeal wall. The surgical approaches to salivary gland masses within the parapharyngeal space are discussed in detail in a later chapter.

■ Submandibular Gland

The submandibular gland, weighing 7 to 16 g, is located in a triangle of the neck bordered superiorly by the inferior edge of the mandible and inferiorly by the anterior and posterior bellies of the digastric muscle. Referred to as the submandibular triangle, this area likewise corresponds to level 1 in the neck staging system. Accordingly, the submandibular gland has an

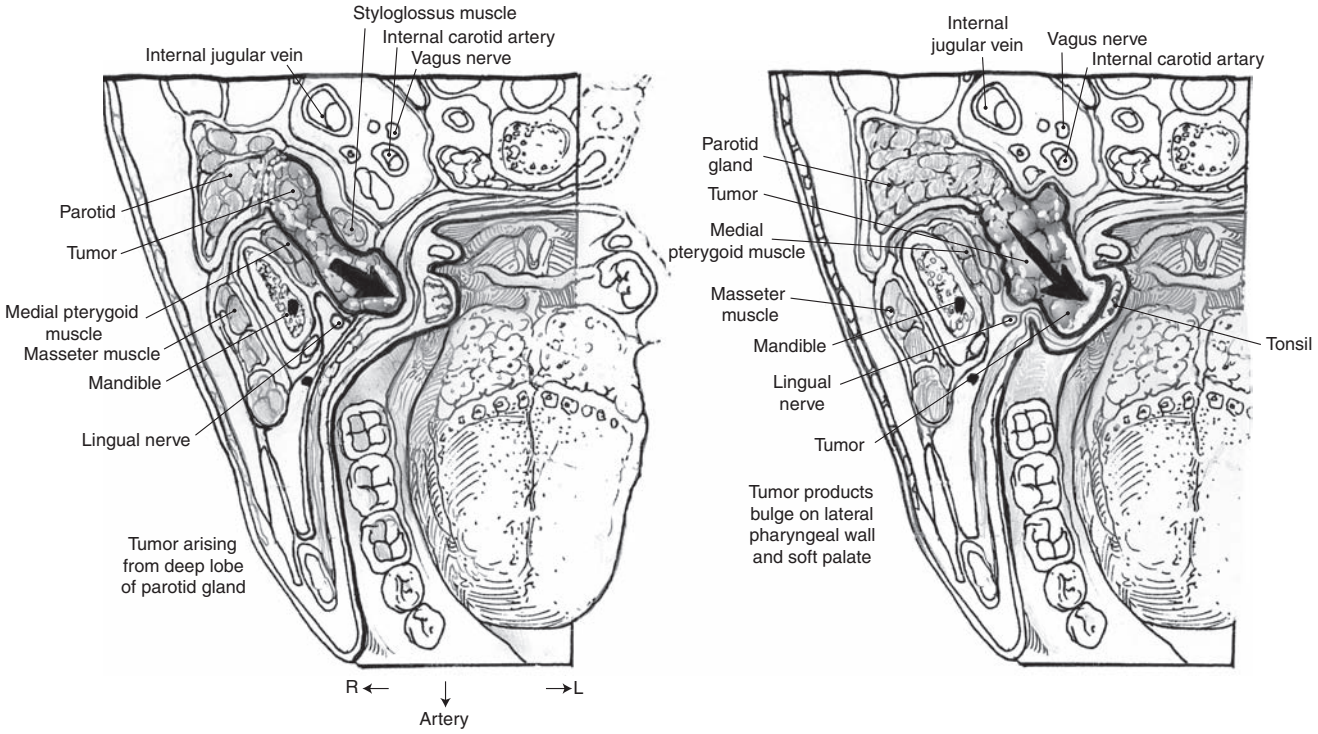

FIGURE 1–9 Tumor produces bulge on lateral pharyngeal wall.

intimate relationship with the mandible, hyoglossal muscle, mylohyoid muscle, posterior belly of the digastric muscle, facial artery and vein, lingual nerve, and hypoglossal nerve.

The submandibular gland is a horseshoe-shaped structure wrapped around the mylohyoid muscle (**Fig. 1–10**). The smaller sublingual portion is located anteriorly, while resting superior and deep to the mylohyoid muscle. The majority of the gland is located inferior to the mylohyoid muscle in the submandibular triangle. In older patients the gland may lie more inferior in the neck, below the digastric muscles, and is described as ptotic.

Fascial Anatomy

The submandibular gland is surrounded by the middle layer of the deep cervical fascia. This layer is distinct from the superficial layer of the deep cervical fascia that surrounds the platysma muscle. The submandibular fascia is clinically relevant during surgery of this region because the marginal mandibular branch of the facial nerve lies superficial to this fascia and facial vein. Similarly, this facial nerve branch is deep to the fascia surrounding the platysma muscles. Any surgical procedure to this region, whether it is direct removal of the submandibular gland, neck dissection encompassing this region, or external approaches to mandibular fractures, must include a directed effort to preserve the integrity of the marginal mandibular nerve. The surgeon can approximate the location of the nerve as lying superior to a line two finger breadths below the angle of the mandible. In appropriate cases, the surgeon can protect the nerve without direct identification by dividing the anterior facial vein at the inferior surface of the gland and elevating the vein with the fascia. As the nerve runs superficial to the vein, it will be protected during dissection inferior to this plane. However, in clinical settings in which malignancy is suspected, one should strongly consider directly identifying and preserving the marginal mandibular nerve, allowing the fascia to be resected in an en bloc fashion with the gland.

Arterial Anatomy

The facial artery branches from the external carotid system just superior or in combination with the lingual artery. The facial artery courses deep to the posterior belly of the digastric muscle entering the submandibular triangle. It continues superiorly, usually indenting the posterior portion of the submandibular gland. The artery is intimately involved with the gland in this region, giving off small branches to supply the gland. Exiting the superior aspect of the gland, the artery then loops around the inferior border of the mandible, leaving a small indentation in the bone, known as the facial notch. Here, the artery is in close approximation

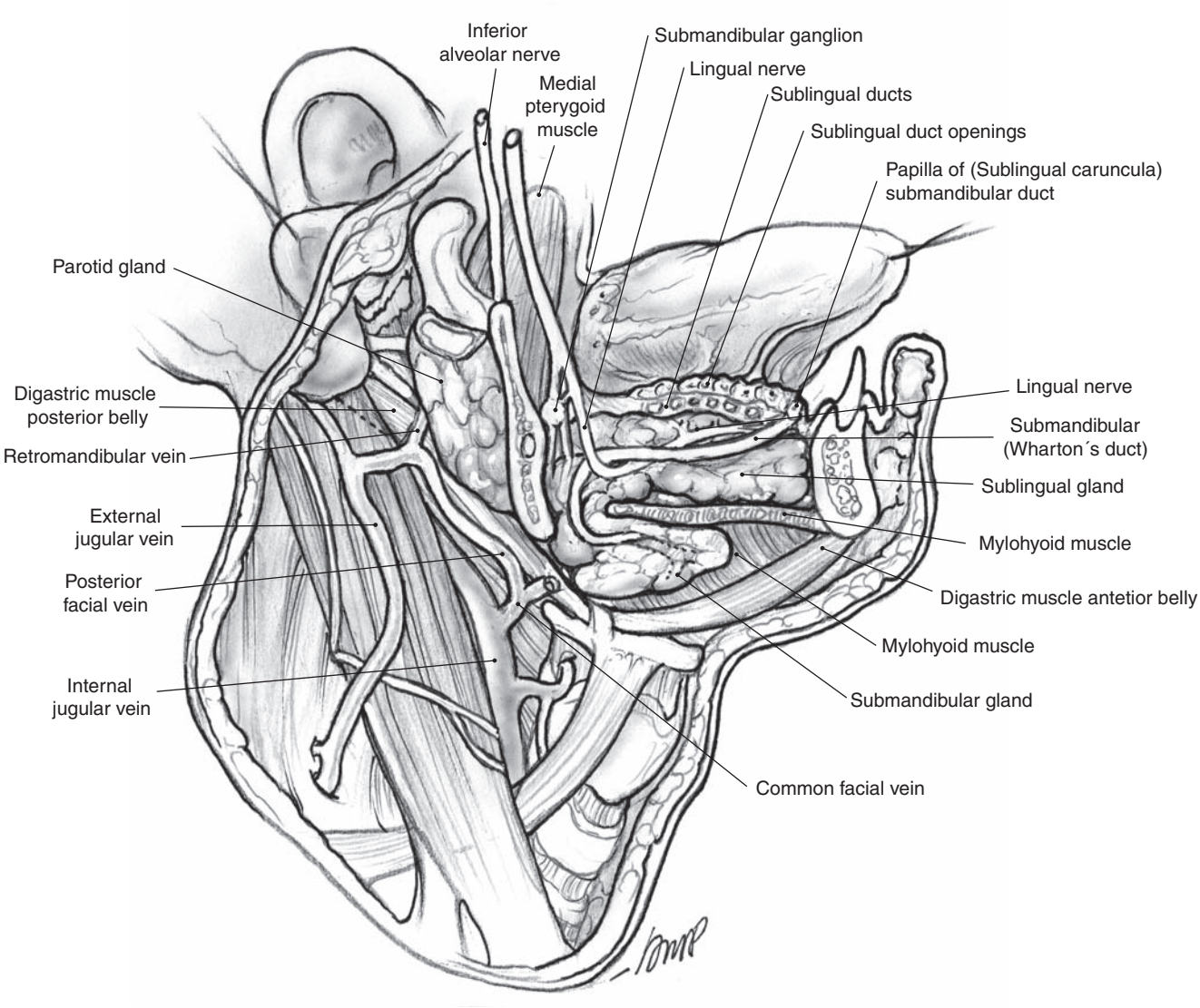

FIGURE 1–10 Submandibular gland and related anatomy.

to the lower branches of the facial nerve as it courses superiorly into the face. Although the artery is standardly ligated in two positions, at the inferior border of the mandible and superior to the posterior belly of the digastric muscle during submandibular gland surgery, its integrity can be preserved in certain clinical settings.

Venous Anatomy

The anterior facial vein is adjacent to the facial artery as it descends from the face over the inferior border of the mandible. The anterior facial vein then coalesces with the posterior facial vein and descends over the midportion of the gland forming the common facial vein. Inferiorly, this vein lies lateral to the gland as it exits the lower aspect of the submandibular triangle to ultimately join the internal jugular vein. Although numerous variations exist for the course of the common facial vein, the importance of this structure to the surgeon has already been discussed.

Wharton's Duct

The ductules comprising the drainage pathway of this secretory gland coalesce into the submandibular duct, which emerges from the sublingual portion of the gland. The duct then courses anteriorly between

the hyoglossus and mylohyoid muscles to form Wharton's duct as it enters the floor of the mouth. Along its course, the submandibular duct runs deep to the lingual nerve and medial to the sublingual gland. It then opens as a papilla in the floor of the mouth adjacent to the frenulum of the tongue.

Neural Anatomy

The facial nerve (CN VII) provides the secretomotor innervation for the submandibular and sublingual glands (**Fig. 1–11**). The fibers originate in the superior salivatory nucleus in the brainstem and exit via the nervus intermedius before joining CN VII in the internal auditory canal. The fibers then leave CN VII via the chorda tympani nerve in the mastoid segment of CN VII. The chorda tympani nerve courses through the middle ear and enters the petrotympanic fissure to the infratemporal fossa. It then joins the lingual nerve, a branch of the mandibular division of the trigeminal nerve. The fibers then synapse in the submandibular ganglion, and the postganglionic fibers innervate the submandibular gland. Other fibers return to the lingual nerve to innervate the sublingual glands.

Lingual Nerve

The lingual nerve, which provides somatosensory and taste function to the anterior two thirds of the tongue arises from the third division of the fifth cranial nerve, V_3 (**Fig. 1–12**). After exiting the foramen ovale, V_3 courses laterally toward the inner surface of the ramus of the mandible. The nerve then branches into the mandibular nerve, which enters the mandible, and the lingual nerve, which travels anteriorly and inferiorly along the lateral surface of the floor of the mouth. A small motor branch to the mylohyoid muscle will separate from the posterior aspect of the nerve under the mandible. This nerve becomes visible when the gland is mobilized inferiorly during removal. Sacrifice of this motor branch is necessary in the majority of cases. The lingual nerve is attached to the deep surface of the submandibular gland at the submandibular ganglion. The nerve carries preganglionic parasympathetic fibers into the submandibular ganglion from which emerge postganglionic

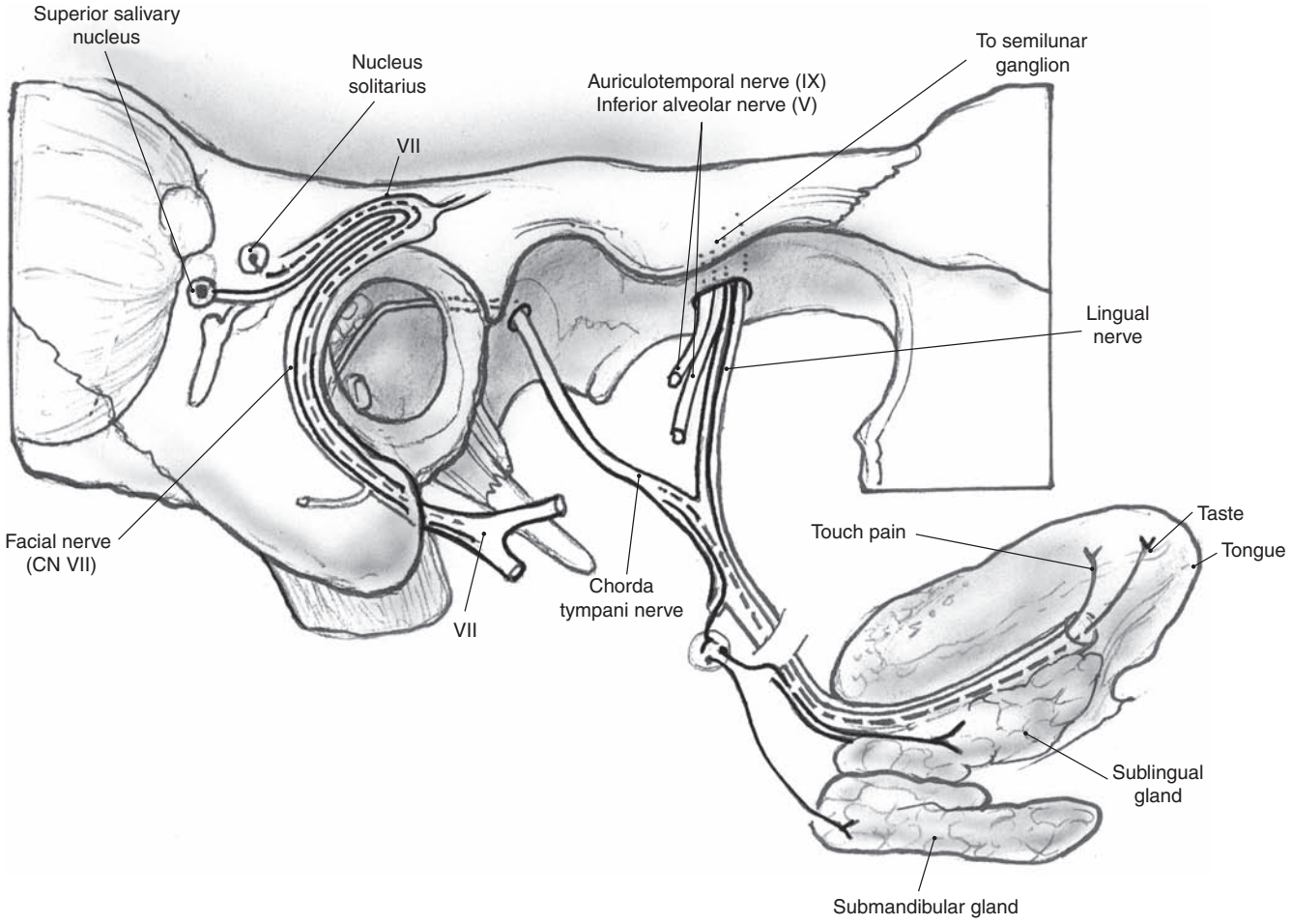

FIGURE 1–11 Autonomic nerve supply to the submandibular gland.

parasympathetic fibers to the gland. Traveling anterior to the ganglion, the nerve lies adjacent and superior to the submandibular duct. The lingual nerve and submandibular duct are exposed during dissection when the posterior edge of the mylohyoid muscle is retracted anteromedially.

The Hypoglossal Nerve

The hypoglossal nerve, which provides motor function to the tongue, enters the submandibular triangle just posterior and deep to the junction of the anterior and posterior bellies of the digastric muscle at the lesser cornu of the hyoid bone (**Fig. 1–12**). The nerve runs in

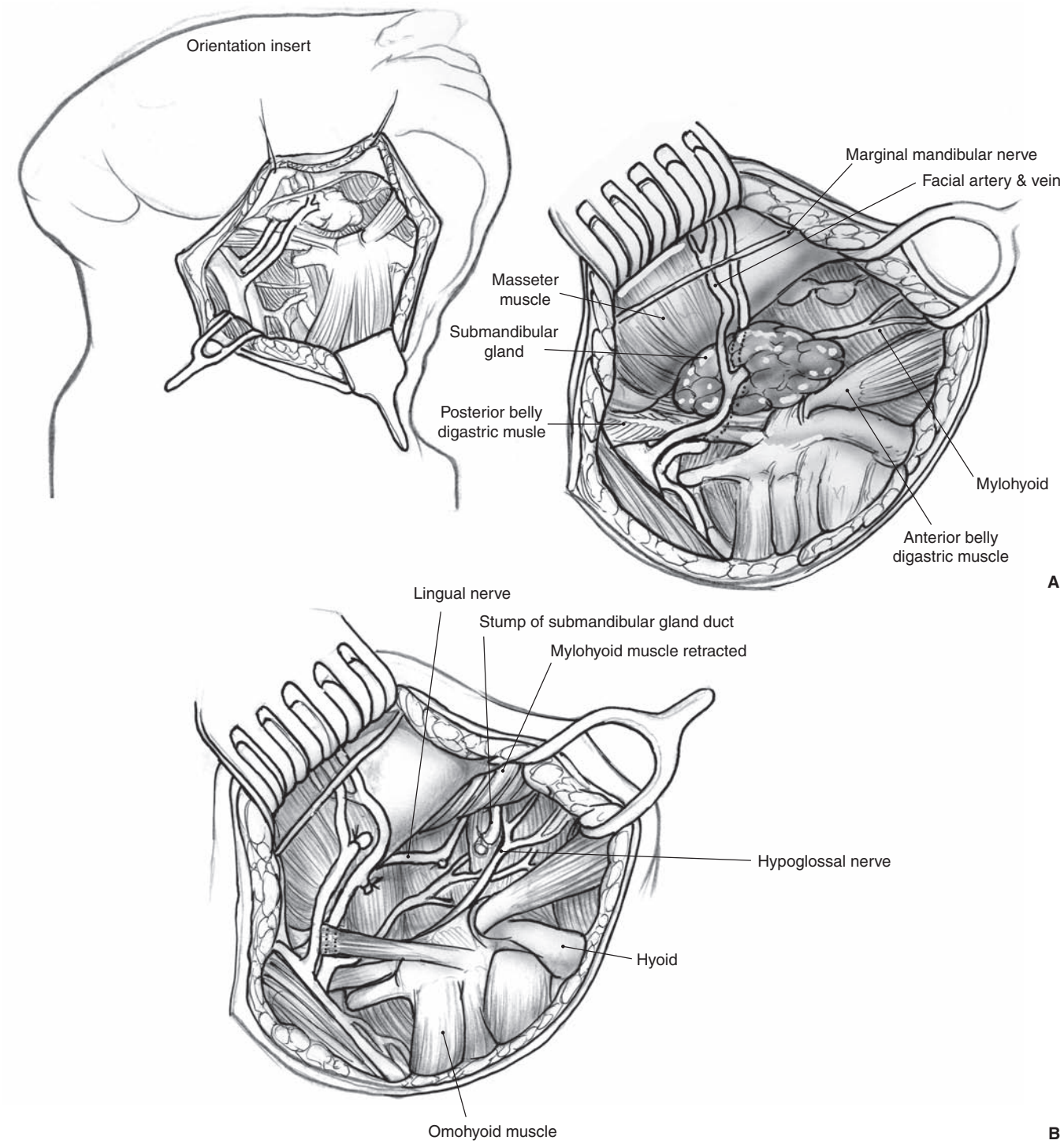

FIGURE 1–12 (A) The submandibular gland is removed, the marginal mandibular nerve is retracted superiorly, and **(B)** the hypoglossal and lingual nerves are visualized.

a plane deep to the submandibular gland and its associated structures and is paralleled in its course by a prominent venae comitantes system. The hypoglossal nerve will travel anteroinferiorly to the lingual nerve and is deep to the lingual nerve and submandibular duct. Care is taken to identify the hypoglossal nerve during dissection on the deep surface of the submandibular gland to preserve the integrity of this important motor nerve. The hypoglossal nerve can be readily identified in the submandibular triangle with gentle dissection just posterior to the junction of the anterior belly of the digastric muscle with the inferior attachment of the mylohyoid muscle.

Lymph Nodes

The lymph nodes associated with the gland are found superficial to the fascia. They can be located superior to the gland and are associated with the facial artery and vein. These nodes are called prevascular and postvascular nodes. They are important for oral cavity cancers, particularly those of the floor of the mouth. Unlike the parotid gland, the submandibular gland does not contain lymph nodes or lymphoid follicles.

■ Sublingual Gland

The sublingual gland is the smallest of the major salivary glands, weighing 2 to 4 g. It is a flat structure lying in the floor of the mouth superior to the mylohyoid muscle (**Fig. 1–13**). The sublingual glands are paired glands lying opposite the lingual frenulum. The sublingual gland is covered only by oral mucosa. The gland does not have a single duct but rather several ductules that open into the floor of the mouth (Rivinus ducts) or submandibular duct (Bartholin's duct). The sublingual glands are innervated by secretomotor fibers of CN VII from the superior salivatory nucleus in the brainstem.

Cysts or mucoceles of the sublingual gland, so-called ranulas, can form in the floor of the mouth and extend or ''plunge'' into the neck inferior to the mylohyoid muscle. Ranulas will be discussed in greater detail in another chapter.

■ Minor Salivary Glands

Minor salivary glands are found in the lips, tongue, buccal mucosa, palate, retromolar trigone, pharynx,

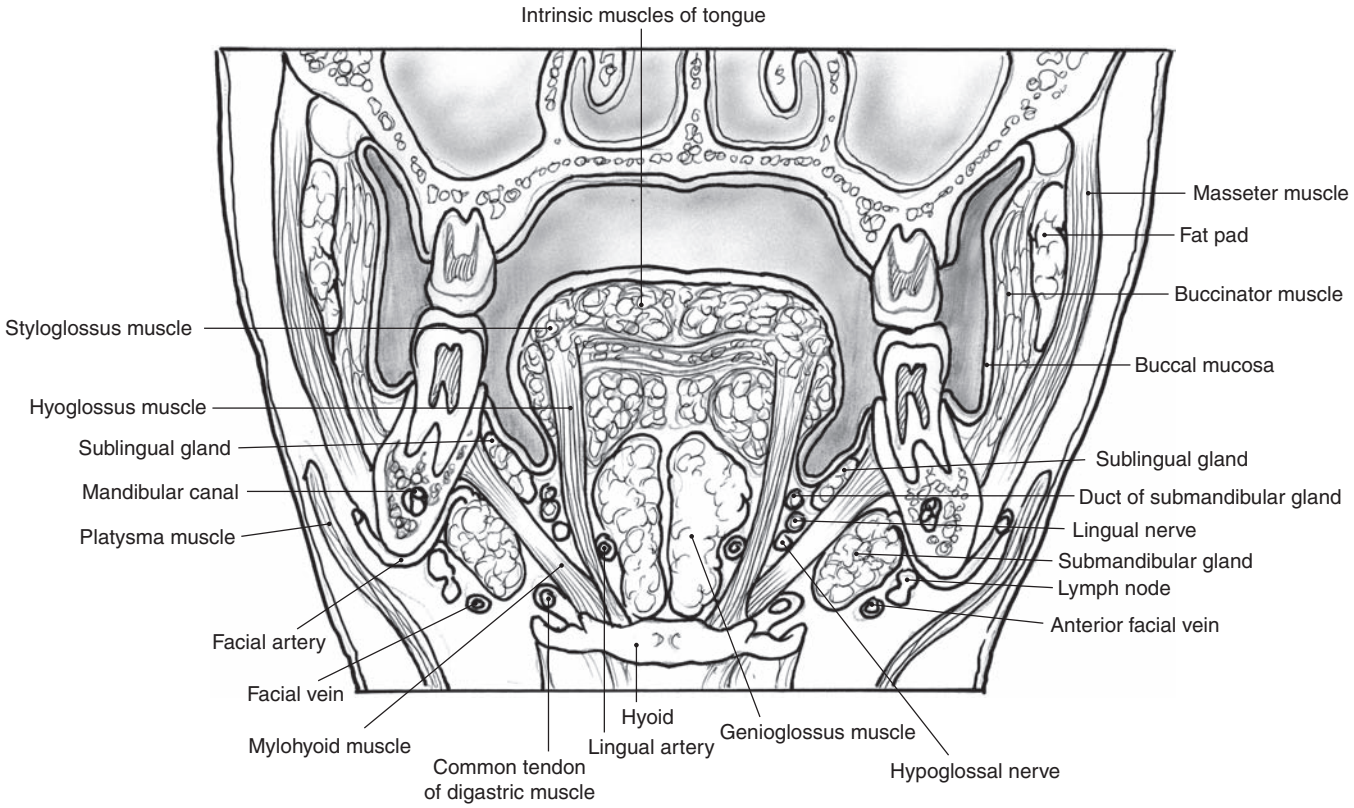

FIGURE 1–13 The floor of the mouth.

supraglottis, and paranasal sinuses and number ~600 to 1000. They are 1 to 5 mm in size. Each gland has its own duct emptying into the oral cavity, pharynx, or paranasal sinuses. They are concentrated in the lips, tongue, buccal mucosa, and palate. The lingual nerve supplies the postganglionic parasympathetic fibers to the majority of the minor salivary glands, though the more superior palatal glands receive innervation from the sphenopalatine ganglion. Salivary gland neoplasms can arise at any of these sites.

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2

Imaging of the Salivary Glands

LAURIE A. LOEVNER AND MADHAVI L. BATTINENI

The imaging algorithm for assessing the salivary glands depends on the clinical scenario with which the patient presents to his or her physician. There is a spectrum of imaging studies that may be used to assess salivary gland pathology, including computed tomography (CT), magnetic resonance imaging (MRI), ultrasound (US), and sialography. However, CT and MRI have sensitivities over 95% in detecting masses of the salivary glands and have largely replaced sialography in the evaluation of salivary masses.[1]

Many of the disease processes that affect the salivary glands may not require imaging of any kind. Such processes include self-limited entities like viral parotitis, mumps, and sialosis. At the other end of the spectrum are the infiltrative, deep lobe parotid masses/malignancies that usually require cross-sectional imaging, including CT or MRI, to assess for perineural spread of disease, infiltration of the skull base, intracranial extension of disease, and/or vascular involvement. In Europe and Japan, in the hands of an experienced sonographer, ultrasound is frequently the first imaging modality used to assess superficial salivary gland lesions.[2,3]

Patients with salivary gland pathology may present clinically with a suspected mass or with suspected obstruction and/or inflammation (diffuse unilateral or bilateral glandular enlargement). Although there may be overlap with many of the clinical entities, the initial imaging study desired may change depending on each of these presentations. In the discussion that follows, the role of imaging in assessing salivary gland pathology will be addressed and will be divided into the evaluation of neoplastic lesions, obstructive/inflammatory lesions, and systemic disorders affecting the salivary glands.

Neoplasms of the Salivary Glands

A painless mass is usually due to a neoplasm (benign or malignant), although neoplasms may occasionally present with dull pain and suggest an inflammatory process. In the parotid region, a painless mass may also be caused by intraparotid or periparotid lymph nodes or a parotid cyst.

The superficial layer of the deep cervical facial fascia encapsulates the parotid gland late in the second trimester of gestation; as a result, it is the only salivary gland to incorporate lymphatic tissue and lymph nodes.[3,4] Therefore, the potential for lymphadenopathy in the parotid gland exists. It is important that the radiologist determine if the pathologic lymph nodes are within the parotid gland or extraparotid at the time of imaging. Malignant adenopathy is typically seen in the setting of dermatologic malignancies (basal cell carcinoma, melanoma, and squamous cell carcinoma) (**Fig. 2–1**).[5,6] Occasionally, metastatic adenocarcinoma (breast, colon, lung) or metastatic squamous cell carcinoma from a primary aerodigestive tract malignancy may result in parotid lymphadenopathy.[5,7] In addition, lymphoma may occur primarily in the parotid gland as a dominant mass or infiltrative lesion, or may secondarily affect the parotid gland in the setting of systemic disease.[7]

Bilateral parotid gland masses are usually due to lymphadenopathy or Warthin's tumors and rarely acinic cell carcinoma.[8] Human immunodeficiency virus (HIV) frequently has bilateral parotid masses corresponding to a combination of lymphoepithelial cysts and lymph nodes,[9,10] as is also seen in Sjögren's syndrome.[11,12]

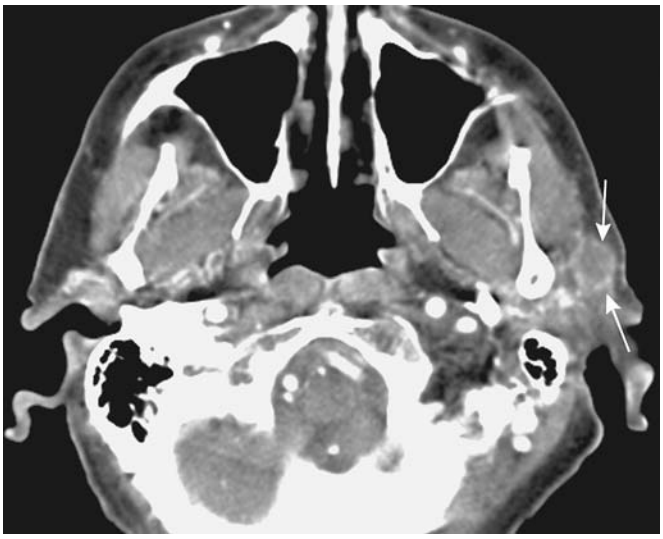

FIGURE 2–1 A 55-year-old male with a prior history of squamous cancer of the scalp presented with a new left cheek mass due to metastatic squamous cell carcinoma to an intraparotid lymph node. Axial contrast-enhanced computed tomography (CT) image shows an 8 mm mass (arrows) in the superficial left parotid gland.

Multiple painless masses within a single parotid gland may be caused by Warthin's tumors,[13] lymph nodes, and, less commonly, acinic cell carcinoma, metastatic disease,[14] and oncocytomas.[15]

Many would advocate MRI as the primary modality for assessing neoplasms of the salivary glands.[16–19] If the referring clinician is highly confident that the glandular process is neoplastic, then MRI is the first, and frequently the only, imaging technique used. However, if there is even a slight chance that the mass could be related to sialadenitis or sialolithiasis, then unenhanced CT utilizing thin (1–3 mm) sections should be performed first, as MRI is not as sensitive or accurate in detecting small calculi (while over 90% of these are seen on CT).[20–23]

There are many reasons why MRI is the preferred modality in assessing the patient suspected of having a neoplastic lesion of the salivary glands. MRI, due to its multiplanar capabilities, as well as the multiple pulse sequences available to assess such lesions (unenhanced T1-weighted, fat-suppressed T2-weighted, and enhanced axial and coronal fat-suppressed T1-weighted), is the best modality to ''map'' the extent of neoplasm.[24] Fat is hyperintense (bright) on T-1 weighted images, whereas tissue with abundant water content is hypointense (dark) on T1-weighted imaging and hyperintense on T2-weighted imaging. Gadolinium is an intravenous contrast agent with paramagnetic effects resulting in hyperintensity (''bright'' signal) that is taken up to varying degrees by neoplasms and inflammatory processes depending on their cellularity and vascularity.

In adults, the parotid gland has a high fat content with numerous thin interstitial septae. The intraglandular ducts and facial nerve are usually not visualized on CT, but can be identified on MRI[25,26] using special pulse sequences. Stensen's duct is well seen usually only when dilated. The retromandibular vein and external carotid artery are noted within the gland posterior to the ascending ramus of the mandible. Almost all parotid lesions are readily identified on unenhanced T1-weighted MRI (**Fig. 2–2**, **2–3**) as being hypointense (dark) relative to the intrinsic high signal intensity of the fat comprising a large portion of the normal parotid gland.[16,18,27] To confirm the presence of a parotid mass, T1-weighted images are most sensitive.[18] One cannot rely on T2-weighted images alone, as some lesions (including some Warthin's tumors and carcinomas) are similar in signal to the normal gland on this pulse sequence.[18] Unenhanced T1-weighted images are useful for assessing the extent of neoplasm within the parotid gland itself (including superficial and deep lobe involvement) (**Fig. 2–4).** In addition, unenhanced T1-weighted images are useful in assessing for invasion of the adjacent bone (the ascending ramus of the mandible, mastoid tip, and skull base marrow) because in the setting of neoplastic infiltration

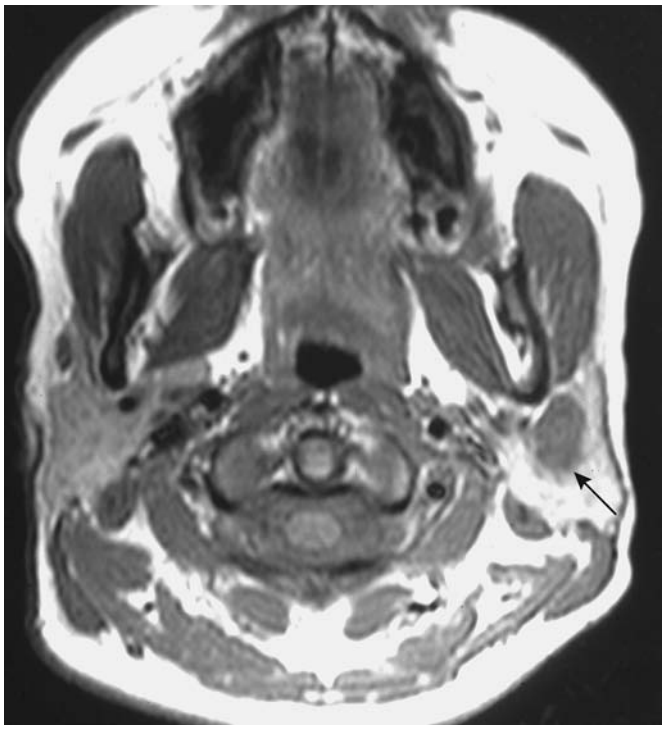

FIGURE 2–2 A 27-year-old woman with an incidental left parotid mixed tumor, detected on a brain magnetic resonance imaging (MRI) study, that was aspirated using CT guidance. Unenhanced axial T1-weighted MRI shows 1.2 cm hypointense mass of the left parotid gland (arrow). Note the hyperintense signal of the surrounding normal parotid gland due to its fat content.

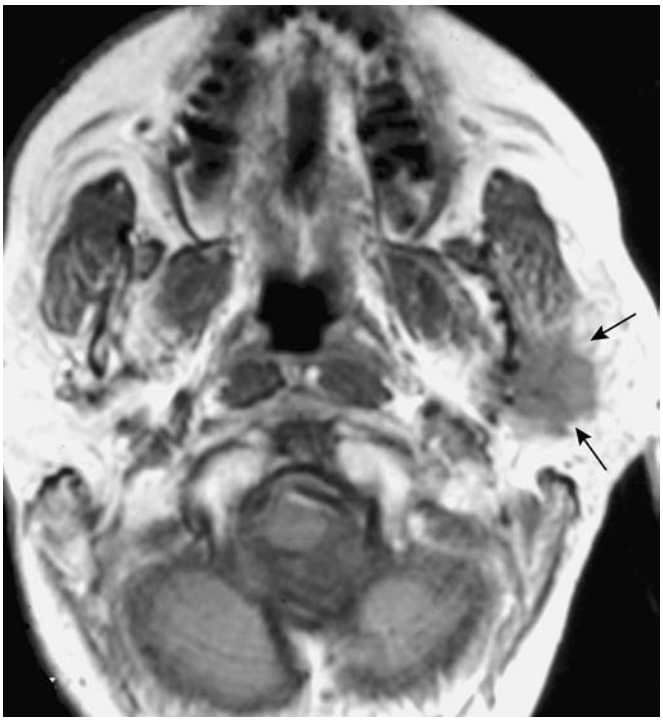

FIGURE 2–3 High-grade mucoepidermoid carcinoma of the left parotid gland. Axial unenhanced T1-weighted MRI shows a poorly demarcated hypointense mass (arrows).

in these locations, the normal hyperintense high signal intensity fat is replaced with hypointense/low signal intensity tissue (usually reflecting a combination of water and pathologic cells) (**Fig. 2–4**).[28] On fat-suppressed gadolinium-enhanced T1-weighted images, the normal fat-containing bone marrow of the mandible and skull base should be hypointense (suppressed); however, in the setting of neoplastic infiltration, enhancing (hyperintense) tissue replacing this normal hypointense background is noted. Similarly, in the presence of perineural spread of disease, one should see replacement of the normal high signal intensity fat in the marrow and the skull base foramina on unenhanced T1-weighted images. Corresponding hyperintense enhancing tissue on the gadolinium-enhanced T1-weighted images is indicative of neoplastic infiltration (**Fig. 2–5**).[8,24,29] In particular, the foramina must be closely assessed by the radiologist in the setting of malignant neoplasms of the parotid gland, including the stylomastoid foramen (seventh cranial nerve, CN VII), foramen ovale (CN V_3), and foramen rotundum (CN V_2). Finally, MRI is the most accurate imaging modality in detecting intracranial spread of disease, including involvement of the leptomeninges.[30–32] MRI is accurate in demonstrating perineural, vascular, and dural invasion that may be present with parotid malignancies, particularly adenoid cystic carcinoma.[31]

In many cases, discrimination between benign and malignant tumors is not possible on MRI. There are studies suggesting that the presence of poorly defined tumor margins may best suggest the presence of malignancy.[33] However, tumor margins and inhomogeneity cannot reliably predict benign from malignant disease (**Fig. 2–6**).[16] Therefore, it may not be possible for the radiologist to distinguish benign from malignant disease in the setting of an isolated, contained intraparotid mass. The presence of infiltration into the adjacent extramucosal spaces, including the masticator space, parapharyngeal space, and the adjacent skull base, is

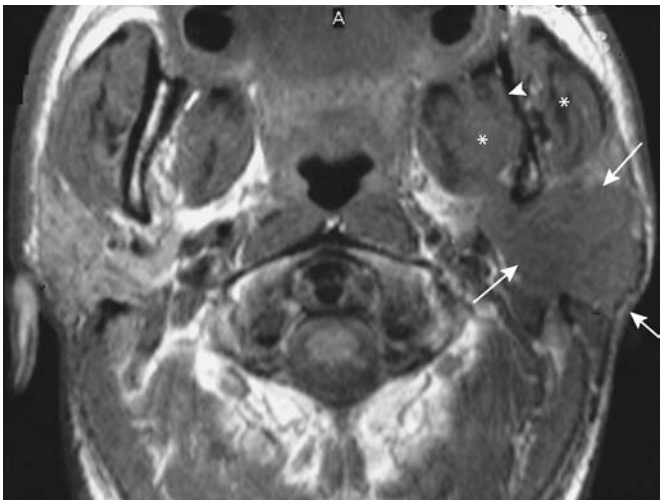

FIGURE 2–4 MRI of adenocarcinoma of the parotid gland with extensive extraglandular spread. Axial unenhanced T1-weighted MRI shows a poorly demarcated hypointense mass involving the superficial and deep lobes of the left parotid gland (arrows). There is spread to the mandibular foramen (arrowhead) and the masticator space (*).

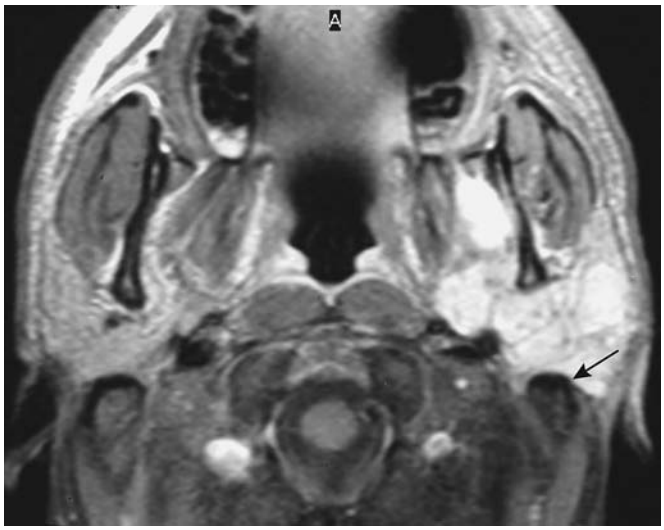

FIGURE 2–5 Enhanced axial T1-weighted MRI shows enhancement of the tumor that abuts the mastoid tip (arrow).

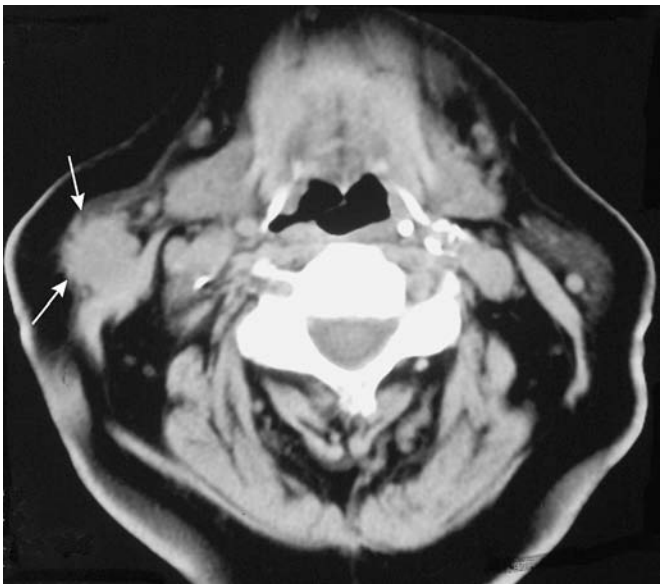

FIGURE 2–6 Axial CT image shows a poorly demarcated, spiculated mass in the right parotid tail (arrows) that represented a benign mixed tumor.

highly suggestive of a malignant lesion.[8] Furthermore, the presence of regional pathologic lymphadenopathy or perineural spread of disease is also usually indicative of neoplasm.[17,34]

T2-weighted MR images tend to be most reliable (~75%) in suggesting the possibility of malignant disease.[18] Typically, a lesion that is hyperintense on T2-weighted images is benign (**Fig. 2–7**), whereas a mass of intermediate or low signal intensity on T2-weighted images is of concern for malignancy (**Fig. 2–8**).[18,27] This is because highly cellular tumors with a high nuclear-to-cytoplasmic ratio (usually high-grade malignancies) frequently are intermediate to hypointense (dark) on T2-weighted images, whereas the less cellular, differentiated masses (benign tumors and low-grade malignancies) tend to be hyperintense on T2-weighted imaging due to higher water content.[27] Most high-grade mucoepidermoid carcinomas (**Fig. 2–8**), undifferentiated carcinomas, adenoid cystic carcinomas, and occasional squamous cell carcinomas of the salivary glands demonstrate intermediate to low signal intensity on T2-weighted images.[18,27] However, some malignancies do exhibit increased signal intensity on T2-weighted images, including low-grade mucoepidermoid carcinomas, some adenoid cystic carcinomas, and, rarely, adenocarcinomas.[16] It is also important to emphasize that pleomorphic adenomas may be hypointense on T2-weighted imaging, especially when cellular. Because they are far and away the most common parotid neoplasm, they will account for a significant number of the masses appearing dark on T2-weighted images; however, a malignant mass should always be excluded.

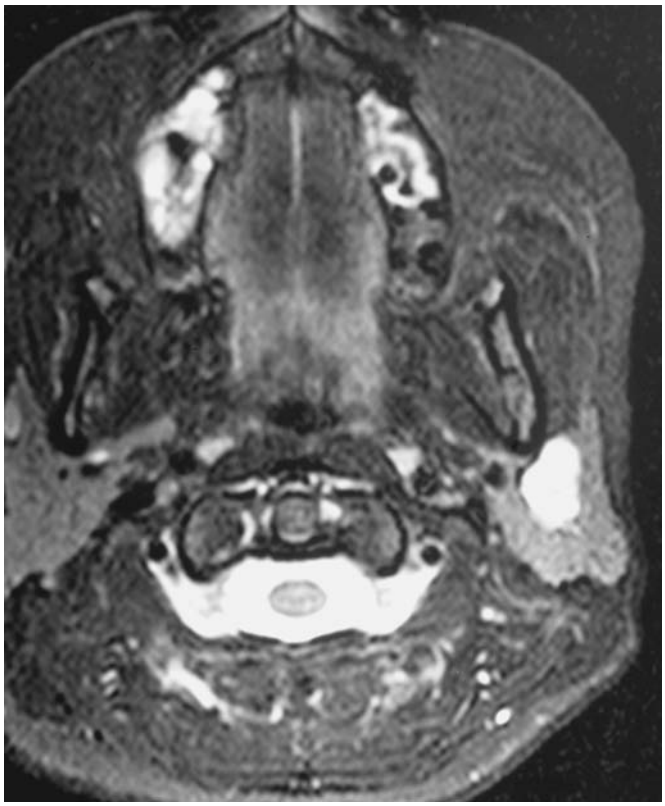

FIGURE 2–7 Same patient as in **Fig. 2–2**. Axial T2-weighted MRI shows the mass to be well demarcated and homogeneously hyperintense, typical of a mixed benign tumor.

The benign mixed tumor, like most benign tumors, is typically hyperintense on T2-weighted images (**Fig. 2–7**) due to extracellular water content, as well as intracellular water content due to a relatively low

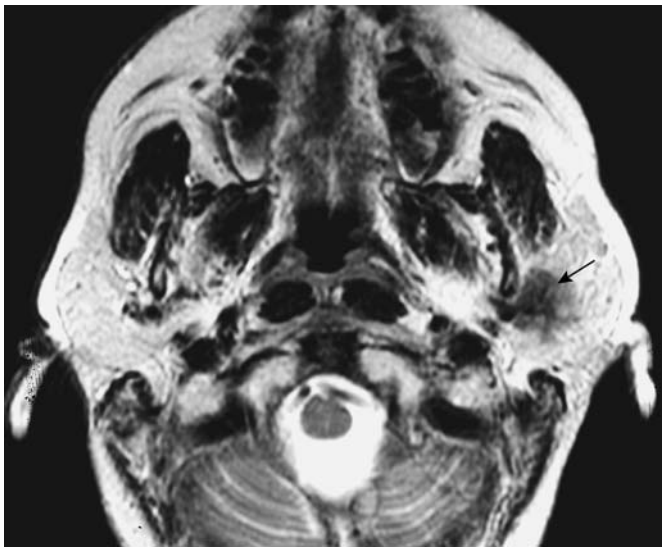

FIGURE 2–8 Same patient as in **Fig. 2–3**. Corresponding axial T2-weighted image shows that the mass is hypointense (arrow).

cellular-to-cytoplasmic ratio.[8,18,27] Among the benign masses that may not always be hyperintense on T2-weighted images are the cellular (less myxoid) mixed tumor and Warthin's tumor.[6] Therefore, a low signal intensity mass on T2-weighted imaging is not specific for a high-grade malignancy, but malignancy must be excluded. Other disease processes, including crystal deposition, fibrosis, and granulomas, can also be relatively T2-hypointense. In addition, chronic sialadenitis may appear hypointense on T2-weighted images.[27] This variability has led some to suggest that the signal intensity on T2-weighted images is not of significant value.[16]

Caution is required in differentiating purely cystic lesions from tumors with solid and cystic components. Warthin's tumors are typically complex lesions on T1- and T2-weighted images, containing areas that are solid and cystic.[35,36] Septae are not uncommon, and they are frequently lobular (**Fig. 2–9**). One important imaging differential is the presence of T1-hyperintensity on unenhanced imaging corresponding to proteinaceous cysts with cholesterol crystals or hemorrhage.[27] Fluid with a high protein concentration, as seen in the presence of blood products or mucoid material, may be hyperintense relative to normal cerebrospinal fluid.[35] However, the signal characteristics of the fluid, especially on unenhanced T1-weighted imaging, will depend on the fluid's viscosity and protein concentration. Simple fluid is usually hypointense on T1-weighted images and hyperintense on T2-weighted images.[15] Benign cysts (including lymphoepithelial cyst, mucus retention cyst, sialocele, first branchial cleft cyst, and ranula) are also commonly hyperintense on T2-weighted images. Administration of contrast is essential to distinguish a cyst from a mass. Specifically, a cyst typically demonstrates rim enhancement, whereas a mass typically demonstrates more solid enhancement.[15] It is important to note that some lesions that appear as simple cysts on unenhanced T1-weighted and T2-weighted images may demonstrate solid enhancement following contrast administration, reflecting that these are not cysts at all, but rather neoplasms[24] (**Fig. 2–10**). The value of contrast enhancement also applies to CT imaging (**Fig. 2–11**).

In the patient with prior parotid surgery for a malignant neoplasm and postoperative irradiation, fibrosis may be difficult to distinguish from recurrent neoplasm, as both are hypointense on T1- and T2-weighted images. In this scenario, positron emission tomography (PET) and/or imaging guided fine-needle aspiration (FNA) or biopsy may be indicated.[29] In the follow-up imaging evaluation of patients operated on for mixed benign tumors, MR is clearly the imaging modality of choice as recurrent pleomorphic adenomas have a somewhat

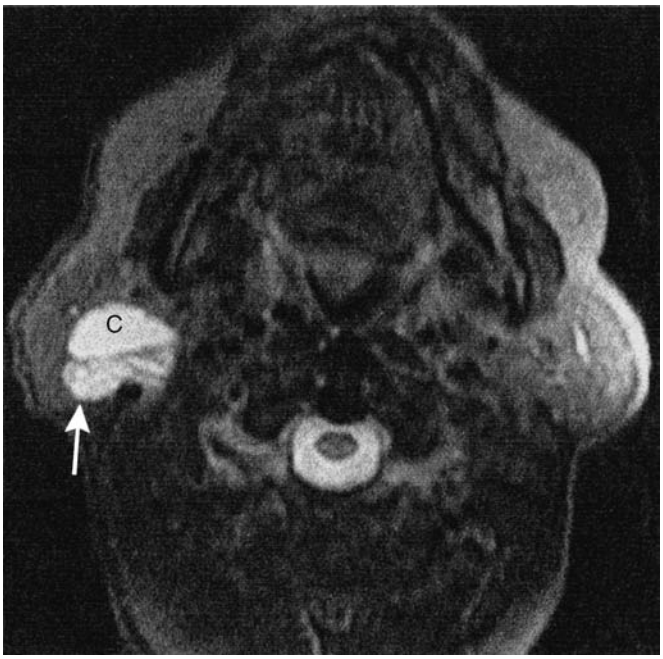

FIGURE 2–9 MRI of a complex cystic and solid Warthin's tumor in the right parotid gland. Axial T2-weighted MRI shows the cystic (c) component of the mass that is homogeneously hyperintense (similar to cerebral spinal fluid), and the more solid component posteriorly (arrow). Also, note the septations within the tumor.

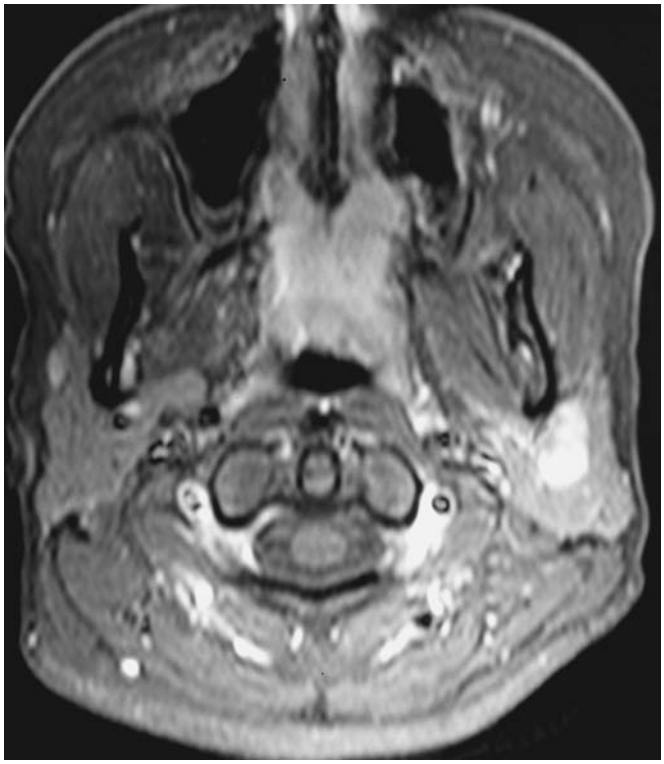

FIGURE 2–10 Same patient as in **Fig. 2–2**. Axial contrast-enhanced fat-suppressed T1-weighted MRI shows that the mass homogeneously enhances.

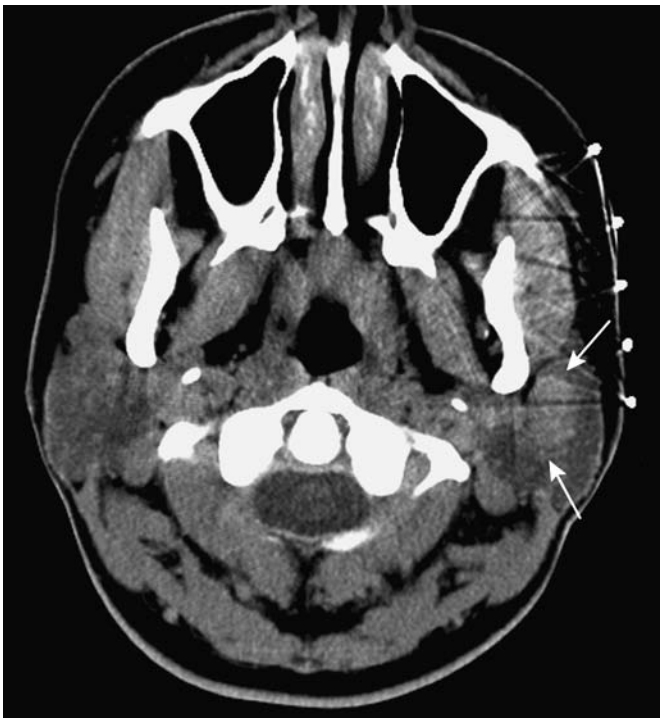

FIGURE 2–11 Same patient as in **Fig. 2–2**. Delayed enhanced axial CT image obtained approximately 6 minutes after injection shows the mass (arrows) is now clearly identified. For reasons not clearly understood, benign mixed tumors are frequently best delineated on CT using delayed imaging.

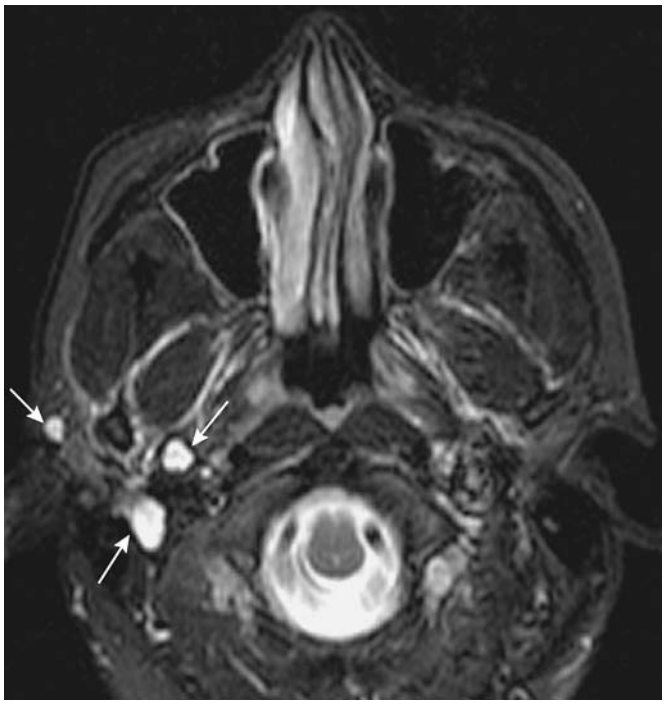

FIGURE 2–12 Recurrent pleomorphic adenoma 3.5 years following initial parotidectomy. Axial T2-weighted image shows the characteristic appearance of recurrent tumor, with multiple T2-hyperintense cystic-appearing nodules (arrows).

characteristic appearance, typically there are multiple T2-hyperintense cyst-like nodules (**Fig. 2–12**).

The attenuation of parotid masses on CT imaging allows one to distinguish a benign cyst from a solid mass, and distinguishes lipomas, but otherwise does not help in predicting histological diagnosis because most solid masses have a similar appearance on CT imaging.[3,15] Because the appearance of a mass on CT is not a good predictor of histological diagnosis,[37] and because MR imaging is more accurate than CT imaging in determining the extent of disease,[38] MR imaging is advocated as the best imaging modality in the clinical setting of a suspected salivary gland mass.[5] Computed tomographic images are also more susceptible to degradation by dental artifact.[7] Although bone marrow involvement is better demonstrated on MR imaging, early cortical involvement of the mandible or skull base (mastoid tip) is best visualized on CT. Because neither study is histologically specific, FNA or biopsy is frequently performed to establish a histological diagnosis necessary to plan therapy.[5,15,32]

Nuclear scintigraphy may be useful in diagnosing Warthin's tumors and oncocytomas. These neoplasms are unique in that they show increased radiotracer uptake on technetium Tc 99m pertechnetate imaging.[1] Because these lesions are not associated with significant malignant potential, in patients who are elderly or who have surgical contraindications, observation may be advocated. Positron emission tomography (PET) has not been a reliable predictor of histological diagnosis, with an accuracy rate of $\sim 60-70\%$.[39]

In Europe and Japan, ultrasound is frequently the first imaging technique utilized in assessing suspected masses within the superficial aspect of the parotid gland. Ultrasound can delineate the retromandibular vein and superficial temporal vein, but not the facial nerve. It is not accurate in assessing deep lobe parotid masses. In skilled hands, ultrasound can analyze superficial salivary gland neoplasms with an accuracy similar to CT and MR imaging.[2,40] Gritzmann in a large series demonstrated that $\sim 95\%$ of space occupying major salivary gland tumors could be completely delineated on ultrasound.[41] All neoplasms were hypoechoic relative to the normal hyperechoic fatty glandular tissue; however, ultrasound, like CT and MR, is not always accurate in distinguishing benign from malignant pathology. Ultrasound differentiated extraglandular from intragrandular lesions with 98% accuracy[42] (all misinterpretations were periparotid lymph nodes).

Color doppler ultrasound may also be useful, as malignant salivary gland neoplasms frequently show a higher grade of vascularity compared with benign neoplasms.[43]

Flow alterations in color doppler ultrasound can be a physiologic parameter in disease states such as Sjögren's.

The limitations of ultrasound even in skilled hands include its inability to assess deep parotid masses, obscuration of lesions by the mandible, and poor identification of extra-parotid spread of disease into the extramucosal spaces of the head and neck (parapharyngeal and retropharnygeal spaces).[2] In addition, ultrasound is not good in assessing for perineural spread of disease or intracranial extension. Magnetic resonance and CT imaging have supplanted ultrasound in the evaluation of a salivary gland mass when such extension is suspected.[3,44] Ultrasound guided FNA may be utilized in the evaluation of a superficial parotid mass that is either not readily palpable, or has both a solid and cystic component.

There is controversy as to the reliable identification of the facial nerve below the skull base.[25,26,45–47] A line connecting the lateral surface of the posterior belly of the digastric muscle and the lateral surface of the mandibular ascending ramus has been used to separate superficial (lateral to the facial nerve) from deep (medial to the facial nerve) parotid masses on imaging.[26,48–50] The differentiation of deep from superficial parotid masses is critical as this will dictate the extent of dissection needed to separate the nerve from the tumor, the attendant risk to the facial nerve, and in the case of tumors involving the parapharyngeal space, the need for a cervical approach with or without mandibulotomy.[44,51,52]

CT and MR imaging play an important role in assessing parapharyngeal space masses including deep lobe parotid tumors, minor salivary gland tumors, and schwannomas (**Fig. 2–13**, **2–14**). Deep lobe parotid tumors and minor salivary gland tumors in the parapharyngeal space lie in the pre-styloid compartment anterior to the carotid artery. Deep lobe parotid tumors are connected to the parotid and can displace the parapharyngeal fat medially. One of the largest issues the surgeon encounters is whether a lesion is arising from the deep lobe of the parotid gland or primarily from minor salivary gland tissue in the parapharyngeal space.[53] With large lesions this can be difficult to determine with certainty. In the post-styloid compartment (the carotid space), common lesions include schwannomas and paragangliomas. They arise posterior to the internal carotid artery and displace it anteriorly. Schwannomas and paragangliomas enhance with gadolinium. Paragangliomas may be further characterized by the presence of serpintine flow voids (salt and pepper appearance) due to the marked vascularity that these lesions can have.

Increasingly, CT image-guided aspirations have become very useful in the assessment of a painless mass of the salivary glands. The most common request for CT-guided aspirations is in the assessment of deep lobe parotid or incidental parapharyngeal space

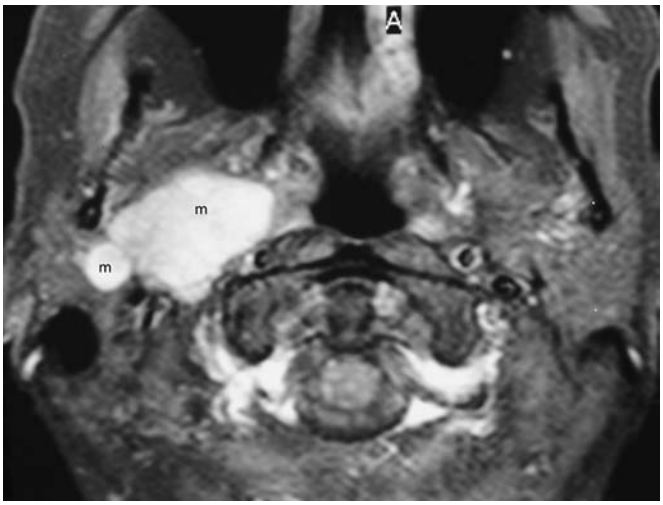

FIGURE 2–13 Mixed benign tumor of the deep lobe of the parotid gland. Axial enhanced fat-suppressed T1-weighted MRI shows a multilobular, enhancing mixed mass (m) of the deep lobe of the right parotid gland, extending to the prestyloid parapharyngeal space.

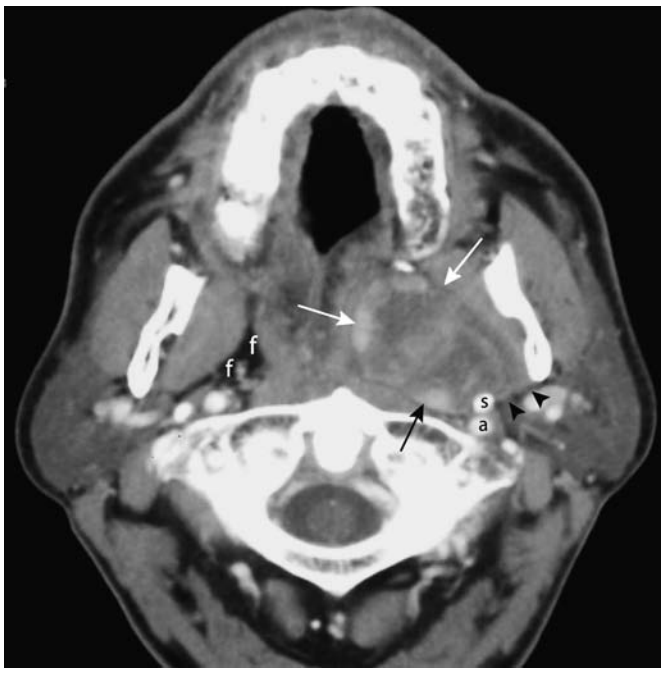

FIGURE 2–14 Schwannoma of the parapharyngeal space. Axial enhanced CT image obtained at the skull base shows a well-defined, heterogeneously enhancing mass (arrows) arising in the left parapharyngeal space. There is a fat plane (arrowheads) separating the mass from the deep lobe of the parotid gland. There is sclerosis of the styloid process (s), suggesting the mass has been there a long time. a, left internal carotid artery; f, fat comprising the normal right parapharyngeal space.

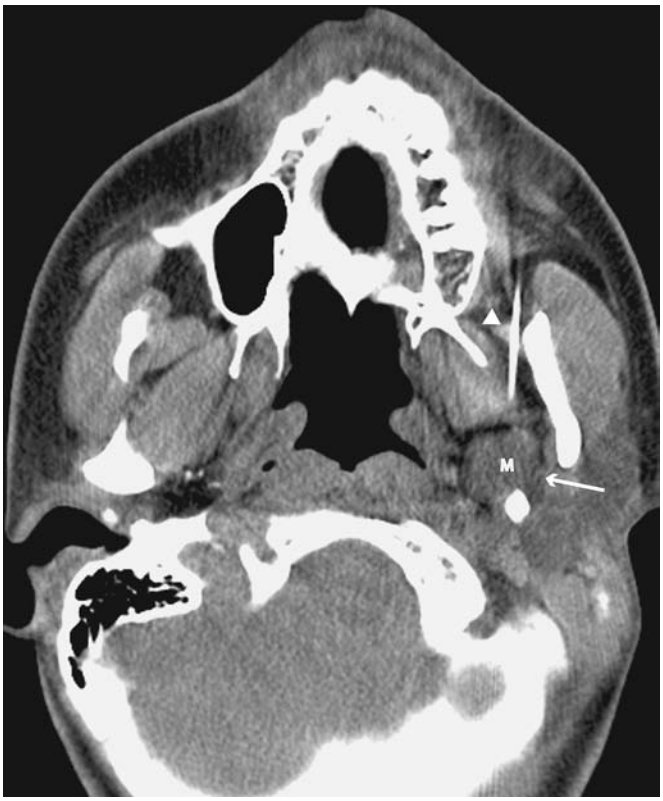

FIGURE 2–15 CT-guided fine-needle aspiration of a left parapharyngeal space mass; cytology revealed mixed benign tumor. Axial unenhanced CT image shows a 14 mm mass (m) in the left parapharyngeal space. Note the hypodense fat plane (arrow) separating the mass from the deep lobe of the parotid gland, and the needle (arrowhead).

masses (**Fig. 2–15**).[54] Frequently, these lesions are not palpable and difficult to approach endoscopically.

■ Obstructive or Inflammatory Lesions

The classic signs of pain and swelling of the involved gland are typical in patients presenting with sialolithiasis (calculi of the salivary glands).[20,55–57] Sialolithiasis is the second most common cause of salivary gland disease after viral infection or mumps. Typically the gland may be diffusely or focally enlarged with a sialolith in the proximal duct. Sialolithiasis most commonly affects the submandibular gland.[40,58] Approximately 80% of sialoliths occur here because the saliva from this gland is more alkaline, thicker, and viscous. Calculi may be multiple (25%), and may occur within intraglandular ductal tributories or within the main ducts. When in the gland itself, the symptoms may be relatively minor, whereas a main ductal sialolith usually has a more acute presentation.

Imaging is extremely valuable in localizing sialoliths. Computed tomography,[20] ultrasound,[59,60] and plain film radiography accurately identify sialoliths (see Chapter 7). Most important is distinguishing intraductal versus intraglandular calculi. Ultrasound is less accurate than CT in distinguishing clusters of stones from single, large stones.[57,60] In general, CT is the imaging modality of choice, and should be performed using thin section (1–3 mm) images. Intravenous contrast should not be administered as small opacified blood vessels may mimic small sialoliths. If an associated inflammatory process or infection is clinically suspected, then contrast enhanced imaging can be performed following unenhanced imaging.[15]

In recent years, some investigators have suggested fast T2-weighted MR imaging with thin sections to noninvasively evaluate ductal architecture and to identify stones.[21,61] Although the ductal system can be nicely demonstrated with thin section T2-weighted MR images, tiny intraglandular calculi, and stones within the main ducts can be overlooked with MR images because of the signal void associated with the calcified stone.[61] In cases of a painful salivary gland associated with chronic sialadenitis without a calculus seen on CT, ultrasound, or plain film radiography, the appearance of the ductal system that MR imaging affords may provide information regarding the etiology of the painful gland. Strictures may be identified in the site of a prior sialolith. In other cases, sialadenitis may not be from calculi, but from other conditions such as autoimmune disease, and the ductal appearance may suggest the cause. For example, pruned or truncated main salivary ducts with globular collections within the peripheral gland parenchyma is typical for autoimmune inflammatory conditions.[62,63] Large ducts are typically spared.

Sialography is contraindicated in the acute setting of suspected sialadenitis because of the possibility of exacerbating the symptoms associated with the infection.[62] Retrograde injection of contrast material may force inflammatory products into the peripheral parenchyma of the gland. Furthermore, instrumentation may cause post-traumatic edema within the duct or stricture formation, leading to reduced drainage of the infected saliva.[15] CT is more sensitive than sialography in demonstrating calculi. Sialography has been used because calculi rarely cause complete obstruction. A filling defect representing the calculus occurs as contrast flows around it. Chronic inflammatory lesions give similar sialographic change including segmental strictures and dilation, saccular dilation of the terminal ducts (punctuate, globular, cavitary, and destructive), and pseudocyst formation. Sialography remains of value in assessing penetrating trauma. Radiosialography using technetium has a limited role in assessment of parenchymal function.

Magnetic resonance sialography has the advantage of not requiring cannulation of the duct, and has a heightened sensitivity to edema in the salivary gland.[64,65] However, in general, the need to perform conventional or MR sialography is limited to a handful of instances when clinical assessment, serology (autoimmune disease) conventional radiography, and/or CT cannot facilitate the diagnosis of chronic sialadenitis.

On cross-sectional imaging, an inflamed gland is usually enlarged, with abnormal attenuation or signal intensity, and prominent enhancement. There is frequently soft tissue stranding in the surrounding subcutaneous fat and tissues. The involved gland will be hyperintense on T2-weighted MR imaging. There may be adjacent enlarged lymph nodes or intraglandular lymph nodes in the setting of parotitis. Inclusion of CT and MR images in the coronal plane to assess inflammatory conditions of the parotid and submandibular glands may be valuable. The relationship of the inflammatory mass to the floor of the mouth for submandibular lesions, and the skull base for parotid gland lesions, is important regarding surgical approach.

A ranula can be completely characterized regarding its relationship to the mylohyoid muscle allowing the surgeons to determine surgical approach.[15] A ranula that plunges through the muscular floor (a plunging ranula or pseudocyst, not epithelial lined) may be excised through a transcervical, submandibular incision.

■ Systemic Diseases

There are numerous imaging manifestations of chronic sialadenitis, most importantly chronic sialolithiasis may result in a small atrophic gland with focal intraglandular calcifications. Systemic disorders that may affect the major salivary glands include autoimmune disease, HIV infection, Sjögren's, and sarcoidosis. CT may be the best way to image these patients because calculi may be responsible for the acute symptoms related to the systemic disorder. Sjögren's syndrome and sarcoidosis predispose patients to stone formation (**Fig. 2–16**). The attenuation within the gland may be increased with both Sjogren's disease and sarcoidosis. Focal masses may be present including cysts, nodules, and lymph nodes in all of the autoimmune diseases. In most cases, the diagnosis of Sjogren's disease; however, can be made clinically based on the sicca syndrome and the connective tissue disorder (i.e., rheumatoid arthritis) combined with serology of antinuclear antibodies. Sialography may occasionally be a value in staging Sjogren's syndrome. Punctate, globular, and destructive glandular ductal patterns may be discerned with MR sialography.[15] There is an increased risk of lymphoma within the parotid gland in patients with Sjögren's

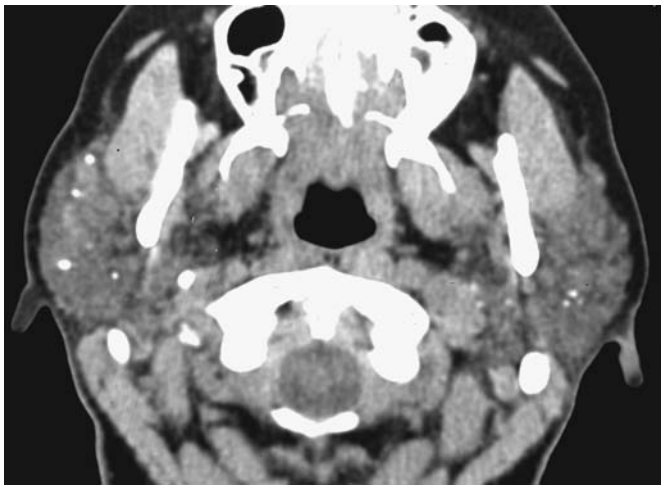

FIGURE 2–16 Axial enhanced CT image shows chronic sialadenitis in a patient with Sjögren's syndrome. Note the increased density/attenuation of the bilateral parotid glands, as well as multiple, tiny, punctuate intraglandular calcifications/calculi.

syndrome by more than 4,000%.[66] Any dominant parotid mass in a patient with Sjögren's syndrome should be considered to be lymphoma and requires fine-needle aspiration or biopsy. MR imaging may be particularly useful in discerning cysts from dominant masses within the parotid glands.[66]

Som et al used the phrase ''acquired immunodeficiency syndrome-related parotid cyst'' to describe the cysts associated with HIV infection that have a similar appearance to Sjogren's related benign lymphoepithelial lesions.[11] In HIV infection, cysts and lymphoid nodules/lymph nodes may be present in the parotid glands (**Fig. 2–17**). Additional findings include cervical lymphadenopathy, as well as hypertrophy of the adenoidal tissue.[51,67]

Sialosis refers to bilateral, painless enlargement of the salivary glands caused by systemic disorders such as diabetes mellitus, hyperthyroidism, alcoholism, and malnutrition. Certain medications have also been associated with sialosis.[62] This disorder is rarely imaged but usually shows enlarged parotid glands with increased attenuation and slightly increased T2-weighted signal intensity. If there are calcifications within a painless parotid mass, benign mixed tumor, granulomatous disease, and occasional venous malformations are the most likely diagnoses.[62] Sarcoidosis predisposes to glandular calcifications.

In summary, most disorders affecting the salivary glands will manifest with a few discrete clinical presentations that will guide imaging selection if necessary for further evaluation. Because sialolithiasis may have a spectrum of clinical manifestations, unenhanced CT should be the mainstay of imaging. Optimal imaging of the salivary glands may require unenhanced (to identify

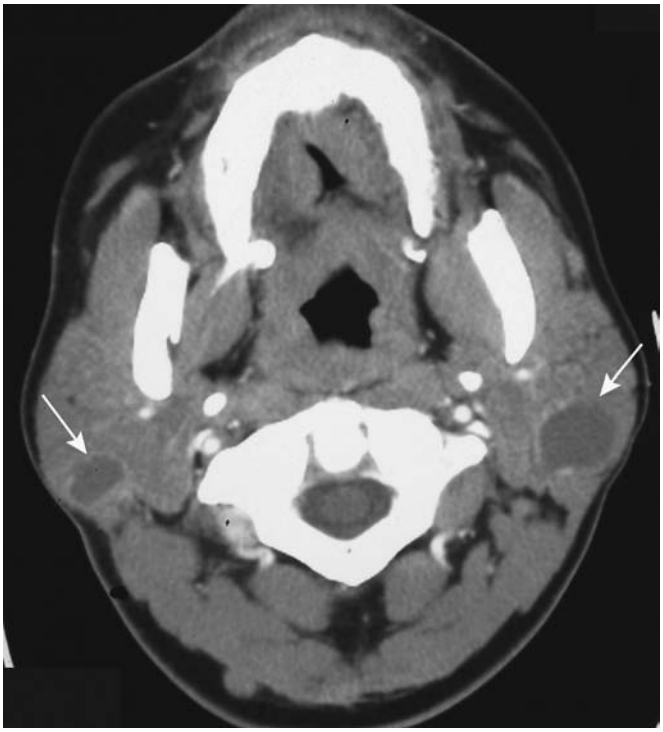

FIGURE 2–17 Axial enhanced CT scan shows lymphoepithelial cysts (arrows) in the bilateral parotid glands in this patient with human immunodeficiency virus (HIV) infection.

calculi), enhanced (to identify a mass), or both unenhanced and enhanced CT scans (for painful masses for which one cannot exclude sialolithiasis). However, for a nonpainful, noninflammatory mass in which there is a high degree of clinical suspicion for a neoplasm, contrast enhanced multiplanar MR imaging is the study of choice. Sialography, may occasionally be indicated and can be noninvasively performed with thin section heavily T2-weighted MR techniques. With CT, assessment of salivary gland tumors requires the administration of intravenous contrast to increase lesion conspicuity when there is a suspected neoplasm.

Imaging of the salivary glands has shifted away from predominantly utilizing plain films and conventional sialography to CT and MR imaging, as well as ultrasound.

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3

Embryology, Physiology, and Biochemistry of the Salivary Glands

KENNETH R. NISSIM, ROBERT L. WITT, AND JONATHAN A. SHIP

Embryology

Salivary glands are present in amphibians upward. Parotid glands are first present in mammals. The major salivary glands start to develop as outpouchings of oral ectoderm into the surrounding mesoderm. The connective tissue in the glands is derived from neural crest cells. The salivary glands originate from solid epithelial buds.

The primordial parotid gland starts to develop in the seventh embryonic week at the site of the eventual duct orifice near the angle of the stomodeum. Three stages are described in the development of the salivary glands.[1] The first stage includes the anlage and the development of branched duct buds that are dichotomous. Two cell types are present: ciliary epithelial cells that line the lumen, and myoepithelial cells covering the external surface. The early presence of myoepithelial cells is evidence that these cells are of ectodermal origin. Branching morphogenesis of the developing salivary glands is initiated by the formation of shallow clefts in a globular bud that deepen to generate new buds. Similar to lung and kidney, salivary gland branching results in repetitive epithelial cleft and bud formation, leading to complex three-dimensional branching structures. Epithelial basement membrane components such as laminin and proteoglycans are required for salivary branching and epithelial functions in general.[2,3] Fibronectin, an extracellular matrix protein, is essential for cleft formation during the initiation of epithelial branching.[4] A second stage includes early formation of lobules and canalization of the ducts. Myoepithelial cells are found around primitive acini and the distal segment of the duct. These functional units, which include endoplasmic reticulum and supranuclear Golgi zones, are completed at the seventh embryonic month. A dysfunction during this second stage may lead to congenital polycystic parotid. The third stage leads to further differentiation of the acinar cells and intercalated ducts with a reduction of the interstitial connective tissue. A study of 22 normal human fetus salivary glands of varying maturities removed at autopsy revealed that the functional maturity of the fetal gland occurs at 21 weeks into gestational maturity. The acini and ducts undergo distinct alterations in antigen expression with growth and maturation until 33 to 40 weeks of gestation, when they resemble adult salivary gland.[5]

Whereas the parotid anlage grows posteriorly, forming tubuloacinar systems, the facial nerve grows anteriorly. The gland eventually envelops the proximal extratemporal facial nerve and its major branches. An examination of human embryos and fetuses revealed no evidence of the parotid gland becoming a bilobate structure as a result of the course of the facial nerve.[6] The interstitium that the parotid moves into is rich in lymphocytes. Mesenchymal tissue surrounds and penetrates the gland, entrapping lymph nodes in the process. A true capsule is not formed around the parotid gland. The parotid gland reaches its final position at the end of the third embryonal month, being the salivary gland farthest removed from its place of origin in the oral cavity. During embryonic maturation, the number of myoepithelial cells decreases, but subsequently increases after birth. The striated ducts are not recognized until birth. The first salivary secretion does not occur until after birth on the stimulation of feeding.

The medial paralingual groove constitutes the anlage of the submandibular glands that appears in the sixth embryonal week. It develops from endodermal buds in the floor of the stomodeum and grows posteriorly and lateral to the developing tongue. During the early stages of development, ducts are surrounded by a one- or two-layer thickness of cells. Acini form at 12 weeks. Myoepithelial cells lie on the external surface of the ducts and acini. Electron microscopy demonstrates desmosomes with microvilli, glycogen granules in the cytoplasm, and secretory granules in the primitive acini.[1] A complete capsule is formed, and its final position, like all salivary glands, is achieved in the third embryonic month. Intraglandular lymph nodes are a rare finding.

The sublingual gland anlage forms at the ninth gestational month. It develops from multiple endodermal epithelial buds in the paralingual sulcus. The glands are penetrated by sublingual connective tissue, and a capsule is therefore absent. Intraglandular lymph nodes are not generally observed. The sublingual glands do not form major ducts. They are aggregations of minor salivary glands, which empty either directly into the oral cavity individually or through openings into the Wharton's duct.

Minor salivary glands form directly as individual units from upper respiratory ectoderm as simple tubuloacinar systems.[7,8] They appear at about the 12th week of intrauterine life. Staining for mucin suggests secretion begins in intrauterine life.[9]

■ Physiology and Biochemistry

Autonomic Nervous System

The flow of saliva is regulated predominantly by the autonomic nervous system. Control of most other gastrointestinal secretions is hormonal. There is a minimal impact from endogenous factors such as bradykinin, aldosterone, estrogen Y1, and antidiuretic hormone on saliva. The salivary glands appear to have roughly equal innervations by sympathetic and parasympathetic fibers. Although both sympathetic and parasympathetic stimulation produces saliva, the parasympathetic system is dominant.

Parasympathetic denervation leads to atrophy of the glandular tissue and decreased production of saliva, whereas sympathetic denervation yields no significantly observable effect on salivary flow.[10,11]

Autonomic innervation extends to vascular, acinar, and myoepithelial cells, as well as intercalated ducts. Neurotransmission by acetylcholine and vasoactive intestinal polypeptide (parasympathetic) and norepinephrine (sympathetic) is nonsynaptic. The receptors reside directly on the cell membranes, and the postganglionic axons from both types of fibers may terminate on or near the same cells. These axons can be either hypolemmal (penetrate the basement membrane) or epilemmal (do not penetrate the basement membrane). The majority of hypolemmal axons are cholinergic, although adrenergic ones also exist.[11,12] Because there is no synaptic transmission, there can be a spillover effect of neurotransmitter from one cell to another.

Although parasympathetic stimulation is dominant and longer lasting, normal salivary physiology depends on the interplay between both sides of the autonomic nervous system.[13,14] This autonomic duality is a common theme in animal neurophysiology; however, in the case of the salivary complex, the effects of the two sides of the autonomic nervous system are more complementary than antagonistic. The parasympathetic system is the primary stimulus for fluid formation, stimulation of glandular metabolism and growth, transport activities of acinar and ductal epithelium, and vasodilation.[14] Parasympathetic stimulation has a limited role in regard to protein secretion and exocytosis and produces a high volume of saliva with low protein content. The sympathetic system is the primary stimulation of exocytosis, modulating protein composition in saliva and constriction of blood vessels, resulting in a decreased salivary gland blood flow. It has a small role in fluid secretion, possibly additive to the parasympathetic system. Both systems induce contraction of myoepithelial cells and stimulate salivary flow (**Table 3–1**). The sympathetic system is synergistic to the dominant parasympathetic system.

Receptors for neurotransmitters for exocrine glands are on the basolateral membranes (cells distal from the lumen).[15] After the interaction of the neurotransmitter with the receptor, activation of an effector process to create a cellular response either occurs directly or via a second messenger. Predominant cholinergic, but also α_1-adrenergic, stimulations are responsible for fluid and electrolyte secretion and, to a lesser extent, protein secretion. The cholinergic stimulation is mediated through the neurotransmitter, acetylcholine, binding

TABLE 3–1 Functions of Autonomic Nervous System

Parasympathetic
Fluid formation
Glandular metabolism
Glandular growth
Transport activity in acinar and ductal cells
Vasodilation
Sympathetic
Exocytosis
Protein metabolism modulation
Constriction of blood vessels
Parasympathetic and sympathetic
Stimulation of salivary flow
Constriction of myoepithelial cells

to M_3 muscarinic cholinergic receptors. Heterotrimeric guanine nucleotide–binding proteins (G proteins) are subsequently activated in the acinar cell and bind to the receptor. G proteins have α, β, and γ components (heterotrimeric). G protein binding to the receptor leads to a dissociation of the α component of the G protein, leading in turn to activation of phospholipase C. This results in the formation of inositol triphosphate and the subsequent release of Ca^{2+} as a second messenger (**Fig. 3–1**). The second messenger Ca^{2+} is instrumental in fluid and ion transport across the apical membrane and into the ductal lumen. The neurotransmitter, norepinephine, acting on α receptors, is an additional mediator that releases Ca^{2+}. Atropine binds to this same M_3 muscarinic receptor and can block acetylcholine. Substance P, vasoactive intestinal peptide, neuropeptide Y, and galanin are additional mediators of the parasympathetic system that are atropine resistant. When G proteins activate phospholipase C, they also form diacylglycerol that activates protein kinase C, resulting in protein exocytosis, a minor pathway for protein secretion.

The sympathetic stimulation produces saliva of low volume and is the major modulator of salivary protein composition and exocytosis.[14] Beta-adrenergic stimulation via the sympathetic system is mediated through the binding of norepinephrine to β-adrenergic receptors (α and β receptor categories are further subdivided into α_1 and α_2 and β_1 and β_2) and the subsequent activation of another G protein. This G protein activates adenylate cyclase, converting adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP). The second messenger, cAMP, activates cAMP-dependent protein kinase A, leading to protein exocytosis. Vasoactive intestinal polypeptide also serves to increase the cAMP in acinar cells.[16] Alpha-2, β_1, and β_2 receptors affect cAMP either by stimulation (β_1 and β_2) or inhibition (α_2). In summary, calcium is the predominant second messenger for voluminous fluid secretion and cAMP the predominant second messenger for a secretion rich in

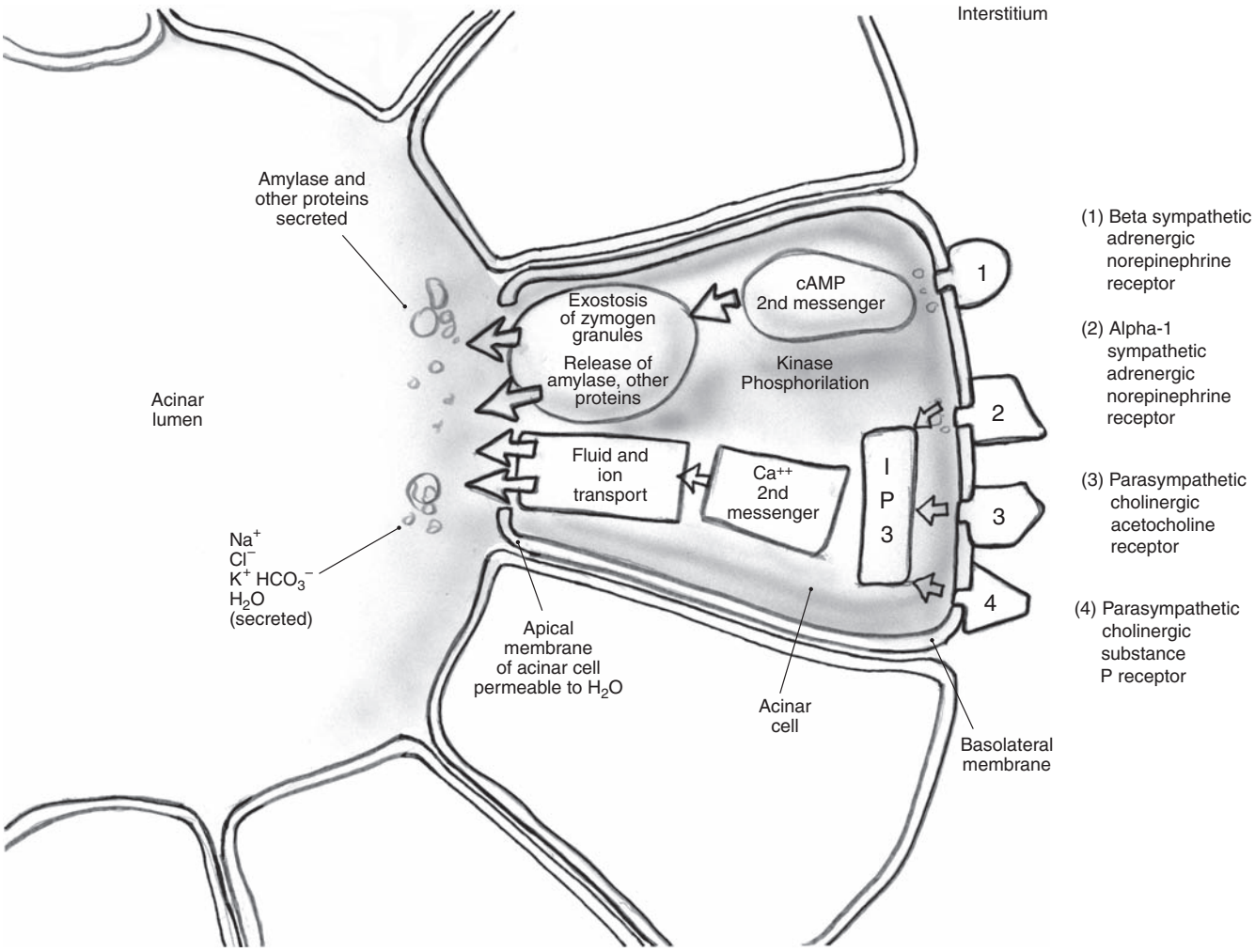

FIGURE 3–1 Autonomic nervous system.

amylase, mucin, and other proteins. The opposite is true for the pancreas.

The activation of the effector process can be a direct effect of the neurotransmitter/receptor binding or via second messengers, including the release of intracellular calcium and/or activation of adenylate cyclase, leading to a buildup of cAMP. Both of these second messengers in turn activate kinases that phosphorylate a multiplicity of effector process proteins, such as myosin, plasma membrane ion pump proteins, and granule membrane associated proteins. In the case of excretory glands such as the salivary apparatus, the cellular response of this complicated process is exostosis of zymogen granules (resulting in the release of amylase and other salivary proteins), ion and fluid transport across the acinar cells and ductal cells, absorption of sodium chloride by the ductal epithelium, vasodilatation and myoepithelial contraction, as well as resetting of the surface and transmembrane potentials (**Table 3–2**). Other substances such as muscarinic agonist medications, hormones, and kinins can also activate these receptors.[11,17–19]

Acinar and Ductal Protein Secretion

Most protein secretion occurs in the acinar cells. Amino acids cross the basolateral membrane via an active transport mechanism and enter acinar cells from the interstitium. Proteins and other macromolecules (principally amylase and glycoproteins) found in saliva are produced intracellularly in the rough endoplasmic reticulum (RER) (see Chapter 4, **Fig. 4–1**). They are segregated in the cisternal space of the RER. Intracellular transport via an ATP mechanism carries secretory products to the Golgi complex in condensing vacuoles. Terminal glycosylation occurs in the Golgi complex. The Golgi complex has a high-permeable membrane. Concentration to secretory (zymogen) granules (a low-permeable membrane) is followed by temporary storage and subsequent release of their contents by fusion of secretory granules with the plasma membrane (exocytosis) after activation of granule membrane proteins by cAMP and calcium activated kinases.[20] The principal pathway, responsible for the secretion of newly synthesized parotid proteins, is through storage of newly synthesized secretory proteins in the secretory (zymogen) granules, followed by regulated extracellular release in response to β-adrenergic stimulation. Ductal cells secrete a small percentage of salivary protein in the ductal lumen.

TABLE 3–2 Structures of Autonomic Nervous System

Parasympathetic	Sympathetic
Cholinergic stimulation	β-adrenergic stimulation
Acetocholine neurotransmitter	Norepinephrine neurotransmitter
M_3 muscarinic receptor	β-adrenergic receptor
Ca^{2+} (2nd messenger)	cAMP (2nd messenger)
↘	↙
Kinase phosphorylation of effector process proteins and cellular response	

cAMP, cyclic adenosine monophosphate

Acinar Electrolyte Secretion

Most of what is understood regarding salivary gland electrolyte secretion is derived from rat and rabbit animal models. The acinar cells are the site of all fluid generation. The liquid component of saliva is derived from the surrounding vasculature. Associated capillaries are extremely permeable, allowing rapid transit of water across the basement membrane. Recently discovered water-specific channels, or aquaporins (aquaporin-5 in salivary glands), may play an important role in the molecular basis of water movement across membranes (transcellular water transport pathway).[21]

Na^+K^+ adenosinetriphosphatase (ATPase) and $Na^+K^+2Cl^-$ are postulated pump and cotransporter, respectively, located in the basolateral membrane (cells distal from the acinar lumen) of the acinar cell that power intracellular Na^+ down its electrochemical gradient, while K^+ (via the Na^+K^+ ATPase pump) and Cl^- (via the $Na^+K^+2Cl^-$ cotransporter) accumulate against their gradient[22] (**Fig. 3–2**).

Therefore, in the resting unstimulated state, K^+ and Cl^- are concentrated in the acinar cell above the electrochemical equilibrium. With autonomic stimulation, Ca^{2+} (the second messenger) sensitive ion channels permeable to K^+ (at the basolateral membrane) and Cl^- (at the apical membrane) open.[17,18,23] Cl^- leaves the acinar cell into the lumen via the apical membrane. This negative charge in the acinar lumen draws Na^+ from the interstitium to pass through tight junctions between the acinar cells into the lumen. Water is carried from the interstitium to the acinar lumen via an osmotic gradient produced by the NaCl in the lumen.

In the preceding model, mass and charge balance in ion transfer must be in a steady state in the acinar cell (**Fig. 3–2**). At the basolateral membrane, the $Na^+K^+2Cl^-$ (via cotransporter) goes through three cycles of entry into the acinar cell from the interstitium. This allows $3Na^+3K^+$ and $6Cl^-$ to enter the acinar cell. The Na^+K^+ ATPase pump at the basolateral membrane results in the extrusion of $3Na^+$ from the acinar cell to the interstitium and the entry of $2K^+$ into the acinar cell from the interstitium at the energy cost of 1 ATP. The $3Na^+$ extruded from the acinar cell by the Na^+K^+ ATPase pump is balanced with the entry of $3Na^+$ into the acinar cell from the $Na^+K^+2Cl^-$ cotransporter. Na^+ remains in charge and mass balance. In the resting state, there is $5K^+$ in the acinar cell ($3K^+$ from the

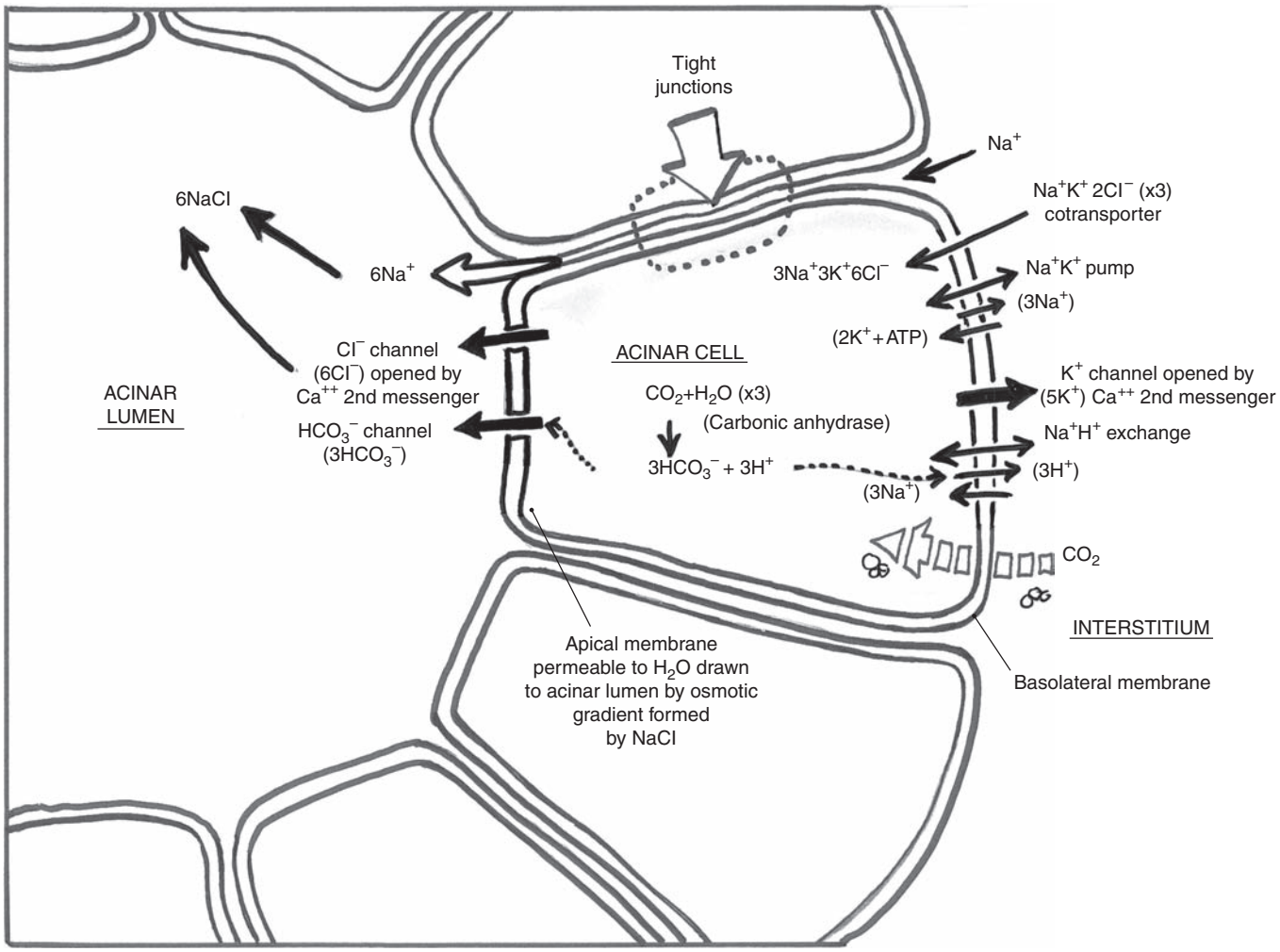

FIGURE 3–2 Acinar cell electrolyte secretion.

cotransporter and $2K^+$ from the ATPase pump). With autonomic stimulation, Ca^{2+} (the second messenger) sensitive ion channels permeable to K^+ at the basolateral membrane allow the release of $5K^+$ from the acinar cell to the interstitium, maintaining a neutral charge balance of K^+. When the autonomic stimulation is complete, the resting state in the acinar cell returns to $5K^+$. Meanwhile, in the resting state, there is $6Cl^-$ in the acinar cell (from three cycles of the $Na^+K^+2Cl^-$ cotransporter). With autonomic stimulation a Cl^- channel opens at the apical membrane, resulting in the release of $6Cl^-$ into the acinar lumen from the acinar cell, maintaining mass and charge balance for Cl^-. The $6Cl^-$ in the acinar lumen draws $6Na^+$ from the interstitium to the lumen via tight junctions between the acinar cells. The 6NaCl draws water via transepithelial movement from the interstitium into the lumen from the osmotic gradient. With cessation of autonomic stimulation (Ca^{2+} mediated), the Cl^- channel at the apical membrane and the K^+ channel at the basolateral membrane close, and $6Cl^-$ and $5K^+$ are reaccumulated in the acinar cell.

A second proposed mechanism of Cl^- secretion (not diagrammed in **Fig. 3–2**) is an acinar cell $Cl^-HCO_3^-$ exchanger in parallel with the Na^+H^+ exchanger, both at the basolateral membrane, resulting in the secretion of $3Cl^-$ across the apical membrane into the acinar lumen. Another Cl^- channel (not diagrammed in **Fig. 3–2**) is a volume-sensitive Cl^- channel activated by cell swelling and inhibited by cell shrinkage. Lastly, in the resting state, voltage-activated Cl^- channels in the apical membrane may also exist.

Acinar bicarbonate secretion (HCO_3^-) into the acinar lumen results from the following postulated mechanism (**Fig. 3–2**). CO_2 diffuses across the basolateral membrane. CO_2 and H_2O are converted to HCO_3^- and H^+ by carbonic anhydrase. The HCO_3^- crosses the apical membrane via an anion channel (possibly the same anion channel used by Cl^-), while H^+ is extruded across the basolateral membrane via the Na^+/H^+ exchanger.

Mass and charge balance in ion transfer must again be in a steady state in the acinar cell (**Fig. 3–2**). The Na^+K^+ ATPase pump drives the extrusion of $3Na^+$ from the acinar cell to the interstitium in exchange for $2K^+$ entering the acinar cell from the interstitium at a cost of 1 ATP. The parasympathetic-stimulated Ca^{2+} mediated channel allows the exit of $2K^+$ from the acinar cell back out to the interstitium for K^+ balance. The Na^+H^+ exchanger brings the $3Na^+$ back into the acinar cell from the interstitium for Na^+ balance. Three cycles of CO_2 and H_2O are converted to HCO_3^- and H^+ by carbonic anhydrase. The $3H^+$ produced in the acinar cell is balanced by a $3H^+$ extrusion from the acinar cell into the interstitium via the Na^+H^+ exchanger. The ultimate result is the release of $3HCO_3^-$ from the acinar cell to the lumen (at an energy cost of 1 ATP).

Ductal Electrolyte Secretion

At the time that saliva is secreted by the acini, it is just slightly less than isotonic with plasma, but this is actively modified as it moves through the intercalated and probably the striated ducts (composition of the primary secretion is altered, but not the volume). The Na^+K^+ ATPase located in the basolateral membrane of the ductal epithelial cell maintains the electrochemical potential gradient of Na^+ and K^+ that powers most of the other ionic transfer processes in the cell (**Fig. 3–3**). Ductal cells do not express detectable levels of $Na^+K^+2Cl^-$ cotransporter activity. Therefore, low concentrations of Cl^- exist in the ductal cell, providing a more favorable condition for Cl^- entry into the ductal cell when the Cl^- channel opens.

As the primary secretion moves through these ducts, it becomes higher in potassium and bicarbonate concentration (potassium and bicarbonate are secreted) and lower in sodium and chloride concentration (sodium and chloride are reabsorbed), but always hypotonic to plasma. Na^+ and Cl^- in saliva are less than measured in serum, but K^+ is always much greater in saliva compared with serum. When salivary flow rates are very low, the secreted salivary K^+ levels are high. The more slowly

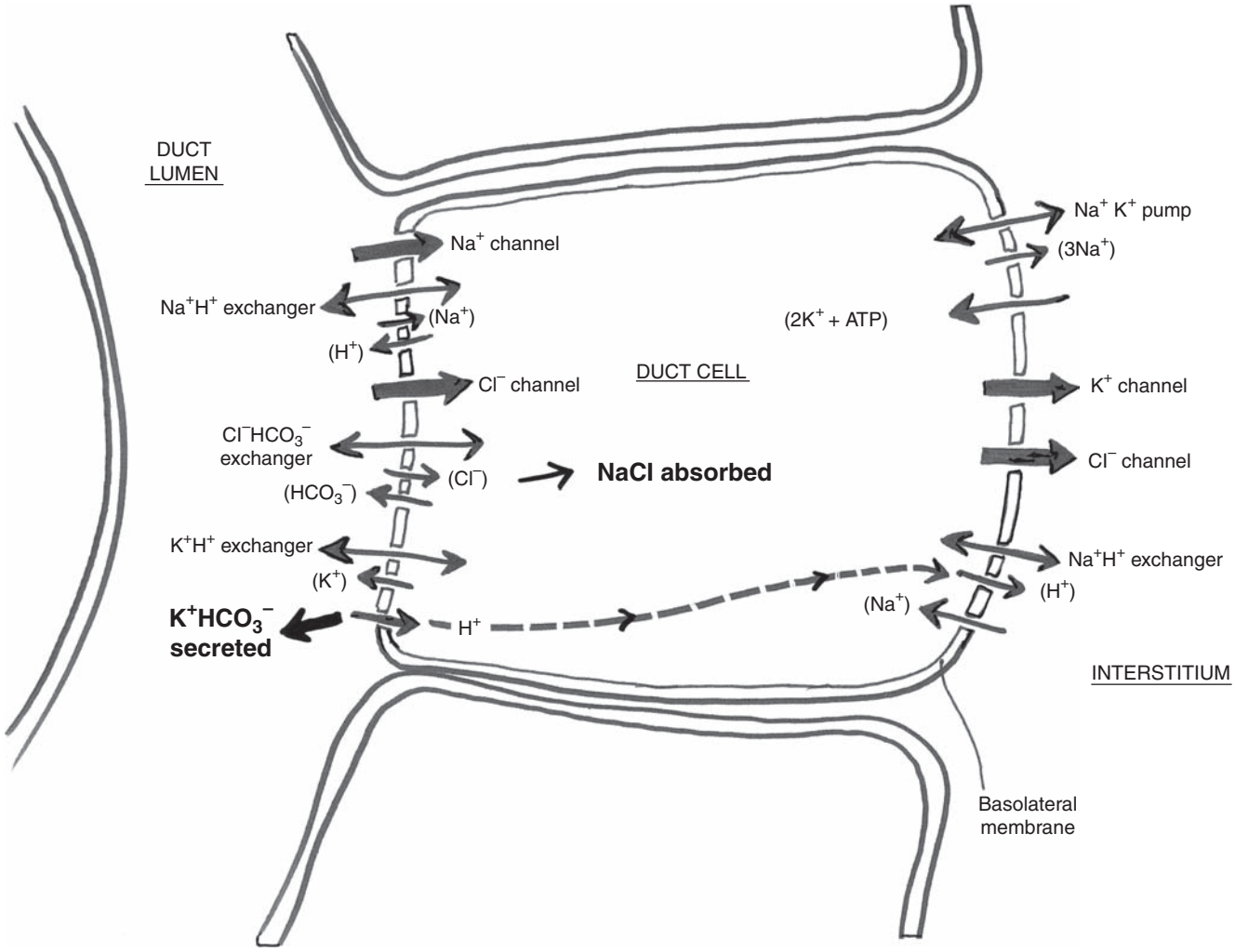

FIGURE 3–3 Ductal cell electrolyte secretion.

flowing basal secretions are considerably hypotonic to plasma, but stimulated salivary secretions flow rapidly and are thus less modified by the ductal system and only slightly hypotonic. At maximal flow rates the tonicity of saliva is 70% of plasma.

Mass and charge balance in ion transfer must be in a steady state in the ductal cell as well. The Na^+K^+ ATPase pump again at the basolateral membrane draws $3Na^+$ out of the ductal cell into the interstitium in exchange for $2K^+$ to enter the ductal cell at an energy cost of 1 ATP. Some K^+ leaves the ductal cell back to the interstitium at the basolateral membrane via a K^+ channel. K^+ that enters the ductal cell from the interstitium via the Na^+K^+ pump can exit the ductal cell by the above-mentioned K^+ channel at the basolateral membrane or an apical K^+H^+ exchanger. When K^+ is secreted from the ductal cell into the ductal lumen by the apical K^+H^+ exchanger, H^+ enters the ductal cell. This H^+ can leave the ductal cell into the interstitium via a basolateral Na^+H^+ exchanger. The overall result is a low intracellular concentration of Na^+. Na^+ can now be absorbed into the ductal cell from the ductal lumen from either the Na^+ channel (primary mechanism of uptake) or an apical membrane Na^+H^+ exchanger. Cl^- to maintain charge balance in the ductal cell is absorbed into the ductal cell from the ductal lumen from a Cl^- channel (primary mechanism of uptake) or the $Cl^-HCO_3^-$ exchanger. When Cl^- is absorbed from the ductal lumen to the ductal cell via a $Cl^-HCO_3^-$ exchanger, HCO_3^- is secreted into the ductal lumen. Cl^- subsequently leaves the ductal cell at the basolateral membrane via a Cl^- channel drawn out by K^+ through the K^+ channel mentioned above. The end result is that NaCl is absorbed into the ductal cell from the ductal lumen, and $KHCO_3$ is secreted from the ductal cell into the ductal lumen.

In addition to parasympathetic cholinergic (second messenger Ca^{2+}) activated Cl^- channels in ductal (and acinar) cells, there is a sympathetic β-adrenergic stimulation activated second messenger, cAMP, that activates a duct Cl^- channel. cAMP may be required for efficent NaCl absorption in many ductal cells. cAMP activates the cystic fibrosis transmembrane conductance regulator located in the apical membrane, resulting in the opening of a Cl^- channel and absorption of Cl^- into the ductal cell. Mutations of this gene result in cystic fibrosis, characterized by reduced flow rate and elevated Na^+ and Cl^- and subsequent mucous plugs.

Sialochemistry

Proteins

Whole saliva is composed of ~99.5% water and therefore has a much lower protein concentration than plasma. The remaining 0.5% is composed of large organic molecules, including proteins, glycoproteins, and lipids; small organic molecules, including glucose and urea; and the electrolytes, chiefly potassium, bicarbonate, sodium, chloride, calcium, and phosphates. Saliva has a specific gravity, depending on flow rate, of 1.002 to 1.012.

Humans secrete between 0.5 and 1.5 L of saliva daily. The parotid and submandibular glands together produce ~90 to 95% of the basal (unstimulated) total salivary flow (**Table 3–3**). The submandibular gland saliva is more viscous due to its higher mucin content. It has a higher basal flow rate than the parotid. However, this relationship is reversed upon stimulation. During eating, the parotid gland produces about two thirds of the salivary flow, a proteinaceous, watery secretion.[24,25] Sublingual gland isolates are more viscous than submandibular gland secretions, with a higher mucous content. The minor salivary glands are purely mucous glands and produce ~5% of the total saliva.

Proteins, which are actively transported, make up the vast majority of the organic components of saliva. Most salivary organic molecules are produced in the acinar cells, with a smaller quantity produced in the ducts or transported into the saliva from blood. The protein content of the parotid gland saliva is higher than that of the submandibular gland even though the viscosity of saliva from the latter is greater.[10,25]

Alpha-amylase is the most important and abundant protein found in saliva, comprising, 10% of salivary protein. Electrophoresis demonstrates that α-amylase is composed of several isoenzymes. Total amylase production for humans is estimated to be 1.5 g a day, with the pancreas secreting 60% and the salivary glands 40%.[10] The parotid glands secrete 70% of the salivary amylase.

There are many salivary glycoproteins produced by the acinar cells. Glycoproteins are involved in tissue coating, lubrication, buffering, digestion, and microbial clearance.[26] Salivary glycoproteins have a polypeptide

TABLE 3–3 Salivary Gland Secretion

Parotid gland secretion
Proteinaceous, watery, serous secretion
Two thirds of salivary flow during gustatory and olfactory stimulation
Organic (proteins including enzymes) and inorganic materials are higher
Submandibular gland secretion
High mucin content, viscous/serous secretion
Higher basal flow rate
Calcium is higher
Sublingual gland secretion
Higher mucin content than submandibular gland
5% of salivary flow
Minor salivary gland secretion
Purely mucous glands
5% of salivary flow

core and oligosaccharide side chains. These vary between the serous parotid (*N*-linked oligosaccharides such as α-amylase, salivary peroxidase, and proline-rich glycoproteins) and mucous submandibular, sublingual, and minor salivary glands (*O*-linked oligosaccharides), producing cells that are the main determinant of viscosity of saliva. The mucins (mucous glycoproteins) are subdivided into mucin 1 (gene designation MUC5B) and mucin 2 (gene designation MUC7). Mucin 1 is a high molecular weight multisubunit molecule that is highly glycosylated (a larger carbohydrate component). Mucin 2 is a low molecular weight single-polypeptide molecule that is glycosylated.[26]

Blood group reactive substances are glycoproteins found on the cell membranes and in low concentrations in saliva, predominantly in labial minor salivary glands.[10] The ability to secrete blood group reactive substances (A, B, AB, and O) is inherited as a dominant factor independent of the ABO blood classification system and is absent in recessive homozygotes, information important in the forensic sciences.

Other enzymes (proteins) secreted in saliva include muramidase, phosphatases, hydrolases, dehydrogenases, arginase, and esterases.[27] Many other proteins have been isolated from saliva,[28] including albumin, amino acids, polypeptides and proline-rich, histatin-rich, and tyrosine-rich proteins. The histatin-rich proteins have antifungal properties, whereas another salivary protein, secretory leukocyte protease inhibitor (SLPI), has antiviral capabilities. Albumin passively diffuses into the saliva from plasma and functions as a carrier protein. The concentration of organic (and inorganic) substances is highly variable and depends on which gland is being measured and the flow rate. Smaller organic elements such as urea, glucose, amino acids, and lipids are passively diffused from the plasma and are therefore directly correlated to serum concentrations.

Several polypeptides have been isolated from mammalian submandibular glands. These include nerve growth factor, epidermal growth factor, renin, kallikrein, and peptidases.[27,29] Most of these are androgen dependent, and their secretion is mediated by α-adrenergic control.[27] They are found in or considered to be secreted by the striated ductal cells. These salivary polypeptides have also been found in blood. This raises the issue of a possible endocrine or paracrine function of the salivary glands.[29] The functions of salivary kallekrein, nerve growth factor, and renin are unknown. Salivary epidermal growth factor may have a role in oral wound healing and head and neck cancer.

Electrolytes

The sodium, chloride, and calcium of the salivary secretion rise during stimulation (they are not reabsorbed by the ductal system), whereas phosphate, urea, ammonia, uric acid, and magnesium fall.[25,30] Increased salivary flow correlates with an increase in osmolality.[19,31] In the unstimulated parotid gland, the secretion of potassium ion concentration is higher than the sodium ion concentration; with stimulation, the ratio is reversed because of decreased Na^+ reabsorption in the salivary ducts at higher rates.[31] Salivary electrolyte concentrations are different than those found in serum because of the active transport of ions across the acinar and ductal cells. The large number of variables that influence electrolyte concentration reduces the accuracy of reliable laboratory ranges compared with serum electrolyte concentrations.

In general, the concentration of both organic (proteins including enzymes) and inorganic materials is higher in the parotid than in the submandibular gland, with the exception of calcium.[25] The concentration of calcium in the unstimulated submandibular gland is 2 to 8 mmol/L, compared with 0.2 to 2.5 mmol/L in the parotid gland.[31] Calcium is flow dependent only at very high rates.[22] Calcium in the parotid gland exists in an ionized and protein-bound form in a 1:1 ratio. Calculi (also referred to as sialoliths) are more common in the submandibular gland than in the parotid gland. Magnesium concentrations are equivalent in all salivary glands and are two thirds of the plasma concentration.[26]

The concentration of bicarbonate (HCO_3^-) in saliva is greater than plasma concentration except at the lowest flow rates. The hydrogen ion concentration (pH) hovers around neutral, with the unstimulated parotid and submandibular glands having slightly acidic values.[31] With increasing flow rate, HCO_3^- increases, dihydrogen phosphate ($H_2PO_4^-$) decreases, and the pH increases to an alkaline state.[31] The pH rises from a low of 5.75 (unstimulated, slow flow) to nearly 8.0 (stimulated, rapid flow).[10] Bicarbonate ($H_2CO_3^-/HCO_3^-$) and, to a lesser extent, phosphate ($H_2PO_4^-/HPO_4^-$) are two buffer systems that, coupled with proteins, provide saliva with a buffer capacity.

Salivary fluoride is similar to plasma but is increased in individuals who drink fluorinated water or use fluorinated toothpaste. There is a slow, prolonged release of fluoride into the oral cavity from soluble deposits on the teeth that prevent dental caries.[26]

Sialometry

Sialometry measures the flow rate of saliva. Unstimulated saliva should be collected 2 hours after eating or after an overnight fast. Whole saliva (a total product of all salivary glands) can be measured by a variety of volumetric and gravimetric techniques, including drooling, spitting, suction, and swab. Isolated parotid

secretion can be obtained by placement of a suction cup over the Stensen's duct, usually referred to as a Carlson-Crittenden cup or Lashley cup. Collection of unstimulated saliva requires a person to drool quietly into a preweighed collection vial, expectorating each minute, for up to a total of 5 minutes.[32] Stimulated saliva can use a masticatory stimulus (flavorless gum base or paraffin wax chewed 60 times/min) or a gustatory stimulus (citric acid) with a similar collection period.

Dynamic radionuclide scintigraphy measures uptake, concentration, and secretion of salivary glands using intravenously injected technetium 99m pertechnetate. It provides an assessment of the functional capacity of the major salivary glands; sequential scanning demonstrates technetium 99m pertechnetate uptake from the vascular system and secretion in saliva. In diseased states there is decreased and delayed uptake, and in the severely atrophic gland there is diminished output from the glands into the mouth. Sialography, computed tomography, and magnetic resonance imaging (MRI) have largely replaced scintigraphy. In vivo nuclear MRI has been used to analyze salivary production in the unstimulated and stimulated parotid gland.[33]

Normal values for salivary flow rates are difficult to establish because of circadian rhythms and other factors that vary the flow rate. There is a nearly 50% normal variability in salivary flow rates in healthy individuals over time.[34] Salivary production rates drop to their lowest levels during sleep. Emotional states are associated with expected higher flow rates.[35,36] Climate, light, age, gender, physical activity, hydration, and personality potentially impact salivary flow. Empty mouth clenching does not appear to be a stimulus of salivary flow.[35] There are also enormous variations of flow rates, both stimulated and unstimulated, between study subjects selected free of subjective complaints or signs of salivary gland dysfunction.[37]

The average daily saliva secretion as stated above is 0.5 to 1.5 L daily. Averages for resting flow rates for whole saliva are 0.3 to 0.4 mL/min, rising to 1 to 2 mL/min in paraffin-stimulated saliva.[38] Unstimulated whole salivary flow rates of less than 0.1 mL/min and stimulated whole flow rates less than 0.4 mL/min are considered to be one criterion for severe salivary hypofunction.[39] Oral dryness is typically noticed when the stimulated rate drops below 0.2 mL/min/gland.[25] Change in an individual's salivary flow rate is a more reliable sign of dysfunction than comparison to normative data, and it has been suggested that individual decrements of more than 45% of normal values are indicative of salivary hypofunction.[34] In experiments designed to reduce salivary production with anticholinergic drugs, dryness was noted when the flow rates were reduced by 50% of the individual's pretreatment flow rate.[40]

The metabolic rate of salivary tissue, as in other secretory organs, is quite high. Spontaneous activity from the salivatory nuclei in the brainstem results in continuous secretion of saliva (unstimulated) without gustatory and masticatory stimuli and serves as a protective secretion. Saliva can increase to a maximum of $\sim$1 mL/min/g of tissue in response to the marked release of neurotransmitters. At this rate the glands are producing their own weight in saliva each minute. This assists in food bolus formation and swallowing. The increase in salivary production is paralleled by an increase in blood flow, which can approach 10 times the rate of blood flow in actively contracting skeletal muscle.[27] Maximal β-adrenergic stimulation of the parotid gland can result in the discharge of 70 to 80% of total stored secretory proteins within 1 hour. This process involves rapid fusion of granule membranes with the apical membrane (exostosis) and with membranes of other organelles.

Eighty to 90% of salivary production occurs with stimulation. The highest flow rates are achieved with stimulation during eating. Gustatory receptors in the oral cavity will stimulate the salivary nucleus in the medulla, resulting in autonomic stimulation of the salivary glands. Acid tastes create the highest salivary flow, and sweet tastes the least. The mechanical act of chewing stimulates saliva production. Olfaction will also increase the flow rate, but to a lesser degree.

Partial surgical removal of one parotid gland does decrease flow in that gland but is not associated with complaints of xerostomia and may even cause compensatory increase in secretion from other glands.[41] Cunning et al[24] reported a decrease in unstimulated salivary flow in patients undergoing unilateral submandibular gland excision with increased subjective complaints of xerostomia. Stimulated flow was not significantly different. In general, subjective postoperative complaints of dryness after unilateral submandibular gland resection are not common.

Salivary Gland Function

There are three major functions of the salivary glands: nutritional intake, communication, and host protection (**Table 3–4**). Saliva production is critical for efficient

TABLE 3–4 Function of Saliva

Digestion
Lubrication
Buffer
Transport to taste receptors
Antimicrobial
Dental protective
Excretory

mastication and deglutition and thus is a significant component of the digestive process and overall nutrition. Alpha-amylase, secreted in high quantities by the human salivary glands, begins the enzymatic process of digestion of starch while the food is still in the oral cavity. Amylase reduces starch to oligosaccharide molecules by cleaving α-1,4-glycosidic bonds. More then half of the starch may be reduced to oligosaccharides by the action of salivary amylase in a well-chewed meal. In the absence of salivary amylase, digestion of starch is still possible because of pancreatic amylase. The optimal pH for amylase is 7, but starch digestion can occur between a pH of 4 and 11. Its activity is terminated below a pH of 4 in the stomach antrum. Alpha-amylase initially continues to digest starch in the gastrointestinal tract because the food bolus protects it from gastric acid. The main end products of amylase digestion are maltose, oligosaccharides, and free glucose.

Lingual lipase produced by the minor salivary glands of the tongue initiates the digestion of triglycerides. It stays active in the stomach because of its acid pH. Proteolytic function is not demonstrated to a significant degree in saliva in contrast to pancreatic secretions.

Saliva lubricates the crushed food, allowing for bolus formation, enzymatic digestion, and swallowing. The lubrication function of saliva is dependent primarily on mucous glycoproteins (and to a lesser extent on proline-rich polypeptides) that bind to water and keep the oral cavity hydrated. Mucins are present in higher concentration in the submandibular, sublingual, and minor salivary glands. Mucins form long end-to-end oligomers to manifest their lubricating properties.[42] Salivary mucins coat the oral mucosa, preventing desiccation. Dry mouth from diminished saliva production is a common complaint. Desiccated mucosa is uncomfortable and more prone to trauma and infection. Some patients with stomatodynia (burning mouth) complain of xerostomia,[43–45] which could be due to changes in salivary composition and flow,[46] especially in the minor salivary glands.[44] The lubrication process is a prerequisite for speech, mastication, and swallowing.

The lubrication function of saliva is also essential to the sense of taste. Saliva transports the bolus to the taste receptor and protects the receptor. Saliva helps dissolve and carry tastants to the taste buds, and is therefore a critical component of the gustatory system.[47] Subjective taste disturbances and oral pain from dry mouth lead to decreased appetite and therefore potentially to malnutrition.

Saliva buffers acids (saliva has a slightly alkaline pH) and dissipates heat. Saliva buffers and dilutes noxious substances that can be expectorated by copious salivation. The chief buffer is bicarbonate (HCO_3^-) and, to a lesser extent, urea, phosphate, and histidine-rich proteins. The bicarbonate concentration in saliva is higher at stimulated (higher) flow rates. Hot solutions are diluted and their temperature lowered. During emesis saliva buffers and dilutes gastric acids.

TABLE 3–5 The Role of Salivary Proteins in Antimicrobial Clearance

Secretory immunoglobulin A (sIgA), IgG, IgM—antibacterial and antiviral properties
Mucin 2—prevents the adhesion and promotes clearance of microorganisms to the oral cavity
Amylase when coupled with mucin 1 clears bacteria from saliva
Peroxidase—antimicrobial function
Lysozyme—hydrolyzes a major component of bacterial outer membranes and activates autolysins
Histatine-rich proteins—antifungal properties
Lactoferrin—chelates iron, reducing the ability of microorganisms requiring iron
Secretory leukocyte protease inhibitor (SLPI)—antiviral activities
Proline-rich peptides inhibit herpes simplex virus I
SLPI antiviral activities
High- and low-weight glycoproteins—inhibit HIV infection

HIV, human immunodeficiency virus

Immune-mediated antimicrobial proteins (**Table 3–5**) associated with the major salivary glands include secretory immunoglobulin A (sIgA) and, to a much lesser extent, immunoglobulins G and M.[28] Dimeric IgA (two IgA macromolecules covalently linked by a J chain) is formed by the plasma cells in the interstitium of the salivary gland. It is transported into the acinar cell by an active transport mechanism. The ''secretory component'' of salivary IgA, both bound to dimers of serum type IgA and ''free,'' differs from serum IgA and is synthesized on the basolateral surface of acinar cells.[10,28] It helps in the transport of IgA across the apical membrane of the acinar cell into the duct. sIgA is stimulated by bacteria and viruses reaching the mucosa. Mucins and enzymes are non-immune-mediated agents that protect the oral cavity from microorganisms. Mucin 2 prevents the adhesion and promotes clearance of microorganisms to the oral cavity. Mucin 1 cradles other salivary molecules such as enzymes (amylase, histatins, proline-rich proteins, and statherin) and immunoglobulins and carries them to their eventual target sites. Amylase when coupled with mucin 1 helps clear bacteria from saliva when it is in solution. Amylase and salivary glycoproteins bind to a select group of *Streptococci*. Lysozyme hydrolyzes a major component of bacterial outer membranes and activates autolysins. Lactoferrin chelates iron, reducing the ability of microorganisms (and neoplasms) that require iron for growth. It is also bacteriocidal. Histatins exhibit antibacterial and candidal activity. Proline-rich peptides play an important role in inhibition of herpes simplex virus l,[48] and SLPI purportedly has antiviral (especially human immunodeficiency virus [HIV]) activities. Peroxidase also has antimicrobial functions.[49,50]

The tooth surface has a protective film of mucin (produced by the submandibular gland and sublingual gland) and proline-rich glycoprotein (produced by the parotid gland) that protect against wear. Mucin 1 adsorbs to the tooth enamel, protecting the tooth from acid. Salivary mucins aggregate oral bacteria, assisting in the prevention of dental plaque formation, and thus help promote normal tooth development.[51] Salivary amylase and mucin complexes can also help promote enamel breakdown, if they are absorbed to the tooth surface, by breaking down starches into simpler sugars that are used by bacteria to create enamel-destroying acids.[26,27,52] Demineralization occurs when acids from attached bacteria erode through enamel. The basic pH of saliva helps prevent dental caries. The salivary bicarbonate (buffer) neutralizes acid. Demineralization is also retarded by proteins in concert with calcium and phosphate ions in saliva. Saliva has been shown to contribute to tooth enamel formation (remineralization) by supplying inorganic ions, including calcium, phosphates, fluoride, and magnesium.[49] The salivary protein statherin, a small phosphoprotein rich in tyrosine and proline, functions to stabilize inorganic ions in solution, promoting remineralization. Statherin prevents precipitation of calcium phosphates from supersaturated solutions, which also plays a role in preventing salivary calculi.[26] Salivary proteins (mucins, histatin, proline-rich proteins, and statherin) also bind to hydroxyapatite on the tooth surface, adding dental protection. Chewing sugar-free gum has become accepted as an adjunct of oral hygiene because of its stimulation of saliva. Decreased salivary flow rate is associated with accelerated tooth decay (dental caries), microbial infections, and subsequent loss of teeth.

Human salivary glands have an excretory function secreting exogenous elements, such as viruses (including rabies, polio, hepatitis B, and HIV), as well as antibiotics and other inorganic elements, such as mercury, lead, sulfur, and iodine. HIV may be recovered from whole saliva or individual glands. Saliva inhibits HIV infection by the action of high molecular weight components in combination with low molecular weight components from serous as well as mucous saliva affecting different stages of the infection cycle.[53] The end result is the mouth is not a transmission route for HIV infection.

The preceding discussion on salivary function suggests that salivary proteins are multifunctional with overlapping roles. This redundancy allows deficiency of one protein to be compensated for by another. Salivary proteins can also cause contradictory outcomes; that is, amylase and mucin can clear bacteria from saliva when it is in solution and yet bind bacteria on tooth enamel, resulting in dental caries.

Pathophysiologic States

Systemic Diseases

Autoimmune diseases are a heterogeneous class of immunoregulatory disorders that usually affect multiple organ systems. The most common systemic disease associated with salivary disorders is Sjögren's syndrome (SS), an autoimmune exocrinopathy that affects primarily postmenopausal females, with signs and symptoms of xerostomia and xerophthalmia (see Chapter 5).[54,55] The American European Consensus Group recently revised the classification criteria for SS, which includes serological, oral, and ophthalmological evaluations and subjective complaints of dry eyes and xerostomia, and it can be used for diagnosing primary and secondary SS.[56] Reported prevalence for primary SS varies from 0.05 to 4.8% of the population,[57] with approximately one million people in the United States estimated to have the disease. The onset of disease is often insidious, and accordingly, diagnosis may be delayed for many years. The female to male ratio has been estimated to be 9:1, although reported ratios vary considerably. Collagen-vascular diseases associated with Sjögren's syndrome (i.e., rheumatoid arthritis, systemic lupus erythematosus, and scleroderma) also cause decreased salivary flow, changes in salivary protein secretion, and alteration of ductal electrolyte absorption.[54] A patient with a connective tissue disorder that manifests as an advanced autoimmune arthritis such as rheumatoid arthritis may not have salivary dysfunction, whereas another who has minimal joint disease may have fulminate SS.

Less commonly reported is autoimmune pancreatitis that is correlated with decreased salivary function that improves with steroid therapy.[58,59] Hashimoto's thyroiditis and hypothyroidism have decreased salivary flow.[60,61] Patients with graft versus host disease from a bone marrow transplant present with sicca syndrome and lymphocytic infiltration of the salivary glands. The xerostomia resulting from an interaction between the bone marrow transplant and salivary gland tissue can be as profound as after head and neck radiation therapy. Sarcoidosis can involve the parotid gland in 10% of patients. It is characterized by bilateral glandular enlargement and xerostomia. HIV infection, which is not an autoimmune process, though it directly affects the immune system, can cause a diffuse infiltrative lymphocytosis syndrome (DILS) characterized by the persistence of CD 8 cells and lymphocytic infiltration of the salivary glands.[62]

Endocrine disorders, including diabetes, tend to cause protein alterations and glandular enlargement (sialosis). Individuals with diabetes have greater complaints of dry mouth,[63] but not necessarily lower salivary flow rates.

More likely, it is the poor glycemic control that is associated with a dry mouth.[64] Hypertension leads to a decrease in salivary sodium levels but probably does not contribute to salivary hypofunction. Medication for hypertension rather than hypertension itself leads to reduced salivary flow rates.[65] Chronic renal failure in patients receiving renal dialysis can lead to decreased excretory function.[66] Patients with alcoholic cirrhosis have lower stimulated and unstimulated salivary flow rates and lower concentration of electrolytes and proteins.[67] Protein and vitamin deficiencies can also cause salivary gland hypertrophy or swelling (sialosis).

Genetic Disorders

Ectodermal dysplasias are a heterogeneous group of conditions comprised of developmental defects of two or more ectodermal derivatives, including the hair, nails, teeth, and sweat glands. Patients with these dysplasias appear to have reduced salivary flow rates, especially of the submandibular glands.[68]

Cystic fibrosis (mucoviscoidosis), an autosomal recessive disorder, leads to abnormal chloride regulation in exocrine glands, including sweat glands and pulmonary and salivary mucous glands. Chloride channels can be found on apical and basolateral membranes of acinar cells and are critical for fluid secretion and NaCl resorption.[69] The ultimate effect of these changes is increased protein, sodium, chloride, calcium, and urea concentrations[27] in saliva, with a decrease in flow rate resulting in an inspissation of secretions and sludging. These changes can lead to stone formation, obstruction, and infection. Microscopic examination of glands shows acinar atrophy and ductal ectasia.[22]

Head and Neck Radiotherapy

Radiotherapy, a common treatment modality for head and neck cancers, causes severe and permanent salivary hypofunction with persistent complaints of xerostomia[70] (see Chapter 13). Patients frequently experience the spectrum of oral health problems associated with salivary hypofunction, including new and recurrent dental caries, oral candidiasis, dysphagia, dysgeusia, difficulty with mastication, impaired use of removable prostheses, and an altered quality of life.[71]

The serous acini that produce saliva are considered to be highly radiosensitive and undergo interphase cell death by apoptosis when exposed to external beam radiotherapy. Within 1 week of the start of irradiation (after 10 Gy has been delivered), salivary output declines by 60 to 90%, with later recovery only if the total dose to salivary tissue is < 25 Gy.[72,73] Most patients receive therapeutic dosages that exceed 60 Gy, and their salivary glands undergo atrophy and become fibrotic.

Therapeutic doses of iodine 131 for thyroid cancer result in occasional long-term salivary damage because of the uptake of iodine 131 by the salivary glands. Fortunately, most cases are transient and can be treated with sialagogues.

Medications and Toxins

The most common cause of salivary disorders is prescription and nonprescription medications (**Table 3–6**). For example, 80% of the most commonly prescribed medications have been reported to cause xerostomia,[74] with over 400 medications causing a side effect of salivary gland dysfunction.[75] Polypharmacy, regardless of the actual medications taken, is associated with subjective complaints of xerostomia as well.[76]

All drugs acting on the autonomic nervous system impact the salivary glands. Although certain cholinergic agonists are known to cause increased salivation, a far greater number of pharmacologic agents cause decreased salivary output due to their anticholinergic and/or antiadrenergic effects.

The anticholinergic effects of the plant *Atropa belladonna* have been known throughout history. Belladonna was a poison used in classical times and has also been used medicinally for centuries. Jimson weed and stink apple are also known for their toxic effects. Both of these plants contain the alkaloid atropine. *Hyoscyamus niger* contains the closely related alkaloid scopolamine. These compounds cause decreased salivation as well as other anticholinergic effects.

The most common types of medications causing salivary dysfunction have anticholinergic effects, which will inhibit the movement of fluid from serum, through salivary acinar cells, into the ductal system and ultimately into the mouth. Several drugs are used specifically for their anticholinergic effects and will cause profound salivary inhibition, including atropine, scopolamine, methscopolamine, tolterodine glycopyrrolate, and ipitrobium bromide. Any drugs that inhibit neurotransmitter binding to acinar membrane

TABLE 3–6 Medications and Xerostomia

Anticholinergic drugs: atropine, scopolamine, methscopolamine, tolterodine glycopyrrolate, and ipitrobium bromide
Antidepressant drugs: phenothiazines, selective serotonin reuptake inhibitors
Antihistamines (first-generation): ethanolamines, ethylenediamines, alkylamines, piperazines, and phenothiazines
Antihypertensives: β-blockers, clonidine (inhibits central α-adrenergic receptors), guanethidine and methyldopa (inhibit the postganglionic sympathetic stimulation), diuretics (intravascular volume depletion)
Seizure medication: carbamazepine
ADHD: atomoxitine (norepinehrine uptake inhibitors)
Chemotherapy: recombinant interleukin-2 (rIL-2)

ADHD, attention deficit/hyperactivity disorder

receptors, or that perturb ion transport pathways, may also adversely affect the quality and quantity of salivary output. These medications include tricyclic antidepressants, sedatives and tranquilizers, antihistamines, antihypertensives (α- and β-blockers, diuretics, calcium channel blockers, angiotensin converting enzyme inhibitors), cytotoxic agents, and antiparkinsonian and antiseizure drugs.[75–83] Antidepressant drugs are among the strongest inhibitors of salivation due to their anticholinergic side effects. These include phenothiazines such as chlorpromazine, tricyclic antidepressants, and newer selective serotonin reuptake inhibitor antidepressants that have reduced peripheral anticholinergic effects yet are still associated with dry mouth symptoms. Venlafaxine, another antidepressant, is both a serotonin and a norepinephrine reuptake inhibitor that causes clinical xerostomia in some patients. Bupropion, an antidepressant, whose mechanism of action is not well understood, also causes dry mouth.

Virtually all of the first-generation antihistamines, including the ethanolamines, ethylenediamines, alkylamines, piperazines, and phenothiazines, cause significant dry mouth due to their anticholinergic effects. The newer ''second-generation'' antihistamines, such as astemazole, terfenadine, fexofenadine, cetyrizine, and loratadine, have markedly less central nervous system and anticholinergic effects. A notable exception is cetyrizine, which is derived from hydroxyzine, an anxiolytic and antihistamine, and keeps some of its anticholinergic properties. Antihypertensives, especially β-blockers, are associated with xerostomia. Their use results in decreased protein secretion as well as decreased salivary flow.[76] Clonidine inhibits parasympathetic innervation by stimulation of central α-adrenergic receptors. Guanethidine and methyldopa inhibit the postganglionic sympathetic stimulation. Diuretics are a common cause of xerostomia, although this effect is usually indirect through intravascular volume depletion. Pain in the parotid gland with gustatory stimulation can be caused by antihypertensive drugs.

Carbamazepine, which is used to treat seizures, commonly causes dry mouth. Amphetamines and norepinephrine uptake inhibitors, such as atomoxitine, which are commonly used to treat attention deficit/hyperactivity disorder (ADHD), are known as a class to cause salivary dysfunction.

Chemotherapy for cancer treatment has also been associated with salivary disorders.[84] Fortunately, these changes appear to occur only during and immediately after treatment, and salivary function returns to pre-chemotherapy levels in most patients after completion of therapy. Recombinant interleukin-2 (rIL-2) utilized as a chemotherapeutic agent for cancer is known to cause xerostomia. Recent studies have demonstrated that salivary flow rates are reduced during rIL-2 treatment. Salivary composition is markedly altered on measurement of basal flow, but not stimulated flow.[85]

There are cholinergic agonists that can increase salivary output. South American natives have long known that chewing the leaves of the *Pilocarpus* plants caused salivation and sweating. Pilocarpine is used to promote salivary flow and reduce symptoms of xerostomia in patients with Sjögren's syndrome[86,87] and in patients who have received head and neck radiotherapy for cancer.[88] Another muscarinic agonist, cevimeline hydrochloride (an M_1- and M_3-specific receptor agonist), has demonstrated effectiveness for patients with Sjögren's syndrome[89,90] and is used in patients undergoing head and neck radiotherapy (see Chapter 13).

Metochlopramide and urecholine are found to promote gastrointestinal and bladder motility but are known to cause salivation as a side effect. Bethanachol and carbachol are choline esters that stimulate muscarinic receptors. Guaifenesin has been said to improve mucosal hydration through increased salivary production by an unknown mechanism, although its clinical effects appear to be limited.

Sialorrhea

Drooling can be caused by excessive salivary secretion or loss of oral competence. Medication effects and toxicity such as from household pesticides should be considered. In younger patients it can be from birth or trauma-related neurological disorders and/or dysautonomias that lead to poor oral motor competence. Treatment is often pursued because of the difficulties of maintaining proper hygiene and due to impaired social interactions (see Chapter 8). Anticholinergic medications can be tried if side effects such as hypersomnolence and gastroparesis are tolerated.

Elderly patients are also subject to this problem. Drooling can be caused by aberrant autonomic control (diabetic autonomic neuropathy, Parkinson's disease) and/or by poor oral competence from neuromuscular diseases (cerebral palsy). Surgery for oral or oropharyngeal disorders, gastroesphogeal reflux disease, or simply loss of teeth that leads to a reduction of mandibular mass and volume are causes of sialorrhea. Antisialagogues are generally contraindicated in this group of patients, typically due to potential complications with concomitant medications and to the potential for significant side effects in the elderly. Low-dose radiation therapy to the parotid and/or submandibular glands has uncommonly been recommended in this population, although its practice in a younger population would be strictly contraindicated due to the risk of delayed neoplasms.[91]

Salivary Physiology with Aging

The aging salivary glands are known to undergo structural changes. The lobule structure becomes less ordered, acini vary more in size and eventually atrophy, interlobular ducts become more prominent, and the percentage of fibroadipose tissue increases.[27] These changes noted in the submandibular gland and, to a lesser degree, in the parotid[92] include shrinkage of cells, dilation of ducts, oncocytic transformation, increased adiposity, fibrosis, focal microcalcifications with obstruction, and chronic inflammation. Similar changes occur in the minor salivary glands with aging.

Approximately 20 to 25% of the elderly population complains of dry mouth.[93] Many authors conclude the frequent complaint of dry mouth in the elderly is secondary to systemic disease and medications and not a by-product of aging itself.[94–98] The lack of increased age-related variability in parotid salivary flow rates over repeated measures in one report suggests that parotid glands have a large secretory reserve.[99] A recent study using isoproteronol, cAMP analogues, and carbachol to study protein fluid secretion showed a decrease in response to all of these compounds in cell lines from patients over 70 years old compared with younger patients. This suggests that there is a decrease in secretory reserve with age.[100] This diminished secretory reserve has clinical sequelae: The older person is more vulnerable to the deleterious effects of medications and systemic diseases associated with salivary disorders.[34]

In contrast, an uncontrolled English population study showed age, female gender, and medication to be independent risk factors for xerostomia.[101] Similar findings have been reported elsewhere.[83,102–104] A decreased flow in the intensively stimulated submandibular gland of the aged has been reported, but this same study did not show a significant change in stimulated flow within the parotid gland.[105] Hydration status may play a role in age-related changes, as many older adults have insufficient fluid intake and are more susceptible to the effects of diminished fluid intake on salivary output.[106] Several scientific reports show decreases in the number and salivary flow of minor salivary glands with age.[107–109] Aging salivary glands are more adversely affected by antisialagogues.[110,111] Rodents show an age-dependent decrease in flow as well as a decrease in the production of mucins and amylase.[112] There are contradictory studies in the literature regarding the effects of age on the rate of stimulated and unstimulated salivary flow in the major salivary glands.[97,105,113] One of the expected major problems in studying this issue is that salivary flow rates vary by as much as 45% in the same individual at different times.[114]

Human parotid saliva has been shown to have less electrolyte content and therefore decreased osmolality with age.[115] IgA increases with age.[105,116,117] There also appears to be a decrease in histatins with age, which may leave patients more susceptible to fungal infections.[118] Mucin content increases as amylase decreases, creating more viscous saliva that can be difficult to clear from the throat.[119]

Finally, there has been speculation that estrogen deficits may produce symptoms of xerostomia in older adults, but replacement therapies including estrogen have not been shown to have any significant effect.[116,120] In summary, there are structural changes in salivary glands that occur over the course of the human life span, but they may not be sufficiently profound to significantly affect salivary output. However, these histomorphological changes predispose salivary glands to clinically significant qualitative and quantitative decrements when older adults experience multiple medical disorders, are exposed to head and neck radiotherapy, or take multiple prescription and nonprescription medications. Accordingly, the older adult must take precautions to the potentially deleterious oropharyngeal effects of salivary dysfunction.

■ Future Physiologic Research

Pharmacological research into medications that selectively promote salivary secretion may depend more on regulating ion channels and second messengers rather than simply stimulating the parasympathetic nervous system, as is currently done with pilocarpine and its derivatives.[121]

The use of gene transfer technology in vivo has demonstrated salivary endocrine pathways. Salivary glands can be used as target tissues for systemic applications of gene therapeutics. Salivary glands are advantageous for this application because intraoral delivery of a vector is possible through the excretory duct, and salivary gland encapsulation prevents vector dissemination.[122]

Saliva meets the demand for a noninvasive, accessible, and efficient diagnostic medium. Salivary transcriptome diagnostics relies on the detection of ribonucleic acid (RNA) in saliva. Distinct cancer-associated molecules in saliva have been accurately measured to distinguish between healthy people and those diagnosed with oral squamous cell carcinoma. One report documents that distinct patterns of cancer-linked messenger RNA can be measured in saliva and indicate the presence of a developing tumor.[123]

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4

Histology, Epithelial Metaplasias, and Noninflammatory and Non-neoplastic Lesions of the Salivary Glands

MARY F. CUNNANE AND GREGORY J. ARTZ

Like exocrine glands generally, the salivary glands are composed of both acini, which in this case produce saliva, and a duct system, which transports the saliva to the oral cavity. Only serous acini are found in the parotid gland. By contrast, the submandibular and sublingual are mixed glands that are composed of both serous and mucinous acini. With a few exceptions, the minor salivary glands are purely mucinous (**Fig. 4–1**, p. 46).

Cellular Composition of Glands

The Parotid

The parotid acini are roughly spherical and are enclosed in loose connective tissue. They are composed of pyramidal cells with their apex at the acinar lumen. The basally situated nucleus is surrounded by a cytoplasm rich in secretory granules, which are more prominent at the apical aspect of the cell. The granules are more or less numerous depending on the secretory activity of the acinar cell. The lumen of the acinus is small and irregular and may not be visible in all acini. Myoepithelial cells are interposed between the serous cells and the basement membrane. They are slender stellate cells with several elongated cytoplasmic processes that surround the acinar cells and are inconspicuous in light microscopic preparations. The myoepithelial cells have a contractile function and propel the saliva into the acinar lumen and into the duct system.

The intercalated ducts are the smallest ducts and are situated within the lobules. Their cuboidal lining cells have nuclei equivalent in size to the acinar cells. They appear larger, however, because the nuclear-cytoplasmic ratio is higher.The intercalated ducts converge to form the intralobular striated ducts. The striated ducts are so named because their tall columnar lining cells have closely spaced, longitudinal basal ridges. The cytoplasm of the striated duct cell stains intensely eosinophilic, owing to the high content of mitochondria (**Fig. 4–2**, p. 47). Both intercalated ducts and striated ducts are secretory ducts.[1] That is, they modify the composition of, as well as transport, the saliva. The large ducts, the interlobular ducts, and the main excretory ducts serve only to transport the saliva.

Interlobular ducts are dispersed in the connective tissue among the lobules. These ducts are lined by a multilayered epithelium composed of tall columnar cells with interposed goblet cells that surmount small cuboidal basal cells. Occasional cells have conspicuous mucinous vacuoles. The main excretory duct, the Stensen's duct, is lined by similar cells, which at the distal aspect of the duct are replaced by a stratified squamous mucosa that merges with that of the oral cavity at the orifice of the duct.

During embryonic life, lymph nodes develop in close proximity to the parotid gland. They persist as poorly formed nodules or as organized lymph nodes within the adult gland itself. Inclusions of parotid acinar and ductal elements may be found in these intraparotid lymph nodes (**Fig. 4–3**, p. 47). Lymph nodes are more common in the superficial lobe of the parotid gland and are infrequently found in the deep lobe.[2]

Fat cells are present among the acinar cells in the parotid gland. Only a few adipocytes are present during

childhood and adolescence. They increase during adult life, however, and may be the predominant feature in elderly individuals. Nevertheless, xerostomia is rarely a consequence, as sufficient acini generally remain to meet physiologic demands.

The facial nerve runs through the parotid gland, thereby dividing the gland into superficial and deep lobes. Branches of the facial nerve are routinely noted in microscopic sections. Though rare, melanocytes have been identified in the interlobular duct of the parotid gland.[3]

The Submandibular Gland

The submandibular gland is composed of tubular acini that are predominantly serous. About 10% of the acini are mucinous. The mucinous cells are large and roughly triangular, with central nuclei and clear cytoplasmic mucin vacuoles of variable size. Groups of serous cells form crescents at the periphery of the mucinous acini (''demilunes'') (**Fig. 4–4**, p. 47). The acini are arranged in lobules, with intercalated ducts, which are longer than those in the parotid gland, and striated ducts, which are shorter.[4] These ducts drain into the main excretory duct, the Wharton's duct. Although a few lymphoid cells may be present in the connective tissue of the submandibular gland, lymphoid aggregates or lymph nodes are not found normally.[5] Fat cells may be present, but they are not as numerous as in the parotid gland. Nerves are not found in the gland parenchyma.

The Sublingual Gland

The subingual gland is also a mixed gland. In contrast to the submandibular gland, however, the secretory lobules of the sublingual gland are primarily mucinous, with a minor component of serous cells. The duct system is similar to that of the other major glands, with the exception that, in addition to the main duct, the Bartholin's duct, which drains into the submandibular duct, there are several smaller ducts (Rivinus ducts), which open directly onto the floor of the mouth. Fat, lymph nodes, and nerves are not present in the sublingual glands.

Minor Glands

The minor salivary glands are distributed throughout the oral cavity, on the lips, tongue, floor of mouth, buccal mucosa, and soft palate. Notable exceptions are the gingiva and the anterior aspect of the hard palate, which are devoid of these glands. Minor salivary glands are present, however, on the posterolateral aspect of the hard palate and in abundance on the soft palate, including the uvula. The minor glands are located in the submucosa, or among muscle fibers, and are surrounded by a thin fibroconnective tissue. They are not encapsulated. Their alveoli are arranged primarily in lobules. With the exception of the serous Ebner's (deep posterior salivary glands of the tongue) glands, the minor glands are mucinous or seromucinous. The mucinous cells of the acini are similar to those in the major glands, with basal nuclei and large mucin vacuoles in the cytoplasm. In many minor glands, serous demilunes are present. Occasionally, individual serous cells are found in mucinous acini. Less commonly, serous acini are present. The duct system is far less complex than that of the major salivary glands. The intercalated ducts are longer, and striated ducts are either absent or rudimentary.[6] The intercalated ducts are lined by cuboidal cells and drain into intralobular ducts, which are lined by columnar cells. Excretory ducts are lined by columnar cells with interspersed goblet cells that surmount a layer of flattened basal cells. Ciliated cells are found in the excretory ducts of Ebner's glands. These cells are more common at the most terminal part of the excretory duct. Squamous cells line the ducts at the point of entry into the oral cavity. In older individuals, oncocytes are occasionally encountered amid the columnar cells of the excretory ducts. Melanocytes have been reported in minor glands, in the connective tissue surrounding ducts and acini.[7]

■ Ultrastructure of Cells that Compose Glands

The most prominent features of serous cells are the membrane-bound secretory granules, which vary in electron density with secretory activity of the cells. The granules are more numerous and more prominent at the apical aspect of the cell, near the lumen (**Fig. 4–5**, p. 47). The intervening cytoplasm is occupied by organelles that are important for secretory activity, including the endoplasmic reticulum, Golgi vesicles, and mitochondria. The basal plasma membrane is extensively folded. It interdigitates with the nearby cells, thereby increasing its surface area. At the apical aspect of the cell, zonula adherens are present between adjacent acinar cells, whereas desmosomes form the attachments at the basal aspect. Lying between these attachment points are the secretory capillaries, which are continuous with the lumen of the acinus. Numerous microvilli protrude into the secretory capillaries from the adjacent secretory cells. These microvilli are similar to those that protrude into the acinar lumen at the apex of the cells.

In mucinous cells the cytoplasm is filled with mucin vacuoles, and the cytoplasmic organelles (Golgi vesicles,

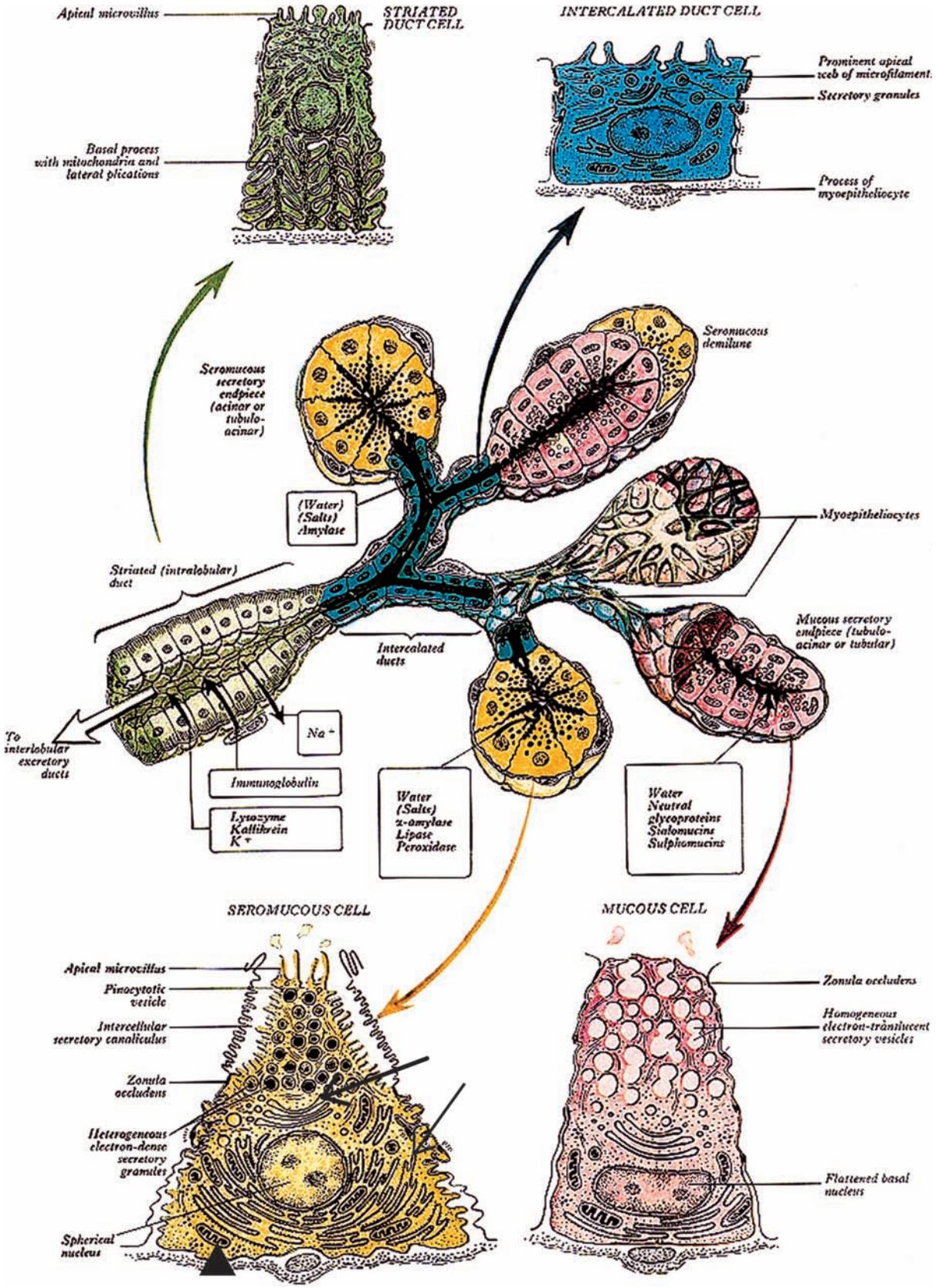

FIGURE 4–1 Diagram of the architecture of a generalized salivary gland, including ultrastructural details. Solid and outlined black arrows indicate direction of saliva transport. (Seromucous cell, arrowhead: mitochondria, thin arrow: rough endoplasmic reticulum, thick arrow: Golgi complex). (From Williams. Alimentary system. In: Gray H, Williams PL, Bannister LH (eds.). Gray's Anatomy: The Anatomical Basis of Medicine and Surgery, 38th ed. New York: Churchill Livingstone; 1995, with permission.)

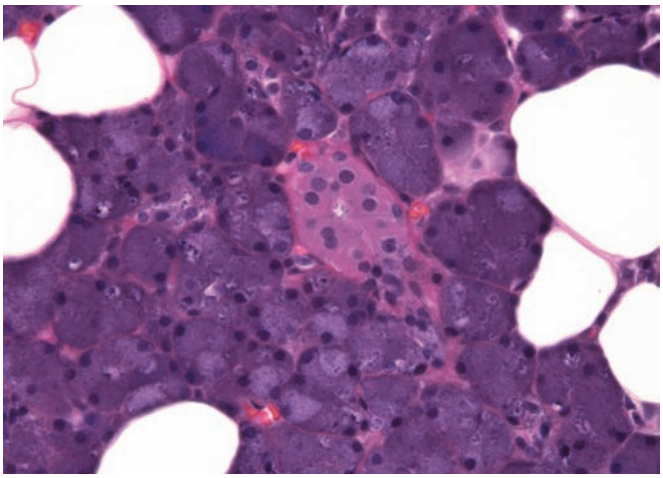

FIGURE 4–2 Parotid gland. Serous acini surround a striated duct (H&E ×400).

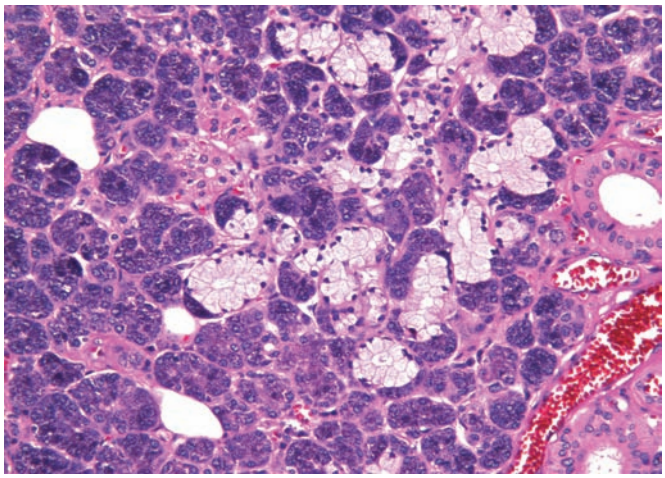

FIGURE 4–4 Submandibular gland. Serous acinar cells form a crescent at the periphery of a mucinous acinus (H&E ×200).

endoplasmic reticulum, and mitochondria) are less numerous than in the serous cells. These organelles occupy the basal zone of the cytoplasm, lateral to the nucleus. Folds in the basal plasma membrane are less prominent than in the serous cells.

Myoepithelial cells are stellate cells, with dendritic processes spread on the surface of the acinar cells. The myoepithelial cells lie between the secretory cells and the connective tissue border of the acinus. These specialized contractile cells have features of both smooth muscle and epithelial cells. They contain myofilaments and actin, as well as pinocytotic vesicles at their basal aspect. Mitochondria, Golgi vesicles, and endoplasmic reticulum are found in the remaining cytoplasm. Myoepithelial cells are connected to the secretory cells by desmosomes.

The few cytoplasmic organelles of intercalated duct cells, principally mitochondria and endoplasmic reticulum, are localized to the basal zone. Occasionally secretory granules may be present, usually in cells close to the acinus. The duct epithelial cells are connected to adjacent cells by junctional complexes and a few desmosomes. Interdigitations are prominent at the lateral aspects of adjacent cells. Myoepithelial cells are present at the periphery of the epithelial cells of the intercalated ducts and occasionally along the striated ducts. They are connected to the epithelial cells by desmosomes (**Fig. 4–6**).

The columnar cells of the striated ducts are characterized by prominent folds in the basal plasma membrane, which extend apically to the midzone of the cells. The folds also ramify laterally and interdigitate with the adjacent cells, thereby greatly increasing the surface area. They correspond to the striations noted on light microscopy. Between the folds are numerous vertically arranged mitochondria. At the apex, microvilli

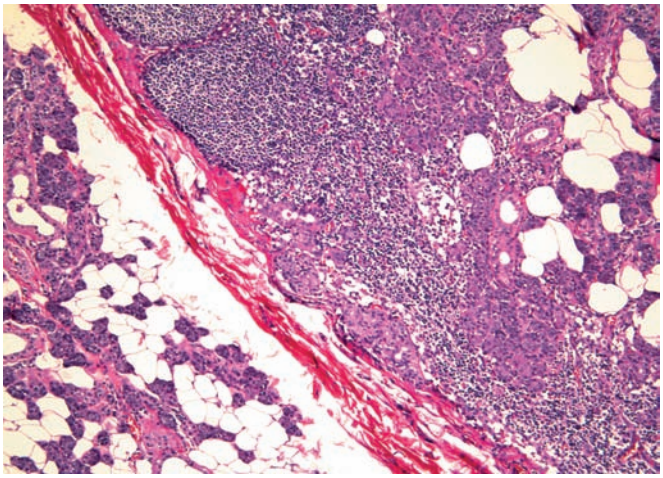

FIGURE 4–3 Intraparotid lymph node with salivary inclusions (H&E ×40).

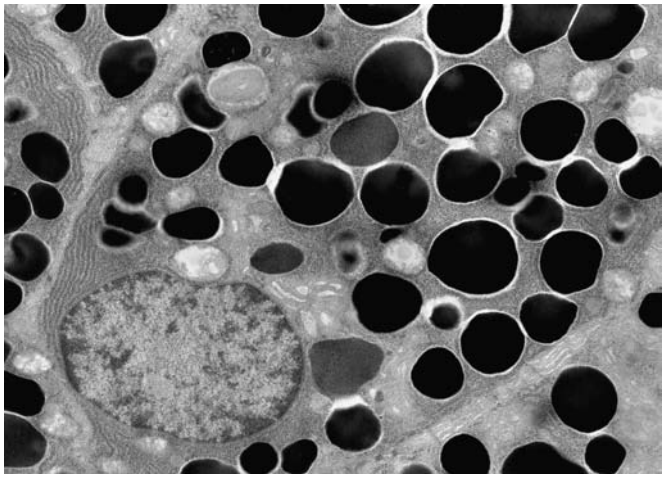

FIGURE 4–5 Serous cell with numerous secretory granules (electron micrograph ×5000 courtesy of Renato Iozzo, M.D.).

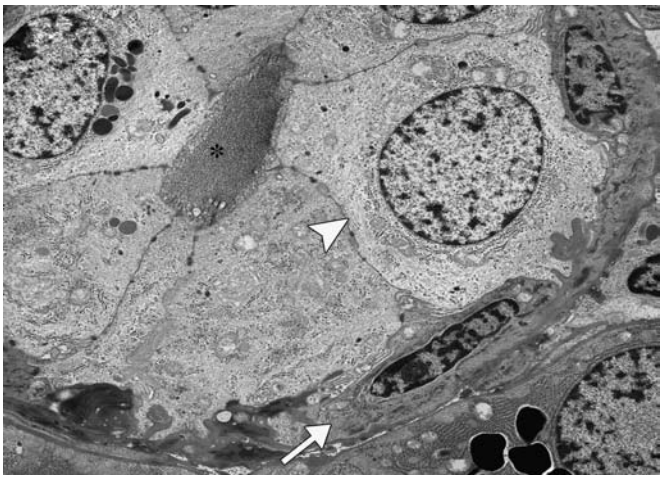

FIGURE 4–6 Myoepithelial cell (arrow) surrounding epithelial cell (arrowhead) of intercalated duct lumen (asterisk) (electron micrograph ×2700 courtesy of Renato Iozzo, M.D.).

project into the lumen. Junctional complexes and desmosomes form sites of attachment to adjacent cells.

The ultrastructural features of the minor glands differ in some respects from those of the major glands.[8] One such variation is the absence of basal folds in the serous cells of Ebner's glands. There are instead numerous folds on the lateral border of the cell.[9] Also in Ebner's glands, many secretory granules are present in the intercalated ducts, as are a well-developed rough endoplasmic reticulum and Golgi apparatus. These features suggest an active secretory role for these cells in the formation of saliva. There are no striated ducts in Ebner's glands. In all minor glands, intercalated duct cells are rich in mitochondria.

■ Immunohistochemistry

Early reports of the immunohistochemical profile of the salivary glands were frequently conflicting, because of the variability in tissue preparation (frozen vs paraffin sections), the antibodies employed, and the detection methods (immunofluorescence vs peroxidase-antiperoxidase). Based on formalin-fixed, paraffin-embedded tissue, recent reports describe more consistent findings.

Cytokeratins are the intermediate filaments found in epithelial cells. The development of antibodies to specific classes of cytokeratin polypeptides has led to an understanding of the heterogeneity of the salivary epithelium, as expressed in the cytokeratin profile. When exposed to a cocktail of antibodies to high and low molecular weight cytokeratins (AE-1/AE-3), acinar cells stain weakly, but much brighter staining is noted in ductal cells.[10] CK-5 and CK-14 are consistently expressed in basal cells in the interlobular and excretory ducts,[11] and these cells react strongly to antibodies to high molecular weight cytokeratins (CK-18 and CK-19).[12] Myoepithelial cells are positive for antibodies to smooth muscle actin and smooth muscle myosin heavy chain,[13,14] as well as CK-14 and CK-17.[15] Epithelial membrane antigen (EMA) stains the serous cells and the luminal surface of ductal cells, but it does not stain mucinous cells.[16] Although there have been reports to the contrary,[17] most investigators have found that S-100 is negative in acinar, ductal, and myoepithelial cells.[18,19] Antibodies to vimentin and desmin are consistently nonreactive.

■ Hyperplasia, Atrophy, and Regeneration

Adenomatoid Hyperplasia

This is a rare benign disorder of mucinous salivary glands that may mimic a salivary gland neoplasm.[20] Patients are asymptomatic, and the nodule is often discovered only incidentally during a dental examination. The hard palate is the most common location, although other intraoral sites are described.[21,22] In most cases, biopsy reveals minor salivary glands indistinguishable from normal. A few reports describe glandular crowding or an increased number of glands.[23] The cause of this localized hyperplasia is unknown, and excision is curative. No relationship to benign or malignant salivary gland tumors has been shown.

Sialadenosis

Sialadenosis refers to recurrent, painless, usually bilateral enlargement of the major salivary glands, particularly the parotid.[24,25] It is associated with endocrine disorders, alcoholism, and metabolic disturbances, including malnutrition and bulimia.[26–30] It has been reported as a side effect of certain drugs, particularly antihypertensive agents and antidepressants.[31] The etiology of sialadenosis appears to be related to a disorder of the autonomic nervous system. Microscopically, hypertrophy of the acinar cells is striking. The cells are enlarged to 2 to 3 times their normal size, and there is an increase in the intralobular fat. There is no inflammation. Ultrastructurally, myoepithelial cells exhibit features of atrophy, and there are degenerative changes in neural elements.[32] Diagnosis may be made by aspiration cytology and morphometry.[33] Treatment is directed at the underlying condition. In long-standing cases, atrophy of the gland eventually occurs.

Atrophy

This is a normal consequence of aging salivary glands and is characterized by the loss of acinar cells, which are

replaced in turn by fat. Most individuals are asymptomatic because of the considerable normal reserve. Atrophy also occurs in association with pathologic processes, such as compression atrophy adjacent to tumors, and distal to duct obstruction caused by sialoliths or intraductal tumors. With chronic inflammation, atrophy and fibrosis follow acinar destruction. An important iatrogenic cause of atrophy is ionizing radiation.[34,35]

Regeneration

Regeneration of salivary tissue is limited. Studies of patients following surgery or radiation therapy indicate that both acinar and ductal cells may undergo mitosis, but significant regeneration of acinar tissue does not occur, and acini are replaced by fat and fibrosis. Hyperplasia of the basal cells in larger ducts and squamous metaplasia of ductal cells may be conspicuous. In experimental animals, regeneration of both acinar tissue and ducts can occur following short-term duct obstruction, but little information is available in human subjects in this setting.[36,37]

Epithelial Metaplasias

Oncocytic Metaplasia

This is the replacement of normal epithelial cells of both ducts and acini by large, eosinophilic cells (**Fig. 4–7**). Ultrastructural studies indicate that the cytoplasm of oncocytes is expanded by an increased number of mitochondria, to the virtual exclusion of other organelles. The mitochondria are enlarged and atypical, with a variety of abnormal morphologic features.[38] Oncocytes may occur singly or in clusters. Occasionally, they form tumors, which are usually benign.[39,40] Oncocytic metaplasia, as well as tumors of oncocytes, are most common in the parotid. It is less common in the minor salivary glands, but nodular oncocytic hyperplasia may occasionally be found incidentally in biopsy specimens in minor glands throughout the upper aerodigestive tract.

The cause of oncocytic metaplasia is unknown, but it appears to be a degenerative phenomenon related to aging. Rare in individuals younger than 50, oncocytes are frequently seen in older subjects. By the age of 70, they are nearly universal.

Oncocytes are not unique to the salivary glands. They occur in many organs, particularly endocrine organs, including thyroid (Hürthle cells), parathyroid, and adrenal, as well as breast and kidney. Oncocytic tumors may form at these sites as well.

Sebaceous Metaplasia

Sebaceous cells are normally found in the major salivary glands. They are most often seen in the parotid, are infrequently identified in the submandibular glands, and are rare in the sublingual glands.[41] Sebaceous cells are also found in the oral mucosa of normal subjects, where they are known as Fordyce's granules. Rarely, they are present in intraparotid and periparotid lymph nodes.[42] In the salivary glands, single cells or groups of sebaceous cells replace the cells of intercalated ducts, or form diverticular outpouchings from the wall of striated ducts or interlobar ducts[43,44] (**Fig. 4–8**). Their morphology is identical to the sebaceous cells found in the dermis: clear cells of variable size, with numerous cytoplasmic vacuoles filled with lipid. Their secretion is extruded into the lumen of the duct and appears in the saliva.

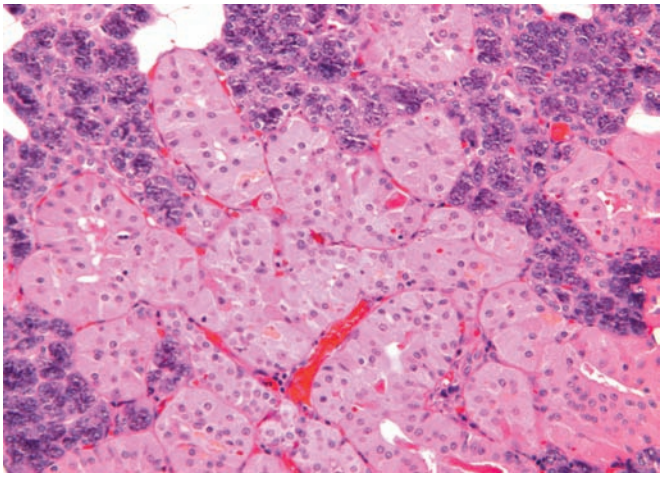

FIGURE 4–7 Oncocytic metaplasia of parotid acini (H&E ×200).

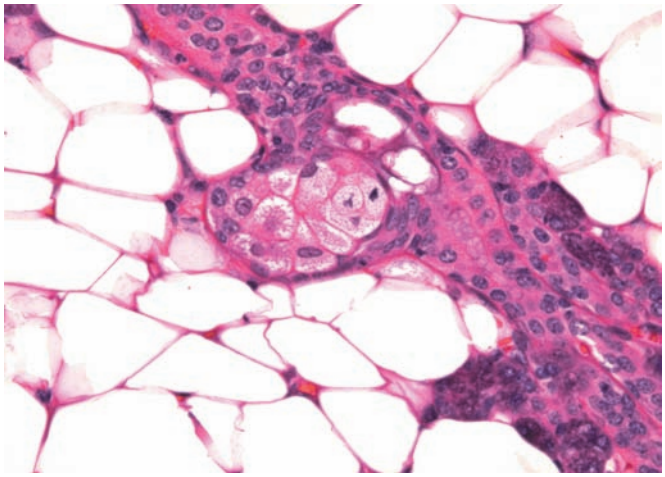

FIGURE 4–8 Sebaceous cells form a diverticulum from the striated duct in parotid gland (H&E ×400).

The origin and function of sebaceous cells in the salivary glands are unknown. They are present in normal glands and have been described in young children. These observations support the hypothesis that they are a variant of normal differentiation. They have been found in inflamed glands and in those containing tumors, but they appear to be independent of these processes. Heterotopia and metaplasia have both been proposed as possible etiologies. Salivary gland neoplasms with sebaceous differentiation, both benign and malignant, have been described but are rare.[10]

Squamous Metaplasia

Replacement of acinar and ductal epithelium by squamous cells does not occur in normal glands. Most commonly, squamous metaplasia is a consequence of an inflammatory process or is associated with a calculus.[45,46] Necrotizing sialometaplasia is a noteworthy example of exuberant squamous metaplasia. It is an inflammatory response to an ischemic insult affecting minor salivary glands, usually in the oral cavity.[47–49]Necrotizing sialometaplasia is characterized by ulceration, with necrosis of acini and replacement of the residual acinar and ductal cells by mature squamous cells. The lobular architecture is retained, and spontaneous resolution ensues. Misinterpretation of this reactive response as a neoplastic process has led to serious diagnostic errors.[50]

Goblet Cell Metaplasia

Goblet cells are normally found in small numbers in the lining epithelium of interlobar ducts. Their numbers increase in inflammatory processes, and in association with calculi and retention cysts. It is speculated that these cells are the origin of mucoepidermoid carcinoma.[51]

■ Accessory and Heterotopic Salivary Gland Tissue

An accessory salivary gland is defined as ectopic salivary gland tissue with a duct system. This is in contradistinction to heterotopic salivary gland tissue, in which only acini are present in an abnormal location, but are not associated with a duct system.[52] The most common example of accessory salivary tissue is accessory parotid tissue. The usual location for the accessory gland is adjacent to, but distinctly separate from, the main parotid gland, unlike the facial process, which is a small anterior projection of glandular tissue along the duct.[53] An accessory parotid gland is usually located anterior to the main parotid gland. It lies superior to the parotid duct, adherent to the masseteric fascia, and in close proximity to the buccal division of the facial nerve. The accessory parotid gland drains into the main parotid duct by one tributary.

Accessory parotid tissue is separated from the main gland by an average of 6 mm and is usually 3 cm or less in size. Histologically, accessory parotid tissue is distinctive, because mucinous cells as well as serous cells may be present in the acini. Autopsy studies have revealed accessory parotid tissue in 21 to 56% of normal adults.[54]

Any disorder that affects the parotid gland may affect accessory parotid tissue. Interestingly, 1 to 8% of parotid tumors arise from accessory tissue, and a higher percentage of these lesions are malignant (50% as compared with 20–25%).[55–57] Symptomatic patients usually present with a painless, mobile midcheek tumor. Confirmation of accessory parotid tissue requires imaging studies to establish that the main gland and mass are indeed separate.

Salivary gland heterotopia refers to the occurrence of salivary tissue at sites other than the normal anatomical locations of the major and minor salivary glands. The most common site of heterotopic salivary tissue is in the cervical lymph nodes.[58] Other locations included the middle ear,[59] parathyroid[60] and thyroid tissue, pituitary glands[61] (as a remnant of Rathke's pouch), the cerebellar pontine angle,[62] the soft tissue of the lower neck, and medial to the sternocleidomastoid muscle.[63] Rare examples of heterotopic salivary gland tissue in sites remote from the head and neck include the stomach, rectum, and vulva.[64–66]

Heterotopic salivary gland tissue in cervical lymph nodes is related to the close association of developing lymphoid and salivary tissue in the embryo, a situation that explains the frequent presence of lymph nodes in the parotid and the inclusions of salivary tissue in intraparotid and periparotid lymph nodes. Heterotopic salivary tissue in other head and neck locations is attributed to the persistence and abnormal development of tissue associated with the branchial apparatus and the primitive foregut. Lower cervical heterotopias are thought to result from the failure of closure of the cervical sinus of His associated with the first and second branchial arches.[67] The middle ear also develops from the branchial apparatus, and the cranial nerves and their ganglia develop on the dorsal aspect of the branchial arches. The intimate admixture of branches of the facial nerve with ectopic salivary tissue in the middle ear is a consequence of this relationship. The rare occurrence of heterotopic salivary tissue in organs remote from the head and neck remains unexplained.

Neoplasms in heterotopic salivary tissue are rare, but they can pose challenging clinical problems. The presence of salivary gland tumor in cervical lymph nodes

may be mistaken for metastatic tumor from a normally situated gland. Alternatively, it may be misclassified as a metastasis from an unknown primary. In either case, inappropriate treatment may result.[68–70]

■ Noninflammatory, Non-neoplastic Disorders

Amyloidosis

Amyloidosis refers to a group of disorders characterized by the localized or systemic deposition in a variety of organs of characteristic extracellular proteins. The fibrillar amyloid proteins are folded as a β-pleated sheet, a feature responsible for their morphologic and staining properties.[71] The diverse causes of an amyloid protein deposition include neoplasia, inflammatory processes, and familial syndromes. The clinical presentation and course of the disease depend on the organ(s) affected. Common sites of amyloid deposition include the kidneys, heart, tongue, and brain. Virtually any organ, however, may be affected.[72] A diagnosis of amyloidosis depends on the identification of an extracellular amyloid protein in histologic sections, where it appears as an amorphous, eosinophilic substance with a uniform, somewhat glassy hue. The diagnosis is confirmed by staining with Congo red. Amyloid proteins bind this dye, and under polarized light they exhibit a characteristic green birefringence. Ultrastructurally, the protein fibrils are linear, parallel, and 7.5 to 10 nm in diameter.

Historically, amyloidosis was classified as primary, secondary, or localized, depending on the clinical setting in which it arose. It has become evident, however, that this classification is overly simplistic. The current classification system is based on the specific protein responsible for the amyloid deposits.

Involvement of the salivary glands in amyloidosis may be the first clinical evidence of the disorder.[73,74] Alternatively, it may be a late feature in a more generalized process.[75] Both major and minor salivary glands may be involved. Clinically, xerostomia or bilateral, painless salivary gland enlargement can be present. The frequent (asymptomatic) involvement of the minor glands has been exploited by utilizing biopsy of these glands for diagnosis when amyloidosis is suspected.[76]

Lipomatosis

Lipomatosis is a condition characterized by an abnormally localized or tumor-like accumulation of intraparenchymal fat tissue. With respect to the salivary glands, a distinction can be readily made between lipomatosis and a lipoma. A lipoma has a fibrous capsule that results in a discrete, localized mass in the salivary tissue. By contrast, lipomatosis is present diffusely throughout the gland. The parotid is the most frequent site; however, lipomatosis of minor salivary glands has been reported.[77,78]

Lipomatosis can be caused by many localized or systemic conditions. Fatty infiltration of salivary tissue often accompanies aging, associated with atrophy. It has been documented in patients with diabetes mellitus, cirrhosis, chronic alcoholism, malnutrition, and hormonal disturbances.[79,80] Recently, parotid lipomatosis has been described in patients positive for the human immunodeficiency virus (HIV) receiving protease inhibitors.[81] It has rarely been reported in the pediatric population.[82,83]

Lipomatosis presents as a soft, diffuse, painless enlargement of the salivary gland, similar to a benign salivary gland tumor. Appropriate diagnostic and imaging studies are indicated, with surgical excision when necessary.

Hemochromatosis

Hereditary hemochromatosis is a common autosomal recessive disorder of iron metabolism characterized by excessive iron absorption and the toxic accumulation of iron in parenchymal cells, particularly the liver, heart, and pancreas. Otolaryngologic manifestations most commonly include xerostomia, due to a loss of salivary gland function as a result of iron deposition.[84,85] The definitive diagnostic test is a liver biopsy. However, because of the diffuse systemic nature of this disease, less invasive diagnostic tests have been reported. Labial biopsies have been successful in revealing hemosiderin deposition within the minor salivary glands.[86]

Cheilitis Glandularis

Cheilitis glandularis is a rare chronic inflammatory condition usually present on the lower lip of adult males.[87] Its etiology is unknown. The affected lip is swollen, and on palpation it is nodular, firm, and sometimes tender. Thick saliva can be expressed with digital manipulation. The vermillion border may be everted. Histologic findings are nonspecific and include hyperplasia, hypertrophy, fibrosis, and salivary ductal ectasia. A case associated with squamous cell cancer has been reported.[88]

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5

Sialadenitis

KELLY M. MALLOY, DAVID ROSEN, AND MARC R. ROSEN

Sialadenitis refers to the various inflammatory conditions affecting the salivary glands. It has been recognized as a disease entity since the time of Hippocrates (*c.* 460–*c.* 377 B.C.), who originally delineated a difference between acute suppurative sialadenitis and mumps parotitis.[1] Etiologies of sialadenitis include bacterial infections, viral pathogens, granulomatous diseases, and systemic conditions. These inflammatory processes may affect any of the salivary tissues of the head and neck; however, of the major salivary glands, the parotid gland tends to be the most commonly involved site. This predisposition of the parotid gland to inflammation and infection is felt to be due to its anatomy and the physiology of its salivary content and normal salivary flow. Presentation of sialadenitis typically involves diffuse enlargement of the affected gland, accompanied variably by other signs and symptoms of inflammation. The most common presentation, regardless of etiology, is glandular enlargement; however, a broad differential diagnosis should be kept in mind when assessing affected patients. This differential would include noninflammatory conditions, both benign and malignant, which produce swelling and mass effect of the salivary glands, as well as other sources of neck and facial swelling that may imitate sialadenitis. This differential diagnosis is listed in **Table 5–1** and includes both salivary and other etiologies of facial and neck enlargement. It is the intention of this chapter to thoroughly delineate the infectious and inflammatory diseases that affect the salivary glands and distinguish these from the other sources of salivary gland enlargement that can complicate diagnosis.

Acute Suppurative Sialadenitis

Historically, acute suppurative sialadenitis is a disease of elderly and debilitated patients; it has often been reported in postsurgical patients, particularly after gastrointestinal procedures, which has earned it the nickname ''surgical parotitis'' or ''surgical mumps.''[2] It is also a common problem in critical care settings where patients are often kept NPO (nothing by mouth), are unable to maintain their own oral hygiene, and are prone to dehydration and immunosuppression secondary to their chronic illnesses and the treatments thereof. With improvements in modern critical care medicine, including improved antibiotics and vigorous hydration schemes, acute suppurative sialadenitis is a less common entity today.[3,4] Still, in the inpatient setting, it reportedly occurs in 0.002 to 0.04% of all postoperative patients. Overall, sialadenitis accounts for 0.01 to 0.02% of all hospital admissions.[5] The most recent quoted data found that acute suppurative sialadenitis accounts for 0.03% of hospital admissions in the United States, and 30 to 40% of these cases occur in postsurgical patients.[6] In the outpatient setting, a more commonly encountered form of acute sialadenitis is that which is consequent to sialolithiasis. Although the classic postsurgical sialadenitis most frequently involves the parotid gland, stone-related sialadenitis is more commonly noted in the submandibular gland, as it is more prone to sialolith formation[3,4] (see Chapters 6 and 7).

The common pathophysiology of acute sialadenitis, be it postsurgical parotitis or stone-related submandibular sialadenitis, is salivary stasis. Stasis of saliva in the ducts and parenchyma may result from poor production

TABLE 5–1 Differential Diagnosis of Salivary Gland Enlargement

Inflammatory
Sialadenitis
Bacterial
Viral
Granulomatous
Systemic (e.g., Sjögren's syndrome)
Cervical adenitis
Dental infection or abscess
Buccal, masseteric, or deep neck space infection or abscess
Bezold's abscess or lymphangitis otitis externa
Noninflammatory
Salivary neoplasm
Lymphoma
Branchial cleft cyst
Sebaceous cyst

of saliva, from impaired salivary outflow, or from a combination of the two. Decreased quantity of saliva is often the result of a state of dehydration, which may be secondary to poor oral intake, overzealous use of diuretics, blood loss, or inadequate fluid replacement in the acutely ill patient. Inanition and anorexia contribute to poor production and flow of saliva. Normally, the presence of a food stimulus prompts salivary production and the action of mastication produces massaging effects of the ducts to facilitate salivary flow. Use of anticholinergic medications and diuretics result in decreased volume of salivary secretions, and sialolithiasis and ductal pathology contribute to impaired flow of saliva through the ducts and into the oral cavity.[6]

The presence of salivary stasis predisposes the salivary gland to infection. Normal salivary flow effectively washes out the parenchyma and ducts of any pathogen that may be present. When the production and passage of saliva are diminished, stagnant saliva provides a ready medium for bacterial growth. It is thought that bacteria migrate from the oral cavity in a retrograde fashion up the ducts to infect the parenchyma of the gland; therefore, organisms of the normal oral flora are the most common culprits in bacterial sialadenitis.[7] *Staphylococcus aureus* accounts for 53% of bacterial infections of the salivary glands; an additional 31% is due to *Streptococcus viridans*.[3] Other potential pathogens include *Streptococcus pyogenes* and *Streptococcus pneumoniae*, gram-negatives such as *Haemophilus influenzae* and *Escherichia coli*, and anaerobes. A study of parotid abscess drainage specimens demonstrated the isolation of anaerobic bacteria, particularly *Bacteroides* and *Peptostreptococcus* species, from 57% of patient samples, highlighting the importance of these bacteria in sialadenitis infections.[8] Poor oral hygiene compounds the risk of developing acute bacterial sialadenitis, as an unclean oral cavity acts as a reservoir for bacterial growth. As with any infectious disease, chronically ill and debilitated (particularly hospitalized) patients are more prone to acute sialadenitis, not only because of their diminished immunocompetency but because they frequently cannot maintain adequate oral hygiene, hydration, and normal mastication, all of which place them at risk for acute sialadenitis.

Although the appropriate quantity and normal egress of saliva are the main factors preventing acute bacterial sialadenitis, the quality of saliva is also a determinant of which glands may be involved. In general, saliva has antimicrobial properties that help to prevent dental decay and maintain a clean and healthy oral cavity, inhabited by normal flora. Normal saliva contains various immunoglobulins, lysozyme, lactoferrin, sialoperoxidases, cystatins, and histatins, all of which contribute to the antibacterial nature of salivary secretions. Lactoferrin has particular activity against gram-negative cell walls and is an antistreptococcal enzyme, and the histatins demonstrate both antibacterial and anticandidal properties. Additionally, saliva contains proteins and glycoproteins that inhibit the attachment of bacteria and other pathogens to oral mucosa and dental surfaces.[9,10] Unhealthy or diminished saliva will be deficient in these antimicrobial properties. Parotid saliva is more serous than that of the submandibular gland, which is felt to lend it a lesser bacteriostatic quality. The increased viscosity of the mucinous submandibular saliva traps bacteria, halting their progression to the parenchyma of the gland. This difference in salivary composition may account for the greater predisposition of the parotid gland to infection compared with the submandibular gland. That said, the submandibular gland is more commonly affected by sialolithiasis due to the nature of its saliva; higher mucin content and alkaline pH of submandibular salivary secretions, plus increased levels of calcium and phosphate salts, contribute to stone formation.[3,6] Blockage of Wharton's duct by a calculus clearly can lead to the salivary stasis that may lead to the development of an acute episode of sialadenitis. Indeed, sialolithiasis often presents when obstruction of a salivary duct by a stone produces the clinical manifestations of sialadenitis.[2]

Acute suppurative sialadenitis presents most often with the rapid onset of unilateral painful swelling of the involved gland (**Fig. 5–1**). The patient may complain of referred pain to the ear, cheek, jaw, or neck, and may experience fevers, malaise, and trismus. Any history of prolonged illness, surgery, dehydration, and poor oral hygiene should be noted, as should a history of salivary stone disease or salivary duct pathology, such as strictures or stenosis. On physical examination, one notes the presence of an enlarged, indurated, warm gland with overlying erythema and tenderness on palpation. There may be reactive cervical lymphadenopathy and displacement of the pinna due to the mass effect of an inflamed tail of parotid. On examination of the oral

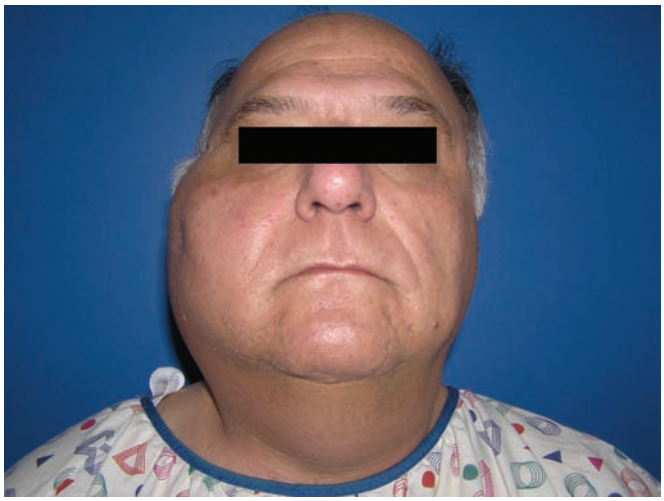

FIGURE 5–1 Acute parotitis. A patient with significant unilateral parotid swelling that was acute in onset and accompanied by pain on palpation and with mastication.

cavity, there may be edema of the duct and ductal orifice, and purulent saliva may be expressed from the punctum with bimanual massage (**Fig. 5–2**). Palpation may also reveal the presence of a ductal calculus.[4]

Diagnosis is typically guided by history and physical examination; however, computed tomography (CT) studies may be undertaken to evaluate for the presence of a nonpalpable stone or abscess formation. One should note that the development of a salivary gland abscess secondary to acute suppurative sialadenitis is typically difficult to detect on physical examination alone, as the dense fibrous capsule of the gland prevents it from feeling fluctuant on exam. Ultrasonography has also been used to evaluate infected salivary glands for the development of abscesses. There are authors who anecdotally report using CT and ultrasound guidance to drain salivary abscesses, but there are no reports comparing these with the standard of surgical drainage.[6] Sialography, which involves the injection of contrast dye into the salivary duct orifice, is contraindicated in the setting of acute sialadenitis both because it is of no diagnostic use compared with other imaging modalities and because the contrast agent may cause increased inflammation and flaring of symptoms.[4]

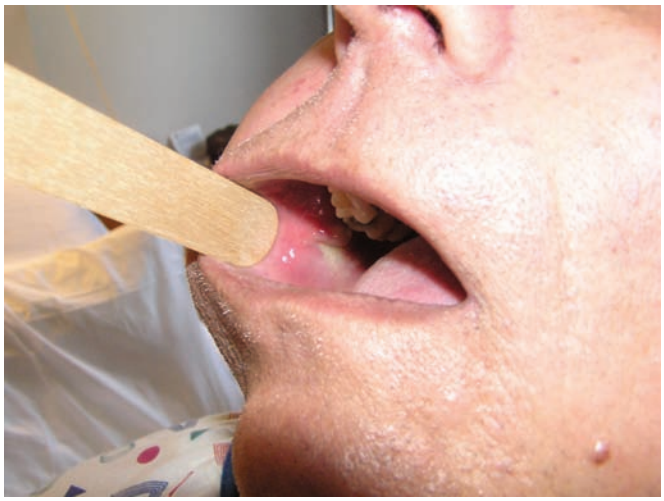

FIGURE 5–2 Acute parotitis. An intraoral view of the same patient's Stensen's duct orifice, which is edematous and expresses purulent saliva with bimanual massage.

Treatment of acute sialadenitis is aimed at eliminating the acute infection and correcting the factors that contributed to the development of the condition. Antibiotic therapy should be administered until clinical improvement is noted, then continued for 1 week after the abatement of symptoms. Although a trial of oral antibiotics is feasible in an otherwise healthy patient, those with underlying exacerbating conditions or with severe constitutional signs should be hospitalized for intravenous therapy.[4] A β-lactamase resistance rate of 73% has been demonstrated by parotitis isolates, highlighting the need for appropriate antimicrobial selection; given the preponderance of bacteria that may be involved in a salivary gland infection, broad-spectrum antibiotics are also wise.[8] Most authors advocate that a β-lactamase-resistant penicillin or first-generation cephalosporin be used as first-line therapy, given that *S. aureus* or a *Streptococcus* species is the most likely pathogen. However, should there be a question whether there is a resistant strain involved (e.g., in a hospitalized patient) or a patient does not improve with standard therapy or is penicillin allergic, other antimicrobials must be used. Vancomycin should be reserved for recalcitrant cases where resistance is suspected. Clindamycin, cefoxitin, imipenem, or a metronidazole-macrolide combination should be used in the case of anaerobic infection or, with the exception of cefoxitin, in penicillin allergic patients.[7,8] One should also remember that gram-negative species may play a role in hospital-acquired sialadenitis.[11] Pus expressed from the duct may be collected for gram stain and culture to guide further antibiotic choice.

Aggressive hydration is also of great importance to correct dehydration and improve salivary production and flow, thus helping to flush pathogens from the gland parenchyma and clear the infection. Patients should be instructed to drink ample fluids, and treating physicians should have a low threshold for admission for intravenous fluids. Sialagogue use also helps stimulate salivary flow, and warm compresses and analgesics help relieve discomfort. Steroid use may be used to reduce inflammation, particularly of the edematous ductal mucosa, and thus improve ductal drainage during the acute phase. Improvement of any deficiency in oral hygiene should be undertaken, as should daily massage of the gland.

Treatment of sialadenitis that develops secondary to sialolithiasis must address the stone disease as well.

Often bimanual massage of the gland will allow one to milk out a smaller stone, or if needed, a small incision in the duct orifice may deliver the calculus. Should the stone be too large for these conservative measures, the acute sialadenitis must be aggressively and adequately treated prior to undertaking any more definitive surgery, such as sialodochoplasty or sialadenectomy for large hilar calculi. Operating on an acutely inflamed gland or duct is technically difficult and may result in postoperative complications of scarring or fistula formation.

Surgical intervention in the setting of acute suppurative sialadenitis may become necessary, however, in the event of abscess formation. As previously mentioned, abscesses of the salivary glands are difficult to diagnose on physical exam. The characteristic fluctuance typical of abscesses is absent due to the tense fibrous capsule of the gland, which envelops the abscess as well. Salivary gland abscess should be suspected in any patient whose sialadenitis fails to improve, or indeed worsens, despite adequate treatment for several days, and prompt CT evaluation is warranted to evaluate for this potentially serious complication. Parotid abscesses can rupture into the external auditory canal or temporomandibular joint. Salivary gland abscesses may also fistulize through the skin of the cheek or neck and extend into the deep spaces of the neck; abscesses originating in the salivary glands have been known to invade the prestyloid parapharyngeal space, the poststyloid space around the carotid sheath, the submandibular space, and the carotid triangle. These abscesses obviously pose a potential threat to the airway, and prompt evaluation and drainage are warranted.[3] Surgical drainage of a parotid abscess is demonstrated in **Fig. 5–3**. This procedure has been in use in essentially the same format since the 1920s. A standard parotidectomy incision is made, and anterosuperior skin flaps are raised. Incisions are made into the parotid fascia parallel to the direction of the facial nerve to liberate the pus, followed by irrigation and closure of the wound over a drain.[2,12]

Abscess formation is just one of the multiple complications associated with acute suppurative sialadentitis.

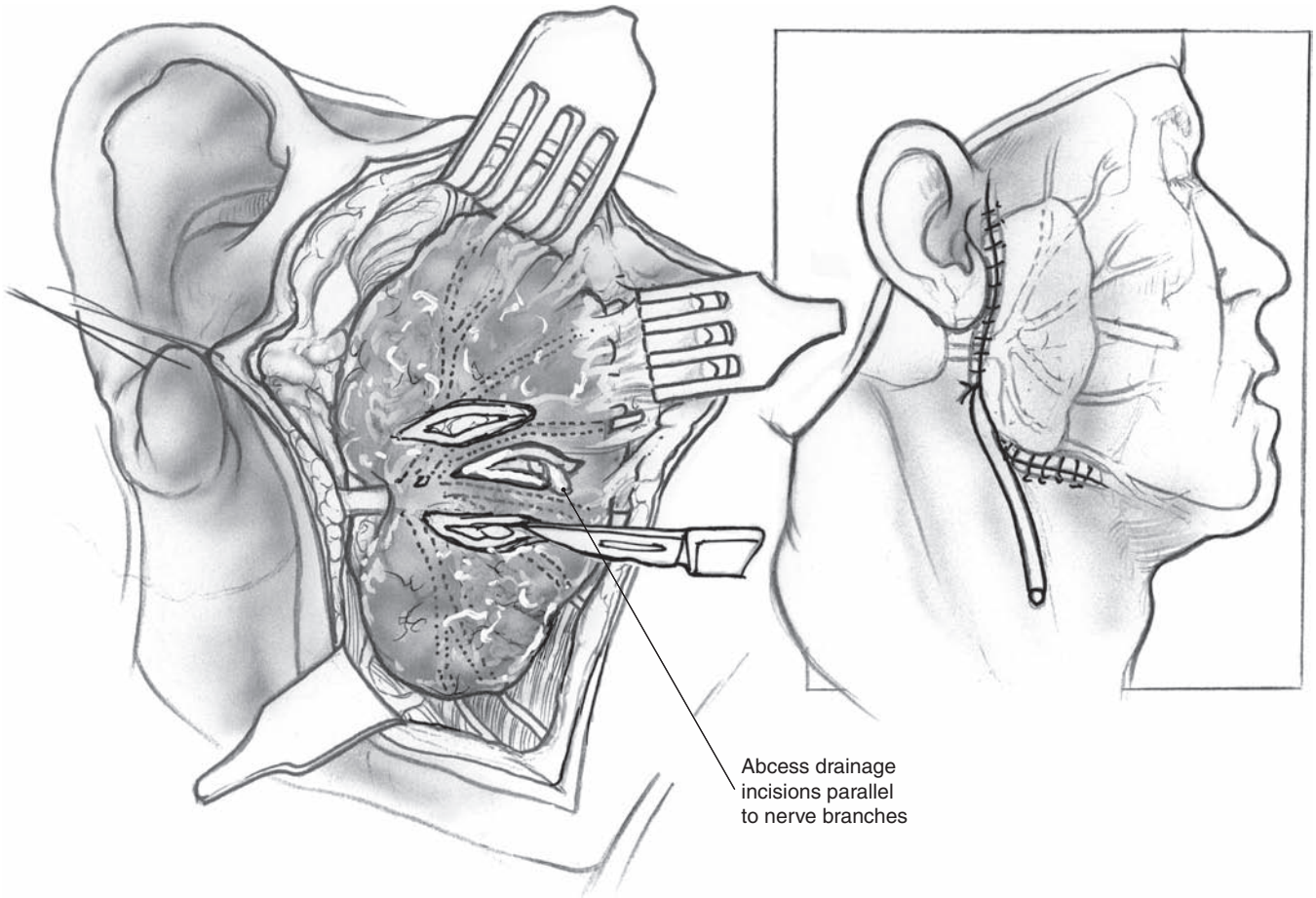

FIGURE 5–3 Surgical drainage of a parotid abscess. An incision is made as per a parotidectomy. Skin flaps are raised anteriorly and superiorly to reveal the parotid gland with its overlying fat and fascial layers. Incisions are made into the parotid fascia parallel to the course of the facial nerve and its branches, and pus is drained from the abscess cavity. After copious irrigation, the wound is closed over a drain.

Chronic sialadenitis may develop after an episode of severe acute sialadenitis that causes irreversible parenchymal and ductal changes (see discussion later in this chapter). Facial nerve paresis has been rarely reported, and is felt to be due to extreme virulence of the offending organism; the resulting intense inflammation causes compression on the nerve or neuronitis. Given that this is so rare a consequence of acute sialadenitis, one must rule out a more likely condition producing salivary gland enlargement and facial paresis: malignancy. Indeed, compression and obstruction of a duct by salivary gland tumor resulting in sialadenitis have been reported as the presentation of salivary neoplasm.[13] Severe and life-threatening complications, though rare, include osteomyelitis, thrombophlebitis of the internal jugular vein, and sepsis.[3] Fulminant necrotizing mediastinitis has also been reported as a complication of acute parotitis.[14] Severe acute suppurative sialadenitis can be so complicated an infection, and has historically affected an already debilitated patient population, that there has been a 20 to 25% increased morbidity linked to the disease.[6] This fact may reflect the poor overall condition and survival of patients who traditionally developed acute suppurative sialadenitis, rather than morbidity due to the sialadenitis itself.

■ Chronic Sialadenitis

Often the factors that predispose an individual to an acute episode of bacterial sialadenitis are not easily eliminated, and stasis of salivary secretions becomes chronic. Sialolithiasis may be recalcitrant, ducts may become scarred and stenotic, and sialadenitis may recur either in the acute suppurative form or as a more indolent subacute process. This recurrent and chronic inflammation of the involved salivary gland causes permanent changes in the gland parenchyma and duct system, including sialectasis, duct ectasia and stenosis, and fibrosis of the parenchyma with loss of functional acini. **Fig. 5–4** demonstrates an enlarged and fibrosed submandibular gland after sialadenectomy for chronic sialadenitis; on histopathology of this gland, the loss of functional acini and replacement of normal parenchyma with fat and fibrosis are obvious (**Fig. 5–5**). This progressive inflammatory destruction of both the functional tissue and drainage system of the involved gland results in diminished secretory function of the gland, establishing a state of progressive salivary stasis and predisposing it to further cycles of inflammation. Once again, the parotid gland demonstrates a greater propensity to chronic sialadenitis than the other major salivary glands.

Clinically, chronic sialadenitis is characterized by repeated periods of pain and swelling of a salivary gland separated by asymptomatic intervals of weeks to months. The patient may additionally complain of thickened and/or diminished saliva, reflecting the decreased secretory capability of a progressively fibrotic gland. Often the patient reports a prior history of a severe episode of acute sialadenitis or ductal pathology such as sialolithiasis, stricture, or prior ductal dilation procedures. Indeed, salivary calculi are the most common cause of chronic sialadenitis, accounting for 30% of all cases. Stricture of Stensen's duct or orifice causes 8%

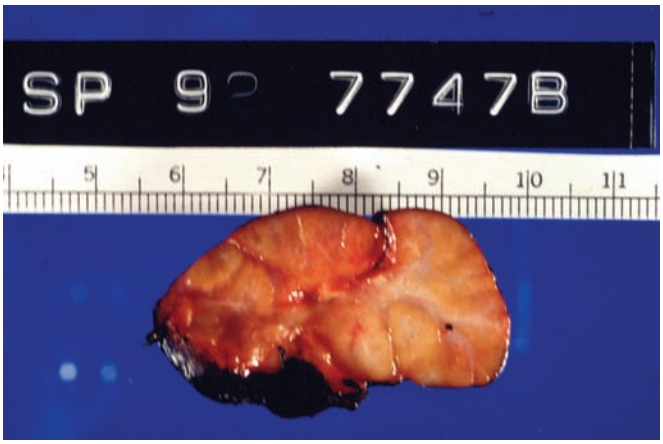

FIGURE 5–4 Chronic sialadenitis. This resected submandibular gland is enlarged in size and demonstrates a lobular appearance on its cut surface. Note the gray-white fibrotic septae that surround and separate the parenchymal lobules. (Courtesy of Mary Cunane, M.D., Thomas Jefferson University Hospital, Philadelphia, PA.)

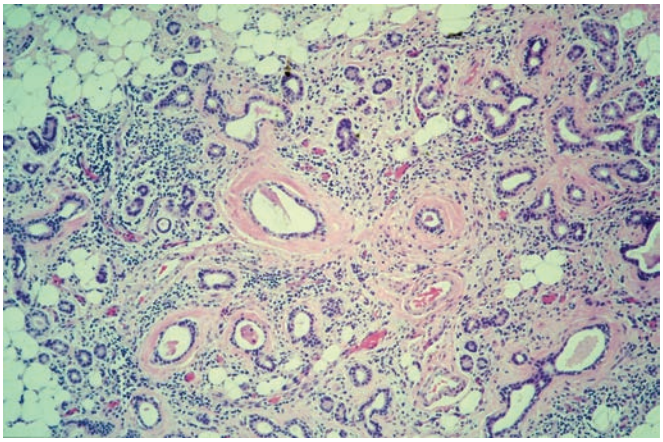

FIGURE 5–5 Chronic sialadenitis. This photo shows the histologic features of chronic sialadenitis within a submandibular gland. Although the overall lobular architecture is retained, the lobules become atrophic and are separated by fibrous bands. There are prominent inflammatory cell infiltrates throughout the specimen and increased replacement of parenchyma with adipose cells. Note the conspicuous periductal fibrosis and ductal dilation as well. (Courtesy of Mary Cunane, M.D., Thomas Jefferson University Hospital, Philadelphia, PA.)

and 4% of cases, respectively, and adjacent scar causes 2% and tumor compression 3%.[15]

Treatment of chronic sialadenitis is challenging. It begins with treating the infection and inflammation as one would acute sialadenitis, as chronic sialadenitis is really a complicated and advanced form of that disease. Antibiotics, vigorous hydration, and sialogogues are used, but they do not appear to alter the chronicity of the disease. Any stone disease or other obstructive pathology of the involved duct should be managed appropriately and only after the current inflammation has subsided. A recent review of the literature found that roughly 50% of patients improve or stabilize with these conservative interventions.[16] Ultimately, as the disease state progresses and the gland becomes increasingly dysfunctional, conservative treatments fail, and often complete excision of the gland is necessary. Other surgical therapies short of removal of the gland have been attempted, such as injection of the duct with sclerosing agents like methyl violet, duct ligation, and tympanic neurectomy. In theory, these interventions would cause the diseased gland to completely atrophy; however, in practice this outcome is variable in its efficacy. Sialadenectomy is the only definitive solution when medical therapy fails, with the advocated procedure being a near-total parotidectomy in most cases. Delaying surgery until any acute exacerbation has resolved is preferable, as there are conflicting data as to the facial nerve being at higher risk for injury during parotidectomy for chronic sialadentitis than during that for neoplasm.[16,17] Preoperative sialography is often advocated to help determine which patients have developed severe enough disease that they might benefit from surgical excision. Those who exhibit moderately severe to severe sialographic changes of irregularly dilated ducts and branches, punctuate sialectasis, and acinar atrophy predictably respond poorly to conservative measures and benefit from surgery. These sialographic changes have been shown to correlate histologically with the severity of the disease.[15]

■ Viral Sialadenitis

Although bacterial sialadenitis produces localized infection and inflammation of the involved gland, viral sialadenitis is a manifestation of a systemic infection. Instead of the gland being directly infected by a pathogen as in bacterial disease, it is infected by a hematogenous spread of virus. Mumps is the classic example of viral parotitis. The advent of the human immunodeficiency virus (HIV) epidemic has led to the discovery of HIV-associated salivary gland disease. Other viruses have been known to infect the salivary glands, such as cytomegalovirus, coxsackievirus, echovirus, Epstein-Barr virus, and parainfluenza and influenza strains.[18] A discussion of all of these entities is beyond the scope of this chapter; however, one should be aware of the potential of these organisms to cause sialadenitis.

Mumps

Historically, mumps parotitis constituted the most common cause of parotid enlargement, and in the prevaccination era it accounted for its alternate name, ''epidemic parotitis.'' It was once a common disease of childhood, producing epidemics among children, with a peak age range of 4 to 6 years. It continues to be the most common viral infection of the salivary glands and most frequently affects the parotid gland. Mumps is caused by a paramyxovirus, which is spread by airborne respiratory droplets and is highly contagious. The virus incubates for a period of 2 to 3 weeks prior to the development of clinical signs and symptoms, and viral shedding can occur for 1 week after the onset of symptoms. Clinically, the patient first experiences constitutional symptoms of fever, malaise, and myalgias, which are followed by the development of bilateral parotid swelling and pain that is exacerbated by eating. The other classic manifestation of mumps infection is orchitis, which causes significant discomfort in the acute phase and may be complicated by infertility in the long term. Other potential complications of mumps include encephalitis, pancreatitis, nephritis, and sensorineural hearing loss.

The diagnosis of mumps parotitis is largely clinical, based on the classic presentation of a young patient with bilateral painful parotid swelling and often in the context of an outbreak of mumps in an unvaccinated population. That said, the diagnosis may be confirmed by serologic testing consisting of hemagglutination antigen testing, mumps S and V antigens, and complement fixation testing, or by isolating the virus from urine. As with many viral syndromes, treatment of mumps is largely supportive. Similar to the treatment of other etiologies of sialadenitis, special attention should be paid to keeping the patient well hydrated, not only to support the patient through the systemic viral infection, but also to assist with good saliva production and flow. Comfort measures such as analgesics and warm compresses may additionally be used. One should note that the swelling of the glands, which may be significant, can take weeks to resolve, but it does typically resolve completely. The patient should be followed for chronic sequelae of the infection, including chronic sialadenitis, infertility, and hearing loss.[18,19]

Human Immunodeficiency Virus

HIV infection may manifest itself as salivary gland enlargement and dysfunction. Salivary gland enlargement

in adult HIV patients can also be caused by follicular hyperplasia, viral, bacterial, fungal, and parasitic infections, a Sjögren's syndrome variant of lymphoepithelial sialadenopathy, diffuse infiltrative CD8 lymphocytosis syndrome, or neoplasms including lymphoma (i.e., mucosa-associated lymphoid tissue lymphoma) and Kaposi's sarcoma.[20]

HIV-associated salivary gland disease (HIV-SGD) may be the presenting sign of HIV infection, and it has been noted both in HIV-positive and high-risk HIV-negative populations.[20] It is particularly noted in children born to HIV-infected mothers, as well as in adult infected patients. Fifteen to 30% of HIV-infected children demonstrate the bilateral parotitis known as HIV-SGD.[21]

The lymphoproliferative and cystic changes in HIV-SGD ultimately lead to glandular dysfunction.[22] It is not known whether the gland becomes infected primarily or if salivary involvement is a manifestation of systemic viral dissemination; we do know that HIV can be found in low levels in saliva of infected individuals, but it is not thought that these concentrations are infective.

HIV infection results in a high concentration and rapid turnover of HIV in hyperplastic lymphoid tissue, in and adjacent to the parotid parenchyma. The fact that the parotid gland as a preferential site for benign lymphoepithelial cysts is probably due to intraparotid lymph nodes, absent in other salivary glands. HIV cytokines and lymphoid hyperplasia stimulate the adjacent ductal epithelium to produce secretions, then secretions cause cyst formation and ductal dilation as well as squamous metaplasia.[23]

In terms of clinical presentation, HIV-SGD causes gradual nontender swelling of the involved gland, most commonly the parotid glands. Glandular enlargement may initially fluctuate, but eventually it becomes persistent. Benign lymphoepithelial cysts form that are bilateral, multiple, and can become large and disfiguring.[24] They can manifest in the superficial or deep parotid lobe and can affect the salivary gland parenchyma and intrasalivary lymph nodes. They are neither invasive nor prone to malignant degeneration.

Along with the classic bilateral parotid enlargement, patients may experience xerostomia, xerophthalmia, and arthralgia, a sicca syndrome not unlike that of Sjögren's syndrome. It is postulated that this common presentation of HIV-SGD and Sjögren's syndrome may be related to the fact that both have an autoimmune mechanism to their pathology. Interestingly, glandular biopsy results demonstrate similar inflammatory changes in the gland parenchyma; serologic testing, however, clearly differs between the two disease entities. HIV-positive serology is obviously inherent in the diagnosis of HIV-SGD. Autoantibody SS-A and SS-B titers associated with Sjögren's are absent in those with HIV-SGD.[25]

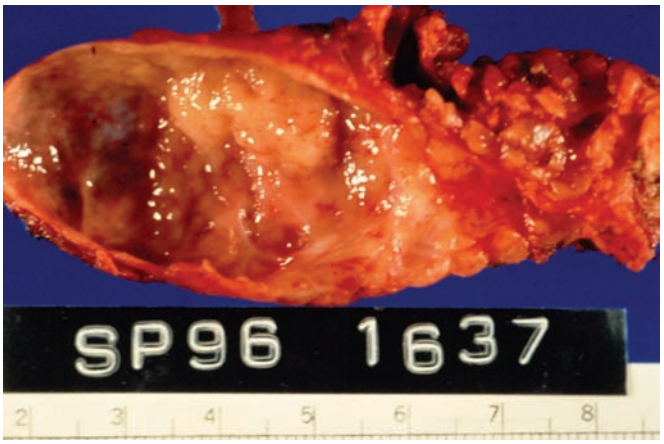

FIGURE 5–6 HIV-related lymphoepithelial cyst. This is a gross pathology photo of the section surface of a parotid gland lymphoepithelial cyst in an AIDS patient. Note the nodular protrusion of lymphoid tissue into the lumen of the cyst. It was this irregularity that was picked up on imaging and led to the complete resection of the lesion to rule out malignancy. (Courtesy of Mary Cunane, M.D., Thomas Jefferson University Hospital, Philadelphia, PA.)

On gross pathology, the involved salivary gland demonstrates cystic enlargement of the gland and diffuse proliferation of associated lymphoid tissue (**Fig. 5–6**). Fine-needle aspiration demonstrates a heterogeneous lymphoid population, macrophages, and anucleated squamous cells (**Fig. 5–7**). The cytology of benign lymphoepithelial cyst in patients with and without HIV infection and with and without Sjögren's syndrome is indistinguishable.[26] When clinical findings and cytology suggest cystic disease, the chance of malignancy is 1%, and nonsurgical management can be considered. The incidence of malignancy in a solid mass of the parotid in an HIV patient is nearly 40%.[27]

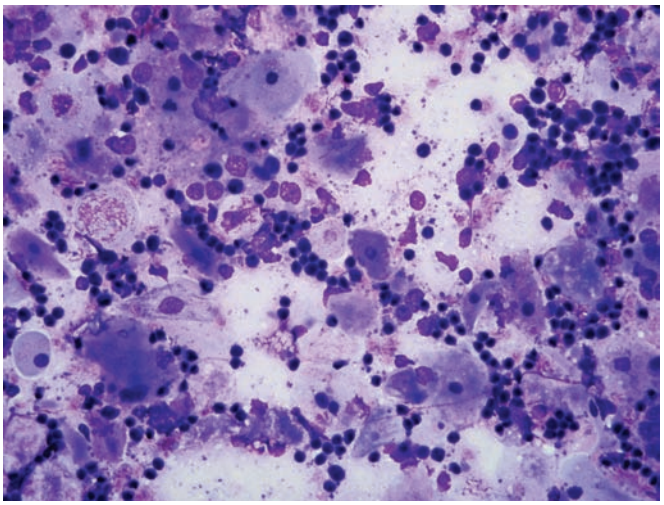

FIGURE 5–7 Fine-needle aspiration of HIV-associated lymphoepithelial cyst. Smears show a mixed population of benign squamous cells (large, flat, pale cells) and small benign lymphocytes (Diff-Quik, ×400).

A change in the growth pattern may warrant repeat fine-needle aspiration.

Histopathology reveals multiple epithelial lined cysts of varying size, which arise in the lymphoid tissue of the gland. The cysts are filled with thin yellow fluid containing lymphocytes, macrophages, and cholesterol crystals. Prominent germinal centers are also noted in the lymphoid tissue surrounding the cysts (**Fig. 5–8**).[25,28]

When diagnosing HIV-SGD, one must bear in mind that the presentation is essentially of painless salivary gland enlargement. Even if an associated diagnosis of HIV is suspected or known, one must work up the salivary gland lesion as a salivary gland mass and keep in mind that differential diagnosis includes the possibility of neoplasm.

Imaging studies, such as CT and magnetic resonance imaging (MRI), may be helpful to determine the extent and nature of the lesion, as well as to look for a soft tissue component or any associated lymphadenopathy (**see Chapter 2, Fig. 2–17**). The lymphoepithelial cysts characteristic of HIV-SGD may be seen on such imaging and guide diagnosis. Cervical adenopathy and nasopharyngeal swelling on clinical examination and imaging can distinguish HIV-positive patients with multiple large cysts from solitary lymphoepithelial cysts in patients without HIV.

Tissue biopsy is needed to rule out malignancy, and fine-needle aspiration and possibly even surgical removal of the gland for definitive diagnosis should be considered. Indeed, the latter is still considered the gold standard for diagnosis of HIV-SGD. That said, in the context of known HIV infection with a typical presentation, confirmatory imaging studies, and a negative fine-needle aspiration for neoplasm, some advocate following the lesion closely without proceeding to surgical removal immediately.[25,29] The fact that HIV-positive patients have an increased incidence of lymphoma (10% greater than the general population) should also cause one to have a low threshold for obtaining a tissue diagnosis.

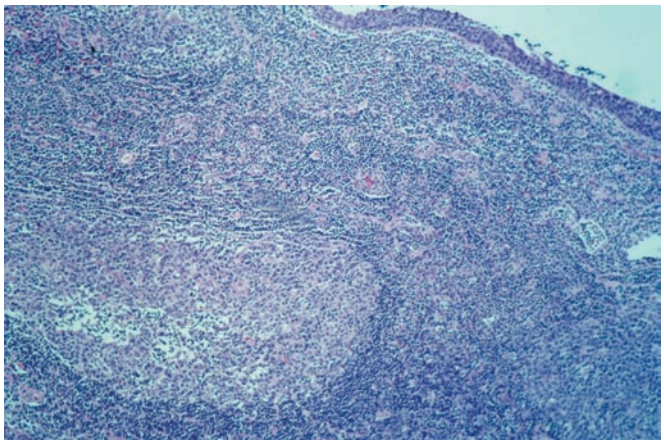

FIGURE 5–8 HIV-related lymphoepithelial cyst. This low-power view shows the inner epithelial lining of the cyst in the upper right corner, as well as a large lymphoid follicle or germinal center in the lower left corner. Note the predominance of lymphoid cells throughout the specimen. (Courtesy of Mary Cunane, M.D., Thomas Jefferson University Hospital, Philadelphia, PA.)

Conservative treatment of HIV-SGD can be similar to that of other causes of sialadenitis. Adequate hydration is very important, particularly in the context of diminished secretory function and progressive sicca syndrome. Use of sialogogues may help; however, sugar-free sialagogues are preferred, as the diminished flow of saliva predisposes the patient to dental decay. For that very reason, vigorous oral hygiene should be practiced, with use of topical fluoride.

Combination therapy with antiretroviral agents, when associated with undetectable HIV branched-chain deoxyribonucleic acid (DNA) levels and increased CD4 lymphocyte counts, effectively reduces viral replication, lymphoid hyperplasia, and cyst formation.[23] Steroids to suppress the inflammatory process underlying HIV-SGD, and the antiretroviral zidovudine have been used to treat the disease.[25,30] Medical management supplemented by cyst aspiration for large cysts provides effective control of this problem and improved patient self-esteem. Noncompliant or those with persistent cysts can be managed with fine-needle aspiration or superficial parotidectomy if the patient is stable and a complete informed consent is established.

Radiation therapy with 24 Gray produces durable parotid control for HIV-associated lymphoepithelial lesions, with failures being uncommon after 2-year follow-up.[31] The duration of survival continues to improve, and the issue of radiation-induced secondary malignancy requires consideration. Alternatively, doxycycline as a sclerosant is effective, avoiding the risks of surgery and radiation. It is best suited for small cysts in the early stage of development, often as it leaves the patient with a residual parotid mass particularly if the cyst was large at the onset of sclerotherapy.[24]

■ Granulomatous Diseases

Multiple granulomatous diseases, both acute and chronic in nature, may affect the salivary glands. Specifically, these diseases affect the lymphatic network associated with the gland, and once again, the parotid gland tends to be more frequently involved compared with the other major salivary glands. Although it is the lymphatic tissue that is predominantly affected, in fulminant disease the inflammatory process infiltrates the adjacent gland parenchyma, impacting its function. These diseases tend to present with gradual enlargement

of a nodule within a salivary gland, which is otherwise asymptomatic. As such, one must approach diagnosis as with any solitary salivary gland mass or enlargement, and consider neoplasm, both of the benign and malignant varieties.

Tuberculosis

Involvement of the salivary glands in *Mycobacterium tuberculosis* infections has been increasingly noted in recent years, reflecting the increased incidence of tuberculosis as a result of the HIV epidemic and new immigrant populations. The salivary glands may reflect either primary infection or secondary or systemic tuberculosis infection. Primary infection of the salivary glands is felt to occur through the intraglandular lymph nodes or via direct infection of the parenchyma. The parotid gland is most commonly involved, and infection typically produces localized glandular disease without constitutional symptoms. Two patterns are noted on histopathology: a diffuse pattern characterized by variably sized nodules occurring throughout the parenchyma, and a localized type consisting of a solitary mass or nodule. Secondary or systemic infection most commonly occurs following primary tuberculosis of the lung and infects the salivary glands via hematogenous spread. It more commonly involves the submandibular and sublingual glands, and the constitutional symptoms characteristic of tuberculosis, fevers, night sweats, and weight loss, are more likely to be present.[32]

Tuberculosis of the salivary glands initially presents as a rapidly enlarging painless swelling or mass within the involved gland. Due to the lack of concomitant signs and symptoms of inflammation, a differential diagnosis must include salivary neoplasm, lymphoma, and other types of indolent sialadenitis. As the infection progresses, inflammation may become more apparent; the gland becomes tender, and the skin overlying it develops a red or purple hue. The skin may then soften and even rupture, and the resulting sinus tract drain a thin, curdlike fluid.

This clinical picture will lead one to suspect a mycobacterial infection. To confirm diagnosis, a purified protein derivative (PPD) test should be placed, and the salivary mass evaluated with fine-needle aspiration. The fine-needle aspiration is useful in several ways. It may be examined for the presence of acid-fast bacilli (AFB), it provides tissue for AFB culture, and it helps to rule out other causes of salivary gland swelling such as malignancy. The patient should also have sputum cultures taken and have a plain chest radiograph performed to evaluate for cavitary lesions. If diagnosis is not confirmed by these methods, then surgical excision of the gland with histopathologic examination will provide a definitive diagnosis. Inflammation of the parenchyma with the presence of acid-fast bacilli-containing macrophages may be noted on pathology, as are the presence of Langhans' giant cells. Treatment of tuberculosis infection consists of multidrug regimens, usually consisting of three to four drug combinations taken for 6 to 9 months. Possible agents include rifampin, isoniazid, ethambutol, and pyrazinamide.[33,34]

Atypical Mycobacteria

Infections of the salivary glands by mycobacteria other than *Mycobacterium tuberculosis* may present in a fashion similar to that of salivary tuberculosis. There is a multitude of atypical mycobacteria that may produce salivary infection, including *M. avium, M. avium-intracellulare, M. malmoense, M. scrofulaceum*, and *M. bovis*. The exact route by which these pathogens infect the salivary glands remains unknown; however, possible conduits of infection include the oral cavity, gingival, lips, tonsils, and throat. Infections are most commonly seen in children 16 to 36 months of age, and both the parotid and submandibular glands have been known to be involved.

The classic presentation is one of a rapidly enlarging salivary gland mass, which develops a violaceous hue to the overlying skin. Progressive disease may become complicated by sinus tracts. Constitutional signs are noticeably absent. A diagnostic work-up similar to that for suspected salivary tuberculosis should be undertaken, given the similarity in clinical presentation. The requisite chest radiograph is negative for the cavitary lesions of tuberculosis, and the PPD is nonreactive. Diagnosis, therefore, is largely clinical and is predicated on the exclusion of other salivary mass entities. Fine-needle aspiration biopsy is preferred to incisional biopsy and will help to rule out other causes of salivary swelling; acid-fast staining is unlikely to be diagnostic, and culturing the tissue is difficult and time-consuming, taking as long as 6 weeks to grow. Incisional biopsy or incision and drainage attempts may facilitate the formation of sinus tracts and unsightly scars. Complete excision of the infected gland is considered to be curative, while there is recent evidence in favor of incision and curettage of the diseased gland. There are no proven effective medical therapies; however, investigations as to the worth of an antibiotic trial are under way. Drugs under consideration include clarithromycin, ethambutol, rifabutin, azithromycin, and fluoroquinolones in adult populations.[35]

Actinomycosis

Actinomycosis is yet another granulomatous infection of the head and neck that can affect the salivary glands. It is caused by the gram-positive anaerobe actinomyces, which is found in the normal flora of the oral cavity.

Within the oral cavity, actinomyces is most prolific in the tonsils and in carious teeth, and infection of the salivary gland occurs via retrograde invasion of the salivary gland duct. Obviously, poor oral hygiene is a key contributor adding to the risk of actinomyces infection; mucosal trauma and disruption, as well as impaired immunity such as that seen in steroid use, diabetes mellitus, and malnutrition, have also been implicated as risk factors. *Actinomyces israelii* is the most common species and accounts for most infections, but *A. bovis* and *A. naeslundi* are also possible culprits.

Actinomycosis of the salivary glands presents as a firm mass within the gland, which may or may not be tender. There is often a history of recent dental work or disease, oral trauma, or oral surgery. The time course of the infection may be rapid and acute, with suppuration much like other causes of sialadenitis, or it may follow an indolent course and produce chronic fibrotic changes within the tissue and the pathognomonic sinus tracts of the disease. These sinus tracts, which are often multiple, drain sulfur granule–containing pus. Other findings on physical exam include induration and erythema of the duct papilla, which may drain purulent saliva. The disease may be complicated by osteomyelitis of the mandible. Constitutional symptoms such as fever or malaise are rare, as is the development of leukocytosis or lymphadenopathy.

Actinomycosis is diagnosed by the presence of sulfur granules and filamentous gram-positive rods on gram stain of swabbed pus or of tissue obtained on fine-needle aspiration. This tissue may also be sent for culture to confirm the diagnosis. If a biopsy of the gland is performed, one will note the presence of multiloculated abscesses surrounded by tough fibrous tissue and containing white-yellow pus. Treatment of actinomycosis consists of a 6-week course of intravenous penicillin G, followed by an additional 6-month oral course of the same. Penicillin G is the antibiotic of choice and produces cure in over 90% of cases. Erythromycin, clindamycin, and doxycycline are also reasonable alternatives. For those cases that prove to be recalcitrant to antibiotic therapy, are suspicious for neoplasm, or if the infection is rapidly progressive and suppurative, surgical excision of the gland is recommended.[2]

Cat Scratch Disease

The entity known as cat scratch disease is a granulomatous lymphadenitis postulated to be caused by *Bartonella henselae*, a rickettsial pathogen. Exposure occurs most commonly through domestic cat scratches; 90% of affected persons report some contact with a cat, and 75% recall a scratch or a bite. Canines, however, are causative in 5% of cases.[36] The head and neck are the most frequently affected areas of the body, and infection often involves the skin and lymphatics associated with the salivary glands (**Fig. 5–9**). Clinically, the patient notes a papular lesion that develops at the site of an animal scratch or bite, typically within 2 to 3 days of inoculation. The papule then becomes vesicular and, in some instances, pustular. Within 2 weeks, the proximal lymph nodes enlarge and become tender and erythematous. In more complicated disease, the lymphadenopathy may become suppurative, and encephalitis, arthritis, neuroretinitis, osteomyelitis, or hepatitis may ensue.[37]

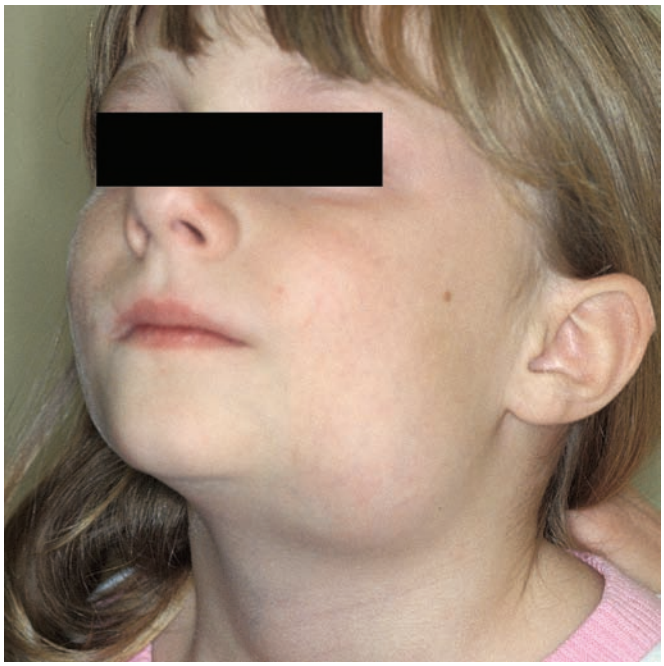

FIGURE 5–9 Submandibular cat scratch adenopathy.

To diagnose cat scratch disease, three out of the four following criteria must be met: (1) a history of animal (typically feline) contact resulting in a scratch, dermal or ocular abrasion; (2) regional lymphadenopathy occurring within 2 weeks after animal contact, as well as sterile cultures of lymph node aspirate and laboratory results to exclude other causes; (3) a positive cat scratch disease skin test; and (4) a lymph node biopsy demonstrating pathologic features consistent with those of cat scratch disease. Biopsy demonstrates reticular cell hyperplasia, granuloma formation, and widening of arteriolar walls. As the inflammatory process continues, one may observe areas of focal necrosis, which can coalesce to form microabscesses.[2] The disease is typically self-limited and requires no specific treatment. Lymphadenopathy should resolve completely within 2 to 4 months; however, aspiration of the node may be of both diagnostic and therapeutic value. Although the disease requires no antimicrobial therapy for complete remission, use of azithromycin has been demonstrated to reduce the duration of lymphadenopathy. Erythromycin,

doxycycline, and rifampin have also been used to treat cat scratch disease.[38]

Toxoplasmosis

The pathogen *Toxoplasma gondii* is a protozoan parasite, which is most often discussed as a source of congenital abnormalities secondary to maternal infections. Toxoplasma infections have also been more prevalent since the beginning of the acquired immunodeficiency syndrome (AIDS) epidemic; as an opportunistic disease, it affects immunocompromised populations and is an AIDS-defining illness. The organism has a three-phase life cycle, existing as an oocyst in the host cat and as a trophozoite in infected beef, lamb, and chicken. Transmission is through the consumption of these undercooked or raw meats, or through contact with cat feces. The trophozoite, as the infectious agent, travels to the lymphoreticular system by hematogenous spread, and as a part of the lymphoreticular tissue, the periparotid and intraparotid lymph nodes may become infected. The typical presentation involves isolated neck adenopathy; however, HIV-infected or other immunocompromised patients may develop a disseminated form of the diseases, with myalgias, anorexia, hepatosplenomegaly, pericarditis, or myocarditis. Diagnosis is by isolation of the organism, but acute and convalescent titers may aid diagnosis. Treatment is reserved for severe disease and for pregnant and immune-suppressed individuals. Spiramycin is used in pregnant patients during the first trimester; otherwise, pyrimethamine and sulfadiazine are used in combination.[2]

Tularemia

The final infectious granulomatous disease to affect the salivary glands is tularemia. It is caused by a gram-negative bacteria, *Francisella tularensis,* an organism whose host is the cottontail rabbit. Infection occurs when handling infected animals; hunters who skin their rabbits and consumers of rabbit meat are likely patients. The disease may also be transmitted through insect bites (ticks and flies are disease vectors) and even through inhalation. Clinically, an erythematous papule forms at the site of inoculation, which may become nodular and ulcerate. Fever, headache, and tender lymphadenopathy follow 2 to 10 days later. Although the site of lymphadenopathy tends to vary according to the location of the insect bite, the periparotid lymph nodes tend to be affected in head and neck inoculation sites. If the manner of infection was through ingestion of meat or inhalation, then there is no single inoculation site, and lymphadenopathy is diffuse. Diagnosis can be difficult. Patients typically report a history of rabbit handling or tick bite exposure, and serologic testing can be performed. Manipulating the affected lymph nodes in the acute phase for the purposes of obtaining culture or tissue is not recommended for two reasons: The organism is highly difficult to successfully culture, and procedures on the affected nodes may cause dissemination of infection. Streptomycin is the first-line agent for tularemia infection; gentamicin, doxycycline, tetracycline, chloramphenicol, and ciprofloxacin may also be used.[39]

Sarcoidosis

Sarcoidosis is a systemic granulomatous disease of unknown etiology. It is characterized by the development of noncaseating epithelioid cell granulomas in multiple organ systems. It is more prevalent in African Americans ages 20 to 40 and shows a slight female preponderance. The most common sarcoid presentation is that of bilateral hilar lymphadenopathy, pulmonary infiltrates, the cutaneous lesion erythema nodosum, and ocular manifestations. There are both acute and chronic forms, the former of which responds best to steroid therapy. The most common head and neck manifestation of sarcoidosis is cervical adenopathy, which occurs in 48% of patients.[40] More germane to this discussion of sialadenitis is the fact that parotitis occurs in approximately 6% of sarcoid patients, presenting typically as bilateral parotid swelling.[41] Indeed, there is a subset of sarcoidosis called Heerfordt's disease, also known as ''uveoparotid fever.'' This is characterized by acute parotitis, uveitis or iritis, and fever. Facial nerve paresis has also been rarely reported in conjunction with this syndrome. Typically, Heerfordt's disease is self-limited, and no treatment is needed; however, other manifestations and exacerbations of sarcoidosis are best treated with corticosteroids and other immune-modulating therapies.[39] Rarely, sarcoid involvement of the exocrine glands may present with xerostomia and xerophthalmia. In this case, it may be difficult to distinguish from Sjögren's syndrome without biopsy of salivary tissue.[42]

Diagnosis of sarcoidosis relies on biopsy demonstrating the presence of noncaseating granulomas with multinucleated giant cells and epithelioid cells. Minor salivary gland biopsy in patients who have developed signs and symptoms suggestive of sarcoidosis has been proposed in the past as a reasonable and relatively noninvasive way of diagnosing sarcoidosis.[43] In the case of salivary sarcoidosis, biopsy of the affected gland, at least via fine-needle aspiration, is necessary to ensure that the glandular swelling does not represent a neoplasm. Sarcoidosis of the salivary gland has been reported to be diagnosed by fine-needle aspiration; the presence of noncaseating epithelioid cell granulomas and multinucleated giant cells is seen on cytology.[44,45]

Wegener's Granulomatosis

Necrotizing granulomas and vasculitis are the hallmarks of this idiopathic disease. Involvement of the upper and lower respiratory tract and kidneys is associated with cough, hemoptysis, epistaxis, and constitutional symptoms. The salivary glands are rarely involved and usually in association with systemic manifestations. The presentation is a nondiagnostic pattern of chronic inflammation. CT may demonstrate diffuse salivary gland enlargement. Biopsy and a positive serology for the autoantibody, antineutrophil cytoplasmic autoantibody, cytoplasmic pattern (c-ANCA) are diagnostic. Treatment includes steroids, trimethoprim/sulfamethoxazole, and cyclophosphamides.

Sjögren's Syndrome

The original physician to describe the triad known as Sjögren's syndrome is of some historical debate. In 1933, Henrik Sjögren, the Swedish ophthalmologist for whom the disease is named, described a syndrome of xeropthalmia, parotid enlargement, and arthritis. It is not clear, however, that he made an association between xerostomia and xerophthalmia from a pathophysiologic standpoint. Johann von Mikulicz Radecki, a Polish surgeon, wrote in 1892 of a link between the two symptoms and noted similar pathologic changes in specimens of lacrimal and salivary gland tissues in patients with these complaints. This led to the eponym Mikulicz disease to describe this disease state. All told, it was not until the mid-20th century that the distinction was made between primary and secondary Sjögren's syndromes, and that it was a disease of autoimmune mechanism.[46]

Today Sjögren's syndrome is described as a sicca syndrome of xerophthalmia or keratoconjunctivitis sicca, xerostomia, and rheumatoid arthritis. It is the second most common rheumatic disease (the most common is rheumatoid arthritis), and two subsets of the syndrome are recognized. Primary Sjögren's syndrome is characterized by the symptoms of dry eyes and dry mouth without associated rheumatoid disease. Secondary Sjögren's syndrome is noted to feature the sicca symptoms along with those of another connective tissue disease. Thus the classic xeropthalmia and xerostomia are found in conjunction with rheumatoid arthritis, systemic lupus erythematosus, or scleroderma.[47,48] Sjögren's syndrome affects between 500,000 and 2 million patients in the United States, and it is felt to affect between 1 and 3% of the general population. The disease demonstrates a female preponderance, primarily affecting women between the ages of 40 and 60 years. Although the disease is 9 times more common in women than in men, one should note that it does present in both sexes and in all age groups.[46]

The common clinical theme of Sjögren's syndrome is exocrine gland dysfunction. As the immune-mediated destruction of these glands progresses, patients note slowly increasing mucous membrane dryness. The disease is of a chronic and indolent nature, and it is not uncommon for 10 years to pass between the patient's first notation of mucosal dryness and the diagnosis of Sjögren's syndrome. From an ophthalmologic standpoint, patients report the sensation of progressively worsening ocular dryness, poor tear production, and red, irritated eyes, often accompanied by foreign body sensation. On examination, conjunctival injection, corneal ulcers, and detached epithelial filaments with discharge may be seen. Scleritis and inflammatory nodules may be seen in severe disease. The examining physician should perform a Schirmer's test to record the actual impairment of tear production. Five millimeters or less of wetted strip after 5 minutes is considered to be a positive test. Ophthalmologists may additionally perform tear osmolarity and vital dye staining to further objectify tear production and quality in these patients.[46–48]

Xerostomia is the other major complaint of Sjögren's syndrome patients. Dry mouth sensation is again a progressively worsening complaint and may be accompanied by a burning sensation of the oral mucosa. Patients may complain of difficulty with deglutition and fluid speech due to their lack of sufficient saliva. Alterations in taste sensation have been reported, as have changes in oral flora and increased incidence of dental caries, the latter reflecting the importance of the bacteriostatic nature of saliva. Enamel decay is noted initially at the gingival and incisive margins.[49] Oral examination demonstrates dry-appearing mucosa and a lack of salivary pooling in the floor of the mouth. The tongue may appear smooth with flattening of the filiform papillae, and angular cheilitis may be noted as well.[50] One third of affected patients may develop chronic erythematous candidiasis, an atrophic process of the oral mucosa manifested by thin, erythematous patches of mucosa predominantly on the palate and buccal mucosa.[46] This may be complicated by candidal thrush superinfection in as many as 80% of patients.[47]

Salivary gland enlargement (**Fig. 5–10**) is another common manifestation of Sjögren's syndrome and may occur in up to one third of patients with the primary form of the disease.[49] The parotid gland is most commonly affected, although any major salivary gland may be involved. Enlargement may initially be unilateral and intermittent; however, with time, enlargement of the salivary glands becomes permanent and bilateral. The affected glands are nontender on exam and have a

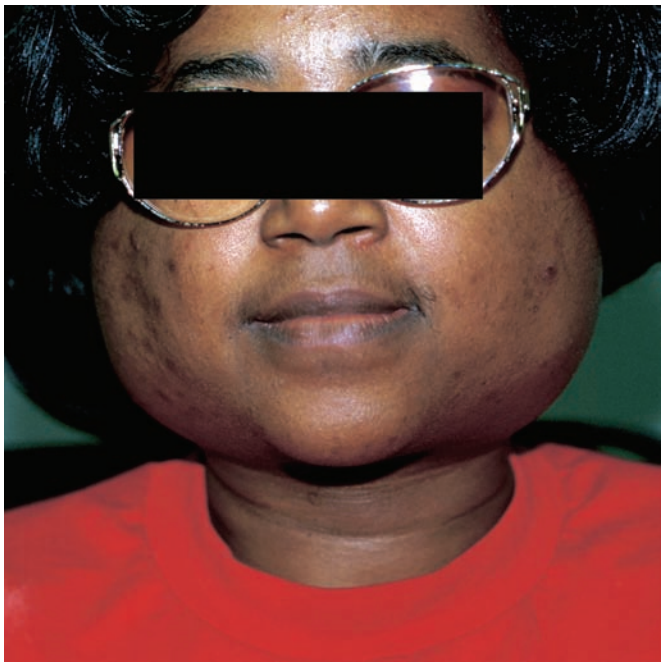

FIGURE 5–10 Bilateral Sjögren's syndrome.

rubbery texture on palpation. The overlying skin may appear tense and erythematous.[50]

Although the clinical signs and symptoms of xerostomia, xerophthalmia, and parotid enlargement may make the physician suspect a diagnosis of Sjögren's syndrome, quantification of symptoms by various testing measures aids in diagnosis. As previously mentioned, xerophthalmia is commonly diagnosed by the Schirmer's test. Similarly, xerostomia may be quantified by salivary flow rate testing, salivary scintigraphy, or contrast sialography. On salivary flow rate testing, an abnormal result is considered to be the production of 1.5 mL or less of saliva in a 15-minute period of time; this is considered to be consistent with a diagnosis of xerostomia.[48] Nuclear imaging such as salivary scintigraphy may also assist in diagnosis and in following the disease progress. Contrast sialography is not of great value during initial diagnosis of Sjögren's syndrome, as the pattern of disease is largely indistinguishable from that of chronic sialadenitis; however, it is helpful in following these patients for disease progression and during consideration of possible gland excision. Finally, labial biopsy to examine the minor salivary glands for lymphocytic infiltration and parenchymal fibrosis firmly establishes the diagnosis of Sjögren's syndrome.[51] The upper lip contains the most minor salivary glands (**see Chapter 2, Fig. 2–16**).

In 2002, a set of diagnostic criteria were developed by the American-European Consensus Group to unify the definition of the disease for both treatment and research purposes. Of the six criteria, one of two mandatory criteria must be met, while a total of four are needed to establish diagnosis of primary Sjögren's syndrome. The two requisite elements are positive anti-Ro (SS-A) or anti-La (SS-B) serologies [Ro (SS-A) and La (SS-B) are ribonuclear proteins] and a focus score of one or more foci of lymphocytic infiltration on labial minor salivary gland biopsy. A focus is defined as 50 or more lymphocytes per 4 mm^2 in the salivary gland tissue. Additional criteria are the presence of ocular symptoms, the presence of oral symptoms, a positive Schirmer's test, Rose Bengal or ocular dye test, and a positive objective quantification of salivary dysfunction or involvement. The latter includes the aforementioned salivary flow rate testing, salivary scintigraphy, and sialography. **Table 5–2** further delineates these criteria. The presence of three out of four of the objective criteria will also classify a case of primary Sjögren's syndrome. The consensus group also defined exclusion criteria, which include a history of head and neck irradiation, hepatitis C infection, HIV infection or AIDS, preexisting lymphoma, sarcoidosis, graft-versus-host disease, and any use of anticholinergic drugs.[52]

TABLE 5–2 American-European Consensus Group Classification Criteria for Sjögren's Syndrome

Criterion	Description
Ocular symptoms	Persistent subjective sense of dry eyes for over 3 months Recurrent foreign body sensation in eye Use of artificial tears 3+ times daily
Oral symptoms	Daily subjective sense of dry mouth for over 3 months Recent or persistent salivary gland enlargement Frequent drinking of liquids to assist with swallowing of solid foods
Ocular signs	Positive Schirmer's test (less than 5 mm in 5 minutes) Rose Bengal/ocular dye score greater than or equal to 4
Biopsy of minor salivary gland tissue	Biopsy positive for Sjögren's pathology: focal lymphocytic sialadenitis with a focus score of greater than or equal to 1, where a focus is defined as an area with 50 or more lymphocytes per 4 mm^2
Objective salivary involvement	Unstimulated whole salivary flow less than or equal to 1.5 mL in 15 minutes Parotid sialography demonstrating diffuse sialectasis in the absence of obstructive process Salivary scintigraphy showing slowed and poor uptake and impaired secretion of nuclear dye
Autoantibodies on serology	Antibodies to Ro (SS-A) and La (SS-B), or both

Data from Mahoney EJ, Spiegel JH. Sjögren's disease. Otolaryngol Clin North Am. 2003;36(4):733–745.

There are many extraglandular manifestations of Sjögren's syndrome that the clinician should be aware of, both within the head and neck and systemically. It is estimated that one third of patients with primary Sjögren's syndrome experience some extraglandular aspect of their disease. Although a full description of these features is beyond the scope of this chapter, one should note that Sjögren's patients may experience sensorineural hearing loss, laryngeal lesions, Hashimoto's thyroiditis and hypothyroidism, and various sinus complaints. There is also a multitude of pulmonary, gastrointestinal, genitourinary, and, of course, musculoskeletal issues that may affect these patients. These associated systemic problems are felt to arise from the same disruption in autoimmune regulation that produces Sjögren's syndrome.[46,50]

Of all the associated disease manifestations of Sjögren's syndrome, the most severe is non-Hodgkin's lymphoma, which equally affects patients with both the primary and secondary forms of the disease, typically late in its course (see also Chapter 12). The increased risk of lymphoma in these patients is significant; it is cited as 44 times that of the general population and is estimated to occur in 4 to 6% of patients with primary Sjögren's syndrome.[53] Sjögren's syndrome–related lymphomas are typically marginal-zone B cell lymphomas, and they often present in the organs affected by Sjögren's syndrome, the parotid and occasionally the submandibular glands. It is postulated that the Sjögren's syndrome–related lymphomas are the result of the prolonged and chronic stimulation of autoreactive B cells that characterizes Sjögren's syndrome and that eventually results in their mutation and abnormal proliferation. Sjögren's patients should be under close surveillance for the development of lymphoma, particularly if they demonstrate any of the following associated risk factors: chronic parotid enlargement, lymphadenopathy, splenomegaly, anemia, lymphopenia, peripheral neuropathy, skin vasculitis, and type II mixed monoclonal cryoglobulinemia.[50,53]

The pathophysiology of Sjögren's syndrome is not yet fully understood. It is recognized to have its origins in a disruption of normal immune regulation where exocrine gland tissue is no longer recognized as self and is instead presented as autoantigen. The immune system's attack response to these autoantigens results in its destruction of exocrine tissue, and hence glandular dysfunction. Exactly what incites this chain of events is unclear, yet several leading theories have been developed. Immune, neuroendocrine, and genetic factors are all felt to contribute to the evolution of the disease, and it is felt that inherent abnormalities in glandular development may be key to the perception of the gland as nonself.

The immune factors that play so elemental a role in the development of Sjögren's syndrome are felt to originate in defective glandular tissue, which is errantly recognized as nonself antigen by the immune system. Exactly what the defects in the glandular tissues are or what causes them is currently unknown. The presence of these autoantigens in a competent immune system necessarily leads to infiltration of the tissue with lymphocytes and the production of autoantibodies, namely the Ro and La autoantibodies detectable on serologic testing. CD4 T cells appear to be the predominant cell type coordinating the attack, releasing interleukin-1 (IL-1), tumor necrosis factor (TNF), and interferon-γ. This induces other lymphocytes, both T and B cells, to join the attack, with the B cells secreting autoantibodies to further augment the response. This self-perpetuating process leads to the destruction of the majority of the glandular parenchyma in most cases. It should also be noted that the vigorous and chronic nature of this autoimmune response may contribute to the development of lymphoma in Sjögren's patients. Chronic stimulation of autoreactive B cells may lead to their mutation, resulting in B cell lymphomas. It has also been shown that there is a failure of apoptosis in autoreactive T cells in the Sjögren's immune response, which may favor the development of malignancy.[46]

Although the immune destruction of glandular tissue is the pathophysiologic crux of the disease, it cannot fully account for the degree of salivary and lacrimal gland dysfunction we see clinically. The reason for this is that histopathologic examinations of Sjögren's affected salivary tissue consistently demonstrate destruction of 50 to 60% of acinar and ductal cells, leaving 40 to 50% to continue to secrete.[46,54] Some other factors must render the remaining tissue insufficient to maintain appropriate function, thus accounting for the severe xerostomia and xeropthalmia of which patients complain. It is felt that the cytokine release inherent to the autoimmune response of Sjögren's syndrome impairs normal exocrine activity of the remaining viable cells; TNF and IL-1 have been shown to inhibit neural release of acetylcholine, which is necessary for glandular stimulation. Additionally, antimuscarinic receptor antibodies have been noted in studies using animal models of Sjögren's syndrome, which would further inhibit normal glandular stimulation.[55] Thus these neuroendocrine factors are felt to contribute significantly to the pathogenesis of Sjögren's syndrome.

Finally, there are notable genetic factors that appear to contribute to the pathogenesis of Sjögren's syndrome. The most common human leukocyte antigen (HLA) genotype in Sjögren's syndrome is HLA-DR, with a preponderance of HLA-DR3 among Caucasian patients. There is also evidence that aberrations in glandular development may lead to inherently defective cells that are predisposed to autoimmune recognition.[46,50]

FIGURE 5–11 Benign lymphoepithelial lesion (BLL) of Sjögren's syndrome. This submandibular gland is enlarged with nodules of varying size replacing normal parenchyma. (Courtesy of Mary Cunane, M.D., Thomas Jefferson University Hospital, Philadelphia, PA.

Although the diagnosis of Sjögren's syndrome involves pathologic confirmation by labial minor salivary gland biopsy, the histopathologic pattern of Sjögren's syndrome in major salivary glands should be noted. The pathologic lesion associated with Sjögren's syndrome is benign lymphoepithelial lesion (BLL). Grossly, the involved gland demonstrates a nodular pattern of glandular enlargement (**Fig. 5–11**). Histologically, the affected parenchyma demonstrates lymphocytic infiltration, acinar atrophy, and areas of epithelial proliferation called epimyoepithelial islands (**Fig. 5–12**). These changes are progressive and may develop into nearly complete replacement of functional parenchyma with lymphoreticular infiltration.[56]

Treatment of patients with Sjögren's syndrome continues to focus on symptomatic control rather than disease modulation. Artificial tears for comfort, eye protection, particularly at night, and vigilant ophthalmologic surveillance continue to be the core treatment of Sjögren's ophthalmalopathy. Meticulous maintenance of good oral hygiene will help to prevent oral and dental complications of the disease. Fluoride treatments and close dental observation with early intervention for dental caries are key elements. Saliva substitutes help with patient comfort, as do sugar-free sialagogues and adequate overall hydration. Oral interferon-α use is under study, with preliminary data demonstrating improved salivary flow and subjective relief of symptoms. Use of oral muscarinic agents has been shown to improve xerostomia in Sjögren's patients. Pilocarpine, with its muscarinic receptor agonist mechanism, has been shown to improve salivary secretion, yet it does not appear to have a measurable effect on lacrimal tear production. Cevimeline is a newer muscarinic agonist with a longer half-life than pilocarpine, a higher affinity for M_3 muscarinic receptors, and decreased affinity for M_2 receptors. The latter reduces the cardiac stimulatory effects of muscarinic therapy.[54]

Treatment of the connective tissue diseases associated with secondary Sjögren's syndrome has focused on targeting the aberrant immune response responsible for the disease. Steroid therapy in particular is a mainstay of treatment for rheumatoid arthritis and systemic lupus erythematosus, but it has not been shown to affect the sicca complex of Sjögren's syndrome, either subjectively or objectively. Systemic steroids are used, however, to manage severe extraglandular manifestations of the disease, particularly those of the kidneys and lungs. Antimalarial drugs often used in treating other autoimmune diseases have also been studied as Sjögren's syndrome therapies with poor results. Thus there are no immune-targeted therapies currently recommended for use in Sjögren's syndrome.

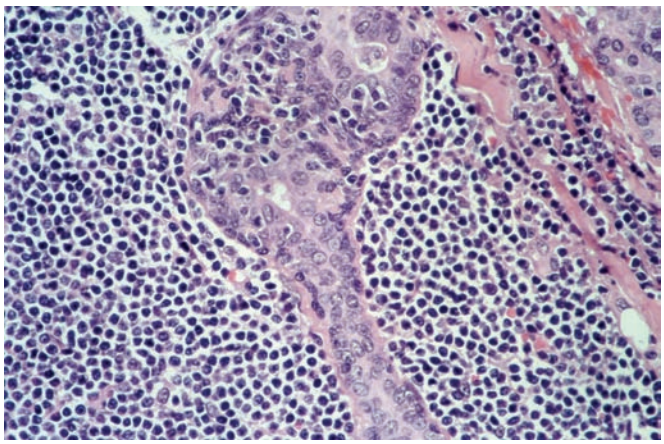

FIGURE 5–12 BLL of Sjögren's syndrome. A high-powered view demonstrating an epimyoepithelial island with a tiny lumen surrounded by a mixed population of lymphoid cells. (Courtesy of Mary Cunane, M.D., Thomas Jefferson University Hospital, Philadelphia, PA.)

■ Conclusion

The causes of sialadenitis are multiple and diverse, ranging from a multitude of infectious etiologies to the errant autoimmune nature of Sjögren's syndrome. The common pathologic crux of sialadenitis hinges upon dysfunctional salivary glands. In the case of acute bacterial sialadentitis and mumps, the dysfunction of the gland is transient, lasting long enough to contribute to the pathogenicity of the disease but not becoming a permanent feature of the gland. Whether due to dehydration, sialolithiasis, or simply inflamed parenchyma, the diminished salivary flow of the gland does typically recover with treatment, or even spontaneously. In contrast to this are the sialadenopathies of Sjögren's syndrome, chronic sialadentitis, HIV-associated salivary

gland disease, and sarcoidosis where continued inflammation and replacement of functional glandular tissue cause continued cycles of salivary dysfunction and inflammation. Sialadenitis is really an umbrella term encompassing a wide variety of causative entities, and recognition of this is useful in diagnosing and treating patients with salivary enlargement.

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6

Histology and Pathology of Sialolithiasis

JOHN D. HARRISON

The background to our present understanding of sialolithiasis starts in 1896, when Küttner[1] published his observations on two patients who had suffered from chronically swollen submandibular glands that had attracted a clinical diagnosis of malignancy. His microscopic examination revealed these were not neoplastic, but chronically inflamed. He found a sialolith in one of the cases, and was of the opinion that the chronic sialadenitis was primary and arose by inflammation that ascended Wharton's duct from the mouth. He considered that the sialolith was secondary and arose from an irregularity in the lining of a duct, in a lobule whose excretory duct was compressed by inflammatory swelling, or in a bacterial deposit. Küttner's seminal publication established chronic submandibular sialadenitis as an entity, which became known as Küttner's tumor in continental Europe. It also made a contribution to the natural history of chronic sialadenitis and sialolithiasis that has recently been shown to be essentially correct.

Thus chronic sialadenitis and sialolithiasis were interrelated from the beginning, and they need to be considered together to understand the etiology and pathogenesis of either. They were reviewed in 1970 in the final edition of *Thoma's Oral Pathology*.[2] On the etiology of chronic sialadenitis, there was little more than salivary calculi are almost exclusively the cause of chronic submandibular sialadenitis, whereas hyposialia of the parotid gland is the most important prerequisite for chronic recurrent parotitis. The notion that sialolithiasis is secondary to sialadenitis had been dropped, and the etiology of sialolithiasis was divided into numerous theoretical causes that included mechanical, chemical, inflammatory, and neurohumoral. These are complex and need not be described here because extensive research has now led to a clear understanding of the natural history of chronic sialadenitis and sialolithiasis.

Natural History of Chronic Sialadenitis and Sialolithiasis

Studies of Experimental Sialomicrolithiasis in Animals

Much of the research into the natural history of chronic sialadenitis and sialolithiasis has been experimental. In the early 1960s, Seifert started to use rat as an experimental model to produce microscopic concretions, called sialomicroliths, and sialadenitis in the submandibular and parotid glands. He and his colleagues[3] continued these investigations over the next 2 decades. These investigations included combinations of hypercalcemia and very high doses of stimulatory agents such as isoprenaline (isoproterenol). The unraveling of the underlying biological processes was an important step in reaching an understanding of the etiology and pathogenesis of chronic sialadenitis and sialolithiasis.[4] Isoprenaline given in repeated high doses soon produces a great increase in the size and weight of the submandibular and parotid glands in the rat as a result of hyperplasia and hypertrophy of the acinar cells. The acinar enlargement is sufficient to result in compression of the intraglandular ducts. Every dose of isoprenaline is followed by an explosive release of secretory material from the acinar cells, which is unable to flow freely

through the lumina of the ducts that are partially obstructed by compression, and the resultant increase of pressure in the lumina of the acini damages acinar cells. This partial obstruction thus results in the stagnation of secretory material that is rich in calcium because of the hypercalcemia. Cell membranes contain phospholipids, which, when exposed because of damage to the membranes, are potent nucleators of calcification.[5–8] Calcium precipitates on these exposed phospholipids to form sialomicroliths that cause ductal obstruction and sialadentitis.[4]

The concept that sialomicroliths could lead to sialadenitis was enhanced by the discovery of sialomicroliths in chronic submandibular sialadenitis[9] and in normal submandibular glands[10] in humans. Because of the possible importance of sialomicroliths in the etiology of sialadenitis and sialolithiasis, an extensive investigation of an archive of normal and experimentally affected salivary glands of cat, in which sialomicroliths had been observed, was undertaken.[11–19] The archival material consisted of ideally preserved specimens of parotid, submandibular, and sublingual glands of cat that comprised normal control glands and glands that had been variously subjected to ductal ligation, stimulation of the parasympathetic and sympathetic nerves, parasympathectomy, and sympathectomy.

Sialomicroliths were detected in 1% of the normal parotids, 10% of the normal submandibular glands, and 27% of the normal sublingual glands. There was a greatly increased occurrence of sialomicroliths in the parasympathectomized submandibular glands, in which they were found in 76%. There were no significant changes in the occurrence of sialomicroliths in any of the other experimental glands. This led to the important realization that the reduction of secretory stimulation resulting from the parasympathectomy had caused the formation of a pathological quantity of sialomicroliths, which led to the suggestion that secretory inactivity was the cause of sialomicrolithiasis in humans.

Sialomicroliths were found in autophagosomes in the acinar secretory cells of the submandibular and sublingual glands of cat, where they arose from degradation of redundant secretory granules and other organelles by the process of autophagy. These secretory granules contain a large amount of sequestered calcium that is present as a cationic shield to allow the condensation of the acidic glycoprotein present in the secretory material. This calcium is released in an ionized form during the normal release of secretory material from secretory granules or during the degradation of secretory granules. The phospholipid of cell membranes that are degraded during autophagy of organelles becomes exposed and is a potent nucleator of calcification.[5–8] The ionized calcium precipitates on the exposed phospholipid to form calcified sialomicroliths in the autophagosomes, and thereby the cell is saved from poisoning by an overwhelming release of ionized calcium. Sialomicrolithiasis thus appears to be a physiological process to safeguard the cell (S. Y. Ali, personal communication, 1991). Sialomicroliths were also found in lumina, where they could arise by expulsion from acinar cells or by formation in stagnant secretory material (**Figs. 6–1** and **6–2**). There appears to be a turnover of sialomicroliths, and means of removal include discharge from acinar and ductal cells luminally to be flushed away in the saliva, and laterally into intercellular spaces and basally into the stroma to be engulfed by macrophages. The lysosomal enzymes and acidity of the phagosomes would be overwhelmed during the formation of sialomicroliths, and the restoration of enzymes and acidity by fusion with primary lysosomes would enable a controlled degradation of sialomicroliths and a harmless gradual release of calcium to occur.

A pathological increase of sialomicroliths occurs only if the balance between formation and removal is disturbed. This happens in the parasympathectomized submandibular glands, in which secretory inactivity leads to autophagy of secretory granules and stagnation of secretory material in lumina, thereby facilitating the formation of sialomicroliths when the sequestered calcium is released as ionized calcium in the presence of phospholipid. However, complete obstruction of the feline submandibular gland by ductal ligation is followed by autophagy in acinar cells and stagnation of secretory material together with degeneration of cell membranes, but there is no increase of sialomicroliths in these glands. The answer to this appears to involve the macrophages, which are present in increased

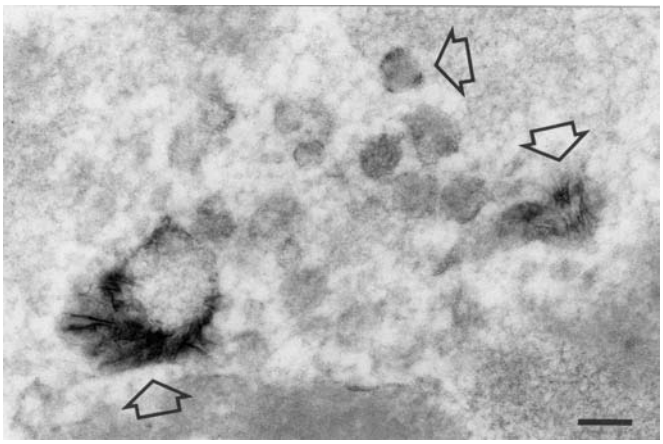

FIGURE 6–1 Needle-shaped crystals of hydroxyapatite (arrows) are associated with membranous debris in the lumen of a duct. Submandibular gland of cat 14 days after parasympathectomy. Tissue immersion fixed in glutaraldehyde and formaldehyde and subsequently in osmium tetroxide, and section stained with lead citrate. ×69,600; bar = 0.1 μm. (Electronmicrograph courtesy of A. Triantafyllou, M.D.)

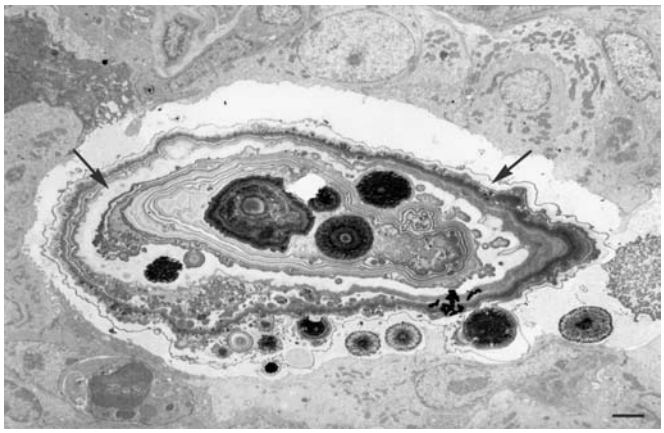

FIGURE 6–2 A large sialomicrolith is present in the lumen of a duct and consists of lamellae and cores variously arranged around single cores, groups of cores and groups of lamellae, and secretory material (arrows), which indicates that many small sialomicroliths had accreted to form the large sialomicrolith. The cores and lamellae consist either of crystals, which are very dense, or granular material, which is less dense. Small sialomicroliths are present in surrounding secretory material. Submandibular gland of cat 21 days after parasympathectomy and sympathetically stimulated. Tissue immersion fixed in glutaraldehyde and formaldehyde and subsequently in osmium tetroxide, and section stained with lead citrate, ×2100; bar = 2 μm. (Electronmicrograph courtesy of A. Triantafyllou, M.D.)

numbers in ligated glands, and may scavenge sialomicroliths so effectively that there is no increase. Also, there may be insufficient calcium in the ligated glands for an increased formation of calcified sialomicroliths, for a decrease of calcium has been detected in ligated salivary glands.

Partial but not complete obstruction is associated with an increase of sialomicroliths, which is seen in the salivary glands of rat stimulated by very high doses of isoprenaline in which partial obstruction is an essential factor.[4] Stimulation of a partially obstructed gland would lead to a release of secretory material from acinar cells that overwhelms the ability of the partially obstructed duct to allow it egress. The resultant acute blockage and increase of pressure in the lumina would lead to a large amount of stagnant secretory material rich in calcium that can precipitate on phospholipid exposed in membranes damaged by the increase of pressure.

Although sialomicroliths were produced experimentally, there was never any formation of sialoliths. However, the feline submandibular glands were only examined up to 42 days after parasympathectomy, and whether longer periods would have led to sufficient accretion of sialomicroliths to produce sialoliths or whether there would have been insufficient dilatation of ducts to allow this remains unknown. However, the feline model produced a wealth of information on salivary calcification that is applicable to the human condition.

Studies of Sialomicrolithiasis in Humans

Scott[10,20] performed an extensive morphometric investigation of the effects of aging on the submandibular gland in humans in the 1970s and found that the parenchyma of normal glands contained sialomicroliths and atrophic foci. Sialomicroliths were associated with the atrophic foci (**Fig. 6–3**), and the occurrence of both increased with age. Scott's finding that sialomicroliths occurred in normal submandibular glands was a breakthrough in the search for the link between normal glands and sialadenitis and sialolithiasis. It was pursued by an investigation[21] in which sialomicroliths were found in all normal submandibular glands and 20% of normal parotids. They were found in parenchymal cells, lumina, and stroma, and appeared to be formed similarly to those in the feline glands. The finding of sialomicroliths in all the submandibular glands and in only a minority of the parotids corresponds to a higher concentration of calcium in the submandibular gland.[22]

The first reported observation of sialomicroliths in humans was in 1965 by Tandler,[23] who observed them with the electron microscope in ductal lumina of a submandibular gland and considered them to be inchoate sialoliths. This suggestion led to a search for sialomicroliths in chronic submandibular sialadenitis, and they were found in all cases.[24] One case was examined with the electron microscope together with a case of parotid sialadenosis.[25] Sialomicroliths in the case of sialadenitis were well calcified and were found in

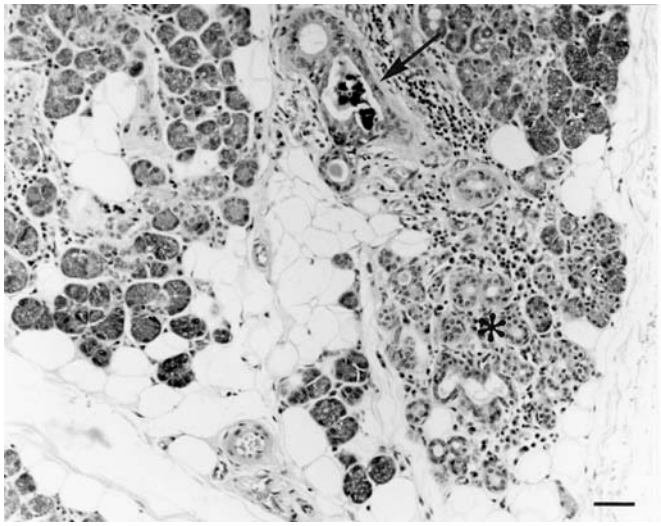

FIGURE 6–3 A group of sialomicroliths (arrow) obstructs the lumen of a striated duct that leads from an inflamed atrophic focus (asterisk). Normal submandibular gland removed during surgery. Section stained with hematoxylin and eosin, ×110; bar = 50 μm.

the stroma, parenchyma, and lumina. They were found less often in the case of sialadenosis, in which they were poorly calcified, and were found in the stroma associated with necrotic acinar cells and in the parenchyma. Sialomicroliths were found in macrophages in both sialadenitis and sialadenosis. The finding of sialomicroliths in the case of parotid sialadenosis contrasts with the rarity of sialomicroliths in normal parotids and appears to relate to the decreased secretory activity of sialadenosis. This would lead to autophagy of secretory granules and release of sequestered calcium, which precipitates on exposed phospholipid to form sialomicroliths in phagosomes. However, when this process is overwhelmed, the released calcium reaches a concentration that kills the cell and then precipitates onto phospholipid exposed in the degenerating membranes of the dead cell, which accounts for the sialomicroliths in necrotic cells. There is also a turnover of sialomicroliths with removal by scavenging macrophages as in cat. The differences in the degree of calcification of the sialomicroliths relate to the amount of calcium sequestered in the glycoprotein of the secretory granules, which is lower in the parotid.[22]

These morphological investigations did not reveal a development of sialoliths from sialomicroliths, and the relation between sialoliths and sialomicroliths was finally established through the investigation of a large series of cases of chronic submandibular sialadenitis by a combination of morphological, clinical, and epidemiological techniques.

Studies of Sialolithiasis in Humans

Seifert and Donath[9] published an important clinicopathological investigation of 349 cases of Küttner's tumor in 1977. They widened its scope from the classic features of chronic sclerosing submandibular sialadenitis described by Küttner[1] in 1896 to encompass cases with only minor histological changes, and thereby made a valuable contribution to our understanding of the etiology and pathogenesis of the condition. They considered that Küttner's tumor or chronic submandibular sialadenitis starts as a secretory disturbance in which there is a condensation of secretory material in lumina with the formation of both calcified and purely organic sialomicroliths that lead to obstruction followed by inflammation, increasing destruction of the parenchyma, fibrosis of the lobules, and a conspicuous lymphocytic infiltrate with lymphoid follicles. The decreased secretory activity as a result of the atrophy favors ascending ductal invasion by microbes that sustain the inflammation; thus a vicious circle ensues, and the manifest sialolith is the final stage.

This concept of chronological progress through increasingly severe changes was challenged in 1981 by Isacsson et al,[26] who found no relation between the severity of the changes in the glands and the duration of symptoms, and considered sialoliths to be the main etiological factor of chronic submandibular sialadenitis and not secondary to it. However, in a subsequent thorough clinicopathological investigation[27] of chronic submandibular sialadenitis in which 154 cases were evaluated and statistically analyzed for 18 different clinical and histological features, which encompassed the wide range of histological appearances established by Seifert and Donath[9] as part of chronic submandibular sialadenitis, it was found that sialoliths, atrophy, fibrosis, parenchymal inflammation, lymphoid germinal centers, mucous and ciliary metaplasia, extravasation of saliva, and accumulation of glycosaminoglycan are related to the total infiltrate of inflammatory cells, which appears to be of great importance in the etiology and pathogenesis of chronic submandibular sialadenitis. The total infiltrate of inflammatory cells, atrophy, fibrosis, and sialoliths, which had been present at some time in the gland or duct of 68% of the cases, was found to be related to the duration of symptoms, which supports Seifert and Donath's concept of chronological progress through increasingly severe histological changes with the secondary formation of sialoliths. Sialomicroliths, in contrast, were found to be related to age as in normal glands and not to duration of symptoms or to sialoliths, which was a surprise, as the suggestion had been made that sialomicroliths occasionally impacted and accreted to form sialoliths.[11,21,24] However, the investigations on the feline glands[12,17] revealed the importance of secretory inactivity in the production of sialomicroliths, and together with the results of clinical and pathological investigations,[27–29] led to the following understanding of the natural history of sialolithiasis (**Table 6–1**).

Secretory inactivity in a normal gland leads simultaneously to increased formation of sialomicroliths and ascent of the main duct by commensal microbes. Impaction of a sialomicrolith in a small intraglandular duct causes focal obstructive atrophy (**Fig. 6–3**).

TABLE 6–1 Natural History of Chronic Sialadenitis and Sialolithiasis

Secretory inactivity in normal gland
Accumulation of sialomicroliths causes foci of obstructive atrophy
Microbes ascend main duct and proliferate in foci of obstructive atrophy
Inflammation with fluid exudate
Compression of surrounding parenchyma with further atrophy
Further ascent by and proliferation of microbes
Further inflammation with fluid exudate
Compression of large duct with partial obstruction
Stagnation of secretory material and released calcium
Formation of sialolith as calcium precipitates on phospholipid of degenerate membranes
Further obstructive atrophy, ascent by microbes, and inflammation

Microbes proliferate in atrophic parenchyma where they are protected from the flushing and microbicidal activity of saliva and from systemic immunity by the associated fibrosis. The diffusion of their waste products and local invasion cause inflammation, the fluid exudate of which compresses surrounding parenchyma and causes further atrophy, which is associated with further invasion by microbes. The process spreads to involve more of the gland until inflammatory swelling and fibrosis secondary to inflammation compress interlobular ducts, which causes partial obstruction that leads to dilatation and intraluminal stagnation of secretory material rich in calcium that precipitates onto the phospholipid exposed in degenerate membranes (**Fig. 6–4**); accretion occurs until a sialolith is formed (**Fig. 6–5**). This causes further obstructive atrophy and reduction in salivary flow, all of which facilitate further ascent by microbes. The process progresses, and the gland becomes increasingly inflamed, atrophied, and fibrosed.

There has not been a comparable investigation into the etiology and pathogenesis of parotid sialolithiasis, and the etiology of chronic parotitis is unclear.[30] Sialomicroliths and atrophic foci occur in the normal parotid,[21,31] and it is likely that the etiology and pathogenesis of parotid sialolithiasis are similar to those of submandibular sialolithiasis. An additional obstructive factor is an albuminous coagulum that forms when plasma proteins leak into the lumina of inflamed glands.[30]

Sialolithiasis of the minor salivary glands is relatively rare, and the peak incidence is later than that of the submandibular gland and is in the fifth to eighth decades.[32–34] The reason for this relates to the spontaneous secretion of the minor salivary glands that occurs in the absence of nervous stimulation, in contrast to the submandibular and parotid glands in which secretion stops in the absence of nervous stimulation.[35] Degenerative changes occur in the minor glands with age and involve acinar atrophy, the occurrence of sialomicroliths in ductal lumina, and an increase of inflammatory cells.[36] This will eventually lead to stagnation of secretory material that is rich in calcium[22] and the formation of sialoliths.

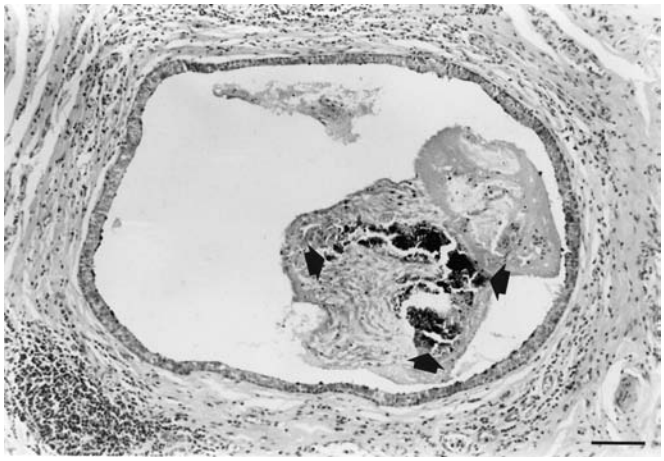

FIGURE 6–4 An inchoate lith consists of foci of calcification (between the three arrows) mixed with secretory material, inflammatory cells, and cellular debris in the dilated lumen of an interlobular collecting duct. Chronic submandibular sialadenitis with sialolithiasis. Section stained with hematoxylin and eosin, ×70; bar = 100 μm.

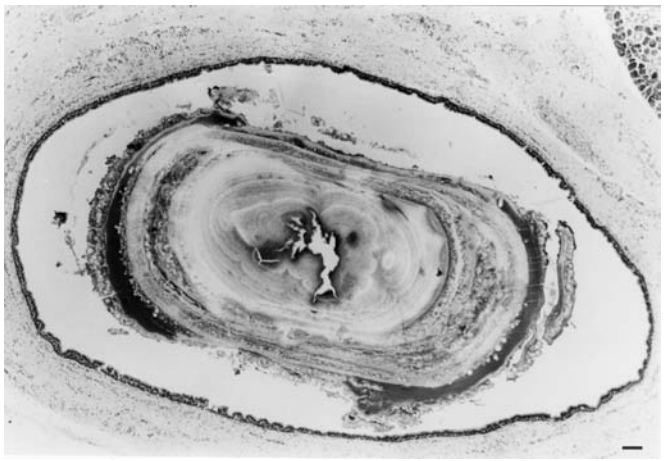

FIGURE 6–5 A sialolith obstructs the dilated lumen of an interlobular collecting duct and contains many lamellae and several central cores, which indicates that accretion had occurred. Chronic submandibular sialadenitis with sialolithiasis. Tissue decalcified and section stained with hematoxylin and eosin, ×27; bar = 100 μm.

The Structure and Composition of Sialomicroliths

A sialomicrolith is defined as a concretion in a salivary gland that can only be seen microscopically and is most often calcified.[14] Sialomicroliths range from consisting mainly of crystals of calcium and phosphorus in the form of apatite to consisting mainly of granular material, which is condensed secretory material, without crystals.[11,14,21,24,25] Some of the sialomicroliths in the parasympathectomized feline submandibular glands are of a florid appearance (**Fig. 6–2**) and consist of complex mixtures of crystals and granular material, which indicates that they grew and fused by accretion and that the presence or absence of crystals relates to the local concentration of calcium at the time that a particular part is forming. Similarly, the sialomicroliths in chronic submandibular sialadenitis are well calcified, which corresponds to a higher concentration of calcium in the submandibular gland, whereas those found in parotid sialadenosis are poorly or not calcified, which corresponds to a lower concentration of calcium in the parotid.[22]

■ The Structure of Sialoliths

A sialolith (**Fig. 6–5**) is defined as a concretion in a salivary gland or main duct that can be seen with the naked eye and is most often calcified. Sialoliths share many features with sialomicroliths, including great variation in structure and in the content of mineral and organic matrix, the latter of which has been found to vary in different parts of sialoliths from 23 to 100% by volume of the part analyzed,[37] as well as being the sole component of some sialoliths.[38] The mineral component has been found to be proportional to the size of sialoliths, which indicates that there is increasing mineralization of the organic matrix with time.[39] The organic matrix contains glycoprotein[40] and lipids derived from secretory material and cell membranes,[5–8,41] which indicates a process of formation similar to that of sialomicroliths, namely a condensation of stagnant secretory material and a precipitation of the sequestered calcium released in an ionized form on to phospholipid exposed in degenerate cell membranes to form apatite (**Fig. 6–4**). This is facilitated by reduced amounts of phytate and magnesium, which are potent inhibitors of apatite crystallization and have been found to be present in reduced amount in the saliva of patients with mineralized sialoliths.[38]

The great variation in the structure of sialoliths (**Fig. 6–5**) is manifest as cores, which are not always present, are single or multiple, and vary from purely organic to heavily calcified; lamellae, which range from being present throughout all but the core to being absent; spheroidal bodies that appear to be condensed secretory material or lipid; bacteria, which are not usually seen in the cores and may be calcified; and a surface coating of condensed secretory material and cellular debris.[37,38,41–49] These variations are caused by variations in the microenvironment between glands and within glands at different times, and parts of sialoliths may change as the microenvironment changes. The core is formed initially, yet it sometimes exhibits a substructure, which indicates a formation by accretion and fusion of smaller sialoliths. This process possibly also includes sialomicroliths.

Direct involvement of bacteria in the formation of sialoliths has been suggested,[45,47] although the absence of bacteria in sialomicroliths indicates that bacteria are not necessary for calcification and the formation of sialoliths. It appears that bacteria are involved later when the partial obstruction caused by a sialolith enables them to ascend more easily from the mouth to reach and colonize the surface of the sialolith.

Sialoliths of a crystalloid structure have been described in the parotid[48] and minor salivary glands.[49] They appear to consist of precipitated protein and to be formed by condensation of stagnant secretory material.

■ The Composition of the Mineral of Sialoliths

The microenvironment determines the type of salt formed and the degree of calcification. The saliva of patients with calcified sialoliths contains more calcium than that of controls and of patients with purely organic sialoliths.[38]

Submandibular sialoliths[5,37,38,42,43,50–52] usually contain apatite, $Ca_5(PO_4)_3OH$, as the principal mineral and often sole mineral. Whitlockite, $Ca_3(PO_4)_2$, is the next most common mineral, appears to be found only in sialoliths from Wharton's duct, is often mixed with apatite, is often localized centrally and in well-mineralized areas, and is not present in lamellae. Octacalcium phosphate, $Ca_8H_2(PO_4)_6.5H_2O$, and brushite, $CaHPO_4.2H_2O$, are seldom present.

Parotid sialoliths[6,50,51] commonly consist of octacalcium phosphate mixed with apatite and sometimes also whitlockite, and consist solely of apatite less often than submandibular sialoliths.

■ Conclusion

The synthesis of many experimental and clinical investigations has led to a radical change in our understanding of the natural history of chronic sialadenitis and sialolithiasis, the etiology and pathogenesis of which are interrelated and inseparable, and has supported Küttner's[1] notion that sialolithiasis is secondary to sialadenitis. The new understanding indicates the importance of good salivary secretory activity not only as a therapy but also as a prophylactic against chronic sialadenitis and sialolithiasis. Another important factor is phytate,[38] which inhibits the formation of sialoliths by chelating the released ionized calcium; a diet with a reasonable content of phytate, which is found in seeds, would appear to be prophylactic.

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7

Classic Approaches to Sialoendoscopy for Treatment of Sialolithiasis

ODED NAHLIELI

Obstructive sialadenitis, with or without sialolithiasis, represents the main inflammatory disorder of the major salivary glands. The diagnosis and treatment of obstructions and inflammations of these glands can be problematic due to the limitations of standard imaging techniques. Satisfactory treatment depends on our ability to reach a precise diagnosis and, in the case of sialoliths, to accurately locate the obstruction. Until recently many of these glands required complete removal under general anesthesia.

Sialolithiasis is a common finding, accounting for 50% of major salivary gland disease.[1,2] The submandibular gland is the most prone to sialolithiasis. In various studies it was found that ~80% of all sialolithiasis cases are in the submandibular glands, 19% occur in the parotid gland, and ~1% are found in the sublingual gland. Sialolithiasis is most often found in adults, but it may be diagnosed in children.[3]

Sialoliths may vary in size, shape, texture, and consistency. They may occur as a solitary stone or as multiple stones. Bilateral submandibular stones are a rare condition (5% of submandibular sialolithiasis cases). Sialolithiasis of submandibular and parotid gland together has not been reported in the literature. The amount of symptomatic and nonsymptomatic sialolithiasis cases is 1% of the population, found in autopsy material.[4]

The symptomatic group of patients admitted to the hospital each year has been estimated as 57 cases per million per annum in the British population, representing 3420 patients per annum.[1] If this incidence is applied to the European or the American population (300 million), then ~17,100 patients per annum will require hospital treatment for sialolithiasis and its complication sialoadenitis. These data do not include patients who were treated as ambulatory (outpatient) cases.

There is a male preponderance,[5] and the peak incidence is between the ages of 30 and 60.[5] Sialoliths grow by deposition and range in size from 0.1 to 30 mm.[6] Presentation is typically with a painful swelling of the gland at meal times, when the obstruction caused by the calculus becomes most acute.[7]

During the past decade, with the introduction of salivary gland endoscopy there has been a major step forward, not only in providing an accurate means of diagnosing and locating intraductal obstructions, but also in permitting minimally invasive surgical treatment that can successfully manage those blockages that are not accessible intraorally.[8–20]

Clinical Presentation

See Chapter 5 for a full discussion of the clinical presentation of sialoliths.

Diagnostic Methods

Clinical Evaluation

Visual scanning of submandibular, preauricular, and postauricular regions is the first step in assessing swelling and erythema (see Chapter 5). This is followed by intraoral examination. Surgical magnification loops (2.5–3.5) are very useful in improving visualization of the orifice of Wharton's and Stensen's ducts. The orifice may be red and edematous and appear as a papilla.

Plaques or whitish secretions from the duct may represent frank infection. Sometimes a small stone can be found in the orifice; occasionally, the white-yellow color of a stone can be seen through the translucent mucosa. Bimanual palpation is particularly important when examining the submandibular gland and duct. It helps to differentiate the gland from adjacent lymph nodes, inferior to the gland, and to ascertain the presence of any firm mass in the take-off of Wharton's duct from the hilum of the gland.

For the parotid gland, manual palpation allows the surgeon to determine the consistency of the gland. One should also massage the gland to milk and inspect the saliva.

Salivary Imaging

Although there are a variety of newly available imaging methods, in this section we focus on those techniques most suitable for patients suffering from salivary gland obstructions (See also Chapter 2). The most effective imaging methods for inflammatory conditions of the submandibular and parotid glands are plain x-rays (occlusal, occlusal oblique, panoramic), sialography, ultrasound, and computed tomography (CT). Scintigraphy will be included in this chapter because of its unique ability to evaluate the gland function. Sialoendoscopy is a newly developed technique that is useful for imaging and treatment. It will be discussed separately.

Plain X-ray

Traditionally, plain radiographs are often used as a simple first-line investigation. Occlusal, occlusal oblique, and panoramic x-rays are excellent for ruling out any calcification in the submandibular region (**Fig. 7–1**). These will not demonstrate radiolucent calculi, which account for 20 to 43% of submandibular stones.[21,22] For parotid stones, panorex and anteroposterior views directed to the parotid region are recommended. The practitioner has to remember that plain x-rays have minimal value in parotid stones because of the amount of radiolucent stones (60–70%). The plain x-ray gives no information on the condition of the affected gland. It is therefore necessary to supplement or supplant plain radiography with another diagnostic modality.

Sialography

Sialography is one of the oldest salivary gland imaging techniques. The first contrast agents used in the early twentieth century were pure mercury. The dye that he used was pure mercury. Nowadays we have better dye options. Although there is a need to penetrate to the ductal system with a catheter through the ductal papilla,

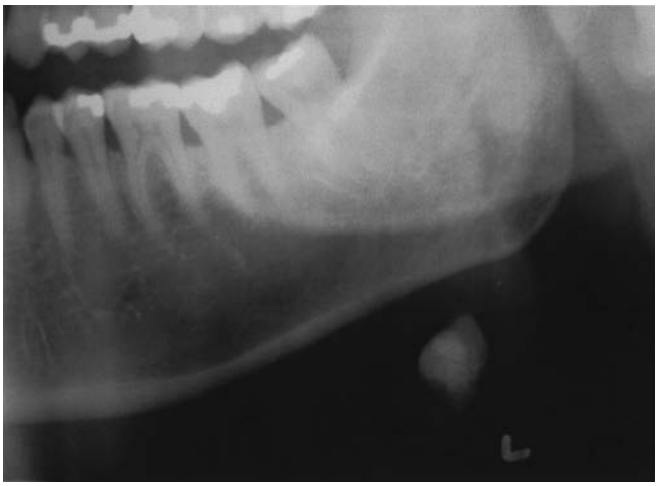

FIGURE 7–1 Panoramic dental x-ray, demonstrating large sialolith in the left submandibular gland.

it is the only method that can give the possibility to examine the ductal system with reasonable cost. Reducing the discomfort during sialography may be achieved by applying topical anesthesia to duct papilla and/or by lavaging the gland through the orifice with 2% lidocaine prior to the injection of the water-soluble dye.

Sialography provides images of the morphology of the ductal system and allows the diagnosis of strictures, dilatations, and filling defects. This technique also provides information on glandular function (**Fig. 7–2A**).

Ultrasound

High-resolution ultrasound is a good imaging method to assess the salivary glands. It is noninvasive, and there is no associated discomfort. It is useful to distinguish the submandibular gland from surrounding lymph nodes and to locate calculi. The portion of Wharton's duct that leads from the hilum of the gland toward the floor of the mouth, precisely after the penetration of the mylohyoid muscle, is difficult to identify.[23] Calculi detection rates vary between 63 and 94%[16] and are close to those for sialography.[24] Ultrasound is able to detect radiolucent stones even though the acoustic shadow is not as marked. The distal portion of the submandibular and parotid ducts can be difficult to visualize using extraoral ultrasound.[25] However, small, high-frequency intraoral probes are now available that overcome this limitation[26] (**Figs. 7–2B, 7–3**).

Computed Tomography

CT scan is especially useful for evaluating inflammatory conditions of the submandibular and parotid glands. Sialoliths are readily identified on CT imaging. The standard images should be 1 mm cuts with three-dimensional reconstruction. In this way the glands and ducts can be visualized in all planes, and stones are less

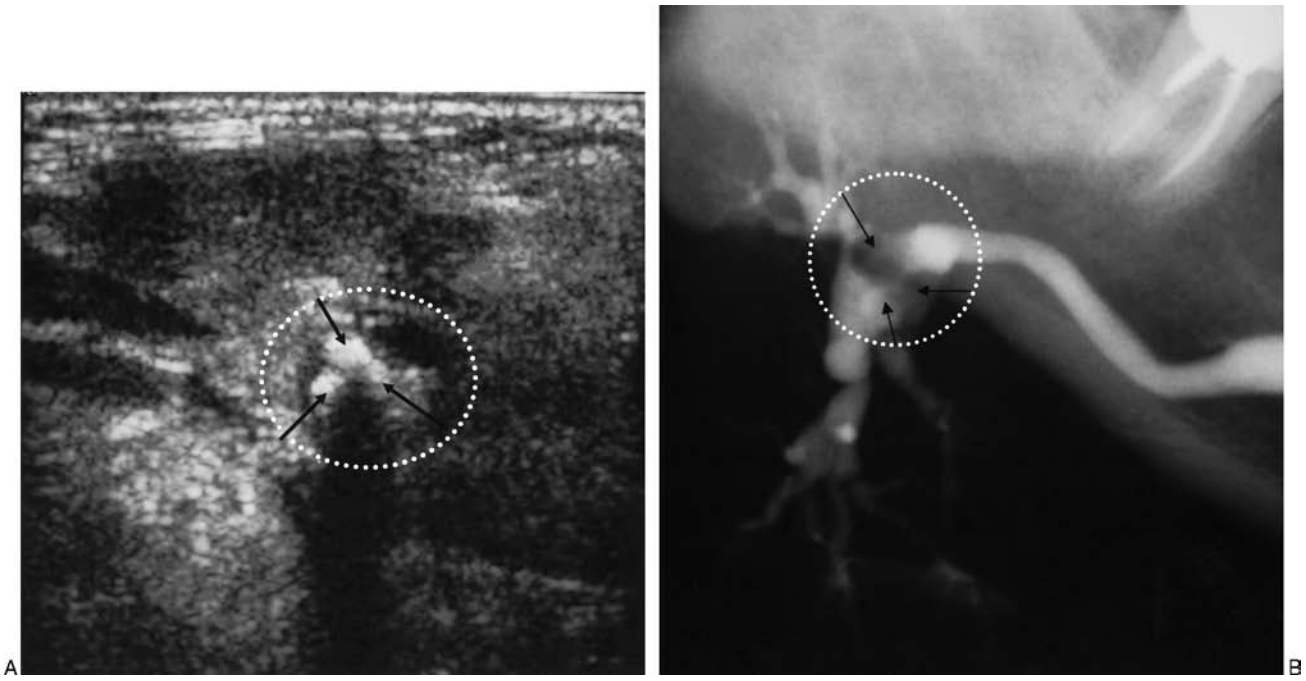

FIGURE 7–2 (A) Ultrasound and **(B)** sialogram of the right submandibular region of patient suffering from multiple swellings. Three stones are demonstrated in the sialogram and in the ultrasound (arrows). The stones appeared as hyperechogenic lesions with acoustic shadow.

likely to be missed. The parotid gland and duct are well demonstrated by CT. Another advantage is the possibility to diagnose and locate intraparenchymal stones and calcifications that are not connected to the gland (phleboliths, tonsiliths, calcifications in the lymph nodes, etc.) (**Fig. 7–4**).

Scintigraphy

In contrast to ultrasound, which depicts architecture, radioisotope imaging of the salivary glands gives some measure of the secretory function and allows comparison between the major glands. The assessment of

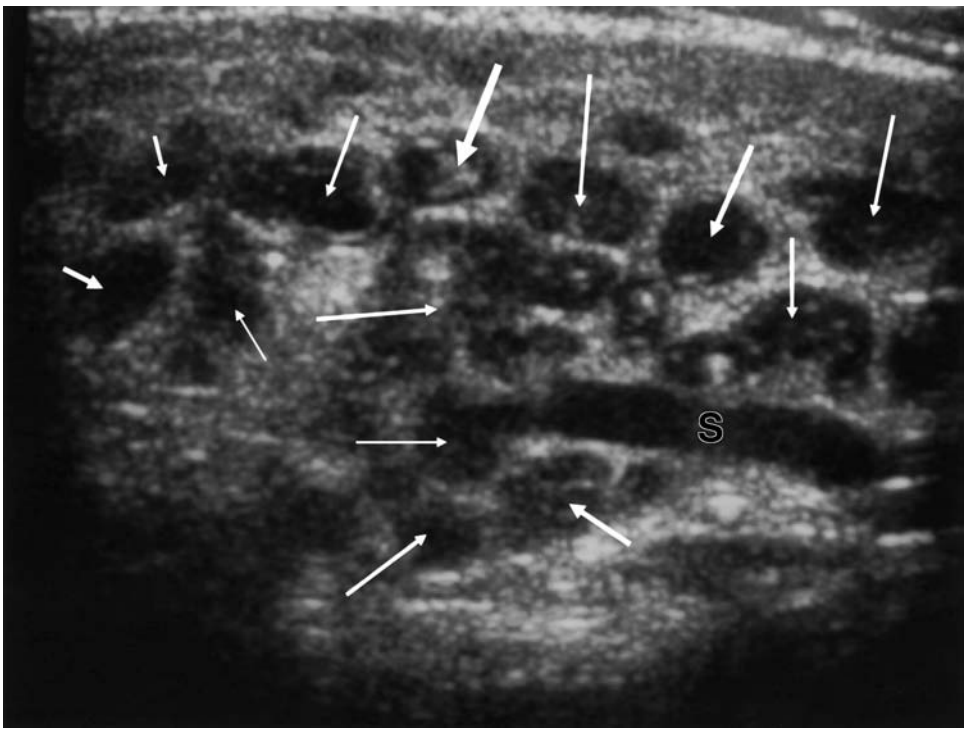

FIGURE 7–3 Ultrasound of parotid gland with multiple hypoechogenic sialectases (arrows) and dilated Stensen's duct (S).

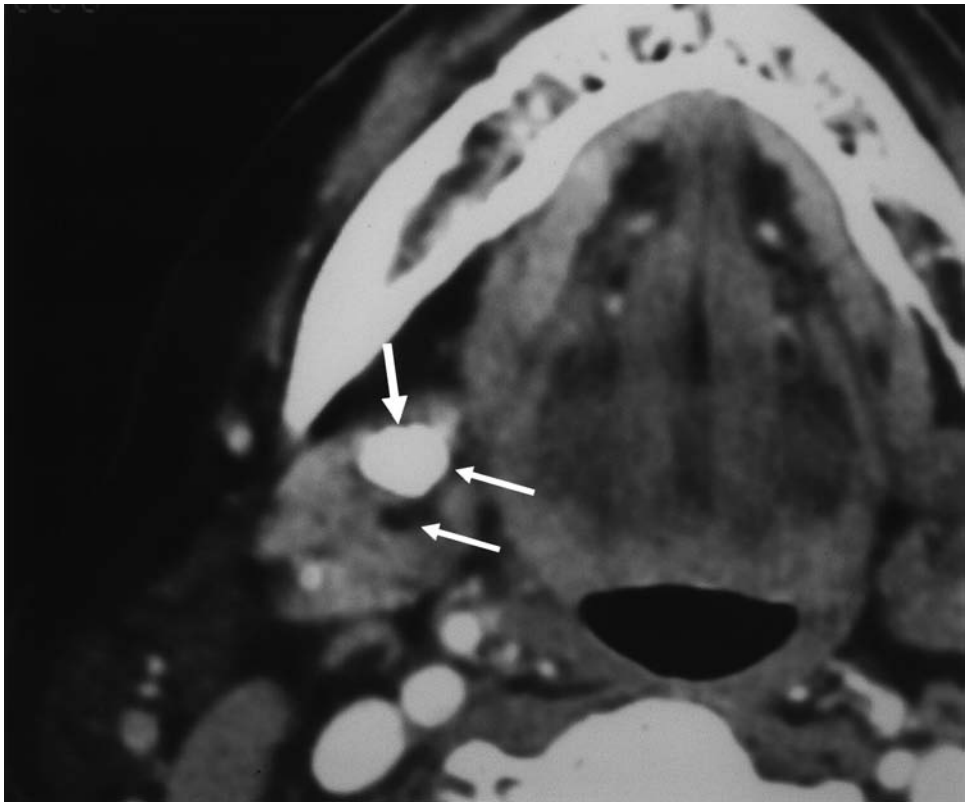

FIGURE 7–4 Computed tomography scan of submandibular gland with stone. The sialolith is marked with arrows.

salivary gland function using a bolus intravenous injection of technetium Tc 99m pertechnetate is easy to perform, reproducible, and well tolerated by the patient.[27] It enables examination of the parenchymal function and excretion rate of the salivary gland and has the further advantage of a short half-life and low radiation dose.[27]

■ Surgical Procedures

This section is problematic because of the enormous and rapid development of methods and technology in recent years. As in other fields of surgery, traditional and more aggressive techniques are being replaced by organ-preserving methods with the help of minimally invasive techniques. The reader needs to be familiar with all techniques. This section includes two parts: traditional and modern approaches.

Traditional Approaches to Submandibular Sialolithiasis

Traditionally, sialoliths in the submandibular duct and gland were divided into two groups: (1) stones that can be removed through intraoral sialolithotomy approaches, including stones up to the first molar tooth, which can be palpated; and (2) stones that cannot be removed from the intraoral approach and require sialadenectomy, including stones posterior to the first molar region, or stones in the middle part of the Wharton's duct that cannot be palpated intraorally.

Intraoral Sialolithotomy

The first step is to locate the stone exactly. This technique is useful only in stones in the anterior and middle part of Wharton's duct up to the first molar tooth. Effectively, only stones that can be palpated easily from the intraoral region are candidates for this technique.

Following administration of local anesthesia, two sutures of 3.0 silk are placed posterior to the location of the stone. The aims of this step are to isolate the stone and to prevent movement of the stone to the inner part of the duct or hilum of the gland. The next step is to cut the mucosa above the stone directly on the stone, which can be done with a cold blade, electrosurgery, or CO_2 laser.[28] The advantages of the CO_2 laser are the hemostatic effect and the easy identification of the stone. The contact between the stone and the laser beam creates a spark that can be easily identified. Following incision of the mucosa and the duct, the stone is exposed and extracted with dental curettes. Following the extraction of the stone, the silk sutures are removed. Milking the gland allows discharge of plaques and saliva and possibly additional stones. Interrupted 4.0 Vicryl sutures are placed to connect the ductal layer to the oral mucosa. The patient is encouraged to

massage the gland and is treated postoperatively with oral antibiotics for 7 days.

The same procedure of sialolithotomy has been described for the more posterior region. The author is strongly opposed to this technique because of the high risk of injury to the lingual nerve and the possibility of severe bleeding from lingual vessels. The technique of extracting such stones is described in the section Modern Endoscopic Approaches to Sialolithiasis.

Submandibular Sialadenectomy

See Chapter 15 for a full discussion of submandibular sialadenectomy.

Traditional Approaches to Parotid Sialolithiasis

Traditionally, sialoliths in the parotid duct and gland were divided into two groups. (1) stones that can be removed through an intraoral sialolithotomy approach, including stones up to the curvature of Stensen's duct above the masseter muscle; and (2) stones that cannot be removed with an intraoral approach, requiring extirpation of the parotid gland. This would include stones posterior to the curvature of the duct.

Intaoral Sialolithotomy

The first step is to locate the stone exactly. This technique is useful only in stones in the anterior part of Stensen's duct anatomically demarcated by the curvature of the duct above the masseter muscle as the duct penetrates the buccinator muscle. Following local anesthesia around the papilla of Stensen's duct, a lacrimal probe is advanced until it reaches the stone. A hemostat holds the papilla and the probe to ensure safe tract to the stone. An elliptical incision around the papilla and the probe is indicated preferably with a CO_2 laser. Blunt and sharp dissection is performed around the duct up to the stone location. The ductal layer above the stone is incised and the stone removed with dental curettes. Following the sialolithotomy, massage of the gland allows release of plaque and saliva. The ductal layer is sutured with several 4.0 Vicryl sutures to the oral mucosa to promote a patent duct.

Superficial and Total Parotidectomy

See Chapter 15 for a full discussion of superficial and total parotidectomy. The difference between removal of the parotid gland with stone and benign tumor is the condition of the gland. Scar tissue, inflammation, and fibrosis inside the gland and around Stensen's duct make the operation difficult and heighten the risk for facial nerve damage and salivary fistulae.[29–31]

Modern Endoscopic Approaches to Sialolithiasis

In the past decade, the advent of salivary gland endoscopy has brought us a major step forward, not only in that the novel techniques provide an accurate means of diagnosing and locating intraductal obstructions, but also that they permit minimally invasive surgical treatment that can successfully manage blockages not amenable to an intraoral approach.[8–20]

In 1997 we (Nahlieli and Baruchin[11]) reported on our experience with the use of a mini rigid endoscope to perform sialoendoscopies on 46 major salivary glands. To date we have successfully managed 892 patients with these endoscopic techniques.

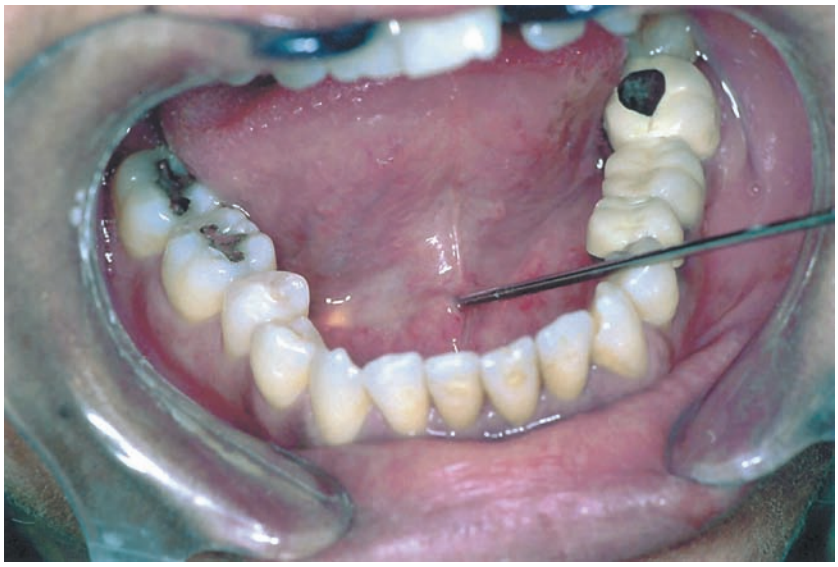

FIGURE 7–5 Introduction of 1.3 mm diagnostic unit through the orifice of the Wharton's duct (following dilatation) into the gland. Note the transillumination effect.

Indications

The indications for sialoendoscopy are the following:

1. For diagnostic purposes, recurrent episodes of major salivary gland swelling without obvious cause
2. Sialolithotomy: removal of deeply located stones (posterior portion of Wharton's duct (''comma area,'' because of its proximity to the lingual nerve) or stones in Stensen's duct posterior to curvature of the duct above the masseter muscle
3. Exploration of the ductal system following calculi removal from the anterior or middle part of the submandibular or parotid ducts
4. Strictures or kinks of the salivary ductal system
5. Treatment of submandibular and parotid sialadenitis
6. Pediatric inflammatory and obstructive pathology

Absolute Contraindication

Acute sialadenitis is an absolute contraindication for sialolithiasis.

Pre-endoscopic Assessment

Following the clinical evaluation, plain x-rays, which include panorex, occlusal, occlusal oblique, sialogram, and ultrasound, are recommended. In the case of a parotid stone in the middle or posterior parts, a CT scan is indicated.

Introduction of the Sialoendoscope

To determine the feasibility of entering the ductal lumen by use of sialoendoscopy, the size of the duct is measured by sialography and ultrasound imaging. Sialography is used for mapping the ductal system for possible variations and assessment of its estimated dilatation capacity.

There are four possible methods for introducing the endoscope into the ductal lumen: (1) introducing the exploration unit (1.3 mm) through the natural orifice of the duct; sometimes there is a need for dilatation, which can be done with lacrimal probes (**Fig. 7–5**); (2) through a papillotomy procedure, performed with a CO_2 laser immediately posterior to the orifice of the duct, thus enlarging the opening; (3) through ductal exploration (''ductal cutdown''), which involves surgical dissection and exposure of the anterior portion of the duct with a microsurgical technique. The duct is then incised longitudinally to allow the intraluminal insertion of the endoscope. If there are any difficulties in introducing the endoscope in the anterior part (e.g., stricture, too narrow ductal lumen), it may be necessary to expose the duct more posteriorly to arrive at a location where the diameter will accommodate the endoscope (**Figs. 7–6, 7–7**); and (4) through a sialolithotomy opening; the endoscope can be inserted through the same opening in the duct where the stone was extracted.

Irrigation during Sialoendoscopy

Irrigation or inflation is crucial in every endoscopy procedure to create an optical cavity. The cavity must be filled with fluid to allow free movement of the instrument, and the area needs to be lavaged to permit good visualization. Isotonic saline is the fluid of choice. An intravenous bag containing isotonic saline is connected to the irrigation port, and the endoscope is moved forward accompanied by a gentle flow of saline. Next, 4 cc of 2% lidocaine is injected through

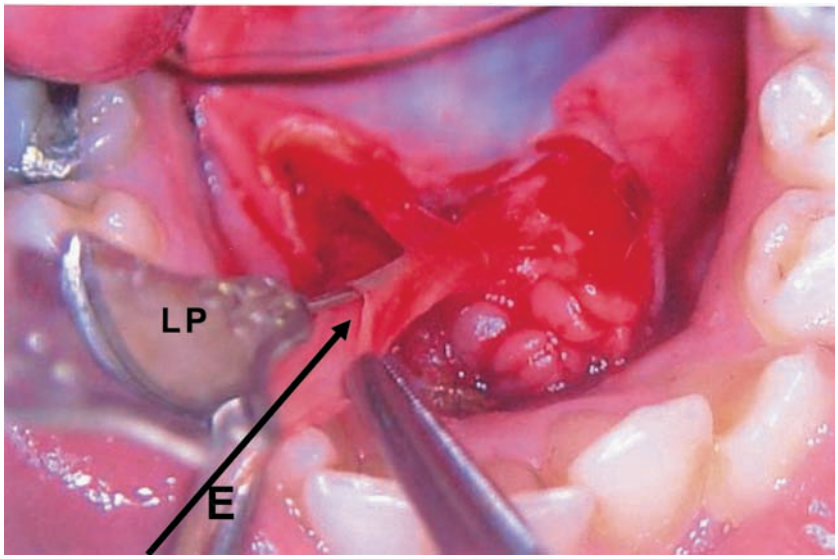

FIGURE 7–6 Exploration of the Wharton's duct. Note the diameter of the duct, sufficient for insertion of the surgical endoscope for interventional sialoendoscopy. Lacrimal probe (LP) is in the duct for correct location. Note the position of the endoscope (E) for accurate insertion.

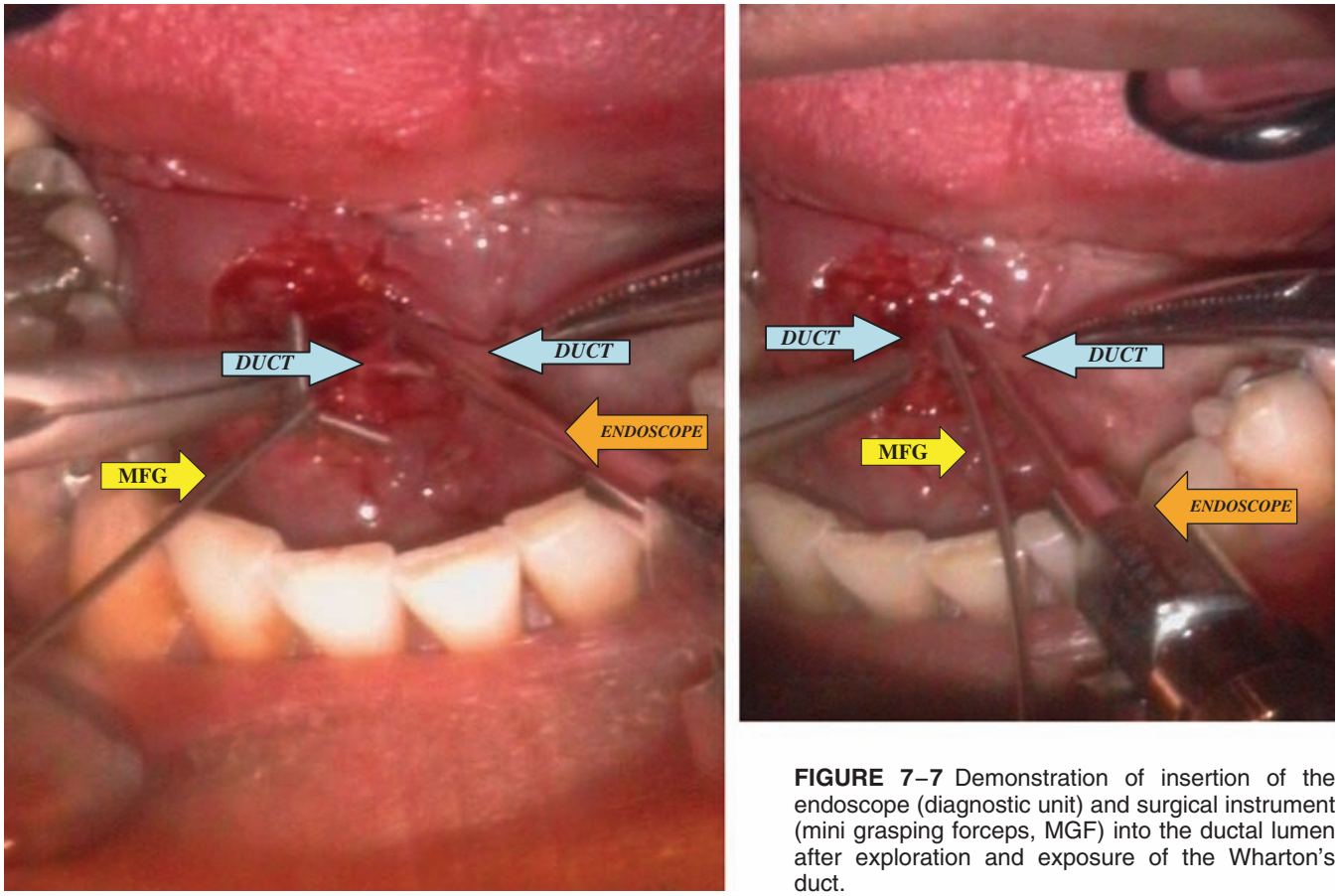

FIGURE 7–7 Demonstration of insertion of the endoscope (diagnostic unit) and surgical instrument (mini grasping forceps, MGF) into the ductal lumen after exploration and exposure of the Wharton's duct.

this port, resulting in the anesthesia of the entire ductal system.

Approaches

An intraductal or extraductal approach is possible. The intraductal approach is a purely endoscopic technique. The extraductal approach is an endoscopically assisted technique (**Tables 7–1 and 7–2**).

Intraductal Sialolithotomy

When a sialolith is encountered, its diameter is estimated using the caliber of the endoscope as a reference, and the method of choice for its removal is selected from four possibilities:

- Removal in one piece by use of grasping forceps, wire baskets, graspers, or balloons (**Figs. 7–8, 7–9**)
- Crushing the calculus with forceps, then removing the fragments using irrigation
- Fragmentation with laser lithotripter
- Combined use of an intracorporeal laser lithotripter or extracorporeal shock wave lithotripter (ESWL), wire basket, and grasping forceps

TABLE 7–1 Determination of the Appropriate Submandibular Sialoendoscopic Technique

Stone location and diameter	Technique used
Sialolith located up to the middle third of the duct	Sialolithotomy and diagnostic sialoendoscopy
Sialolith < 5 mm, located in the hilum area	Grasping forceps
Papillotomy/duct exploration	Grasper or wire basket or balloon
	Lithotripsy (do not use lithotripsy in nonfunctional glands; apply a ductal stretching technique)
Sialolith > 5 mm located in the hilum area	Ductal stretching technique
	Sialolithotomy
	Diagnostic sialoendoscopy and removal of residual sialoliths
Secondary ducts, ductal exploration technique	Grasping forceps
	Lithotripsy

TABLE 7–2 Determination of Appropriate Parotid Sialoendoscopic Technique

Stone location and diameter	Technique used
Sialolith located up to 1 cm from the papilla	Sialolithotomy and diagnostic sialolithotomy
Sialolith < 5 mm, located up to the posterior third of the duct	Grasping forceps
Papillotomy/duct exploration	Grasper or wire basket or balloon
	Lithotripsy
Sialolith > 5 mm, located up to the posterior third of the duct	Ductal stretching technique
	Sialolithotomy
	Diagnostic sialoendoscopy and removal of residual sialoliths
Sialolith > 5 mm, located in the middle and up to the posterior third of the duct, and dilation and intraductul stone removal failed	Endoscope-assisted extraoral approach
Secondary ducts, ductal exploration technique	Grasping forceps
	Lithotripsy
Strictures of anterior location	Balloon dilation (two trials)
	Endoscope-assisted application of grasping forceps

The primary goal is to remove the calculus in one piece. If this fails, the second option is crushing, and the ultimate resort would be intracorporeal lithotripsy. Occasionally, particularly in cases where lithotripsy has been used or multiple sialoliths were encountered, it has been necessary to perform a second sialoendoscopy to clear the involved gland of all obstructions.

Extraductal Sialolithotomy

The following extraductal approaches are available:

- Intraoral techniques. These techniques can be used for submandibular and parotid stones.
- Extraoral technique. This technique is exclusively for impacted parotid stones.

Intraoral Sialolithotomy

We developed the so-called ductal stretching technique to overcome sialolith removal that we cannot solve with the purely endoscopic techniques or a failed attempt to extract the sialolith by purely endoscopic techniques (**Fig. 7–10**). In our experience, indications for this technique include:

- Large-size calculi in the submandibular and parotid ducts, measuring more than 5 mm
- Narrowness of the duct, which effectively rules out the option of attempting an intraductal approach
- Failures of the intraductal techniques

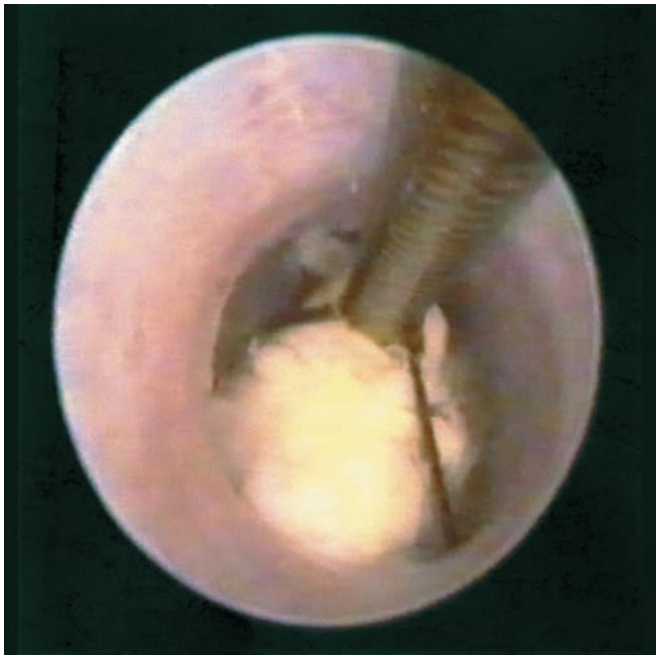

FIGURE 7–8 Endoscopic view of basket retrieval of sialolith from the submandibular hilum.

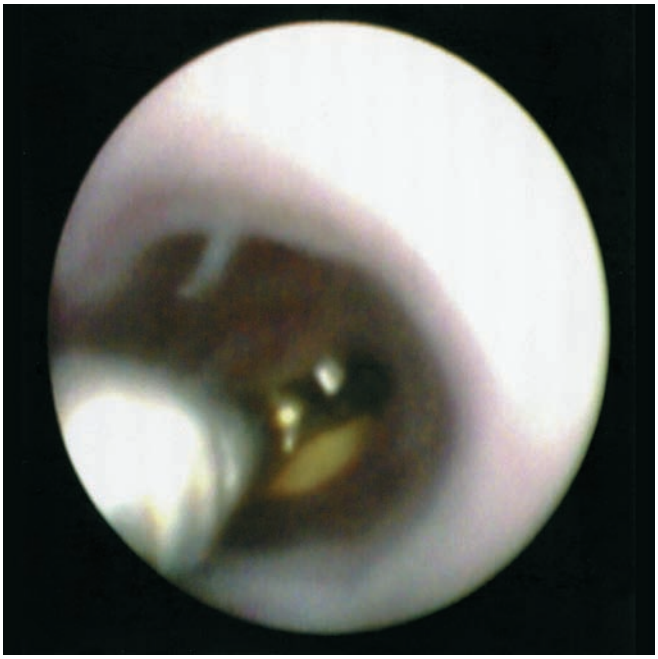

FIGURE 7–9 Endoscopic view of mini grasping forceps retrieval of sialolith from the submandibular hilum.

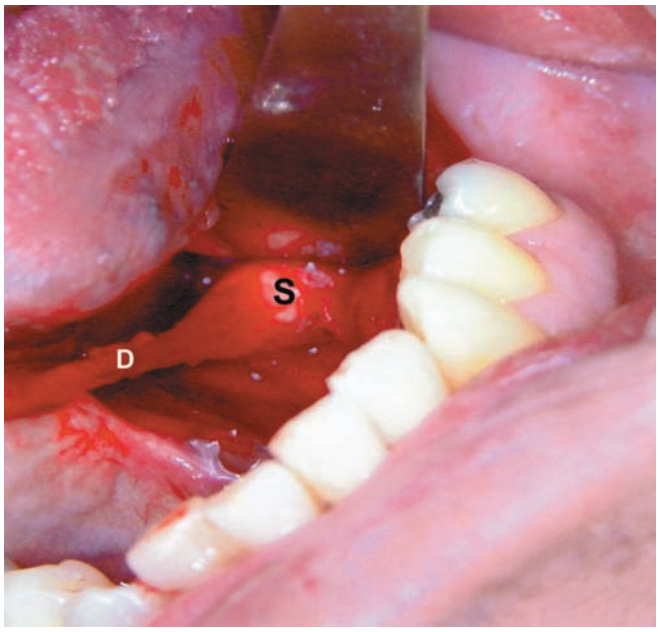

FIGURE 7–10 Ductal stretching technique. A 7 mm stone in the hilum of the submandibular gland with too narrow a duct for pure endoscopic retrieval. D, duct; S, stone.

The ductal stretching technique involves these steps:

1. Introducing the endoscope for exact location of the stone lavage and disconnecting the stone from the ductal attachment
2. Introducing the lacrimal probe into the duct and making an incision above the duct with a CO_2 laser
3. Dissecting and isolating the duct from the surrounding tissues up to the first molar (submandibular) or the curvature of the duct above the masseter muscle (parotid)
4. In submandibular cases, forwarding the gland toward the mouth with digital pressure from the submandibular region
5. Ductal section above the calculus and sialolithotomy
6. Endoscopic exploration for removal of additional calculi and lavage
7. Temporary polymeric stent insertion for 4 weeks

Extraoral Sialolithotomy

This approach is exclusively reserved for removal of impacted parotid stones.[19] The indications for the extraoral approach are:

- Calculus in the posterior third of the Stensen's duct with too narrow duct anterior to it
- Obstruction of the posterior or middle third of the Stensen's duct leading to the calculus
- Large-size (> 5 mm) stones in the middle or posterior part of the duct that cannot be dilated for intraductal removal
- Intraparenchymal stones

Identification of Sialolith

The first step is to identify the exact location of the sialolith. There are two main approaches:

- Sialoendoscopic identification
- Ultrasound identification

The endoscopic approach is indicated when there is a possibility of introducing the endoscope (Nahlieli Sialoendoscope, Karl Storz GmbH, Tuttlingen, Germany, Diagnostic Unit 1.3 mm) into the duct. The ultrasound identification is indicated when there is no possibility to penetrate the duct via Stensen's duct due to ductal obstruction or severe stenosis.

The Calculus Can Be Identified through the Ductal Lumen

Following infiltration of local anesthesia around the orifice of the Stensen's duct and irrigation of the Stensen's duct with 2% lidocaine, the diagnostic unit is introduced, and the calculus is identified. The exact location on the outer skin is marked with the aid of the transillumination effect of the sialoendoscope.

The Calculus Cannot Be Identified through the Ductal Lumen

The gland is evaluated with high-resolution ultrasonographic examination (ATL-300, Advanced Technology Laboratory, Bothell, WA with high resolution 5–12 MHz linear probe). The calculus is detected, and its depth, size, and shape are annotated. Skin coordinates are drawn to the exact surgical location of the stone, and a biopsy wire marker is inserted under ultrasound control to locate the stone.

Removal of Sialolith

The suspected area of the stone is infiltrated with local anesthesia. A 1 cm incision according to the facial lines is performed. Sharp and blunt dissection will lead to the stone. If we have a location difficulty problem during the dissection, the ultrasound probe is used.

We reach the capsule or the scar tissue over the duct around the stone. A No. 11 blade is used to open the capsule or the fibrosis, and the stone is exposed and removed with the aid of curettes. A guide is inserted to the cavity of the stone, and a 1.3 mm Nahlieli endoscope is inserted to screen the area and to remove additional particles. A thorough lavage under direct vision is performed. After removal of the stone and the additional particles, a polyethylene stent is inserted into this region

directed from the location of the stone intraorally. The stent is fixated with 4.0 silk to the oral buccal mucosa.

In intraparenchymal stones there is no need for stent usage. The capsule is sutured with 4.0 Vicryl suture, skin closure with 6.0 nylon. Pressure dressing is applied for 48 hours. In cases where there is obliteration of the anterior part of the duct and no passage to the oral region is identified, a 1.7 mm vein line is introduced (after removal of the stone) from the location of the stone to the oral mucosa. The needle is removed, and the shaft is incised. Using a 4.0 silk suture, the vein line is fixated to the oral mucosa.

Antibiotic coverage follows the procedure. The procedure is done with the aid of magnification loops × 3.5. Pressure dressing is applied for 48 hours. The length of the procedure is 90 to 120 minutes.

Limitations

The depth of the stone from the outer skin surface should not exceed 6 mm, and screening of the surrounding tissue is mandatory for large blood vessels and for phleboliths. In the presence of deep calculi or close relation to a large-size blood vessel, we recommend exploring this region using a face-lift approach.

Postoperative Management and Care

Following interventional sialoendoscopy, a temporary polymeric stent (sialostent) (Sialotechnology Ltd., Ashkelon, Israel) is introduced into the duct and kept in place for 4 weeks (**Figs. 7–11A,B**). After placement of the stent, the surgeon continues in submandibular cases to perform a modified anti-kink procedure to correct the unfavorable angle of Wharton's duct (around the lingual nerve and the mylohyoid muscle). In the author's opinion, this is one of the main causes of the formation of sialoliths.

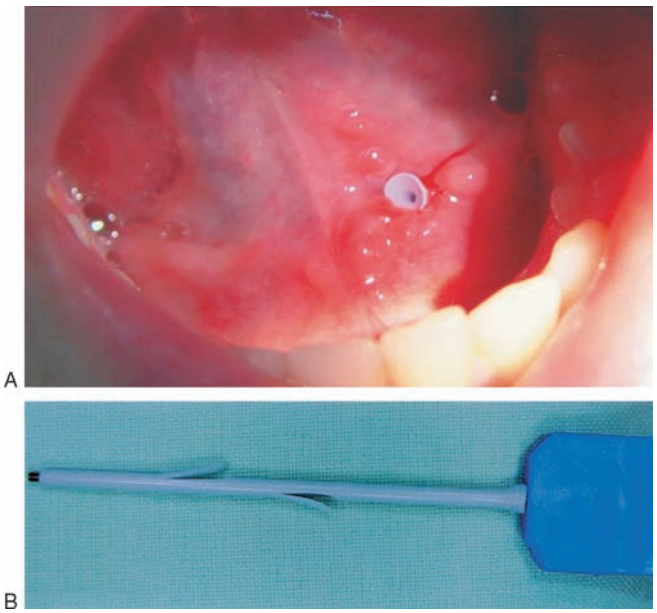

FIGURE 7–11 (A) Sialostent in the Wharton's duct after endoscopic surgical intervention. **(B)** Sialostent.

The aim of this procedure is to prevent recurrence of new stones. Ideally, a 4-week period of retention is most desirable. Its purposes are bridging the gap between the healing process of the oral region (the penetration region of the endoscope), which normally occurs very fast, and the restoration of normal function of gland, which normally takes around 2 to 4 weeks, and the prevention of the obstruction of the ductal lumen by postoperative edema. This also allows any calculus fragments to be washed out by the saliva and acts as a stent in an attempt to reduce the possibility of stenosis. Ductal marsupialization that involves suturing the incised ductal margins to the overlying incised mucosal margins can act as an adjunctive measure to provide added safety for maintaining patency of the ductal opening. All patients are treated postoperatively with antibiotics for 7 days.

Outcomes, Success Rate, Failures, and Complications

Over the past 11 years (1993–2004), sialoendoscopy has been performed on 892 salivary glands, with symptoms of obstructive disease. There have been 442 males and 450 females, with ages ranging from 2 to 96 years. There were 598 submandibular glands, 289 parotid glands, and 5 sublingual glands. Eighty-six percent of the glands were diagnosed with obstruction, and 14% with sialadenitis.

All patients underwent preoperative and postoperative screening, including routine radiography, sialography, and ultrasound. Postoperative examination was routinely performed 1 month following the procedure. Some patients were followed as much as 40 months postendoscopy. The majority of procedures were performed under local anesthesia on an outpatient basis. The time for the procedure ranged from 30 to 90 minutes.

The success rate for parotid endoscopic sialolithotomy was 86%, and the success rate for submandibular endoscopic sialolithotomy was 89%. Immediate failures (introduction of the miniature endoscope failed or proved not feasible) accounted for 1.4% of cases. Intraoperative failures (inability to accomplish any of the endoscopic retrieval techniques) were 6%, and late failures 5%. One patient suffered from temporary lingual nerve parasthesia, 1.7% suffered from postoperative infection, 0.4% suffered from postoperative bleeding, 0.9% developed traumatic ranula, and 2.5% suffered from ductal strictures.

Endoscopic Observations and Treatment in Clinical Practice

In clinical practice, several microanatomical and pathophysiological phenomena have been encountered in the course of sialoendoscopic procedures.

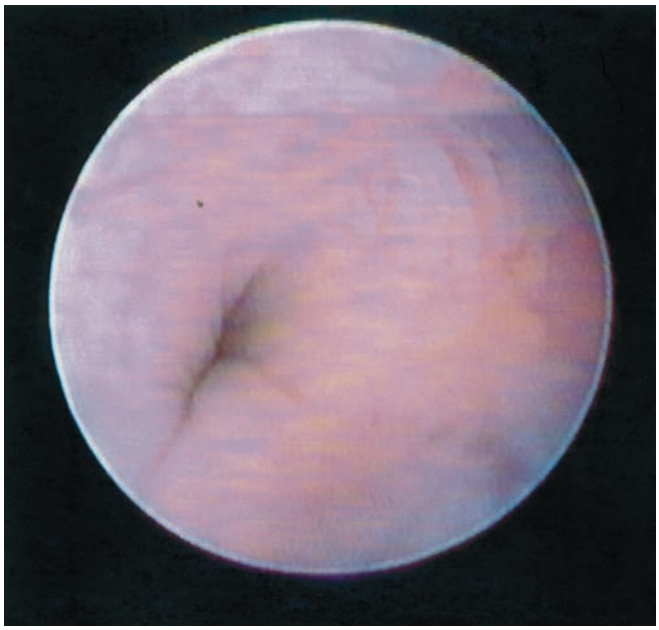

FIGURE 7–12 Sphincter-like system of the Wharton's duct in the closed position.

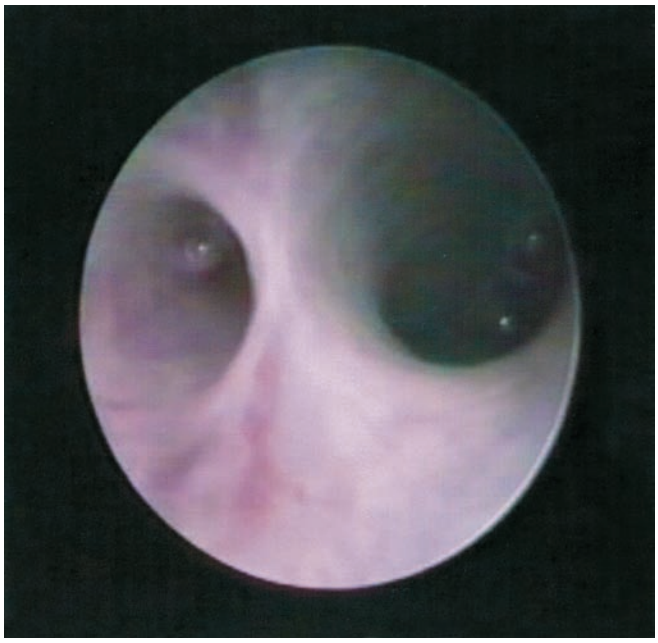

FIGURE 7–13 Open position of the duct; the submandibular gland hilum is observed.

Mason and Chisholm, in their book published in 1975, described the presence of smooth muscle strands around the walls of the Wharton's duct.[32] Katz described them in his article in 1991.[9] We were able to demonstrate this mechanism and publish in 1997[11] (**Figs. 7–12** and **7–13**). Although a search in the literature did not reveal sphincter-like mechanisms in the parotid gland, we were able to observe and document this mechanism in the Stensen's duct. The difference between the sphincter-like systems in the parotid and submandibular gland is in their location. In the Wharton's duct, the sphincter-like system begins near the papilla and runs posteriorly. In the Stensen's duct, it is located posteriorly in the vicinity of the ramification.

During sialoendoscopies we could identify in few cases the sublingual duct opening (Bartholin's duct) in the Wharton's duct. This opening was noted in the anterior part of the Wharton's duct, between 0 and 5 mm posterior to the papilla.

Typical changes in the ductal system during different states of health were noted. In chronic sialadenitis or with long-standing calculi, the lining mucosa of the ductal system had a matted appearance, ecchymosis and a small number of blood vessels. In a healthy gland or in patients with short-term stasis of saliva, there was a shiny appearance of the ductal lining, and proliferation of blood vessels was noted.

Peculiar connections between calculi and the ductal wall were observed in the submandibular and parotid glands. The connections in the Wharton's duct were found posterior to the bifurcation), the point where the duct divides into the inner and the outer lobes, whereas in the parotid gland, they were posterior to the curvature. No such connections were detected anterior to these regions.

Ductal polyps were noted in 12 glands, 8 in the Stensen's duct and 4 in the Wharton's duct. All polyps caused obstructions; four of them in the parotid gland had a history of salivary gland surgery before endoscopy, and three were associated with calculi. All the polyps demonstrated in the sialogram as a filling defect. They were not diagnosed on ultrasound. The polyps were extracted by miniature biopsy forceps or basket.

Intraparenchymal stones located close to the ductal system could be seen with the endoscope, and deeper calculi could not be observed.

We could identify seven foreign bodies in the ductal system, four in the parotid duct and three in the submandibular duct; four of them were hair shafts, and three were parts of a plant most probably (they were washed out during irrigation). Five of them were associated with calculi, and three of them were in children. We observed a formation of sialolith around a hair shaft in two cases.

Due to the more sophisticated equipment and techniques we were able now to better identify, diagnose, and treat the obstructive conditions of ductal strictures and kinks. These malformations were detected in 98 cases, 28 kinks (22 submandibular and 6 parotid) and 70 strictures (26 submandibular and 44 parotid).

We identified an anatomical malformation in the submandibular hilus, a pelvis-like formation (a basin-like structure) instead of a bifurcation or trifurcation. This pelvis formation caused obstructive phenomena

and was demonstrated as a widening of the duct in the hilus region in a sialogram.

We revealed an evagination in a 10-year-old child who suffered from two sialoliths. The sialoliths were identified in the Wharton's duct. During extraction of these calculi from the duct, the formation of an evagination was noted. It obstructed the ductal lumen and was the cause, in our opinion, of the calculi formation. We assume that the intraductal evagination is a form of anatomical malformation.

*Instrumentation (**Figs. 7–14, 7–15**)*

We have now progressed to using a semirigid, moderately flexible endoscopic device (Nahlieli Sialoendoscope) specifically designed for salivary gland endoscopy. It is 1 mm in diameter, 10,000 pixels, with two facilities: an exploration unit with an outer sleeve of 1.3 mm, and a surgical unit with a sleeve of 2.3 mm × 1.3 mm, with three channels for introducing a surgical device with a diameter of 1 mm and an irrigation port device.

Another unit is the type 1 endoscope (pistol). The outer sleeve is 2.3 mm, with a 1 mm (200 mm length) telescope, a sleeve for surgical instruments, connection for irrigation pump, and a valve for control. This type of surgical unit is for exploration following sialolithotomy of large-size stones. The surgical instruments that can be useful are instruments from 1 mm or less. The useful tools are grasping forceps, basket, grasper, balloon-like Fogarty or sialoballoon catheter, biopsy forceps, intracorporeal lithotripter probes, and laser probes. We work under direct vision, so we can use our instruments with meticulous observation. If there is a problem of space and we cannot insert the multichannel endoscope, we can insert the diagnostic unit and the surgical endoscope by its side.

The last option is to work in a semiblind technique, to identify the obstruction with the 1.3 mm diagnostic unit, to remove the 1 mm telescope, and to insert the working instrument through the sleeve. This option is indicated especially in the narrow Stensen's duct.

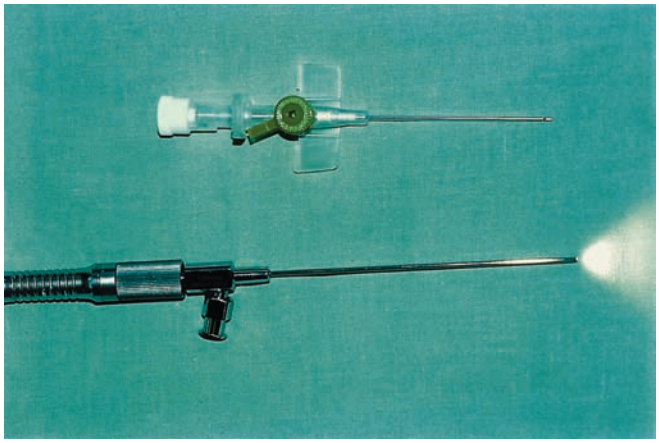

FIGURE 7–14 The 1.3 mm diagnostic unit of the sialoendoscope.

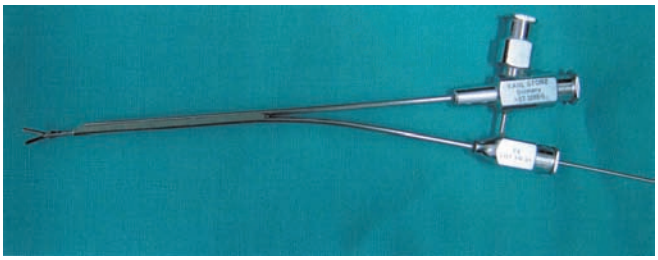

FIGURE 7–15 The 2.3 mm surgical unit with grasping forceps in the surgical sleeve.

A new innovative line of multifunctional instruments (Karl Storz, GmbH, Tuttlingen, Germany) was developed recently with the advantage of a minimal diameter, from 1.1 mm with a channel for irrigation and surgical instruments, to make the sialoendoscopy procedures easier (**Fig. 7–16**).

Choosing the Appropriate Instrument

A calculus that can be bypassed is usually best handled with the basket. Calculi that cannot be bypassed due to narrowness of space can be handled with a grasping forceps or grasper. In the author's opinion, the grasping forceps is well controlled, and the stone can be held and maneuvered easily by this instrument. Lithotripter probes are used to fragment the calculus when the other instruments fail. Balloons are good tools, especially for strictures, but also for a soft small calculus. Biopsy forceps are used for ductal polyps.

Sialolithiasis Lithotripsy

Lithotripsy for kidney stones was first reported in 1980. The first report on the use of shock waves to fragment sialoliths was in 1986 by Marmary.[33] The problems initially were due to the large lithotripsy machine that had very broad focus. They caused removal of dental fillings and periosteal irritation. There are three external lithotripsy methods depending on the system of generating the shock waves: electrohydraulic, electromagnetic, and piezoelectric. The waves are brought to focus through acoustic lenses. The shock waves pass through a water-filled cushion to the sialolith, where two

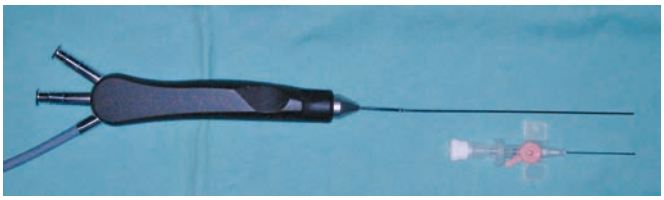

FIGURE 7–16 The 1.1 mm multifunctional sialoendoscope with integrated surgical sleeve and irrigation.

mechanisms, stress and cavitation, act to fragment the calculus. The soft tissue and the water around the stone do not interfere with the passage of the shock waves. A compressive wave is propagated through the stone, subjecting it to stress. The energy from the sialolith–water contact results in the formation of expansion waves, inducing cavitation bubbles.

When the bubbles collapse, a jet of water is projected through the bubbles to the surface of the stone. This force is enough to fragment the stone. Development of smaller machines with a more finely focused beam of waves led to a few centers in Europe using it. From 1989 we can find in the literature articles discussing the results of ESWL. The technique delivers 1000 to 5000 shock waves per session. Usually three sessions are needed. The location of the stone is identified and targeted through an inline ultrasound 7.5 MHz probe.

Reviewing the relevant literature[34–36] demonstrates a success rate from 16 to 63% for stone-free gland proven by ultrasound screening. Most authors have found elimination of the symptoms is a very significant value of the technique. Iro and colleagues achieved complete stone removal in 50 to 58% of the patients, partial elimination of the stone in 35 to 50%, and alleviation of symptoms in 76 to 100%.[34] Escudier et al found 38% stone free and 62% with residual fragments.[35] They also found stone size to be a statistically significant indicator of success, ESWL being less effective on stones larger than 7 mm. The morbidity following the lithotripsy procedures is low and includes ductal bleeding, gland swelling, petechial skin hemorrhage, and secondary infection of the affected gland.

Until recently the low success rate and the very expensive equipment were the main obstacles preventing more surgeons from using this technique. The rapid development in miniaturization of the equipment, the reduction in the equipment price, and the combination with other minimally invasive techniques gave this lithotripsy technique a place in our armamentarium in the treatment of sialolithiasis.

In 2004 we (Nahlieli and Hecht-Nakar) developed miniature ESWL (Sialotechnology Ltd., Ashkelon, Israel).[37] The diameter of the generator is not bigger than a computer box, and the therapy head was reduced dramatically to fit the dimension of the head and neck region. Ultrasound and endoscopy are used to locate the calculus. The endoscope irrigates and inflates the salivary gland using isotonic saline. Additionally, 2% lidocaine anesthetizes the entire gland and protects the salivary parenchyma, generating more substance to produce the cavitation effect. The success rate of the new lithotripter for complete removal of the stone is 63% (37% total elimination, 26% a need for simple endoscopic intervention). The elimination of the symptoms is striking: Ninety percent of the patients were symptom free following the first treatment. The endoscopic removal of the residual stones after the lithotripsy procedures is easier and less complicated. The shock waves disconnect the stone from the ductal wall and reduce the volume of the stone. In the future, as in urology, ESWL will be in many cases the first line of treatment. This treatment is adjuvant technique for deep stones in the hilum of the submandibular and in the posterior parts of the parotid gland.

Intracorporeal Lithotripsy

In this technique the lithotripsy energy is delivered to the target stone through a fine probe. Several methods used to generate the energy for the lithotripsy procedures include the electrohydraulic technique, pneumoballistic technique, dye pulsed laser, and holmium laser.[36,38] The probes are delivered to the location of the stone under the supervision of the endoscope. Electrohydraulic and pneumoballistic techniques are most effective in fragmenting the calculus to small pieces, although the particles are not always small enough for free passage through the ductal lumen. The main disadvantage of these energies is the damage of the shock waves to glandular tissues, especially using the electrohydraulic technique.[38] The holmium laser, which is a gold standard technique in urology, also causes severe damage to the surrounding tissues and can easily cause ductal perforation. Another disadvantage of this technology is the high cost of the equipment. A new and promising development in the intracorporeal lithotripsy field is a new generation of lithotripters designed especially for the salivary glands based on erbium: yttrium-aluminumgarnet (YAG) laser technology.[39] The advantage of this method is the quality of the fragmentation, to a dust that can easily be washed out from the gland with minimal collateral damage to the surrounding tissues. The fragmentation is done under endoscopic supervision and can be done under local anesthetic as an ambulatory procedure. Other important advantages of this technology are the low cost and the availability of the instruments (the basic laser unit is the same as that for dental use).

Acute Sialadenitis Caused by Sialolith

A complete blockage of the salivary duct by stone can cause a saliva collection, and this can easily be infected. The obstruction can be in the hilum region or by a small fragment of stone that was fractured and moved forward to the narrowest place in the distal portion of the duct. The infection can be moderate with swelling of the gland itself, but severe infections with spread to adjacent anatomical spaces is well documented in the literature.[40] The submandibular gland can cause severe infection

due to its anatomical location and has the potential to cause airway obstruction (see discussion in Chapter 5).

The bacterial cause of parotid and submandibular infection due to sialolith is mainly *Staphylococcus aureus*.[41] During the acute phase, probing of the involved duct is indicated. Surgical intervention during the acute phase to remove the stone (hot sialolithotomy) is documented in the literature, especially with CO_2 laser.[28] The author's personal experience is to remove the stone from the duct only if it is in the anterior part of the duct and the sialolithotomy is a simple procedure without a need for dissection.

Another situation in which the patient can benefit from hot sialolilithotomy is in severe infections from the submandibular gland with a need for incision and drainage. In all the other cases the author's preference is to ''cool'' the gland with antibiotic treatment first and to wait with the definitive surgical intervention until the gland is clear from acute infection.

Strictures and Kinks

Following the extensive use of sialoendoscopy, in our department, we encountered new pathologies that cause salivary gland obstruction. From our past and present data, it seems that strictures and kinks are the leading cause of obstruction after sialoliths. Strictures in salivary ducts have been mentioned briefly and anecdotally in the literature, whereas, kinks are a new pathology.[17]

Buckenham et al[42] and Brown et al[43] were the pioneers in the use of balloon technique under fluoroscopic guidance. The endoscopic technique simplified the dilatation techniques, as we can use less complicated instruments combined with our ability to work under direct or semidirect vision.

Diagnosis

Strictures were investigated and diagnosed by sialography and sialoendoscopy. Kinks were diagnosed mainly by sialography, and sialoendoscopy was used to rule out other pathologies and to locate the kink. Occasionally sialography, demonstrating a kink, revealed storage of the contrast dye in the area of the kink. During the postevacuation phase of the gland, blockage is noted in the same area. Strictures are quite obvious in sialogram, and they have a typical appearance in sialoendoscopy.

Treatment

Treatment techniques are based on the diagnostic progress made in identifying and locating pathologies when using the sialoendoscope.

Dilatation

The treatment of strictures is based, first of all, on diagnosing and locating the pathologic process. Dilatation can be accomplished by saline hydrostatic pressure balloons or a mini-forceps expansion maneuver. The first attempt to dilate the stricture is undertaken by saline pressure irrigation, through the irrigation port, while introducing and advancing the diagnostic sialoendoscope. If the saline pressure irrigation fails to induce dilatation, the next step is to insert a sialoballoon (Sialotechnology Ltd., Ashkelon, Israel). The sialoballoon has a high-pressure balloon tip of 2 to 4 mm in length, and an outer diameter of 2.5 Fr (< 1 mm). It can be inflated with air up to 4 mm H_2O pressure at a maximum of 18 Bar. This pressure is sufficient to dilate most of the strictures.

The balloon can be inserted in either of two ways: under direct vision, if there is enough space to insert the sialoendoscope and the balloon; or in a semiblind approach, through the telescope channel of the diagnostic sialoendocope in a semiblind technique. Another technique for dilatation of strictures is to expand the involved region with the use of miniature grasping forceps. The technique involves the use of the grasping forceps as a dilator, in that the opened grasping jaws are gently moved in a retrograde fashion along the inner wall of the stricture region. Following the procedure, we inject 100 mg of hydrocortisone solution intraductally.

A sialostent can be inserted to assist in preventing re-creation of strictures; the stent is kept in place for 4 weeks. All patients are treated postoperatively with amoxicillin 1.5 g per day for 7 days.

Anti-kink Procedure

The treatment of kinks, as in strictures, is preceded by a careful diagnostic workup to provide accurate localization of the pathology. In the submandibular kink, a balloon performs contouring of the kink. The next step ahead is the advancement ductoplasty. This is performed by stripping the duct and removing ~ 5 mm of the anterior part of the duct, pulling it anteriorly, and inserting a sialostent. The anterior edge is sutured to the mucosa and periosteum near the lingual side of the anterior teeth with 4.0 Vicryl suture. For additional support, a 3.0 silk suture is inserted through the oral mucosa lining and the ductal layer and connected to the anterior teeth. The whole maneuver means to extend the angle of the kink. The procedure is completed by injecting 100 mg hydrocortisone into the kink region through the sialoendoscope.

In the event of a parotid kink, the procedure includes balloon contouring, placement of the polyethylene stent, and hydrocortisone injection. All patients are treated postoperatively with oral antibiotics for 7 days. All these procedures are performed under local anesthesia on an outpatient clinic basis.

Conclusion

Sialoendoscopy is a promising new method for use in diagnosing and treating many inflammatory conditions of the major salivary glands. It is an outpatient procedure, utilizing local anesthesia and without major complications. It appears to be the future solution for the management of perplexing inflammatory salivary gland pathology. As more surgeons become involved with endoscopy, more findings and innovations will be forthcoming, adding to its effectiveness.

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8

Pediatric Salivary Gland Disease

RICHARD J. SCHMIDT, STEVEN P. COOK, AND JAMES S. REILLY

The spectrum of diseases of salivary gland origin in children is both different and perhaps less common than that seen in adult populations. However, the anxiety to parents and to pediatricians caused by the presentation of a swelling in the face, oral cavity, or neck will always be high. An attentive, thorough, and thoughtful workup will reassure the family and lead the child safely to the correct series of tests. Basic knowledge of the anatomy, the embryology, and the more common pediatric conditions and their presentations will guide the physician to achieve the correct diagnosis and initiate treatments. The physician must be cognizant that most salivary gland diseases in infants and children are not treated with surgery.

Embryology and Anatomy

The six major salivary glands arise as ectodermal outpouching of the oral mucosa during the sixth to eighth week of gestation. These glandular elements expand into the intercalated ductal structure and eventually into acinar cells.[1] The parotid gland is the first and the largest of the major salivary glands to develop. Located just in front of the pinna, the parotid gland extends inferiorly from the zygomatic arch, posteriorly to the pinna and cartilage of the tragus and ear canal, and anteriorly over the ascending ramus of the mandible and on to the body of the masseter muscle. The inferior border of the gland tapers to lie in the groove between the sternocleidomastoid muscle and abuts the inferior edge of the body of the mandible. The parotid gland is tightly sheathed in the parotid-masseteric fascia, causing slight and poorly defined swellings of the cheek when the entire gland is diseased.

The parotid gland also serves as the host for the main trunk and branches of the facial nerve as the nerve exits the skull at the stylomastoid foramen, and travels laterally and anteriorly within the substance of the parotid gland to reach the delicate muscles of facial expression. These branches of the facial nerve create an arbitrary division of the gland when explored surgically and has significance in that the deeper portion of the parotid gland can extend beneath the styloid process and into the parapharyngeal space. Large tumors or masses of the parotid gland may enter the parapharyngeal space and can displace the ipsilateral tonsil fossa into the oropharynx and cause airway symptoms.

The parotid gland is tightly encased between the superficial and deep layers of the investing fascia. The septations within the parotid gland prevent the spread of infection both within and outside the gland, even when suppuration develops in lymph nodes within the parotid gland.[2,3]

The parotid duct exits from the gland and passes across the masseteric muscle before turning medially through the buccal fat pad to enter the oral cavity as the Stensen's duct orifice. The duct's opening is opposite the primary molar dentition in the child under 10 years. In the older child it is adjacent to the second maxillary molar tooth as in the adult.

The submandibular gland is a rubbery, oval shaped mass bound between the anterior and posterior borders of the digastric muscle. The submandibular gland approaches and goes medial to the body of the mandible, again dividing into a larger superficial lobe

and a smaller deep lobe. The anterior extent of the gland envelopes the posterior border of the mylohyoid muscle and permits the submandibular duct to turn sharply and medially to reach the floor of the mouth, just lateral to the lingual frenulum. The punctum of this gland is identified by the Wharton's duct orifice.

The smallest and least clinically significant of the six major salivary glands are the paired sublingual glands that lie just medial and inferior to the punctum of the Wharton's duct. Approximately 10 small ducts separately enter the floor of the mouth from the sublingual gland. If the ducts are coalesced into a single entity, the duct is renamed the Bartholin's duct and joins with the Wharton's duct inferior to the openings on the floor of the mouth.

Saliva

The secretions of the salivary glands provide over 100 to 500 mL of complex fluid to the oral cavity each day. The saliva provides protection and brings moisture to the mucous membranes of the oral cavity, provides sustenance for young tooth buds and deciduous teeth of the alveolar ridges, and prevents the muscles of the tongue from drying and cracking. A dry oral cavity in an infant or young child is one of the earliest and most important signs of dehydration in a young infant, and a frequent portend of death in countries where cholera is endemic to youth and infant populations. Thirst modulates fluid intake effectively when adequate supplies of safe drinking water are available.

Saliva aids in protection from both local and systemic infections by preventing bacteria from entering the mucosal barrier to the head and neck. Secretory immunoglobulins, which are produced in the tonsils and adenoid tissue, migrate into the major salivary glands. The subunits of immunoglobulin A (IgA) then are expressed with a specific antigen-recognizing configuration to combat diseases that may come in contact with the saliva-moistened mucous membranes. Saliva also contains lysozymes, lactoferrin, and minerals to assist in the post-eruption maturation of the primary and secondary teeth. The calcium and phosphate protect against plaque. Erosion of the incisor teeth in infants can commonly occur from sucking too long on the nipple of a sugary solution within a baby bottle.

Hyposalivation

Dry mouth can occur acutely from dehydration, and assessment of the mucous membranes within the oral cavity is an important physical finding. Intervention is best dealt with by immediate oral, nasogastric, or intravenous rehydration. Infusions and bolus delivery of fluid can be quite rapid because young children have a very strong cardiovascular system and can handle moderate fluid overloads. Rarely, intraosseous fluid administration can be an alternative method of fluid intake. Severe dehydration will quickly lessen salivary gland output, which further dries the oral membranes in the mouth. Stasis and thickening of salivary gland secretions predisposes them to infection or abscess formation (e.g., suppurative parotitis).

Complete agenesis of salivary gland tissue in the infant and child is extremely rare and leads to severe xerostomia and loss of teeth.[4] Diagnosis is confirmed by magnetic resonance imaging or by radionucleotide studies. Hypoplasia of one salivary gland is rare and not associated with xerostomia.

Chronic conditions that lead to a potential decrease in salivary gland output include diabetes mellitus and hypertension.[5,6] Insulin appears to have a direct relationship with salivary gland function in young children.

Radiation therapy for pediatric head and neck malignancies will cause damage to the salivary glands and a subsequent increase in caries within the dentition. Meticulous care of all dental issues and application of dental sealants are both very important prior to commencement of radiation therapy. Squamous cell carcinoma of the nasopharynx, lymphomas, and sarcomatous bone tumors of the mandible, maxilla, or nasal bones are all major risk factors for secondary salivary gland impairment.

Several classes of drugs will induce dry mouth. The perioperative use of the anticholinergic drug atropine is a common example. Postganglionic sympathetic blocking agents have a similar effect. Antidepressant medications that are dibenzoxepine derivatives, including amitryptiline and imipramine, have similar effects on salivary gland secretions. Important mood drugs may need to be discontinued if the side effects are too severe. Titrating medications to reduce drooling may lead to unpleasant dryness of the oral cavity and result in cessation of the medications use and potential benefits.

Intranasal decongestants and antihistamines employed for allergic rhinitis may also cause some dryness of the mouth, but the symptoms are mild and do not result in injury to the oral mucosa. Several medications used to control systemic hypertension may result in chronic mild degrees of oral dryness.

Saliva may change in physical or chemical composition and may go unnoticed if the change is gradual over weeks or months. Patients, particularly children, may not complain. Saliva is generally tasteless, because of a low concentration of glucose and sodium. Active secretion of iodine into the saliva may produce a metallic taste sensation. Cystic fibrosis, which is the most commonly inherited disorder for children, is associated with excessive amounts of salivary calcium

and phosphorus. This disorder predisposes to dental calculi and not salivary calculi.[7] Diffuse parotid swelling without infection in a child less than 2 years old should prompt a sweat chloride test. Salivary levels of uric acid also increase with gout, which is very rare in children, and can produce salivary gland calculi.[8,9] Prader-Willi syndrome (psychomotor and growth retardation, hypotonia, hypogonadism, short stature, and obesity) is associated with a thick saliva.

Overall, chronic xerostomia is quite rare in infants and children.

■ History and Physical Examination

The history that leads us to suspect salivary gland disease is defined by symptoms of pain and facial/neck swelling during eating and physical findings that are localized to the major salivary glands or to the oral cavity. Most families bring their child to their family physician or emergency department. Persistent disease will often prompt referral to a specialist.

If the swelling is unilateral, then viral parotitis, obstructions to the ductal system, or adenitis from glandular infections within the parotid is suspected. Bilateral swelling is more commonly associated with systemic diseases, such as sarcoidosis, cystic fibrosis, diabetes mellitus, and starvation. Most of the swelling that is associated with subtotal salivary duct obstruction comes from distention of the ducts and gradually reduces over 2 to 4 hours. The child will refuse to eat because this is painful.

Infections that are sequestered within the lymph nodes that are intimately connected with the submandibular gland or the parotid gland will generally give rise to skin changes of the surrounding tissues. First, there is swelling and erythema. The skin color slowly darkens and becomes red-purple. These changes foreshadow necrosis of the skin and generally lead to suppurative breakdown of the skin with purulent or serous drainage. Inflammatory conditions do not subside quickly, but will subside over 2 to 7 days.

If calculi are the cause, the stone may pass through the duct; this will give immediate and complete relief of symptoms. Unfortunately, this occurs very rarely. Recurrent parotid and submandibular swellings can occur either from stones or from poorly understood inflammatory conditions. Viral parotitis, bacterial sialadenitis, or autoimmune conditions that attack the salivary gland elements must be considered. Exact and reliable clinical tests to confirm these conditions are often lacking.

Physicians are now much more aware of the risk of human immunodeficiency virus (HIV) disease that can be transmitted to infants and young children through maternal exposure, from sexual activity or intravenous drug use. Bilateral enlargement of the salivary glands can occur primarily from HIV, from secondary infection within lymphoepithelial cysts arising within the substance of the parotid gland.

During the physical examination, parents are always protective of their child, and young children tend to be apprehensive. Therefore, careful and gentle inspection is reassuring to both parent and child. Younger children are most comfortable on their parent's lap. Often, the parent can map out with their index finger the side and site of the swelling. Parents will often be able to estimate the size and describe any associated skin changes of the face and neck. The parents are also very helpful when questioned about skin lesions on the trunk or the extremities because they examine their children regularly with baths and clothing changes.

Palpation should begin only after all information that inspection permits have been obtained. Also, it is important to start with the noninvolved or nontender areas. Gentle, soft, and light fingertip pressure should be applied in a reassuring and nonthreatening fashion. The examiner generally has only one chance to establish reassurance and confidence with the child and the parents. If the child is too fearful to be examined, the examiner may wish to go directly to imaging, which in children is most often accomplished with sedation.

For the older and more mature child, the face and neck are touched, and bimanual palpation is always essential for salivary gland disease. The glands should be carefully palpated for tenderness, areas that are soft and fluctuant, and the mobility of the overlying skin. Granulomatous disease, particularly nontuberculous mycobacterium or sarcoidosis, should be evaluated with skin purified protein derivative (tuberculin; PPD) and chest films. Adenitis of the glands will cause asymmetric swelling.

Bimanual palpation of the salivary gland ducts is critical for complete examination. The ducts are where small calcifications may be detected. These can be only millimeters in size and can slip in and out of the gland itself. Therefore, the gland is massaged from posterior to anterior and from lateral to medial. Small stones, thickened secretions, or blocked puncta can be assessed only when the bimanual palpation is performed in conjunction with careful intraoral visualization of the salivary duct flow and the appearance of the puncta. This part of the examination should be done toward the end because it may evoke some pain and requires very good visualization of the buccal mucosa for the parotid gland and of the floor of mouth for the submandibular and sublingual glands.

Malignant tumors are firm, minimally tender, and can be aggressive and grow quickly. Regional adenopathy

should be investigated by palpation. Malignant tumors will often spread outside the gland, invade the fascia, and be fixed to the surrounding muscle, fascia, or bone. The integrity of the surrounding nerves is essential to evaluate. Weakness or asymmetry of the face, lips, tongue, or neck muscles generally means malignant disease. Consultation with pediatric oncology specialists is essential because many pediatric tumors are treated by clinical trials. Malignant tumors in childhood are very rare, but aggressive growth is often seen when these tumors occur.

Photo documentation is also recommended. This can be done with digital cameras and retained in the electronic medical record for reference and consultation use.

Laboratory Examination

Evaluation of infectious etiologies of salivary gland disease most often involves several laboratory tests. Most often a complete blood count (CBC) with differential diagnosis is obtained. Sedimentation rates and C-reactive protein values are helpful to confirm acute inflammation. HIV testing is useful, particularly if there is bilateral symmetric parotid swelling.

When there is immunodeficiency disease or if there is exposure to a member of the household with tuberculosis (TB), skin tests for TB and/or anergy should be undertaken. Also, multiple views of the chest are very valuable, looking for hilar adenitis.

If there is purulent discharge from Stensen's duct or Wharton's duct, a direct culture should be obtained. However, because the cultures are often contaminated with oral flora, the therapy should have strong gram-positive coverage for *Staphylococcus aureus* and streptococcal species.

Cytological and chemical analysis of saliva and tissue secretions is rarely available or applicable for children. Few pediatric centers see a large case load of malignant disease of salivary gland origin. Therefore, these techniques are not used often enough to maintain and improve skills. Cannulation of the pediatric salivary duct also has been very difficult and is not often performed.

Fine-needle aspiration and cytology, however, have merit, even in children. Cytologic aspirates will require a light, fast general anesthesia. However, when malignancy is suspected and the risks of an open biopsy seem high, this technique will often yield the correct diagnosis when placed in the hands and microscope of an experienced pathologist.

Open biopsies are still preferred when the lesion is demonstrated to be unilateral and confined primarily or exclusively to the lateral lobe of the parotid gland. The submandibular gland can be removed easily, and excisional biopsy should be suggested early if there is a suspicion of malignant disease. Complete removal provides sufficient material and analysis of the tumor borders to better assess prognosis and completion of the excision of the mass. Facial nerve integrity monitors are potentially helpful. Proper surgical technique to identify the trunk of the facial nerve and other anatomical structures adds safety to the surgical experience.

Radiographic Imaging Techniques

Imaging for infants and children involves a variety of techniques (see Chapter 2), from simple plain radiograph films to more sophisticated images, such as computed tomography (CT) scans and magnetic resonance imaging (MRI). Reliable and accurate imaging requires two different elements. First, will the child be awake and immobilized? Second, can sedation be safely and adequately administered to obtain an optimal study? Skilled centers that diagnose and treat high volumes of pediatric patients will most reliably result in a satisfactory study and a happy family and child.

Awake studies include plain radiographs, ultrasounds, and CT or MRI in children 5 years of age or older. Special-needs children, even adolescents, will often require sedation at a site that is in proximity to the imaging department.

Plain films are easy and generally reliable to evaluate the underlying bone structure of the mandible and the skull base. Most plain films are obtained as anteroposterior, lateral, or oblique views. The positioning is important to avoid calcifications that may be hidden by overlying bone structures. Submandibular stones are more often calcified and identifiable (4:1). Dental occlusive views of the floor of mouth are best for submandibular stones. Evaluation of the integrity of the primary and secondary teeth is essential when the area of disease is adjacent to the body of the mandible. Odontogenic abscesses often cause swelling over the mandible or the buccal cheek area.

Sialography is used to image the ductal system, but it is rarely available for children. Placement of catheters within the ducts is very time-consuming, is met with resistance by the child and adolescent, and generally results in high levels of anxiety and frustration. Sialography is optimal for evaluation of ducts for ectasia, strictures, and stones.

High resolution ultrasonography is an effective method to evaluate salivary glands. The parotid gland can be very well visualized. Structures reliably identified include the gland and ductal system, plus the surrounding tissues, including the sternocleidomastoid muscle, mastoid tip, styloid process, carotid sheath, and posterior facial vein.[9] Small punctated areas of ductal disease,

such as ectasia, can be readily identified as echogenic images through out the gland.[10,11]

Ultrasound is also favored because this is a rapid tool to evaluate adenitis and to determine whether the node is within the parotid or submandibular gland or extrinsic to it. The node is evaluated for size and whether the center is necrotic and hypoechoic. There is also the loss of central blood vessel flow on color-flow Doppler that confirms the presence of purulent or necrotic material within the mass.

Ultrasound is safe for repeated use in children because of the absence of ionizing radiation. Young parents are also very comfortable with the ultrasound technology because they may have already experienced this technique, which is often performed during pregnancy. Imaging techniques permit accurate measurement of the mass or nodes and allow sequential measurements over days, weeks, or months to assess progression or regression of the lesion.

CT scans with contrast are the diagnostic image of choice for most pediatric-age lesions.[12] New and faster CT machines provide completed images and scans within a 5-minute window. Less sedation is required, and many children as young as 4 years of age can cooperate fully. Although there is some radiation exposure, the value of CT images lies in the excellent detail and the ability to alter the contrast of the window to enhance viewing bone, soft tissue, and vascular details.

MRI provides exquisite soft tissue detail and is sensitive enough to demonstrate not only the gland tissue but also the route of the facial nerve within the gland.[13] The different spin ratios (T1, T2) permit variations in signal intensity; this leads to recognition of different tumor tissue types. Mixed tumors can be suggested by imaging characteristics. Vascular malformations within the parotid gland, most commonly hemangiomata, are high flow, parenchymatous lesions of intermediate intensity on T1-weighted images and of high intensity on T2-weighted images. MRI techniques are considerably slower than CT. Therefore, children will often need sedation and sometimes general anesthesia for more extensive studies of the torso or head.

■ Pathologic Conditions

Suppurative Parotitis

Bacterial sialadenitis is an acute infection of the major salivary glands that is associated with fever, swelling, and tenderness over the involved gland. The saliva is thickened and purulent, when expressed through bimanual palpation. The salivary punctum will be swollen and erythematous. The infection most often occurs in the very young or weakened infant or child. Purulent parotitis is seen in premature infants, chronically ill children with cerebral palsy or neoplastic diseases, and in poorly nourished children who have undergone major surgical procedures where atropine is administered.

The uncommon neonatal suppurative parotitis is seen mostly in premature babies and male neonates. The higher mucus content and its bacteriostatic protection result in fewer infections of the submandibular gland. Infection can be an oral cavity–derived retrograde ductal infection or from a blood-borne etiology. Fever, anorexia, and failure to thrive are coupled with initially unilateral and subsequent bilateral parotid swelling and tenderness. Parenteral antibiotic coverage for *S. aureus* and gram-negative bacilli is started until culture results are available. Poor response to medical management is treated with drainage.

S. aureus, S. viridans, S. pneumoniae, and *Bacteroides* species account for most cases of parotitis in children.[14] The parotid gland is more frequently infected, and reports relate this to a higher serous content in the parotid gland saliva when compared with that in the submandibular gland.[15] Antibiotic therapy focuses on medications with excellent gram-positive coverage and is combined with very good hydration, as the two main pillars of therapy. Intravenous antibiotics, such as ampicillin/sulbactam, are required for any serious infection with persistent symptoms after 24 hours of oral therapy. Warm compresses, sialagogues, and gentle massage from the gland to the duct's orifice (e.g., milking the gland) are important.

When the medical therapy is not successful, small abscesses may form. These will often require aspiration or incision and drainage. The surgical procedure depends on localizing the abscess with ultrasound or by CT image techniques and may be best performed in conjunction with an interventional radiologist. Occasionally, the abscess may point near the tragal cartilage or even into the external auditory canal through the fissures of Santorini.[16] Dental and periodontal infections are much more common than parotid gland abscess and should be excluded by obtaining dental films in cases where the physical findings are not clear.

Recurrent Parotitis of Childhood

A more common illness is recurrent parotitis that is generally thought to be bacterial and suppurative in nature, but clinical confirmation of this is often absent. What is known is that the condition occurs more often in boys, generally between 3 and 10 years of age. The episodes can reoccur either weekly or monthly, lasting days to weeks. Histological appearance includes dilated intraparenchymal ducts with periductal lymphocytic infiltration.

The treatment and the diagnostic workup tend to remain empiric, and children with persistent disease are often imaged with CT scan. The CT will often show ectasia of the ductal system from chronic inflammation. Serial ultrasounds of the parotid gland are safe and very often useful to identify the presence or absence of intraparenchymal disease.

Empiric therapy with gram-positive coverage is started, and there is often relief of symptoms within 48 hours. Some studies have shown positive cultures of *S. pneumoniae, S. aureus,* and *Haemophilus influenzae*. *S. viridans* has also been reported.[17,18] Supportive care is generally all that is needed with the antibiotics. There is speculation about dental trauma, localized strictures of the ducts, or autoimmune etiologies, but few findings occur to confirm these theories.[18]

Primary management for persistent cases uses serial dilatations of the Stensen's duct and forcing the child to consume adequate to large amounts of fluids to ensure adequate hydration. Most cases resolve during adolescence, and surgical intervention is not common.

Viral Parotitis

Historically, mumps parotitis constituted the most common cause of parotid enlargement, and in the prevaccination era accounted for its alternate name *epidemic parotitis*. It was once a common disease of childhood, producing epidemics among children, with a peak age range of 4 to 14 years. It continues to be the most common viral infection of the salivary glands and most frequently affects the parotid gland. Mumps is caused by a *paramyxovirus*, which is spread by airborne respiratory droplets and is highly contagious. The virus incubates in the upper respiratory tract and parotid gland for a period of 2 to 3 weeks prior to the development of clinical signs and symptoms, and viral shedding can occur for 1 week after the onset of symptoms. Clinically, the patient first experiences constitutional symptoms of fever, malaise, headache (headache is associated with a pleocytosis of the cerebral spinal fluid in 10% of children), neck pain, and myalgias, which are followed by the development of unilateral and then bilateral parotid swelling and pain that is exacerbated by eating. In $\sim$30% of children, the salivary gland swelling may be minimal. The other classic manifestation of mumps infection is orchitis, which causes significant discomfort in the acute phase and may be complicated by infertility in the long term. Other potential complications of mumps include encephalitis, pancreatitis, nephritis, and sensorineural hearing loss.

The diagnosis of mumps parotitis is largely clinical, based on the classic presentation of a young patient with bilateral painful parotid swelling (and rarely submandibular swelling) and often in the context of an outbreak of mumps in an unvaccinated population. That said, the diagnosis may be confirmed by serologic testing consisting of hemagglutination antigen testing, mumps A and C antibodies, or complement fixation testing, or by isolating the virus from urine. If serology for paramyxovirus is negative, antibody titers for other viral agents should be obtained. The virus can be isolated from the saliva from 7 days before and up to 9 days after the onset of swelling. The mumps skin test is not helpful as it does not become positive for 3 to 4 weeks after viral exposure. As with many viral syndromes, treatment of mumps is largely supportive. Similar to the treatment of other etiologies of sialadenitis, special attention should be paid to keeping the patient well hydrated, not only to support the patient through the systemic viral infection, but also to assist with good saliva production and flow. Comfort measures such as analgesics and warm compresses may be used. One should note that the swelling of the glands, which may be significant, can take weeks to resolve, but it does typically resolve completely. The patient should be followed for chronic sequelae of the infection, including chronic sialadenitis, infertility, and hearing loss. The vaccine given in combination with measles and rubella vaccines is administered at age 12 months. Viral parotitis now is very rare due to the efficacy of measles, mumps, and rubella (MMR) vaccines. The vaccine is very effective, with a 97% serum conversion rate of over 95%, and the annual incidence of parotitis continues to decline to fewer than 500 cases annually in the United States.[19]

Human Immunodeficiency Virus

Human immunodeficiency virus infection in children causes a wide spectrum of disease with varied clinical presentation (see Chapter 5). Acquired immunodeficiency syndrome (AIDS) represents the most severe end of the disease process. Parotitis may be present in the earlier stages of the HIV viral infection. Generalized lymphadenopathy often accompanies the mildly symptomatic child, and the presence of cytomegalic viral infection before 1 month of age or oral candidiasis suggests a moderately more aggressive presentation.

Almost one third of children with HIV will have parotid gland enlargement due to lymphocytic infiltration of the gland.[20,21] Adenitis within the parotid gland and intraparotid B cell non-Hodgkin's lymphoma are manifestations of malignant transformation from HIV.[22]

Cytomegalovirus Infections

Some authors have reported primary postnatal infections of the parotid gland with cytomegalovirus

(CMV).[23] CMV is highly species specific, and only human strains produce human disease. Horizontal transmission is the result of salivary gland contamination. Excretion rates can be as high as 70% in the 1- to 3-year age group. Some young children can transmit the disease to their parents. Most often the involvement of the major salivary glands is transient and uncomplicated.

Stricture

Narrowing of a major salivary gland duct may result from faulty chewing habits causing trauma to the punctum, calculi within the duct, or external trauma to the duct. Rarely, multiple strictures may occur as the sequelae of a pneumococcal infection involving the duct. The clinical presentation is one of swelling in a single gland during a meal as reflex secretory pressure increases. This swelling may be associated with pain. As the reflex stimulation decreases, the gland slowly empties, and the swelling subsides. Generally, this takes around 2 hours.[3]

Sialography can be used to diagnose strictures. Dilatation of the duct proximal to the stricture may be seen in long-standing cases (obstructive sialodochiectasis). Strictures may be treated with simple dilation of the duct. Sialodochoplasty is an alternative for refractory cases, with gland excision performed as a last resort.[24]

Sialolithiasis

Although salivary calculi are relatively common among the general population, they are uncommon in children. The reason for this is not completely understood, although the lower salivary calcium concentration and higher rate of salivary flow in children may protect against calculus formation.[25]

Sialolithiasis appears to be related to local factors and affects the submandibular gland much more often than the parotid gland.[26,27] This is most likely related to the higher calcium concentration, more alkaline pH, and higher mucin content of submandibular saliva. Further, the long, superiorly directed course of Wharton's duct is more conducive to stasis of secretions than is Stensen's duct.[27]

In the pediatric population, boys are affected 3 times as often as girls are. The average age at presentation is 10 years, and many have been symptomatic for a prolonged period of time before the diagnosis is made. Symptoms can range from a slight tenderness in the floor of the mouth to acute sialoadenitis. The most common presenting symptom is submandibular swelling, often associated with pain, which increases with eating and gradually improves afterward.[28]

The diagnoses can frequently be made on physical examination with bimanual palpation. Radiography should be obtained, even if a stone is palpated, as multiple calculi may be present. Intraoral occlusal radiographs are useful in detecting calculi in the anterior two thirds of the duct, although distal oblique occlusal radiographs are required to evaluate the posterior one third of the duct.[28] Alternatively, noncontrast CT scans through the floor of the mouth may be useful in identifying calculi throughout Wharton's duct and in the gland itself. Sialography or ultrasound may aid in the diagnoses of radiolucent calculi.[27]

A calculus may occasionally pass through the orifice of Wharton's duct, either spontaneously or with the use of foods to stimulate salivary flow. If this does not occur, dilation of the duct and sialolithotomy are treatment options. Calculi in the posterior one third of the duct or in the gland itself can be treated with sialadenectomy.[27]

Cysts

Salivary gland cysts may be acquired or congenital. Acquired salivary cysts develop secondary to trauma or inflammation, or occur as retention cysts. In addition, a neoplasm may undergo cystic degeneration and radiographically mimic a salivary cyst.

Congenital Cysts and Dysgenetic Salivary Glands

Congenital cysts generally involve the parotid gland. These lesions include dermoids, branchial cleft cysts, and branchial pouch cysts. In general, these lesions can be difficult to distinguish from one another, and definitive diagnosis is often deferred until after pathologic analysis.[29]

Dermoids of the parotid gland may appear as an isolated cystic mass. Dermoid cysts of the floor of the mouth, unlike the ranula, present in the midline. Treatment is by complete surgical excision with facial nerve preservation. Keratinizing squamous epithelium with skin appendages lining the cyst is seen on pathologic analysis of these lesions.

The fetal branchial apparatus is a foregut derivative that develops in the second week of fetal life consisting of four ectodermal clefts, five paired pharyngeal arches, and four endodermal pouches. Less than 5% of branchial anomalies are first branchial cleft malformations. First branchial cleft cysts or fistulas present from the external auditory canal to the angle of the mandible. First branchial cleft cysts have been further classified by Work[29] as type I and type II lesions. Type I cysts are duplication anomalies of the membranous external auditory canal (derived from ectoderm) and occur deep within tissue adjacent to the pinna, external auditory canal, and parotid gland. They have a tract to the membranous external auditory canal. Histologically,

they are cysts lined by squamous or ciliated columnar epithelium and are associated with lymphoid tissue. They can be histologically indistinguishable from benign lymphoepithelial cysts, and diagnosis is assisted by discovery of a sinus tract. The clinical or histological identification of a sinus tract may confirm branchial cleft origin. The less common type II cysts are duplication anomalies of the external auditory canal and pinna (derived from ectoderm and mesoderm). Often there is an associated sinus tract and stoma opening into the upper neck. They run parallel to the external auditory canal, but they do not have a tract to the membranous external auditory canal. These cysts contain squamous epithelium with skin appendages, as well as cartilage, and can be found either medial or lateral to the facial nerve. Both types of first branchial cleft cysts are associated with repeated infections.

Complete surgical excision with facial nerve preservation, after the acute infection has subsided, is the treatment of choice. In type I first branchial cleft cysts the tract is dissected from the external auditory canal, often using a probe. The excised tract in the external auditory canal can be sutured if small or allowed to granulate and heal by secondary intention. A gauze pack with antibiotic ointment is placed in the external auditory canal. Identification of the facial nerve is essential (**Figs. 8–1, 8–2, 8–3**).

Branchial pouch cysts are rare lesions that occur in the parotid region, often deep in the retromandibular region. Complete surgical excision with facial nerve preservation is the treatment of choice. Congenital ductal cysts present as parotid swelling in infancy. Generally, no therapy is indicated unless there are repeated infections.[30]

Another first branchial cleft malformation involves a patent foramen of Huschke. In the third month of fetal development the anteroinferior surface of the tympanic plate is patent, later closing with fibrous tissue. Persistence of this foramen may lead to otorrhea from external auditory canal fistulas and a parotid swelling from sialadenitis. (More commonly, it involves the temporomandibular joint with pain on chewing.) Otoscopy or endoscopy may reveal a defect in the external auditory canal, confirmed by CT of the temporal bone. In symptomatic patients with involvement of the external auditory canal and the parotid, excision of the fistula and cyst with parotidectomy is necessary to prevent ongoing symptoms.[31]

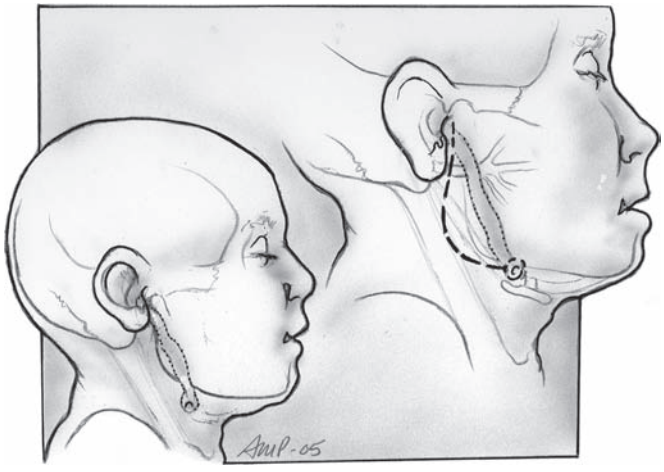

FIGURE 8–1 Type I branchial cleft anomaly.

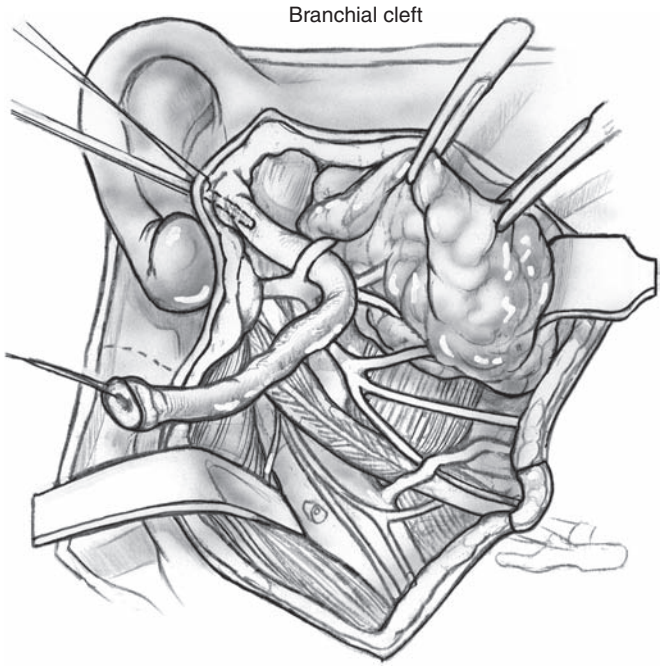

FIGURE 8–2 Excision of the tract requires exposure of the facial nerve.

Preauricular sinuses and cysts are differentiated from branchial abnormalities. They are related to fusion of the ectodermal hillocks from the first and second branchial arches in formation of the auricle. Their location superior to the tragus suggests the tract should not involve the facial nerve. Excision is assisted with the use of a lacrimal probe. The deep plane of dissection is the temporalis fascia. A tiny piece of auricular cartilage is excised where the tract ends. For recurrent preauricular sinuses a wide suprahelical incision down to the temporalis fascia with removal of tissue superficial to this fascia is recommended.

Dysgenetic salivary glands, including the rare congenital polycystic parotid gland, manifests with cysts of varying sizes, with duct differentiation that may include primitive duct buds of the embryonal period or mature intercalated or striated ducts. Duct lumens may contain spheroliths, microliths, or degenerative changes with desquamation. Remnant acini are present between cysts,

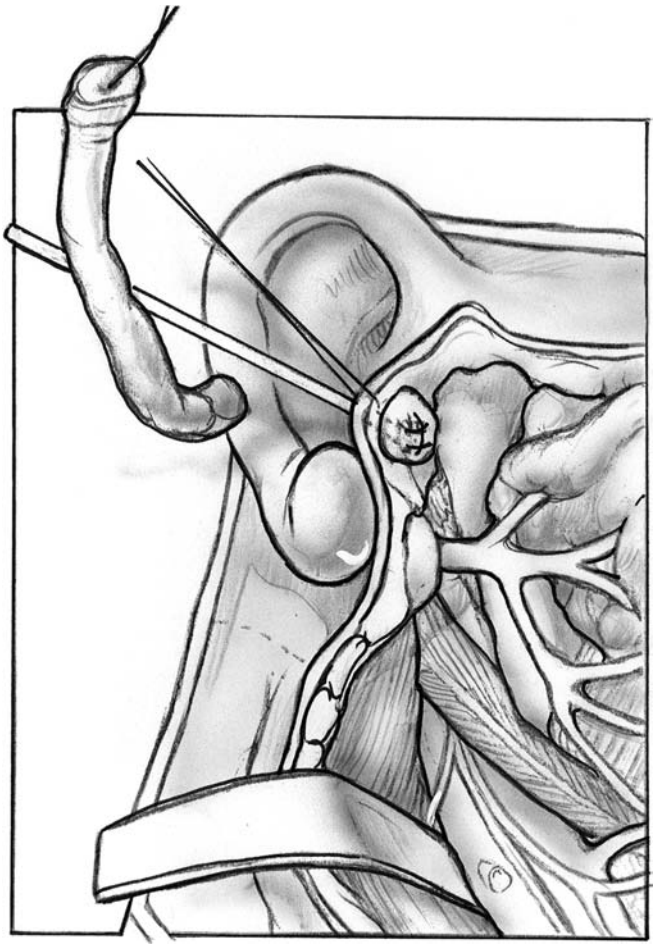

FIGURE 8–3 The external auditory canal defect is sutured.

with no inflammatory cells present. Congenital sialectasia may be unilateral or bilateral and with stagnation of secretions may lead to recurrent sialadenitis. Conversely, duct atresia is rarely reported in submandibular glands. Congenital salivary hyperplasia must be distinguished from sialosis.

Acquired Cysts

Mucoceles are pseudocysts that can occur anywhere that minor salivary glands are found, although the lower lip is the most common location reported. The most common presentation is of a painless, fluctuant swelling. A mucocele develops via extravasation of mucin. Pseudocysts form when salivary secretions leak into surrounding tissues usually as a result of trauma to the gland. These secretions cause an inflammatory reaction, which leads to the formation of a wall composed of granulation tissue. Retention cysts occur when there is obstruction of the salivary duct resulting in its expansion and the formation of a true epithelial-lined cyst. Extravasation mucoceles are more common than retention cysts in young people. This distinction is somewhat academic, however, as the treatment is the same for both lesions. Complete surgical excision along with the associated glandular tissue is the treatment of choice.[32]

Ranula is the term used for a mucocele or retention cyst of the sublingual gland. The term is derived from the Latin word *rana* (''frog'') because the blue translucent swelling typically seen in the floor of the mouth in these patients resembles the underbelly of a frog.[33]

A ranula is classified as being either simple or plunging. A simple ranula involves the sublingual space only, whereas a plunging ranula extends posterior to the mylohyoid muscle into the neck. A simple ranula may be either a retention cyst or an extravasation pseudocyst. A plunging ranula is always an extravasation pseudocyst.[34]

The clinical presentation varies depending on the type of ranula present. The simple ranula will most often present as a bluish, nontender, fluctuant mass on one side of the floor of the mouth. Simple ranulas are mostly asymptomatic, but they can lead to airway obstruction. A soft, painless, ballotable cervical mass is the most common presentation for a plunging ranula. A plunging ranula extends from the floor of the mouth, below the mylohyoid muscle, to the neck. If a cervical cyst is present without intraoral presentation, the diagnosis is more challenging. Plunging ranulas must be differentiated clinically from lymphangioma, dermoid cysts, or hematoma. Imaging, including CT or MRI, may be useful in distinguishing a plunging ranula from a variety of other cystic neck masses.[35]

Several methods of treatment have been reported, including excision of the ranula, with or without ipsilateral sublingual gland excision, marsupialization, cryosurgery, and observation for spontaneous resolution. The latter will generally occur within 5 months, if at all.[33] Recurrence is prevented by excision of the ranula with the sublingual gland; however, one recent study found no increased recurrence rate for simple ranulas treated with marsupialization, compared with those treated with excision of the tumor and associated sublingual gland.[34] Complete excision of the lesion, along with removal of the ipsilateral sublingual gland, is the treatment of choice for a plunging ranula.[34,35] Surgery in the floor of the mouth must be cautious for the presence of Warthin's duct and the lingual nerve.

Granulomatous Diseases

Several granulomatous diseases can produce a chronic inflammatory response in the salivary glands. These are uncommon in children, compared with adults. The parotid is the most commonly involved gland. Although diffuse involvement of a gland is sometimes seen, typically patients present with a painless, slow-growing mass within a salivary gland.[36,37] Without biopsy, these lesions can be difficult to distinguish from neoplasms.

Potential etiologies for granulomatous sialoadenitis include mycobacterial infections, cat scratch disease, sarcoidosis, and actinomycosis.[36]

Infections of the salivary glands by mycobacteria other than *Mycobacterium tuberculosis* may present in a fashion similar to that of salivary tuberculosis. In children, over 90% of these infections are secondary to atypical mycobacterial infections. It presents most commonly in children under 5 years of age. There are a multitude of atypical mycobacteria that may produce salivary infection, including *Mycobacterium avium, M. avium-intracellulare, M. malmoense, M. scrofulaceum*, and *M. bovis*. The exact route by which these pathogens infect the salivary glands remains unknown; however, possible conduits of infection include the oral cavity, gingival, lips, tonsils, and throat. Infections are most commonly seen in children 16 to 36 months of age, and both the parotid and submandibular glands have been known to be involved.

The classic presentation is one of a painless, unilateral, slow-growing, preauricular or upper cervical mass, unresponsive to antibiotics, which develops a violaceous hue to the overlying skin. Progressive disease may become complicated by sinus tracts. Constitutional signs are noticeably absent. A diagnostic workup similar to that for suspected salivary tuberculosis should be undertaken given the similarity in clinical presentation. The requisite chest radiograph is negative for the cavitary lesions of tuberculosis, and the PPD is nonreactive. CT or MRI will demonstrate a mass with central necrosis. Atypical mycobacterial-specific antigens and polymerase chain reaction techniques for detection of atypical mycobacterial DNA and RNA are evolving. Diagnosis remains largely clinical and is predicated on the exclusion of other salivary mass entities. Fine-needle aspiration biopsy is preferred to incisional biopsy and will help to rule out other causes of salivary swelling; acid-fast staining is unlikely to be diagnostic, and culturing the tissue is difficult and time-consuming, taking as long as 6 weeks to grow. Incisional biopsy or incision and drainage attempts may facilitate the formation of sinus tracts and unsightly scars. Complete excision of the infected gland is considered to be curative, but there is recent evidence in favor of incision and curettage of the diseased gland. Lesser procedures, such as incision and drainage, have a high rate of recurrence.[38] Antimicrobial agents have met with limited success. Investigations as to the worth of an antibiotic trial are under way. Drugs under consideration include clarithromycin, ethambutol, rifabutin, azithromycin, and fluoroquinolones in adult populations.

In contrast to atypical mycobacterial infection, mycobacterium tuberculosis infection involving the salivary glands more often has systemic symptoms and a positive PPD. Treatment for such infections includes systemic antituberculosis therapy[36,38] (see Chapter 5). Cat scratch disease is covered in Chapter 5.

Sarcoidosis (see Chapter 5) is an idiopathic granulomatous disease, which can involve any of the salivary glands, although the most commonly affected is the parotid gland. Generally, this is manifested by gland enlargement. About 40% of children with sarcoidosis will develop parotid gland enlargement.[39] Paralysis of the facial muscles can develop when the disease invades the parotid gland. The paralysis is generally transient and may be associated with uveitis (Heerfordt's disease). Biopsy of involved glandular tissue may help to establish the diagnosis. Treatment is usually symptomatic with corticosteroids.[40]

Actinomycosis and Cat Scratch disease are covered in Chapter 5.

Endocrine and Metabolic Disorders

Enlargement of the parotid gland can be seen in up to 10% of patients with diabetes mellitus. This enlargement is due to fatty infiltration of the gland.[16] Hypothyroidism can also produce parotid enlargement. In contrast to what is seen in diabetics, parotid enlargement associated with hypothyroidism is a true hypertrophy of glandular tissue. The condition is reversible with correction of the patient's hypothyroidism. A variety of metabolic disorders, including obesity and malnutrition, are associated with parotid gland enlargement.[38] Up to 30% of patients with bulimia may have transient parotid enlargement.[41]

Neoplasms

Vascular neoplasms are the most common tumors of the salivary gland in children. Some 3.2% of all salivary neoplasms occur in children.[42,43] The same tumors that occur in adults occur in children. A solid salivary gland mass in a child is more likely to be a malignancy than in an adult.[30,42,43] Most neoplasms involve the parotid gland. Tumors in the submandibular or minor salivary glands are more likely to be malignant than in the parotid gland.[24,42] In children there is an overall higher female to male sex predilection for salivary gland tumors in general. This is also true for both benign and malignant tumors in children.[44]

Tissue diagnosis is important in the management of the salivary gland mass. Knowing whether the lesion is benign or malignant allows the surgeon, family, and patient to understand the extent of the planned operation and whether the facial nerve can be preserved.[24] If an experienced cytopathologist is available, fine-needle biopsy can serve as a useful guide to differentiate neoplasm from granulomatous disease. Sensitivity for a positive biopsy with a neoplasm is reported to be 92.3%. Specificity for a negative aspiration for tumor has been

noted to be 99%.[45] CT imaging can be used to increase the diagnostic accuracy when doing a needle biopsy of deep lesions.

Incisional biopsy of the minor salivary gland of the lip is indicated to diagnose Sjögren's syndrome. Incisional biopsy is rarely indicated for lesions of the major salivary glands, however.[44] One should assume that any solid parotid mass in a child is a neoplasm.[24] For this reason, once inflammatory disease is excluded, excisional biopsy is preferred to give the pathologist adequate tissue, avoid tumor contamination of the field, and avoid facial nerve injury. It may also be the definitive treatment.[3,43] Intraoperative frozen section examination may help with decisions during the course of the procedure.[44] Still, radical surgery with facial nerve sacrifice should not be done based on frozen section diagnosis alone.[24]

CT and MRI both have value in demonstrating whether the lesion is confined to the superficial lobe of the parotid gland. MRI demonstrates better differentiation of tumor from muscle. CT and sialography are important for the diagnosis of inflammatory disease.[46] High-resolution ultrasound can also be used to define the relationship of a parotid mass to important adjacent structures.[9]

Benign Tumors

Benign tumors typically occur within the intracapsular portion of the gland.[30] The benign mixed tumor (pleomorphic adenoma) is the most common solid salivary neoplasm and the only one that occurs with any regularity.[9,24,30,42,43,47] In contrast to vascular lesions, which are most common in infants and young children, they occur in an older age group.[30,42] The peak incidence in the pediatric age group is 10 years of age. Benign mixed tumors occur primarily in the parotid gland as a discrete mobile mass. They are usually larger than 1 cm, and they tend to enlarge slowly over time.[30] It has been noted that the delay between initial tumor detection and when medical attention is sought can be well over 1 year. Facial nerve involvement is unusual.[30] Parotidectomy with facial nerve preservation is the treatment of choice.[47] Recurrence is possible.[42,44] Long-term malignant transformation in a recurrent lesion has been reported.[44]

Other types of benign lesions are less common. Basal cell adenoma, papillary cystadenoma lymphomatosum (Warthin's tumor), xanthoma, neurolemmoma, and lipomas can be seen.[30] Neurofibromas are rare but may involve the parotid and submandibular glands in children with neurofibromatosis.[42,48]

In children less than 2 years of age, the main trunk of the facial nerve and divisions are more superficial and inferior. Beyond 2 years the mastoid tip and tympanic ring form, and the facial nerve takes a deeper position. The marginal mandibularis branch of the facial nerve takes a more superficial position over the mandible compared with adults. Facial paralysis is a significant risk in pediatric parotid surgery.

Malignant Tumors

When one excludes vascular lesions, 50% of all pediatric salivary gland tumors are noted to be malignant.[49] The majority of malignant salivary gland neoplasms in children occur within the parotid gland. Pain, rapid growth, cervical adenopathy, and facial palsy are all signs of a malignant tumor.[42,49] Malignant lesions tend to occur in older children.[49]

As in adults, mucoepidermoid carcinoma is the most common (40–50%).[30,44] In contrast to adults, however, undifferentiated malignancies are more common in children.[42,47] High-grade lesions are aggressive and solitary and tend to grow rapidly. Cystic lesions are generally low grade. Low-grade mucoepidermoid carcinoma generally has a better outcome with appropriate surgery, that is, parotidectomy with facial nerve preservation.[43] In high-grade lesions, portions of the nerve may need to be sacrificed.[49]

Adenoid cystic carcinoma is associated with slow growth, high local recurrence, and distant metastasis, yielding a very poor survival rate.[44,49] Pain and facial paralysis are less common.[49] Other malignancies include acinic cell carcinoma, rarely adenocarcinoma, and squamous cell carcinoma.[49] Lymphoma is rare.[3]

Wide local surgical excision is indicated for virtually all salivary gland malignancies. Minor salivary gland malignancies are unusual and can be treated with wide local excision.[38] Radiation is indicated for facial nerve involvement, aggressive histologic features, adenoid cystic carcinoma with perineural invasion, and cervical lymph node metastasis or residual tumor after surgery.[38,47]

Rhabdomyosarcoma is the most common mesenchymal malignancy and rarely occurs in children older than 5 years of age.[38] Treatment involves excision and radiation therapy, possibly in conjunction with chemotherapy.[38,42,49] Metastatic lesions from areas of the face, scalp, and orbit can occur.[3]

Vascular Tumors

The vascular lesions include hemangiomas, lymphangiomas including cystic hygroma, and arteriovenous malformations. The most common pediatric parotid mass is hemangioma.[16,24,44] This lesion represents 20% of all parotid tumors and 50% of those presenting in the first year of life.[30,50,51] Salivary hemangiomas are located in the parotid in 80% of cases. Hemangiomas are solitary in 80% of cases.[24] Females are more commonly affected than males.[30,38] These lesions can be thought of as hamartomas rather than neoplasms[44,52] (**Fig. 8–4**).

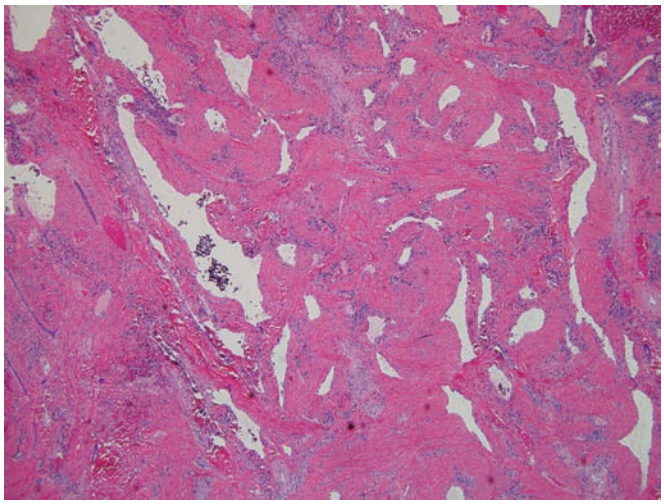

FIGURE 8–4 Hemangioma with medium-size blood vessels present in the subcutaneous tissue (H&E, ×40).

Hemangiomas occur shortly after birth and rapidly enlarge due to cellular proliferation. The acini and ductal structures are unaffected. The parenchyma is replaced by endothelial proliferation. Most are contained within the intracapsular portion of the gland. They can, however, involve skin and surrounding structures with the potential to narrow the ear canal as well as causing significant cosmetic deformity.[52] When the lesions involve skin, they are red, rubbery, and lobulated. They are compressible and enlarge with feeding or straining. The lesions will typically involute over time. This usually occurs within the second to fifth year of life, the vascular growth being replaced with fibrofatty tissue.[30,38] With this in mind, a conservative, nonsurgical therapy including observation is often the best treatment.[38,52] Given the dramatic and occasionally deforming appearance of the child with hemangioma, the family may exert pressure to ''do something.''[48]

Because hemangiomas do tend to involute, accurate diagnosis of this entity is critical to ensure a proper management plan.[50] Various imaging techniques can be used, including ultrasound, CT, and MRI.[24] As with other lesions, MRI offers the benefit of excellent picture quality, definition of tissue planes, avoidance of ionizing radiation, images in several and planes, and may avoid the need for contrast.[46,50]

Hemangioma can be associated with complications that require intervention. Hemorrhage, ulceration, infection, platelet sequestration (a localized consumptive coagulopathy is known as Kasabach-Merritt syndrome) and high-output cardiac failure may preclude a conservative plan of observing the lesion.[38]

Surgery is indicated when these complications occur. Preoperative embolization of feeding vessels can be considered.[38] Superficial parotidectomy with facial nerve preservation is the procedure of choice. Complications of surgery such as facial nerve injury, recurrent disease from incomplete resection, and even death can occur. These problems must be balanced against the wait-and-see approach.[3] If associated vital structures are at risk, such as the orbit or airway, systemic or intralesional steroids may be indicated. Dosing at 3 to 5 mg/kg/day for several weeks can be initiated.[24] Hemangiomas are responsive to steroids in 50% of cases, and the response if effective is often immediate. Interferon use is limited by its toxicity and need for long-term administration.

Lymphangiomas, by contrast, will rarely involute and may enlarge by dilation of existing vessels to encroach on the airway or interfere with feeding. Fifty percent of these lesions are present at birth and 90% by the end of the first year of life.[54] Histologically, they appear as cystic dilatations of the lymphatic system[30,53] (**Fig. 8–5**). Lymphangiomas occur most commonly in the parotid gland. They do not replace normal parotid parenchyma. They may arise as part of a cystic hygroma with extensive involvement of the head and neck. These lesions tend to surround nerves and grow beyond tissue planes.

Excision is the standard therapy; however, the extensive nature of the lesion makes nerve injury a high possibility.[16] Staged resection of massive lesions of the head and neck may be needed.[48] In the hope that the patient may be one of the rare few to experience spontaneous regression, surgery can be deferred until the child is 3 to 5 years of age. Earlier surgery may be needed if the lesion is causing functional problems or getting frequently infected.[48] Airway obstruction is more common in lymphangioma of sublingual or submandibular glands. Surgery carries a high chance of recurrence because it is likely that residual cyst will be left.[3,16]

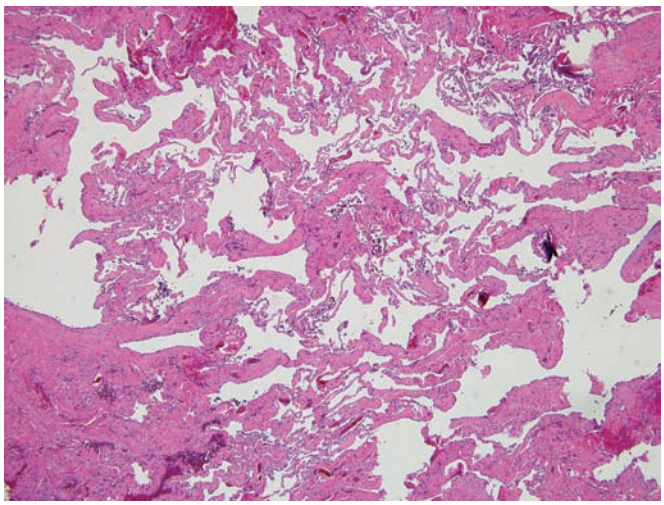

FIGURE 8–5 Lymphangioma with numerous dilated lymphatic vessels present in the subcutaneous tissue (H&E, ×40).

Needle aspiration is discouraged because the fluid will reaccumulate. Furthermore, there is a potential to cause infection or hemorrhage and possibly compromise the airway.[3] In the past, attempts to cause inflammation and sclerosis by injection of various materials have been made with limited success. Picinibil (OK-432 Chugai Pharmaceutical Co., Tokyo, Japan) may be the exception.[55]

Arteriovenous malformations are congenital lesions manifesting early in life. Blood is shunted from arterial vessels directly into the venous system. An arteriogram assists in diagnosing and defining the extent of the problem. Complete surgical resection is preferred.

Sialorrhea (Drooling)

True hypersalivation is a rare condition that is associated with painful oral lesions or heavy metal poisoning with the attendant oral irritation. Hypersalivation is also associated with nausea, Parkinson's disease, and pregnancy. In teething children, excess oral secretion is common.[3]

Drooling is the unintentional loss of saliva from the mouth.[56] It is a common problem in children with physical or cognitive disabilities.[57,58] Although it is normal in children younger than 15 to 18 months of age, in older children it is most commonly associated with neuromuscular disease, particularly cerebral palsy. Poor oral competence and inability to swallow seem to be the primary problem, rather than an excess output of saliva.

Drooling may be associated with perioral skin irritation, dehydration, foul smell, interference with oral intake, soaking of clothing, and damage to electronic communication devices and books. There is a social stigma that potentially may interfere with social interactions and self-esteem. The public views the child as ''impaired.''[59] There is an increased intensity of caregivers' time and effort. Aspiration of pooled oral secretions may lead to potentially life-threatening pneumonia.[60]

Initial assessment should include a determination of how the child holds his or her head, an oral and dental examination, and a full head and neck exam. Adenotonsillar hypertrophy and any condition that causes nasal obstruction, by virtue of leading to mouth breathing, could potentiate drooling.[59]

Various attempts to measure and quantify drooling and salivary flow have been attempted. Collection of saliva has been tried with various techniques such as using a receptacle, collecting sputum, and measuring volume of secretions absorbed on intraoral cotton rolls.[41] Questionnaires to get a subjective idea of the amount of drooling have also been devised.[57,59] A basic assessment can be obtained by asking how many bibs or shirt changes occur per day. Seeking a quantitative or qualitative assessment of the impact of drooling for an individual is important in making management recommendations as well as evaluating the outcome of any treatment.

William Crysdale at the Hospital for Sick Children Toronto, Canada advocates a team approach to include a speech pathologist, otolaryngologist, and pediatric dentist. The speech pathologist determines the potential for improved oral motor control. The dentist assesses the health of the teeth and occlusion. The family is involved in decision making.[61]

Management options include a conservative approach of observation without specific intervention, behavioral modification and working with a speech pathologist, medications to decrease salivary flow, and various surgical procedures.[56,58,61] Radiation therapy should be avoided because of the risk of malignant transformation of the gland and the transient response.[56,62]

Pharmacological Treatment

Treatment with medications is generally aimed at decreasing salivary flow by blocking the cholinergic system's muscarinic receptors. These drugs have wide-ranging systemic effects. Potential complications of anticholinergics include urinary retention, constipation, blurred vision, drying of bronchial secretions, and restlessness. Atropine has both central and peripheral effects. Hyoscyamine and benztropine have been tried as well.

Glycopyrrolate has several advantages over other medications. It does not cross the blood–brain barrier, so there are no central effects.[56] Although it is supplied as an intravenous medication, it can be used orally or via a gastrostomy tube starting at a dose of 1 mg/mL. The dosing can be titrated by modifying the milligram dose or dosing schedule to produce an optimal effect without inducing side effects. If the drug does not produce a full effect, the medication dosage can be increased. If it wears off too quickly, additional dosing can be done.

Scopolamine patches offer the ease of a transdermal route of administration.[60] The drug is continually released over a sustained period of 3 days. The difficulty lies in dosing, particularly for small children. The patch should not be cut or trimmed, as the medication will leak, giving unpredictable dosing. There is the risk of the same side effects that can be associated with all of the anticholinergics.

The clinical applications for botulinum toxin (Botox) have increasingly been defined. Botox binds to the presynaptic membrane of cholinergic nerves and produces a chemical denervation of the target tissue.[63] Several recent publications have noted a decrease in salivary flow from injection of Botox A in the parotid and submandibular salivary glands.[63–65] Patients

can be injected under a general anesthesia or after the application of EMLA cream (Astra Zeneca LP, Wilmington, DE). Using ultrasound guidance, the medication can be injected directly into the substance of the gland. Improvement occurs with dosages of 30 U in the parotid glands and 20 to 30 U in the submandibular glands.[56,62] Onset of action may begin as soon as 72 hours postinjection but generally occurs anywhere from 7 to 10 days.[62,64,65] The amount of response varies.[62,63] Duration of response is variable as well, lasting anywhere from 2 weeks to 6 months. Other than pain at the injection site, complications directly related to the drug have not been noted.[62,64,65]

Surgery

Numerous surgical options have been devised over the years (**Table 8–1**). Surgical options focus on denervation of the glands, rerouting ducts, duct ligation, submandibular gland excision, or combinations of these procedures.

Bilateral tympanic neurectomy requires a tympanotomy to gain access to the middle ear. The chorda tympani nerve, a branch of the seventh cranial nerve, supplies preganglionic fibers to the submandibular gland. Jacobson's nerve, a branch of the ninth cranial nerve, acts on the parotid gland. The chorda tympani nerves are sectioned, and a section of mucosa over the promontory along with Jacobson's nerves is removed. Little long-term improvement has been noted. The risks of tympanic membrane perforation, ossicular injury and hearing loss, and loss of taste generally make this a less than optimal therapy.[56,59,66] Tympanic neurectomy has been combined with submandibular gland excision.[59]

Rerouting the parotid or submandibular ducts directs saliva to a more posterior location in the oral cavity. This technique does not alter salivary volume. The patient with underlying swallowing disabilities may continue to drool. Ranula formation or floor of the mouth edema from submandibular duct rerouting can occur. The rerouted ducts may develop stenosis.[58]

Wilkie and Brody have reported long-term success in control of drooling. They recommend rerouting of the parotid duct in conjunction with submandibular gland excision.[67] Complications include the formation of cysts in the cheek, fistulas with recurrent symptoms, parotitis, and increased dental caries.[67] Postoperative technetium scanning has demonstrated persistent submandibular gland function several years after duct rerouting.[68]

The gold standard surgical modality to control drooling is bilateral parotid duct ligation (**Figs. 8–6, 8–7, 8–8**) and submandibular gland excision. This operation focuses on decreasing salivary flow without creating a dry mouth and the attendant discomfort, difficulty eating, and increased risk of caries. In the resting state, the submandibular and sublingual glands produce 70% of saliva. The minor salivary glands produce another 10% of saliva. The parotid gland produces most of the saliva while eating.[59,66,69]

Removal of the submandibular gland removes a major source of saliva in the resting state. Parotid duct ligation eliminates a major source of saliva with meals.[41,59] The remaining sublingual and minor salivary glands continue to provide enough saliva that xerostomia is not generally a problem.[69] Ligation of the parotid duct causes gland atrophy. Submandibular gland excision avoids the risk of ranula formation and floor of the mouth edema seen when the duct is rerouted. Success in controlling drooling is ~86 to 88%.[59]

Surgical risks from parotid duct ligation include sialadenitis of the parotid with painful swelling and possible infection, and fistulization of the parotid duct with recurrent symptoms. Submandibular gland excision risks injury to the marginal mandibular, lingual, and hypoglossal nerves, and bilateral external incisions on the neck. Hospitalization possibly with an ICU stay is

TABLE 8–1 Surgical Options for Sialorrhea

Tympanic neurectomy
Tympanic neurectomy and submandibular gland resection
Rerouting the parotid duct and submandibular duct
Rerouting the parotid duct with submandibular gland resection
Parotid duct ligation and submandibular gland resection
Ligation of the parotid and submandibular ducts

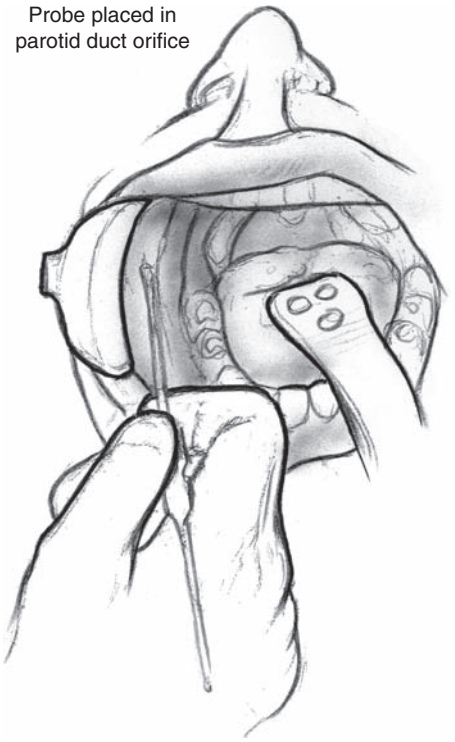

FIGURE 8–6 Lacrimal probe placed in parotid duct orifice.

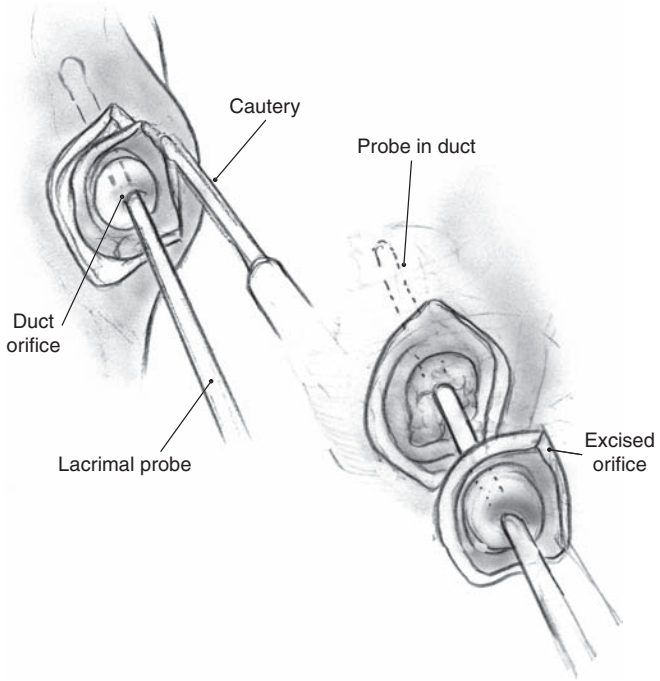

FIGURE 8–7 Excision of duct orifice and surrounding mucosa.

recommended for these severely impaired children to monitor their airway.[69,70] However, it is usually brief.

Recently ligation of the submandibular ducts (**Figs. 8–9, 8–10, 8–11**) in conjunction with parotid duct ligation (four-duct ligation) has been described for chronic salivary aspiration, although its utility for drooling is apparent.[70] This procedure takes less time than bilateral parotid duct ligation with submandibular gland excision and avoids the complications associated with gland excision.

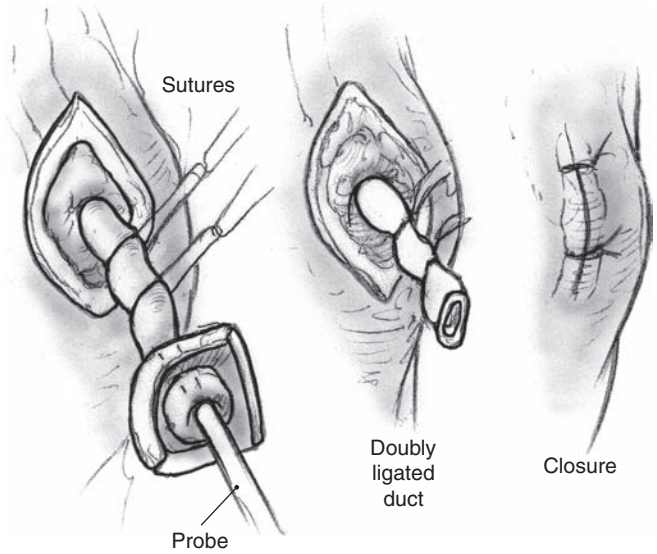

FIGURE 8–8 Duct ligation.

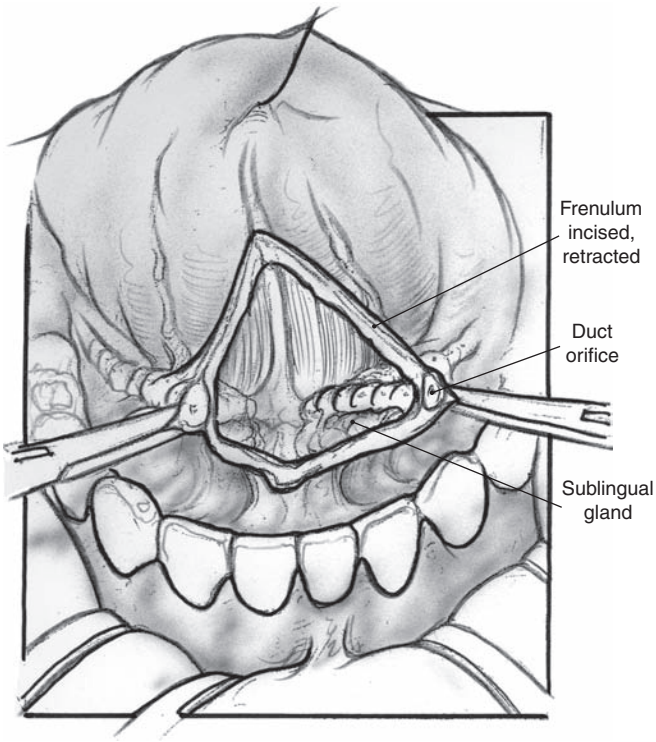

FIGURE 8–9 Midline vertical incision between submandibular ducts (lacrimal probe in duct not shown).

Providing dissection of the submandibular duct is not performed beyond 1 cm of the duct orifice, ranula formation can potentially be avoided. Klem and Mair did cadaver dissections of the floor of the mouth in conjunction with their study.[70] They noted that the sublingual glands send multiple ducts that connect with the submandibular duct. These connections occurred beyond 1 cm of the submandibular duct orifice. This finding explains the risk of ranula formation after submandibular duct rerouting.

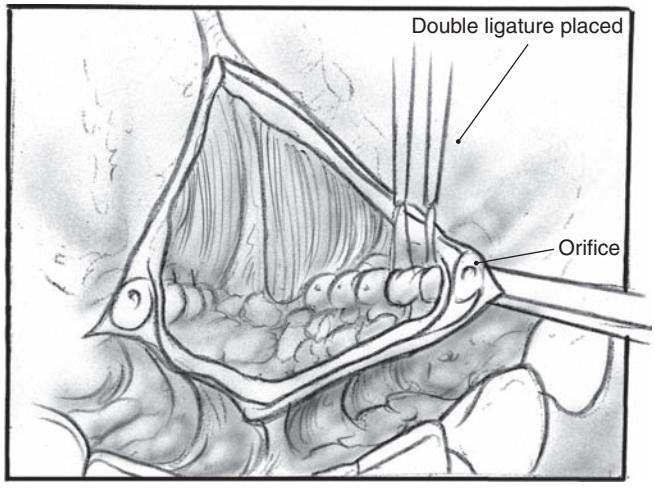

FIGURE 8–10 Double ligation of submandibular duct.

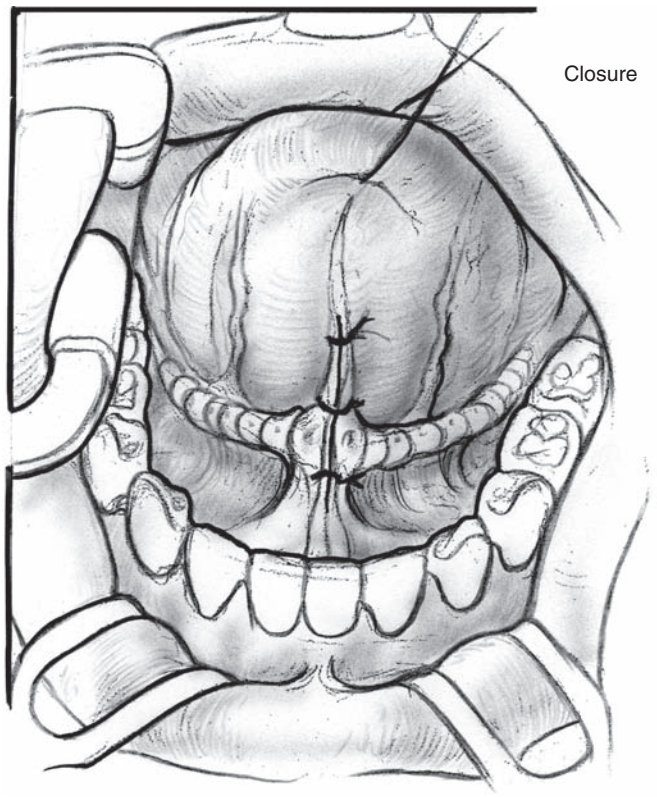

FIGURE 8–11 Loose closure of floor of mouth incision with absorbable suture.

The success rate of four-duct ligation has been estimated at 81%.[66] The ease and speed of this procedure may make it a good first alternative to parotid duct ligation and submandibular gland excision.

Ligation of the parotid duct is performed by first retracting the cheek (**Figs. 8–6** to **8–8**). An injection of a small amount of 1% xylocaine with 1:100,000 epinephrine is made at the duct orifice. The punctum is dilated and cannulated with a lacrimal duct probe. An incision is made around the duct orifice, and the cannulated duct is dissected in the submucosal plane from the surrounding tissues. The duct is doubly ligated with 4.0 silk suture as the lacrimal duct probe is withdrawn. The duct orifice can be cauterized or resected. The mucosa is closed using a 4.0 chromic suture. The procedure is repeated on the opposite side.

Ligation of the submandibular ducts again begins with an injection of 1% xylocaine with 1:100,000 epinephrine (**Figs. 8–9** to **8–11**). The frenulum between the duct papillae is incised, and the papillae are clamped with a hemostat. The duct is dissected in the submucosal plane for no more than 1 cm. The duct is doubly ligated and the orifice cauterized. The procedure is repeated on the opposite side. The incision can be loosely closed with an absorbable suture or left opened. A single dose of second-generation cephalosporin is administered. Children are sent to the intensive care unit (ICU) postoperatively for airway monitoring.[70]

Aspiration

Children with significant swallowing dysfunction are at risk for salivary aspiration and subsequent pneumonia.[71] This potentially can require frequent hospitalizations and the need for supplemental oxygen. If the child has a tracheotomy, caregivers often spend large amounts of time suctioning the child. This limits the child's ability to participate in activities, increases caregiver concerns, and negatively impacts on the lifestyle of the child and his or her family.[72] Because many children with neuromuscular disease have problems with gastroesophageal reflux, aspirated gastric contents may compound this problem. For this reason pure treatment to control salivary output with medications or surgery may not prevent aspiration. Tracheotomy is not effective in preventing aspiration.[72,73] Four-duct ligation and bilateral parotid duct ligation with submandibular gland excision have both been used effectively to control salivary aspiration.[70,74]

Although several additional surgical procedures have been tried to prevent salivary aspiration, laryngotracheal separation (LTS) appears to be the most effective by most reports.[73] The procedure effectively separates the distal airway from the oropharynx. Saliva or refluxed gastric contents cannot enter the lower airway. The procedure is quick, 100% effective in controlling aspiration, with limited complications. LTS can be done in children with or without a preexisting tracheotomy.[72,73]

The radionuclide salivagram is a simple study to demonstrate salivary aspiration. One cc of technetium 99m sulfur colloid 9 (200 uCi) is placed in the mouth of the child, and the child is scanned from the mouth to the abdomen for 1 hour using a gamma camera. The scan shows whether the radioisotope passes into the stomach or is detected in the trachea and bronchi (**Fig. 8–12**). If the radionuclide fails to progress from the oral cavity, this is presumptive of significant swallowing dysfunction and a risk for aspiration. The salivagram has a sensitivity of 94% in predicting which children would benefit from LTS. The specificity was 93%.[75]

Although the procedure is theoretically reversible, it is generally offered to children with devastating neurologic disease. As such, the patient or the family should expect this to be a permanent solution that commits the child to a tracheotomy. The separation of the distal airway from the larynx and oral cavity precludes any verbal communication. Even in the child with severe neurologic impairment, the loss of vocalization has been noted to be a concern to virtually all families prior to the procedure.[37] In the rare child who aspirates but can communicate verbally, other alternative approaches to aspiration should be sought prior to LTS.[74]

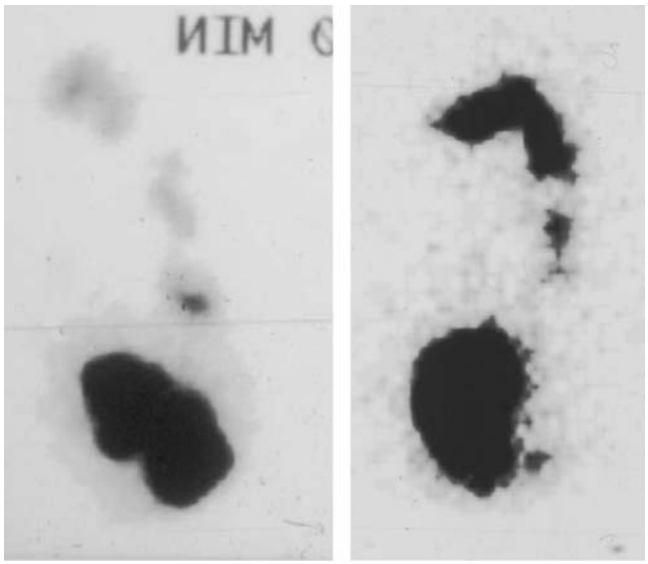

FIGURE 8–12 Salivagram. Image on the left is a negative salivagram showing technetium (Tc 99m) in the stomach 1 hour after instillation of 1 cc in the patient's mouth. Image on the right is a positive salivagram showing Tc 99m in the mouth with aspiration of material into the trachea and extending into the right and left main bronchi.

The procedure begins by securing the airway with an oral endotracheal tube in the child without a preexisting tracheotomy. If the child has a tracheotomy, the stoma is intubated with an armored endotracheal tube. An apron flap is marked off on the anterior neck at two fingerbreadths above the suprasternal notch or just above the tracheotomy tube site. A central semilunar extension is marked to encompass the existing tracheotomy site or, in the virgin neck, to accommodate the future stoma to the distal trachea. The incision is injected with 1% xylocaine with 1:100,000 of epinephrine. The skin is incised, and subplasmal skin flaps are developed superiorly and inferiorly. In the virgin neck the semilunar piece of skin is excised. The peristomal skin and soft tissues of the tracheocutaneous fistula are excised.

The strap muscles are separated in the midline from the thyroid cartilage to the sternal notch (**Fig. 8–13**). The thyroid isthmus is divided in the midline. The trachea is dissected from all surrounding tissues anteriorly and laterally. A preexisting tracheotomy can create significant soft tissue reaction. The trachea is divided at its anterior and lateral portions at the level of the third to fourth tracheal ring, beveling the incision superiorly. If there is a preexisting tracheotomy, the trachea is transected at the inferior aspect of the tracheotomy stoma. In the virgin neck, the oral endotracheal tube is withdrawn and replaced with a sterile endotracheal tube introduced into the distal trachea and passed under the drapes from the sterile field to the anesthesiologist. The anterior portion of the distal trachea is secured to the lower skin flap with a suture of 0 silk. Before incising the posterior tracheal wall, a small bolus of 1% xylocaine with 1:100,000 of epinephrine is injected into the mucosa. The posterior tracheal mucosa is incised, dividing the trachea in half. The posterior tracheal mucosa is separated from the anterior esophageal wall behind the proximal and distal tracheal segments (**Fig. 8–14**).

Attention is directed to the proximal tracheal segment. Vertical incisions are made in the midline of the anterior trachea through the second and third tracheal arches (**Fig. 8–13**). This allows the proximal trachea to collapse upon itself. The proximal trachea is closed as a blind pouch using interrupted stitches of 3.0 nylon or

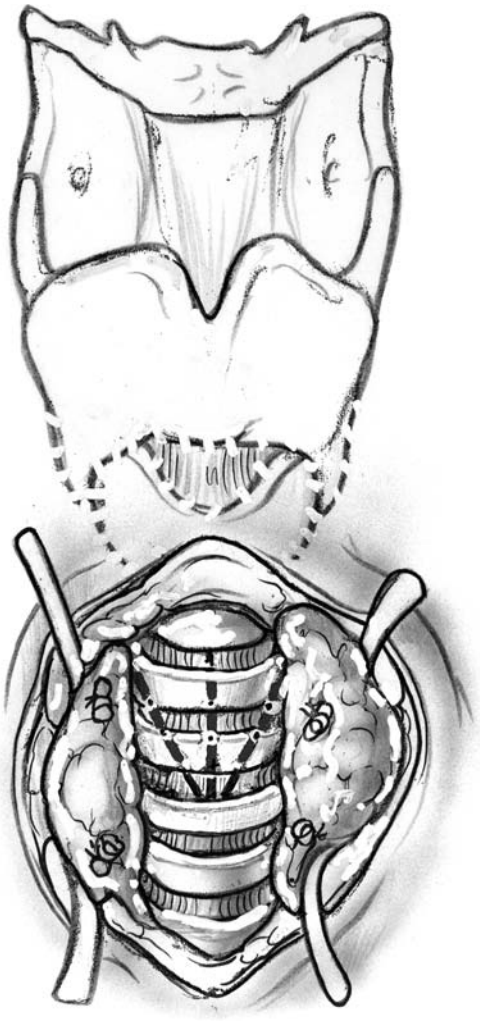

FIGURE 8–13 After division of the thyroid gland, the trachea is exposed, and vertical tracheal incisions are made.

Prolene (Ethicon, Sommerville, NJ) (**Fig. 8–14**). A superiorly based flap of sternohyoid muscle is created and sutured as a second layer over the proximal tracheal closure with 4.0 Vicryl (Ethicon) as a reinforcing layer (**Fig. 8–15**).

The surgical site is irrigated and meticulous hemostasis achieved. Through a small lateral stab incision, a small Jackson-Pratt drain is placed in the deep aspect of the wound, along the anterior esophageal wall. The distal trachea is sutured to the skin with 3.0 silk, as the incision is closed, maturing the distal trachea as permanent tracheostomy (**Fig. 8–16**). Antibiotic ointment is applied, and the endotracheal tube is replaced with a standard tracheotomy tube. The child is sent to the ICU. The drain is removed when output is less than 20 cc/24 hours. Gastrostomy tube feeds can be started the day after surgery, but oral intake is deferred until the 7th to 10th postoperative day. The tracheotomy tube can be changed at any time because the mature stoma allows wide access to the distal airway. Good local care prevents peristomal cellulitis. Sutures are removed slowly over several days, a few at time, beginning on the seventh postoperative day.[73]

Complications are few. Peristomal cellulitis can occur and persist until all sutures are removed. Fistulas are rare and generally managed with local care. Stomal stenosis is possible.[73]

Caretaker satisfaction is high, with fewer reported hospitalizations and pneumonias, and increased ability for the patient to travel. There is also a decrease in home nursing care compared with prior to surgery. Parents generally have concerns prior to the procedure, particularly because of the loss of vocalization, but 100% of families, in one report, noted improved quality of life for both the child and family and would recommend the procedure to others.[72]

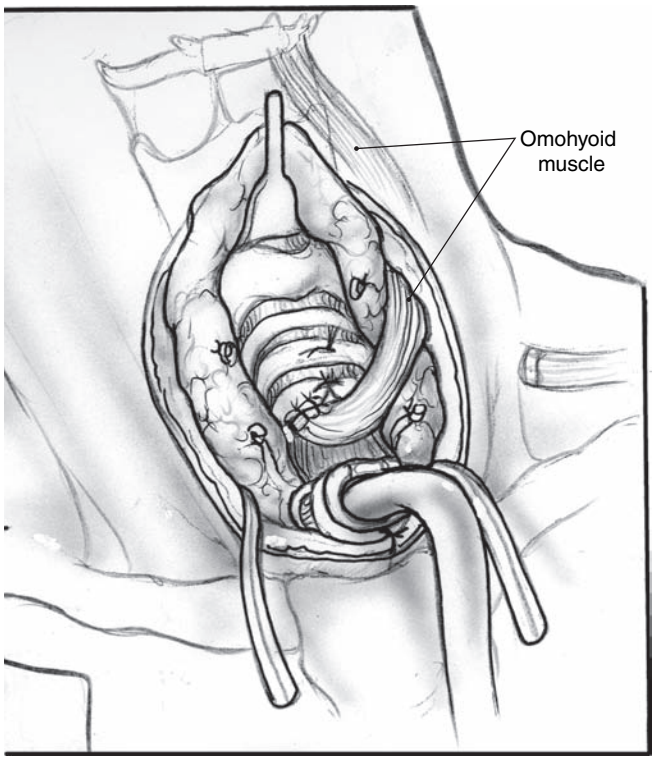

FIGURE 8–15 Strap muscle pedicle flap as a reinforcial layer.

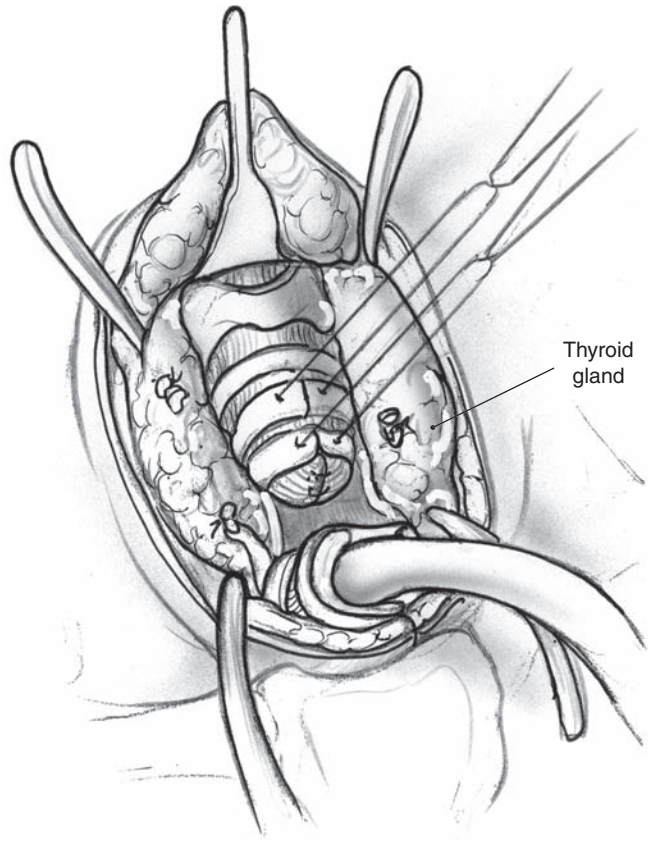

FIGURE 8–14 Closure of proximal trachea.

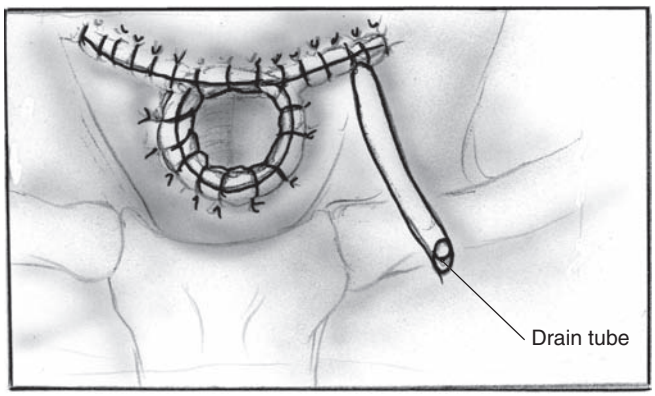

FIGURE 8–16 Closure with suction drain.

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9

Benign Tumors, Cysts, and Tumor-like Conditions of the Salivary Glands

ROBERT L. WITT AND SUSAN J. MAYGARDEN

Three percent of head and neck tumors and 0.5% of all tumors in the body are parotid tumors. Parotid tumors constitute 80% of tumors of the salivary glands, and 80% of parotid tumors are benign.[1,2] Five to 10% of salivary gland tumors are in the submandibular gland, and 50 to 60% of these are benign.[1,2] Ten to 15% of salivary gland tumors occur in the minor salivary glands, and 20 to 25% are benign.[1,2]

Benign Mixed Tumor (Pleomorphic Adenoma)

The use of imaging, fine-needle aspiration, and nerve integrity monitors will be covered in this section on the benign mixed tumor.

Historical Review

The development of parotid surgery can be traced to treatment of the benign mixed tumor. These tumors were first termed *mixed tumor* by Broca in 1866, and this name was later popularized by Minsenn in 1874.[3] Mixed tumor refers to the mixture of epithelial and mesenchymal elements. The term *pleomorphic adenoma* emphasizes the varied histological presentation of these tumors. Early parotid surgery was performed by Siebold (1793), Billroth (1859), and Virchow (1863).[4] Eighteenth- and 19th-century parotid surgery avoided the facial nerve, with intracapsular dissection of the tumor later replaced by extracapsular enucleation. Enucleation was thought to avoid damage to the facial nerve, but it resulted in tumor spillage with associated recurrence rates as high as 45%.[5]

In 1907 Thomas Carwardine reported facial nerve preservation during parotid surgery.[6] Sistrunk[7] identified a facial nerve peripheral branch and traced it in a retrograde fashion to the main facial nerve trunk during parotidectomy. Retrograde dissection of the facial nerve was practiced prior to antegrade dissection. Multicentric recurrences were interpreted as being due to a semimalignant nature of the tumor. McFarland[8] drew attention to high rates of recurrence with enucleation and the benign histopathology of these tumors, stating: ''The complaisance of the surgeon is not infrequently disturbed by the return of his patient with a recurrence of the tumor, and that of the pathologist, by the continued good health of some patient condemned to death upon the histopathological evidence of a supposed malignancy.'' Patey and Thackray[9] advocated wide resection of the tumor by superficial parotidectomy, showing what they termed ''*focal infiltration* of the capsule, and demonstrated how pseudopodia of the tumor could be left behind if the lesion was enucleated.

Not long afterwards it became widely recognized that only the rare tumor with infiltrative and destructive growth had malignant characteristics, and that the vast majority of mixed tumors were in fact benign. The theory that one third of mixed tumors were multicentric was discarded on the discovery that most cases of ''multicentricity'' were in fact due to tangential cutting of tumor projections and were thus multicentric recurrences of benign mixed tumors. Pathologic review repeatedly revealed pseudopodia perforating the pseudocapsule and projecting into salivary gland tissue. Interestingly, surgeons started performing a wider resection of benign mixed tumor, including facial nerve

dissection, because of fears of multicentricity rather than for the more valid reason that enucleation leads to subtotal removal of tumor. More complete parotid surgery led to higher rates of temporary and permanent injury to the facial nerve, postoperative hematoma, gustatory sweating, and facial contour depression. To avoid these complications and reduce recurrences, a return to enucleation followed by radiation therapy was practiced in some centers.[10] The risk of radiation-induced malignancy led to the abandonment of this modality.

Surgery for mixed tumor of the parotid has evolved from enucleation to retrograde and subsequent antegrade facial nerve dissection with adequate margin of normal parotid parenchyma except where the tumor abuts the facial nerve. Modern skillfully trained surgeons perform parotidectomy with a low risk of permanent facial nerve dysfunction and recurrence.

Presentation

The benign mixed tumor is the most common salivary gland neoplasm in adults and children, with most occurring in the parotid gland.[1,11] Eighty-five percent of mixed tumors present in the parotid gland (**Fig. 9–1**). Two thirds of parotid neoplasms are mixed tumors.[2] They present in all ages, with the highest incidence in the fourth decade of life.[1] They present more commonly in females.[1] They are firm except in a tumor that is predominantly myxoid (hypocellular). Extrinsic pressure can result in facial nerve dysfunction on rare occasion. The biological characteristics do not vary by age, and low recurrence rates are expected after appropriate resection.

Parotid mixed tumor is most often diagnosed and treated when the tumor is small (< 4 cm), mobile, and located in the superficial lobe. Eighty percent of the parotid parenchyma is lateral to the facial nerve. Ninety percent of parotid mixed tumors present in the superficial lobe, and 80% are located in the lower pole. Ten percent of mixed tumors extend to or are limited to the deep lobe of the parotid. They may also present very rarely in the accessory parotid gland. The accessory parotid gland, present in up to 56% of individuals, connects to the main excretory duct of the parotid gland and is found on the anterior surface of the main parotid gland or anterior to the parotid.[12]

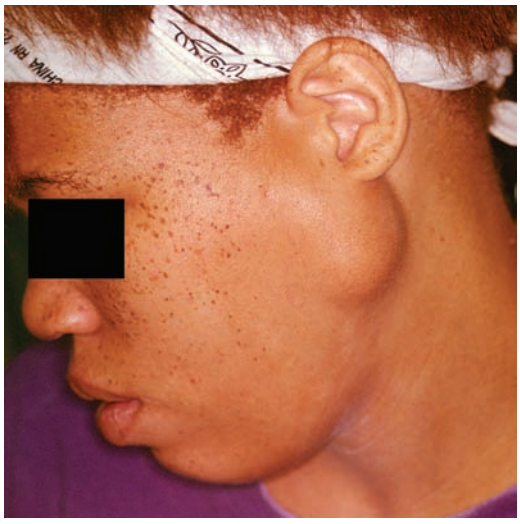


FIGURE 9–1 Parotid mixed tumor.

Parotid deep lobe tumors, including mixed tumors, may extend above or below the stylomandibular ligament in the space between the angle of the mandible and styloid process and present as a parapharyngeal space mass. The stylomandibular ligament runs with three muscles inserted in the styloid process: the styloglossus, stylohyoid, and stylopharyngeus. It inserts in the posterior border of the ascending ramus and angle of the mandible. Tumors that extend anterosuperior to the stylomandibular ligament are dumbbell tumors that are constricted between the mandible, stylomandibular ligament, and skull base. Tumors extending posteroinferior to the stylomandibular ligament are rounded in appearance. Parapharyngeal tumors, including mixed tumors, can result in sleep apnea from associated intraoral swelling and medial displacement of the tonsil and lateral pharyngeal wall, often presenting without trismus. The carotid space vessels and cranial nerves (CN IX–XII) of the poststyloid compartment of the parapharyngeal space are not involved with the tumor as deep lobe parotid tumors present in the prestyloid compartment. Paragangliomas and most schwannomas are found in the poststyloid compartment of the parapharyngeal space. Intraoral biopsy of parapharyngeal mixed tumors will result in tumor seeding and scar tissue, making definitive transcervical resection more difficult.

Mixed tumors are most often solitary tumors with a rare presentation as a synchronous or metachronous tumor in the same gland or contralateral gland. Uncommonly, they can present together with another salivary gland tumor, most commonly a Warthin's tumor, but also with a mucoepidermoid, acinic cell or adenoid cystic carcinoma.[13]

Five percent of mixed tumors occur in the submandibular gland.[2] Fifty to 60% of submandibular tumors are mixed tumors, presenting as a painless swelling.[14] Ten percent of mixed tumors occur in minor salivary glands, and only very rarely do they occur in the sublingual gland.[2] More than half of benign tumors of the minor salivary glands are mixed tumors.[2] They most commonly occur as painless, submucosal masses in the hard and soft palate, with equal incidence, but without ulceration. In the palate they usually present lateral to

the midline. They have poor mobility when on the hard palate because of the underlying bone. They may also present in the upper lip and buccal mucosa, where they are mobile.[2] Mixed tumors can arise in the nasal cavity and paranasal sinuses. Paranasal sinus mixed tumors may cause nasal obstruction or obstructive sinusitis. Pharyngolaryngotracheal minor salivary gland neoplasms, including mixed tumors, may present with hoarseness, dysphagia, cough, or hemoptysis.

Esoteric heterotopic salivary gland rests can develop mixed tumors in the cervical lymph nodes, ear, lacrimal gland, mandible, sellar region, lung, breast, trunk, and lower limbs.[15] In the skin, mixed tumors are called chondroid syringomas. Chondroid syringomas present from the fourth through sixth decades more commonly in males. The tumors have been found in most areas of the skin, but the majority present in the skin of the face and head. They can originate from sebaceous glands, sweat glands, or ectopic salivary glands.[16]

Imaging

Ultrasound can differentiate a benign mixed tumor from a malignant tumor in over 90% of cases.[17] Criteria for malignancy include irregular shape, ill defined and irregular margins, inhomogeneous structure, and the presence of abnormal lymph nodes. High-resolution probes and harmonic imaging can demonstrate histopathological heterogeneity of mixed tumors in many cases[17] (see Chapter 2 for a full discussion).

Computed tomography (CT) and magnetic resonance imaging (MRI) may predict mixed tumor if lobular shape and homogeneous internal echoes are present. CT imaging is less expensive but more prone to degradation artifact than MRI. CT should be performed with contrast enhancement. MRI with gadolinium enhancement is superior at demonstrating the internal structure of the salivary gland and delineating tumor from normal salivary gland. MRI has different signal intensity for tumor, fat, and muscle. An MRI of a mixed tumor typically shows postcontrast enhancement, a high T2 signal, and well-defined margins (unless large enough to be lobulated) that do not invade surrounding tissue planes.[18] CT or MRI will demonstrate deep lobe parotid tumor extension to the prestyloid compartment of the parapharyngeal space. The prestyloid compartment is anterior to the carotid space vessels. The deep lobe parotid tumor displaces the parapharyngeal fat medially. Deep lobe parotid tumors extending into the parapharyngeal space can be seen connected to the parotid and can be distinguished from minor salivary parapharyngeal tumors that are completely surrounded by fat (**see Chapter 2, Figs. 2–13, 2–14**).

Positron emission tomography with fluorine-18 fluorodeoxyglucose has not yet proven useful in classification of salivary gland neoplasms as benign or malignant. A false-positive rate of 31% has been reported in one study.[19]

Pathogenesis

The pathogenesis of the benign mixed tumor is uncertain. The multicellular theory hypothesizes that salivary gland tumors develop from the proximal and distal ectodermally derived differentiated cell types in the adult salivary gland (acinar-duct subunit). The mixed tumor in this theory comes from the distal intercalated and myoepithelial cells and consists of epithelial and myoepithelial elements. The myoepithelial cells are responsible for the extracellular matrix.[20,21]

The bicellular or reserve theory suggests that basal cells of excretory ducts and intercalated ducts are stem cells from which adult salivary gland units and tumors derive.[22] The mixed tumor would derive from intercalated duct stem cells in this theory.[23]

Cytology

Fine-needle aspiration of benign mixed tumor usually yields benign epithelial cells admixed with stroma (**Fig. 9–2**). Varying degrees of cellularity and differing proportions of epithelium and stroma are seen. The epithelial cells may be arranged as sheets, cords, or single cells. The stromal component is acellular, fibrillary material that is metachromatic (magenta-purple) with Romanovsky-type stains (e.g., Diff-Quik or Giemsa,

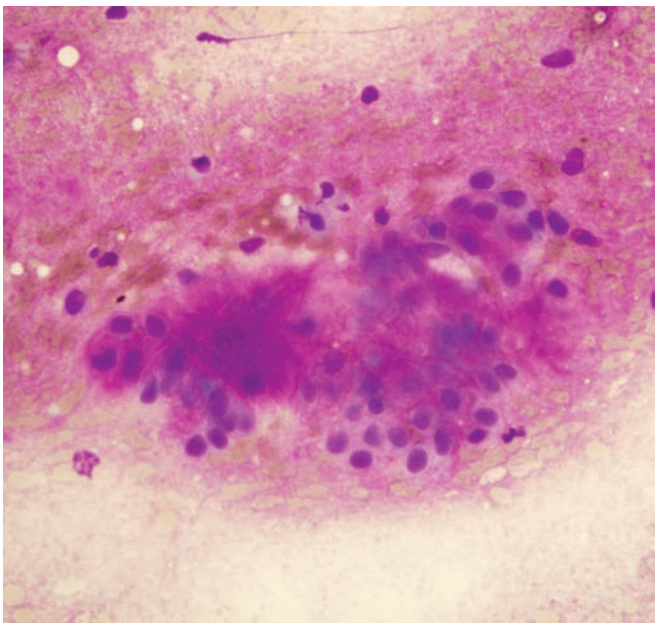


FIGURE 9–2 Fine-needle aspiration of benign mixed tumor, containing benign oval epithelial cells and pink-purple fibrillary matrix material (Diff-Quik stain, ×400).

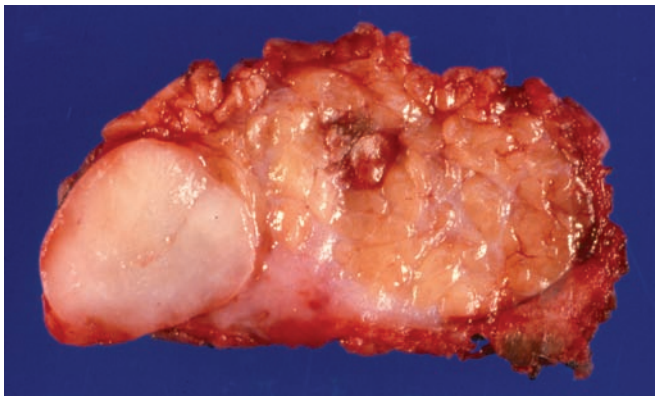


FIGURE 9–3 Gross photograph of benign mixed tumor showing circumscription of the mass.

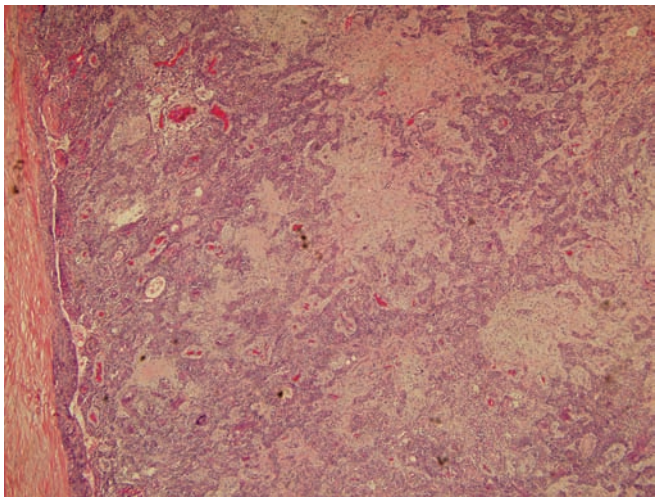


FIGURE 9–4 Histology of usual benign mixed tumor showing a biphasic neoplasm with epithelial and stromal components (H&E, ×40).

which are commonly used for rapid evaluation of specimen adequacy).[24] A typical benign mixed tumor is usually not a diagnostic dilemma. Occasional cases may be highly cellular with minimal stromal component, or contain cystic changes, squamous metaplasia, or necrosis that can mimic other neoplasms. Squamous metaplasia in benign mixed tumor can be mistaken for squamous cell carcinoma.

Alterations in histology following fine-needle aspiration can result in exuberant squamous metaplasia, infarction and necrosis, subepithelial stromal hyalinization, acute and chronic hemorrhage with inflammation with multinucleate giant cells, granulation tissue with subsequent fibrosis, cholesterol cleft formation, pseudoxanthomatous reaction, pseudocapsular invasion, and microcystic degeneration.

Histology

Mixed tumors of the parotid are benign epithelial tumors with an incomplete fibrous capsule of varying thickness. Mixed tumors in the minor salivary glands usually do not have a capsule.[24] Even nonencapsulated mixed tumors show distinct circumscription of the lesion on gross examination and low-power microscopy (**Fig. 9–3**). Protuberances give a lobulated appearance as the tumor grows. Mixed tumors are round, smooth, freely movable, and grossly gray to yellow in color.

Microscopically, mixed tumors are biphasic neoplasms that contain benign epithelial and myoepithelial cells with a variety of patterns, and mesenchymal stroma (**Fig. 9–4**). The term *pleomorphic adenoma* was coined to reflect the large variety of patterns these tumors can assume. The epithelial cell forms are predominantly salivary duct and myoepithelial cells. Closely associated nonductal cells include spindle, round, stellate, plasmacytoid, polygonal, and clear forms. Rarer cell forms include keratinized squamous epithelium, oncocytes, basal cells, and sebaceous cells or goblet cells. The stromal component is usually myxomatous or myxochondromatous, but hyaline, fibrotic, or osseous (bone-forming) areas may also be present in the stroma.[24] It is believed that the stroma is produced by the myoepithelial cells.[25] Tumors may be epithelial-cell rich (cellular) (**Fig. 9–5**) or stromal rich (myxoid) (**Fig. 9–6**). Tumors are more highly cellular (the epithelial component predominates) in their early stages of development, and the amount of chondromyxoid stroma (the mesenchymal component) increases with the duration of the neoplasm.[23] Recurrent mixed tumors are frequently more hypocellular (stromal-rich) with associated higher rates of incomplete encapsulation.[26,27]

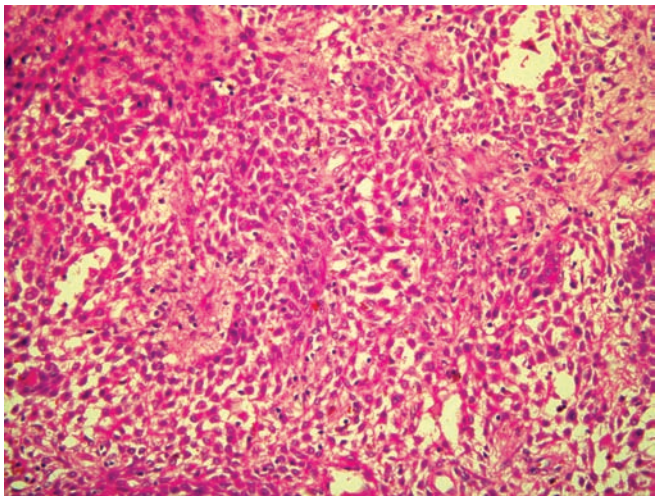


FIGURE 9–5 Histology of cellular benign mixed tumor. These tumors predominantly contain the epithelial component of a benign mixed tumor, with only scant amounts of chondromyxoid matrix (H&E, ×200).

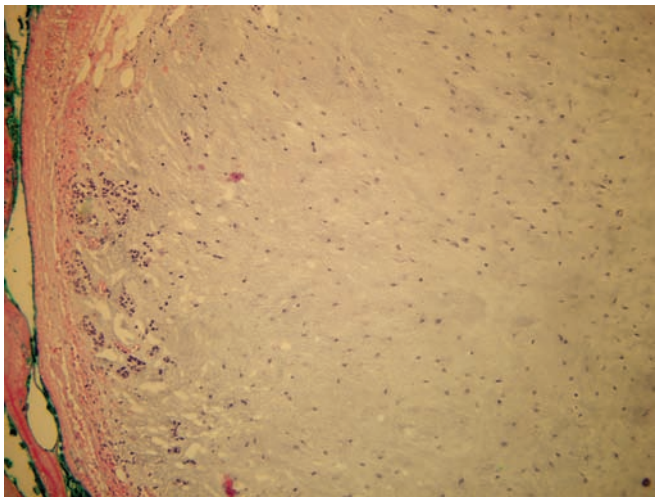


FIGURE 9–6 Histology of stroma-rich benign mixed tumor. These tumors are predominantly myxoid stroma, with only a sparse epithelial component (H&E, ×100).

Genetics

The first observation of recurrent loss of a chromosome[14] was in a meningioma. The mixed tumor was the second type of benign tumor for which nonrandom chromosomal changes were reported.[28] The mixed tumor has been cytogenetically well characterized. In addition to the cytogenetic subgroup with an apparently normal diploid stemline (making up 30% of the cases), three major cytogenetic subgroups with abnormal karyotypes can be distinguished. By far the largest cytogenetic subtype consists of tumors with chromosome 8 abnormalities mainly showing translocations involving band *q12* (*8q12*). Patients with the *8q12* abnormality tend to be younger, and they have more hypercellular tumors. The ectopic expression of the *PLAG1* gene is associated with benign mixed tumor in individuals with *8q12* translocation. The other subgroups involve various translocations involving *12q15* and a group of nonrecurrent clonal abnormalities.[28] Another reported chromosome abnormality involves chromosome bands *3p21*.[29] There is thus far no correlation between these cytogenetic characteristics and recurrence.

The mutation of the tumor suppressor gene *p53* is the most common genetic alteration in human cancers. Immunohistochemistry of the *p53* and the proliferative marker K_i-67 has been absent from primary parotid and submandibular mixed tumors indicating that mixed tumors of the parotid and submandibular gland are histologically similar and that they have a low proliferative rate and good prognosis.[14]

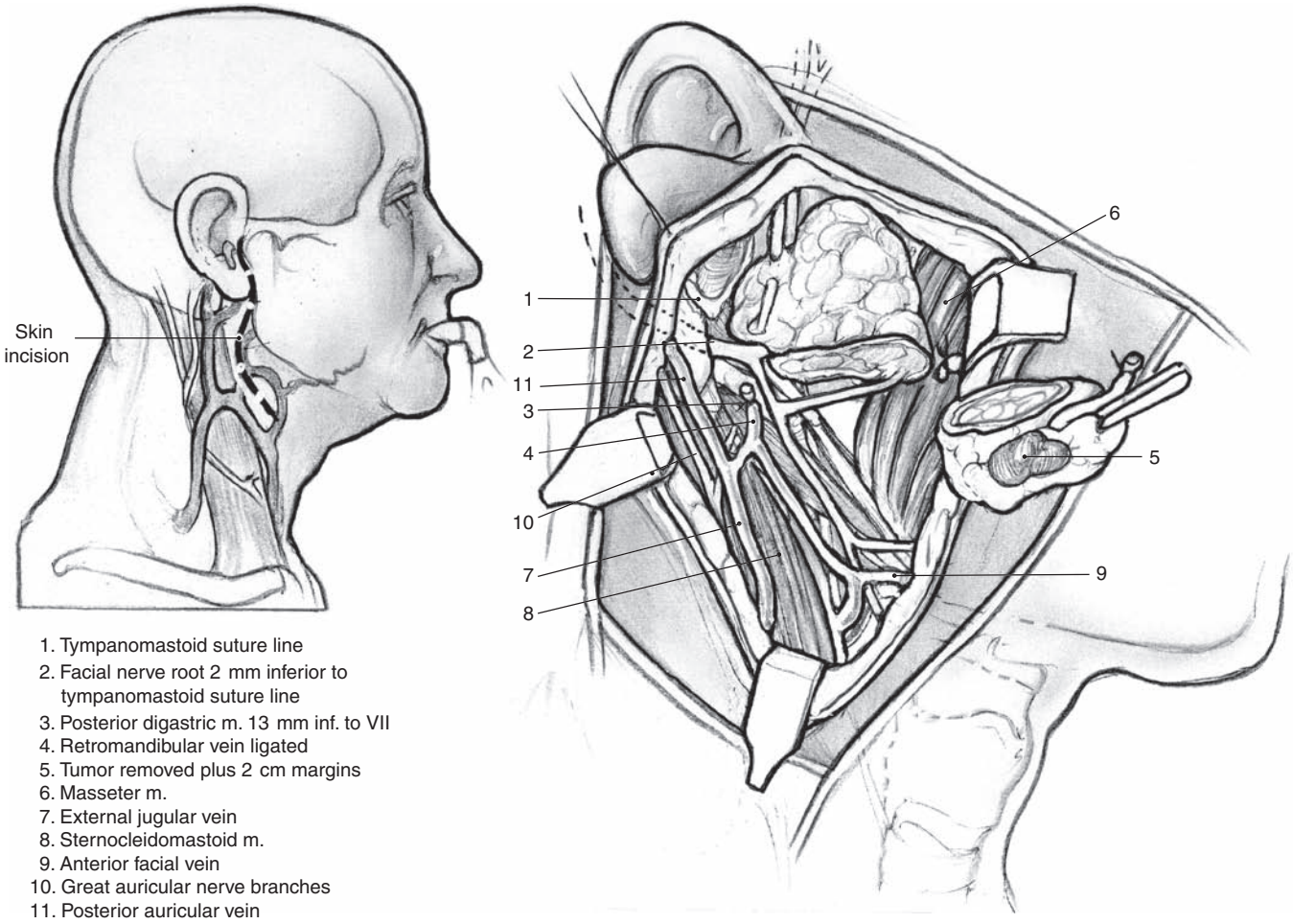
The degree of deoxyribonucleic acid (DNA) instability as revealed by the immunohistochemical staining with anti-single-stranded DNA antibody after acid hydrolysis (DNA instability test) can be used as a marker of malignancy. Twenty-one of 33 (64%) mixed tumors were positively stained by DNA instability test diffusely or sporadically, indicating that mixed tumors can be regarded as ''unstable'' and often contain or predispose to malignant subclones with occasional capsular or extracapsular invasion, reflecting the potential progression to malignancy. In comparison, no sign of potential malignant progression was identified in the seven Warthin's tumors studied.[30]

Treatment

The informed consent for the removal of a parotid mixed tumor should include transient or permanent facial nerve dysfunction, numbness, gustatory sweating, seroma, hematoma, and recurrence. The parotid mixed tumor is most commonly treated with partial superficial parotidectomy (dissection of the facial nerve with a 2 cm margin of normal parotid parenchyma except where the tumor abuts the facial nerve),[31] or complete superficial parotidectomy with facial nerve dissection. The facial nerve is most commonly dissected in an antegrade fashion, but a retrograde approach is still preferred by some and is not associated with a higher rate of complications, including facial nerve dysfunction.[32] The more variable course of the peripheral facial nerve branches has mostly resulted in abandonment of this technique. Total parotidectomy[33] and extracapsular dissection[34] have also been used for benign mixed tumor. Extracapsular dissection differs markedly from other parotid procedures because facial nerve dissection is not performed. Extracapsular dissection is contrasted to enucleation by its advocates as dissection of a small cuff of normal parotid parenchyma just outside the capsule of the parotid tumor.[34]

Regardless of the extent of normal parotid parenchyma that is resected with the tumor, there will be a near universal focal capsule exposure where the facial nerve or superficial fascia abuts the tumor.[31,35] A positive margin with partial superficial parotidectomy or complete superficial parotidectomy will occur in up to one third of cases because of pseudopodia piercing the pseudocapsule where the tumor abuts the facial nerve.[31,35] Few separations of pseudopodia from the main tumor occur with expertly performed contemporary parotid surgery because most of the tumor has a margin of normal parotid parenchyma. Enucleation leads to more positive margins with unacceptable recurrence rates. Capsular penetration occurs where the tumor forms protrusions into the pseudocapsule, sheared off with enucleation.

Partial superficial parotidectomy (**Fig. 9–7**) for small (< 4 cm), mobile tumors of the lateral lobe will result in less transient facial nerve dysfunction, gustatory sweating (Frey's syndrome), facial depression, and operative time compared with procedures (total parotidectomy and



1. Tympanomastoid suture line
2. Facial nerve root 2 mm inferior to tympanomastoid suture line
3. Posterior digastric m. 13 mm inf. to VII
4. Retromandibular vein ligated
5. Tumor removed plus 2 cm margins
6. Masseter m.
7. External jugular vein
8. Sternocleidomastoid m.
9. Anterior facial vein
10. Great auricular nerve branches
11. Posterior auricular vein

FIGURE 9–7 Partial superficial parotidectomy. Note the mean distance from the tympanomastoid suture to the facial nerve is 2 mm. The mean distance from the posterior belly of the digastric muscle to the facial nerve is 13 mm.

complete superficial parotidectomy) that resect a greater portion of normal parotid parenchyma and dissect more of the facial nerve.[31] Extracapsular dissection if improperly performed is enucleation and will result in unacceptable recurrence rates. If a normal cuff of parotid parenchyma is resected without dissection of the facial nerve, a potentially higher risk of permanent facial nerve dysfunction may ensue. A meta-analysis summary effect for permanent facial nerve dysfunction is reported 1.8 times higher for extracapsular dissection compared with superficial parotidectomy.[31] Additionally, the exact procedure indicated for a parotid mass cannot always be determined in the preoperative setting, and successful surgery may require wide exposure with facial nerve dissection, not afforded in extracapsular dissection.

Mixed tumors extending to the parapharyngeal space (**Fig. 9–8**; **See also Chapter 2, Fig. 2–13**) can usually be removed with a transcervical approach after superficial parotidectomy and facial nerve dissection (see Chapter 15). Selected larger, retromandibular mixed tumors approaching the skull base may require mandibulotomy. Lip split, closure of intraoral structures, and midline extension of the cervical incision can be avoided with a vertical mandibulotomy posterior to the lingula of the medial surface of the mandible, preserving the inferior alveolar nerve and intraoral sensation and providing a panoramic view of the parapharyngeal tumor (**Figs. 9–9, 9–10**). Modern plating systems should be contoured and applied prior to the mandibulotomy. They are then removed and reapplied after mandibulotomy and resection of tumor. This approach will minimize the risk of nonunion, malunion, or malocclusion.

The treatment of a submandibular mixed tumor is resection of the gland along with the tumor with a margin of normal tissue where possible. The informed consent should include trauma to the marginal mandibular branch of the facial nerve potentially resulting in a temporary or permanent lower lip asymmetry,

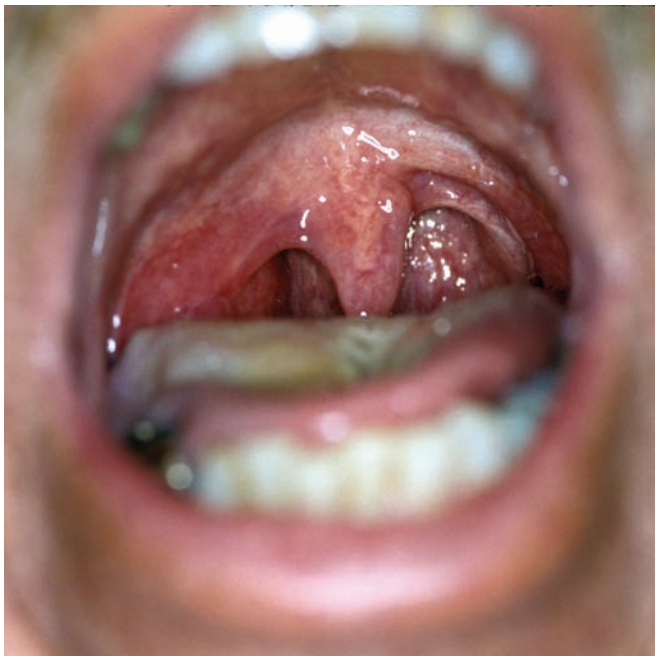


FIGURE 9–8 Right parapharyngeal tumor.

intraoral numbness, and trauma to the hypoglossal nerve resulting in tongue deviation, infection, and hemorrhage. Rare recurrences are possible after this approach. The treatment of a minor salivary gland mixed tumor is resection of the gland with a margin of normal tissue where possible. The informed consent would vary with the anatomical presentation.

Recurrence

Most cancer tumor registries do not track mixed tumors; therefore, follow-up remains deficient. Recurrence rates for mixed tumors are also difficult to evaluate because of the small number of patients and the variability of follow-up times. In most series, parotidectomy with facial nerve dissection results in recurrence rates of 0 to 4%.[31] Recurrences generally occur in the first 10 years, with a mean interval to the first recurrence of 7 years.[36] Late recurrences beyond 20 years occur, although rarely. Recurrent mixed tumors are almost always multinodular.[37] Imaging studies coupled with clinical exam will document the multiplicity of recurrence over clinical exam alone. Seventy-five percent of recurrences are in the superficial lobe (**See Chapter 2, Fig. 2–12**).[38] Time intervals between operation and recurrence are significantly shorter for enucleation compared with parotidectomy and facial nerve dissection.[39] Patients with more than one recurrence tend to have their first recurrence earlier (mean 47 months) than patients who were cured after reexcision of their only recurrence (mean 105 months).[40]

The chief factor for tumor recurrence is enucleation (**Table 9–1**), where pseudopodia of tumor extending beyond the pseudocapsule are sheared off.[36,39–41] The reported meta-analysis summary effect reveals a 9 times higher rate of recurrence for enucleation compared with superficial parotidectomy.[31] Recurrence is also possible, but much less likely in parotidectomy with facial nerve dissection in areas where the tumor

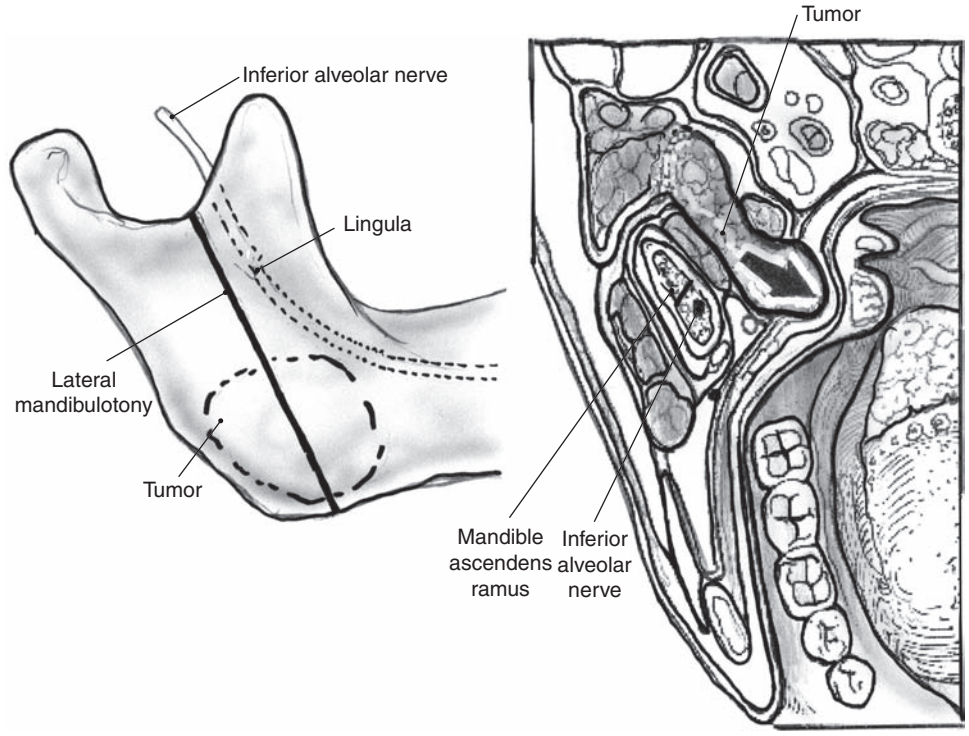


FIGURE 9–9 Vertical mandibulotomy posterior to the lingula of the medial surface of the mandible.

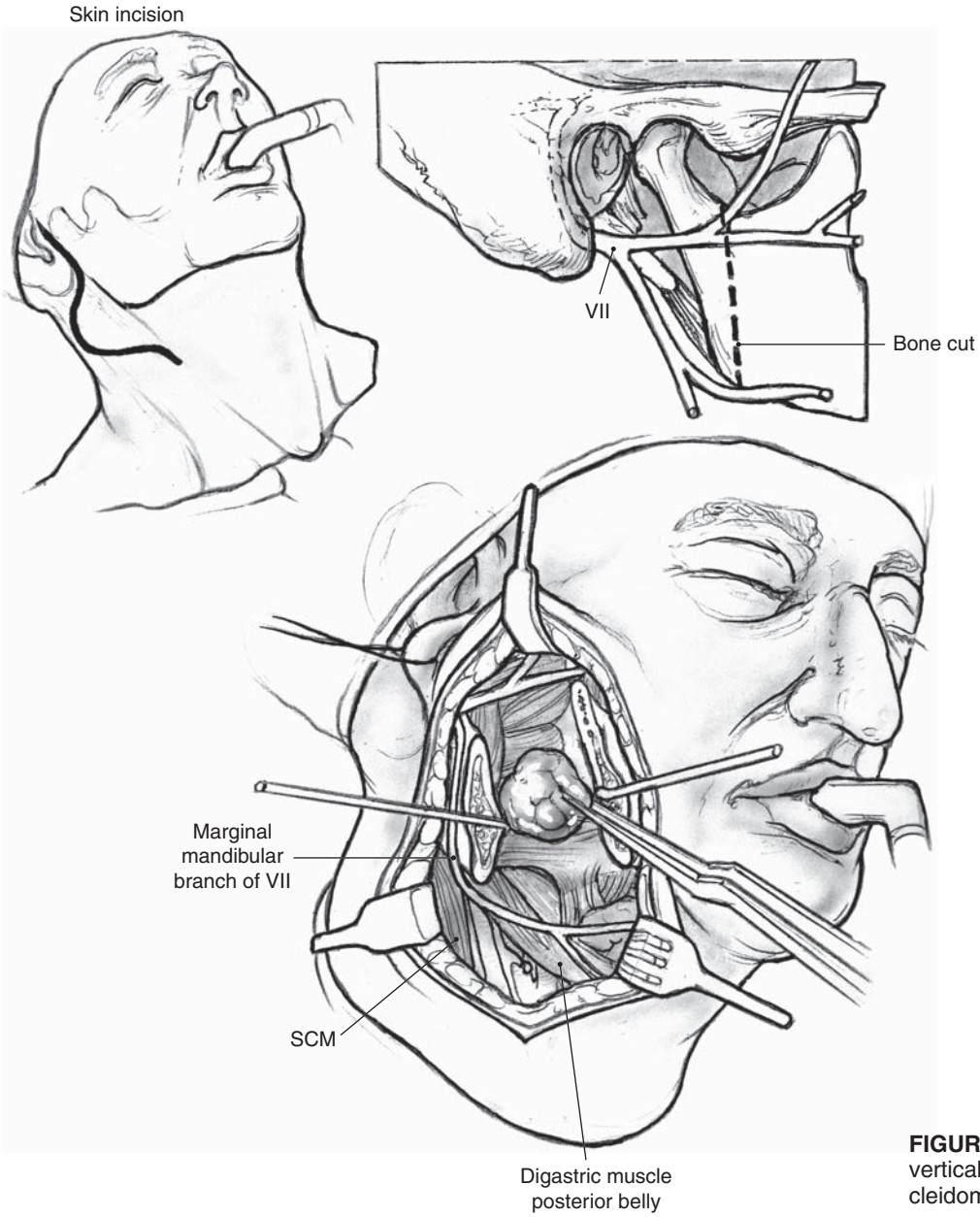


FIGURE 9–10 Panoramic view after vertical mandibulotomy. SCM, sternocleidomastoid muscle.

abuts the facial nerve and a ''partial'' enucleation is performed.[31]

The other major significant reason for recurrence is tumor rupture and spillage. The overall rate of recurrence using superficial parotidectomy with facial nerve dissection is 2.6% in a review of 23 publications with 2366 total patients. When the capsule is ruptured using superficial parotidectomy with facial nerve dissection, the rate of recurrence is 5% ($p < .05$).[31] The percentage of mixed tumors that recur during enucleation is 30%.[31] This high rate is because of the heightened incidence of tumor rupture as well as the shearing of tumor pseudopodia that pierce the pseudocapsule. Older, hypocellular tumors (myxoid-type tumors), with focal absence of encapsulation, are also more friable and prone to rupture.[26,27] Hypocellular tumors show greater focal absence of encapsulation (compared with cellular tumors), with tumor merging into normal parotid gland tissue in 70% of cases.[27]

TABLE 9–1 Risk Factors for Recurrence of Benign Mixed Tumors

1. Enucleation
2. Tumor rupture
3. Hypocellular tumors
4. Deep lobe/parapharyngeal tumors
5. Large tumors
6. Younger/female patients
7. Previously recurrent tumors
8. Increased proliferative activity

Other predisposing factors to recurrence include deep lobe tumors that are at an increased risk for rupture.[42] Removal via the perioral approach will increase the chance of rupture and recurrence.[40] Higher recurrence rates are not uniformly reported in younger and female[33,42,43] patients but are a factor in some series.[40] Recurrence rates are higher for previously recurrent tumors.[44] Subsequent recurrence after an initial recurrence occurs at a rate of 25%.[45] If there is one recurrence, additional recurrences can be expected at a shorter interval.[41] The true primary multicentric mixed tumor is very rare.[39]

Tumors in the upper neck attached to the inferior aspect of the parotid gland can be mistakenly diagnosed as lymph nodes and are therefore at times enucleated through an inadequate incision. A watchful waiting approach under this clinical circumstance will inevitably lead to a high rate of recurrence. This situation is managed with superficial parotidectomy with nerve dissection.[46]

Recurrences may also rarely occur in adequately resected tumor. In these cases there may be a characteristic of the tumor that increases its chance for recurrence. Flow cytometric DNA analysis suggests high S-phase fractions are associated with larger tumor size and tendency to recur.[47] Large tumors may recur because of difficulty in their removal, their increased proliferative activity, or for both reasons.

Immunohistochemical staining of pathologic specimens of mixed tumor has also allowed the evaluation of the expression of cell proliferation associated nuclear antigen (K_i-67). The expression of K_i-67 has been correlated with mitotic activity, histological grade, and clinical behavior of tumors, including salivary gland tumors. Proliferation markers are low in hypocellular, myxoid tumors, both primary and recurrent, but the proliferation activity is higher in the uncommon cell-rich recurrent tumors compared with its primary presentation.[37,48] Proliferation activity is markedly higher in epithelial cells of recurrent mixed tumors compared with nonrecurrent tumors. Immunhistochemical markers on recurrent tumors are also higher for progesterone receptor compared with primary tumors.[49]

The differential diagnosis for a recurrent mixed tumor is a malignant transformation of a previously benign mixed tumor, a neuroma, or a lymph node. Fine-needle aspiration can frequently make the diagnosis. A spectrum of treatment options has been promoted for recurrent mixed tumors. Observation can be appropriate in the debilitated or elderly patient, particularly with evidence of benign tumor on fine-needle aspiration. Observation has also been advocated in selected cases if the recurrence is nonprogressive and asymptomatic, waiting for the presentation of the expected multiple sites of recurrence and therefore avoiding multiple surgeries.

Recurrent mixed tumors are multinodular in up to 98% of cases when clinical exam is supplemented with imaging.[38] Resection of a localized lesion close to the thin layer of fibroblasts that surround the tumor will likely result in later recurrence.[50] Unencapsulated nodules are often embedded in surrounding healthy fat tissue and scar tissue, so that total parotidectomy with facial nerve dissection and resection of scar is the first line of treatment for recurrent mixed tumor.[37] Retrograde facial nerve dissection, particularly the likely undisturbed temporal facial nerve branch, has an important potential role in recurrent mixed tumor. Total parotidectomy with facial nerve sacrifice and grafting is an option exercised in selected cases.[45] Resection and reconstruction of overlying skin with a pectoralis myocutaneous flap or radial forearm free flap may be required.

Radiotherapy after surgery for an isolated recurrence in a patient younger than 40 years of age is not indicated. Hearing impairment and malignant degeneration after radiation therapy must be considered. However, treatment of the patient with multicentric and multiple recurrences, particularly in an individual older than 40 years of age, can include surgery followed by radiation therapy. Treatment of recurrent multinodular disease with surgery alone compared with surgery and postoperative radiation resulted in a reduction in subsequent recurrence from 43 to 4% in one series.[51] Neutron radiotherapy is superior to conventional radiotherapy for malignant salivary gland tumors, and it appears promising in patients with multiply recurrent mixed tumors who are not candidates for surgery.[52] Local-regional control remains less both in conventional and neutron radiotherapy for patients with gross residual disease compared with microscopic disease. Radiotherapy will not be effective if a large mixed tumor load remains (see Chapter 13).

Facial nerve injury after surgery for recurrent mixed tumors occurs in up to 40% of cases and the rate increases with each revision procedure.[51] The chance of new relapse and facial nerve injury will be higher in patients treated with prior parotidectomy with nerve dissection than enucleation.[38] Infiltration of the facial nerve is 8 times greater with recurrent tumors.[53] Deep lobe recurrences, recurrences in multiple sites, and extensive scar tissue will increase the rate of facial nerve injury.[54] Intraoperative monitoring of the facial nerve for recurrent tumors is appropriate.

The potential devastation of recurrence cannot be underestimated. One third of patients with recurrent tumors do not ultimately achieve tumor-free status.[40] Recurrent tumors, although benign, can behave (biologically) as malignant tumors, recurring in the deep parotid lobe, neck, or base of the skull, and present formidable or incurable situations.

Myoepithelioma

Myoepitheliomas, benign tumors composed almost entirely of myoepithelial cells and a minor stromal element, comprise 1% of salivary gland neoplasms. Most myoepitheliomas occur in the parotid gland (40%), followed by the hard and soft palate (21%), and rarely in the submandibular gland.[55] There is no gender predilection. They are painless, slow-growing tumors.

Myoepithelial cells lie beneath the ductal and acinar epithelium, typically lining the basement membranes of the salivary glands. These cells combine features of both smooth muscle and epithelial cells.[56] Myoepithelial cells also occur in sweat glands, mammary glands, and the prostate. They contract, helping to express secretions from glandular acini to secretory ducts in the salivary glands.[57]

In the multicellular theory, tumors develop from ectodermally derived differentiated cell types in the adult salivary gland (acinar-duct subunit), with distal cellular elements consisting of intercalated and myoepithelial cells composed of epithelial and myoepithelial elements. Myoepithelioma may represent one end of the spectrum of mixed tumor when one considers that both myoepithelial cells and ductal/acinar epithelial cells may derive from a single stem cell precuror in salivary glands.[56] This theory is substantiated by a shared chromosome *12q* cytogenetic abnormality in these two types of neoplasms.[57]

Myoepitheliomas are smooth-surfaced tumors with a white-colored interior. They have a thin capsule in the parotid gland and are unencapsulated when located in the palate. Microscopically, myoepitheliomas may exhibit solid, myxoid, or reticular growth pattern. The myoepithelial cells may appear spindled, epithelioid, clear, or plasmacytoid[58] (**Fig. 9–11**). The histological variants do not have prognostic significance. Spindle cell variants are the most common.[59] Ductal structures are either absent or very rare. Some investigators state that one or more ductal structures at medium (× 200) to high (× 400) power field excludes a diagnosis of myoepithelioma, and suggest that even rare ductal structures mean that the tumor is a cellular benign mixed tumor.[56] Others state that no more than 5 to 10% of cells should have duct structures for a diagnosis of myoepithelioma.[60] Most authors feel that the myxochondroid stroma of benign mixed tumor should be absent in myoepithelioma, and, if present, the lesion should best be regarded as a benign mixed tumor.[61] As this discussion illustrates, the distinction between cellular benign mixed tumor and myoepithelioma is somewhat arbitrary.

Myoepitheliomas must be distinguished from other tumors with spindle cells, including extracranial meningioma, schwanomma, paraganglioma, fibroma, and leiomyoma. The plasmacytoid variant must be distinguished from a plasmacytoma. Immunohistochemical studies are positive for cytokeratins, vimentin, and S-100 protein and help confirm the myoepithelial nature of the tumor.[56] The rare malignant myoepithelioma may arise from a preexisting mixed tumor or a benign myoepithelioma or more commonly de novo. Malignant transformation is often preceded by a longer clinical course of multiple recurrent benign tumors.[56] Accumulation of p53 protein, perhaps through mutational events, may play a role in malignant transformation.[62]

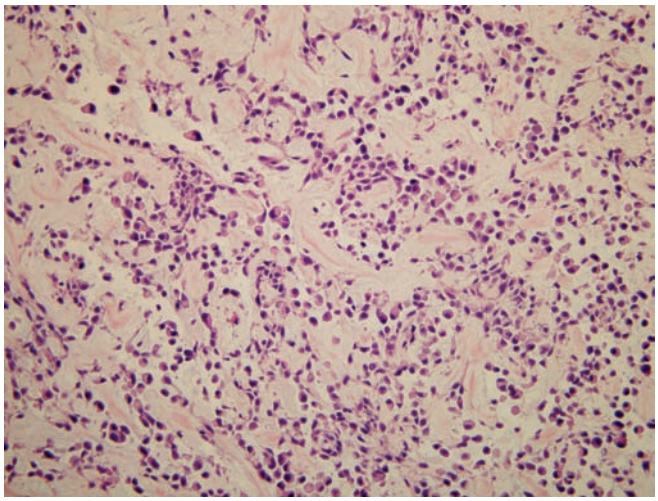


FIGURE 9–11 Histology of myoepithelioma. The cells in this example are plasmacytoid-like, although many other patterns are possible. Immunostaining was done on this neoplasm and showed the cells to be myoepithelial cells (positive staining for cytokeratin and S-100; H&E, ×200).

The treatment of benign myoepithelioma is similar to the mixed tumor, given the similar biologic behavior of the tumor. Recurrence after partial or complete superficial parotidectomy is rare, occurring less commonly than with the mixed tumor.[59] Resection of the palatal presentation would include a cuff of normal tissue.

Warthin's Tumor

The American pathologist Aldred Scott Warthin vividly described two cases as papilliferous in 1929.[63] His eponym is widely used, although Hildebrand has the earliest report in the 19th century.[64]

Presentation

Warthin's tumor, or papillary cystadenoma lymphomatosum, is generally regarded as a true neoplasm confined almost exclusively to the parotid gland. It is the second most common benign neoplasm of the parotid gland, making up 20 to 30% of parotid tumors and

generally occurring between the fourth and seventh decade.[65] The tumor presents as a slow-growing mass, often in the tail of the parotid, although it can become inflamed with a painful presentation and rapid growth after an indolent course for years. Warthin's tumors presenting in minor salivary glands many times are discovered in the lip or palate. They are occasionally found in the parapharyngeal space and submandibular gland. Warthin's tumor can be rarely found in the larynx, lacrimal glands, and nasopharynx.[55]

Multifocal Warthin's tumor occurs in up to 20% of patients.[66] The bilateral presentation in 5 to 6% of cases is a more common finding than in any other salivary gland tumor.[66] Bilateral occurrence has been noted less frequently for oncocytoma, acinic cell carcinoma, and basal cell adenoma.[67] Extraglandular presentation of Warthin's tumor in the neck makes up 3 to 5% of Warthin's tumor.[68] There are sporadic case reports of Warthin's tumor associated with mixed tumor, oncocytoma, or lymphoma.

Warthin's tumor is more common in male patients. An increasing number of female patients are being reported with Warthin's tumor closely correlated with the increase in smoking rates noted in female patients. Thirty to 40% of patients with Warthin's tumor are now female. Over 90% of patients with Warthin's tumor smoke, supporting a correlation between cigarette smoking and Warthin's tumor.[65,69] Warthin's tumor has been considered rare in African Americans; however, an increasing percentage of African Americans are being reported with this tumor.[69] Warthin's tumor is also rare in Africa.[70] Ionizing radiation has been associated with benign and malignant tumors. Study of atomic bomb victims in Hiroshima and Nagasaki, Japan, demonstrates an increased frequency of Warthin's tumor with increasing radiation dose.[71]

Imaging

Nuclear imaging is helpful in Warthin's tumor and oncocytic tumors. Technetium Tc99m pertechnetate uptake is due to the epithelial component (oncocytic portion) of Warthin's tumors, and tumors with a large epithelial component and lesser amounts of cystic spaces show a larger radioactive index.[72] An increased uptake of the isotope is not noted in all Warthin's tumors, and a negative scan does not exclude this tumor.[73] Normal salivary glands and Warthin's tumor concentrate radioactive iodine. This needs to be considered on evaluation of diffentiated thyroid cancer for metastasis.

The tumor contents of Warthin's tumor are best imaged with MRI (**See Chapter 2, Fig. 2–9**). Unilateral, but particularly bilateral, nonenhancing tumor, with well-defined margins on MRI, with a high T2 signal, is likely to be Warthin's tumor.[18] Preoperative imaging with MRI (MRI has superior soft tissue resolution) or CT may determine multifocality or extraparotid origin of Warthin's tumor.

Warthin's tumor may present on imaging as a cystic parotid lesion. Using ultrasound, hypoechoic areas may represent the cystic component of Warthin's tumor. Other cystic parotid lesions include benign lymphoepithelial lesions, branchial cleft cysts, chronic sialadenitis, cystic low-grade mucoepidermoid carcinoma, cystic mixed tumor, lymphangioma, and lymphoma. For unknown reasons positron emission tomography may result in high fluorine-18-fluorodexyglucose (FDG) accumulation in the parotid gland in patients with Warthin's tumor.[74]

Pathogenesis

The pathogenesis of Warthin's tumor is not fully understood (**Table 9–2**). The parotid gland is the first to develop embryologically and the last to be encapsulated. The most popular hypothesis on the pathogenesis of Warthin's tumors is the incorporation of salivary ducts in lymphatic tissue during late encapsulation.[75] Another hypothesis is that the tumor arises from heterotopic salivary ducts within preexisting lymphoid tissue or periparotid lymphoid tissue.[76] In the reserve cell theory, Warthin's tumor derives from intercalated ducts. It has also been proposed that Warthin's tumor is not a neoplasm, but rather a metaplastic process with a secondary lymphoid reaction. The nonclonal nature in one study of Warthin's tumor determined by the polymerase chain reaction method suggests that Warthin's tumor may be a nonneoplastic tumor-like condition.[35] The higher incidence of autoimmune disorders (Hashimoto's thyroiditis, autoimmune hyper- and hypothyroidism) in patients with Warthin's tumor and the higher rates of smoking promote an autoimmune or inflammatory role in the formation of Warthin's tumor.[77] Warthin's tumors that are predominantly epithelial in cellular consistency are smaller than

TABLE 9–2 Theories of the Genesis of Warthin's Tumor

1. Warthin's tumor results from the incorporation of salivary ducts in lymphatic tissue during late encapsulation
2. Warthin's tumor arises from heterotopic salivary ducts within preexisting lymphoid tissue or periparotid lymphoid tissue.
3. According to reserve cell theory, Warthin's tumor derives from intercalated ducts.
4. Warthin's tumor is not a neoplasm but rather a metaplastic process with a secondary lymphoid reaction.
5. Warthin's tumor may initially develop from an adenomatous epithelial proliferation followed by lymphocytic infiltration.
6. Epstein-Barr virus genome is an inciting factor.
7. Enzyme type 2 nitric oxide synthase is a stimulating factor.

the classic or lymphoid predominant tumors, suggesting that Warthin's tumor may initially develop from an adenomatous epithelial proliferation followed by lymphocytic infiltration.[78]

Lymph nodes are found within the parotid gland, and these nodes can contain salivary tissue. The late encapsulation of the parotid may be why lymph nodes adjacent to but separate from the parotid may also contain salivary gland tissue, explaining the finding of salivary tumors in the upper neck, not in continuity with the parotid gland. Warthin's tumor may result from a proliferation of these salivary gland rests.[79]

Using in situ hybridization techniques, the Epstein-Barr virus genome was first detected in the cytoplasm of neoplastic cells of multiple or bilateral Warthin's tumor at a rate of 87% compared with 17% for solitary Warthin's tumor. This suggested a strong association between infection of cells with this virus and the development of multiple or bilateral Warthin's tumor.[80] Other evidence refutes Epstein-Barr virus as a cause of Warthin's tumorogenesis. Ogata et al[81] found Epstein-Barr DNA in 62% of Warthin's tumors; however, in situ hybridization for Epstein-Barr ribonucleic acid (RNA) showed that the nuclei of the neoplastic epithelial cells of all tumors were negative. Although in situ hybridization for Epstein-Barr virus DNA revealed that the nuclei of the neoplastic epithelial cells were positive in 4 of the 21 tumors, the positive cells were sparsely distributed, and there was no evidence of monoclonal proliferation of Epstein-Barr-positive neoplastic epithelial cells.[81]

Immunohistochemical studies have identified prolonged nitric oxide production by the enzyme type 2 nitric oxide synthase implicated in the pathogenesis of many solid tumors. Nitric oxide and type 2 nitric oxide synthase are known to be associated with p53. A significant association between enzyme type 2 nitric oxide synthase and p53 staining is identified in Warthin's tumors.[82]

Cytology

The typical cytologic features of Warthin's tumor are oncocytic epithelial cells and lymphocytes (**Fig. 9–12**). The epithelial cells are usually present in cohesive sheets. The lymphocytes are cytologically benign and may be predominantly small mature lymphocytes or a heterogeneous lymphoid population with mixed small and large lymphocytes, corresponding to follicle formation (germinal centers) in the lymphoid stroma. Many Warthin's tumors have a cystic component, and aspirated cyst contents may have a brown, turbid, ''motor oil'' gross appearance. Microscopically, the cyst fluid contains degenerated cells, proteinaceous fluid, and cholesterol clefts.[83] Various metasplastic changes may occur in the epithelium of Warthin's tumor, including squamous metaplasia, mucinous metaplasia, and sebaceous differentiation.

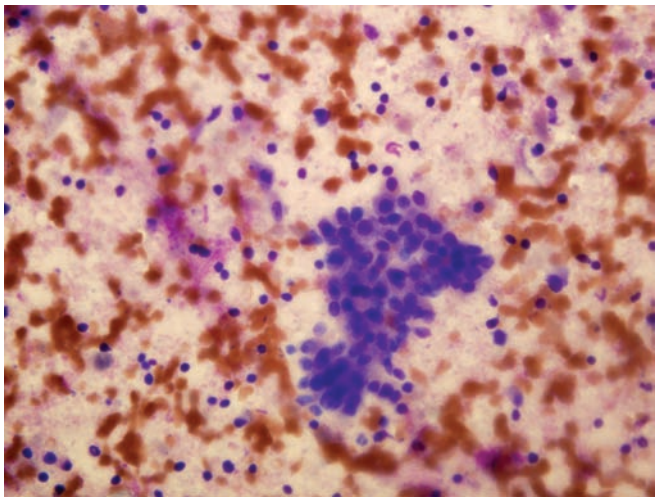


FIGURE 9–12 Fine-needle aspiration of Warthin's tumor, showing mixed oncocytes (the larger, cohesive cells) and background small benign lymphocytes (Diff-Quik stain, ×400).

Fine-needle aspiration of Warthin's tumor may be nondiagnostic if only the cyst contents are aspirated. It is important to sample a residual solid mass if a cyst is aspirated. CT-guided fine-needle aspiration may reduce sampling error, avoiding the pitfall of a nondiagnostic aspiration of the cystic component of the salivary gland mass. If a lymphocyte-rich area is aspirated, an erroneous diagnosis of a lymphoproliferative lesion such as lymphoma may be entertained. If predominantly oncocytic epithelium is sampled, it may be difficult to distinguish Warthin's tumor from oncocytoma. Squamous metaplasia in Warthin's tumor may be mistaken for squamous cell carcinoma or mucoepidermoid carcinoma.[84]

Postaspiration histological changes of Warthin's tumor can include infarction, fibrosis, and exuberant squamous metaplasia.

Histology

Warthin's tumors are encapsulated with a smooth or lobulated surface. Cystic areas on gross cross-sectioning may contain a brownish fluid. Warthin's tumor consists of oncocytic epithelium, frequently with papillary architecture, with a lymphoid stroma and cystic spaces. The columnar oncocytic epithelium is bilayered with oxyphilic granular cells (**Fig. 9–13**). The oncocytic cells contain excessive mitochondria that show frequent structural abnormalities and reduced metabolic function. An increase in mitochondrial DNA damage secondary to smoking has been hypothesized.[85] Immunohistochemistry using antimitochondria antibody may

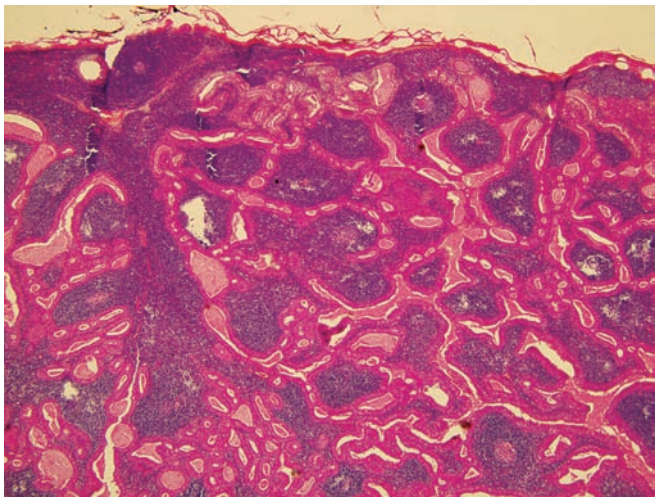


FIGURE 9–13 Histology of Warthin's tumor. These lesions show bilayered oncocytic epithelium and a dense, lymphoid stroma (H&E, ×40).

help in the identification of oncocytic cells.[86] Metaplastic (infarcted) Warthin's tumor is characterized by replacement of the original oncocytic epithelium by squamous metaplasia along with extensive necrosis, fibrosis, and inflammatory change that can be misinterpreted for malignancy. Metaplastic Warthin's tumor may occur spontaneously or after fine-needle aspiration.[87]

Four subtypes of Warthin's tumor have been characterized. Subtype 1 has an epithelial tumor component of 50%. It occurs in 77% of cases. Oncocytic differentiation and focal metaplasia to goblet cells or squamous epithelium are found. Subtype 2 is lymphoid stroma poor with an epithelial component of 70 to 80%. It appears like an oncocytoma in areas and occurs in 14% of cases. Subtype 3 is lymphoid stroma rich with an epithelial tumor component of only 20 to 30%. Subtype 3 is found in 2% of cases. In subtype 4, large areas of squamous cell metaplasia and regressive changes are identified. This subtype is seen in 7% of cases. The different subtypes are not associated with different biologic behaviors.[88]

Immunohistochemistry of cytokeratin expression for Warthin's tumor and its metaplastic variant indicates that both express cytokeratins 7, 8, 18, and 19, typical for columnar differentiation. The expression of cytokeratins 5/14 and 17, which are typical of regenerative cells, is restricted to basal cells in Warthin's tumor but is expressed in basal and also in surface cells in metaplastic Warthin's tumor.[89]

Genetics

Warthin's tumor has been successfully karyotyped, and clonal numerical and/or structural changes have been detected in some of these tumors. Two recurrent abnormalities include the −6p rearrangements and t(11;19) in almost half of Warthin's tumor cases.[90] Clonal alterations in this study support that Warthin's tumor is a true neoplasm rather than an autoimmune- or hypersensitivity-related tumor-like condition.[90]

The follicular lymphoid infiltrate in Warthin's tumor is polyclonal when examined by polymerase chain reaction technology. T- and B-cell markers indicate normal lymphoid populations in Warthin's tumor. DNA is largely diploid.

Treatment

A highly accurate diagnosis of Warthin's tumor by fine-needle aspiration may prompt conservative management in selected cases. An overall diagnostic accuracy rate of 70% by fine-needle aspiration and not higher suggests that histological confirmation is still necessary in many cases.[91] Enucleation of Warthin's tumor has been advocated to reduce morbidity,[92] but without imaging studies it increases the risk of failing to remove multicentric tumor. Partial superficial parotidectomy and complete superficial parotidectomy are standard treatment options.[93] Wide exposure and careful palpation are recommended to appreciate multicentricity. Total parotidectomy has been promoted because of multicentricity. Many clinicians do not advocate long-term follow-up,[93] but metachronous Warthin's tumors even after prolonged follow-up has led some to advocate long-term-follow up.[79] Extraglandular Warthin's tumors make up 3 to 5% of Warthin's tumors and are treated surgically with few recurrences.[79] Malignant transformation of Warthin's tumor most often to mucoepidermoid carcinoma is reported in 1% of cases.[94]

■ Basal Cell Adenoma

In older classification schemes, all benign salivary gland neoplasms that lacked chondomyxoid stroma were termed *monomorphic adenomas*. The various types of tumors that fell under this heading were split out as different named types of monomorphic adenomas in the 1970s, and by the time of publication of the second Armed Forces Institute of Pathology fascicle, eight different types of monomorphic adenomas were recognized.[83] Basal cell adenoma was one of these tumor types. When the World Health Organization revised the classification system once again in 1991, the umbrella term *monomorphic adenoma* was dropped, many of the subtypes were renamed, and several were grouped under the term *basal cell adenoma*.

Basal cell adenomas make up 2 to 5% of salivary gland tumors. Seventy-five percent occur in the parotid and 5% in the submandibular gland. The upper lip is the

most common presentation of a minor salivary gland basal cell adenoma, followed by the buccal mucosa.[55] There is a female predominance of this tumor by a 2:1 ratio. Basal cell adenoma occurs later in life, when compared with a mixed tumor, with a peak incidence in the seventh decade of life. Such tumors rarely occur in children. They appear as solitary masses, excluding the membranous subtype, which is often multifocal.[95] They are hard to palpation, apart from the basal cell adenoma with a large cystic component. They are mobile, except when located on the hard palate.

Basal cell adenomas are solid, well-circumscribed tumors that have a pinkish brown or gray appearance on cut surface. They are encapsulated in the parotid but unencapsulated in minor salivary glands. On aspiration, they are composed of small, basaloid cells with a microacinar architecture. Basal cell adenoma is distinguished from mixed tumor by the absence of the chondroid and myxoid foci that typify mixed tumors and facilitate its recognition on fine-needle aspiration[55] (**Fig. 9–14**). Fine-needle aspiration may distinguish basal cell adenoma from mixed tumor, cyst, lipoma, or lymph node. The most difficult cytological distinction is between basal cell adenoma and other tumors with a predominance of basaloid cells, such as cellular mixed tumor, basal cell adenocarcinoma, and adenoid cystic carcinoma. The distinction between basal cell adenoma and cellular mixed tumor is of little clinical importance, but distinction from the malignant tumors is a serious clinical issue. Clinical factors of facial nerve dysfunction or imaging studies showing invasion point to an adenoid cystic carcinoma. The location in a minor salivary gland would also favor adenoid cystic carcinoma, given that minor salivary glands often host adenoid cystic carcinoma. Cytological features of the cell–stroma interface are useful in distinguishing basal cell adenomas of the solid type and the adenoid cystic carcinoma. The collagenous stroma in basal cell adenomas interdigitates with adjacent cells in basal cell adenoma. In adenoid cystic carcinoma the two are separated by a sharp, smooth border. Given the difficulty distinguishing a basal cell adenoma from the solid form of adenoid cystic carcinoma by fine-needle aspiration, along with the divergent clinical implications, the diagnosis is best left to the histology.[96] On histology the distinction is more evident, with basal cell adenomas being circumscribed and not invading surrounding tissue.

Histology shows basaloid cells in a variety of architectural arrangements with a minimal amount of collaganized stroma, but without the abundant myxoid matrix that is required for the diagnosis of benign mixed tumor (**Fig. 9–15**). Subtypes of basal cell adenoma include tubular, trabecular, solid, and membranous or dermal analogue tumor.[55] Membranous basal cell adenomas are typically located in the parotid gland and are known for a high recurrence rate in part because they are not encapsulated. Bilateral occurrence is reported for the membranous subtype but is not seen in the tubular or other subtypes of basal cell adenoma. The membranous basal cell adenomas have a high rate of malignant transformation, giving rise to basaloid adenocarcinoma ex-monomorphic adenoma.[97] They not infrequently occur in association with dermal adnexal lesions. Membranous basal cell adenoma has a clinical and histological resemblance to dermal cylindroma, sharing similar incidence of alterations at the 16q12–13 region, supporting a common molecular origin.[98]

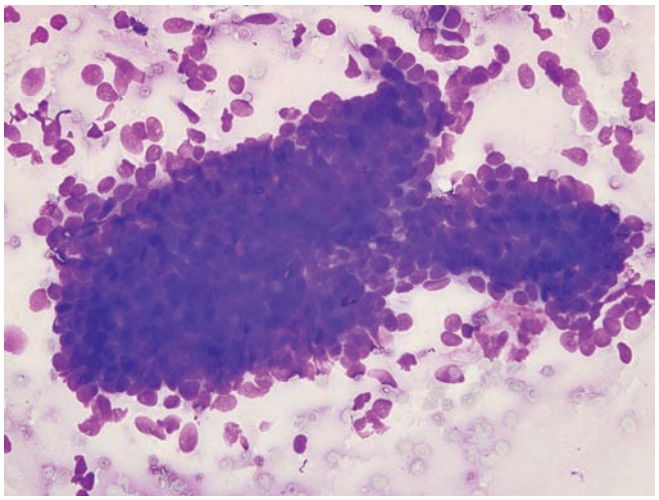


FIGURE 9–14 Fine-needle aspiration of basal cell adenoma. Aspirates of these lesions may show a variety of patterns. All contain small, basophilic cells without fibrillary matrix material (Diff-Quik stain, ×400).

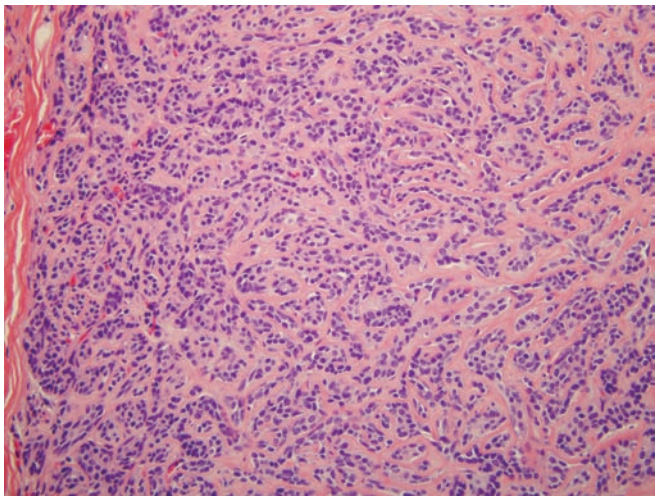


FIGURE 9–15 Histology of basal cell adenoma. The tumor is composed of small nests of basaloid cells surrounded by basement membrane material (H&E, ×200).

Treatment of basal cell adenoma is excision with a normal cuff of surrounding tissue. They uncommonly recur (with the exception of the membranous subtype) when treated by superficial or partial superficial parotidectomy with nerve dissection. The multifocal nature of membranous basal cell adenoma suggests treatment with total parotidectomy.[97] Submandibular or minor salivary gland tumors should be treated with resection of the submandibular gland with the tumor or resection of the minor salivary gland tumor with a rim of normal tissue.

■ Canalicular Adenoma

Canalicular adenomas were separated from monomorphic adenomas and basal cell adenomas in 1991, and they are now classified separately from them.[99] They arise almost exclusively from minor salivary glands and seldom occur outside the oral cavity. Like basal cell adenomas, canalicular adenomas are found more commonly in females and in an older population of patients in their seventh decade of life. These slow-growing asymptomatic masses occur most commonly in the upper lip and are the second most common upper lip salivary gland tumor after the mixed tumor.[55] The second most common site is the buccal mucosa, and they rarely are found in the parotid. They can be multifocal.[100] They are encapsulated with branching and interconnecting cords of double cell thick rows of bland, basaloid, cuboidal to columnar epithelium in a loose stroma without mesenchymal tissue.[15] Myoepithelial cells are usually not part of the tumor, and thus immunostains for smooth muscle actin or smooth muscle myosin are negative.[101] This can be helpful in the distinction between canalicular adenoma and other benign adenomas, such as benign mixed tumor or basal cell adenoma. Treatment is superficial or partial superficial parotidectomy. Recurrences are rare.

■ Oncocytoma

Oncocytomas usually present in the sixth through ninth decade of life as a solitary parotid mass with rare multicentric and bilateral occurrence. They have an equal gender distribution. They account for 1% of salivary gland neoplasms, originate from oncocytes, and are found mostly in the parotid gland, occasionally in the submandibular gland, and rarely in the minor salivary glands. They can be bilateral in up to 7% of cases.[102] When associated with radiation exposure, they occur 20 years earlier than the mean age for patients with oncocytoma not exposed to radiation.[103]

Oncocytes are epithelial cells with accumulations of mitochondria. They are found predominantly in salivary gland tissue but also in the thyroid, parathyroid, respiratory tract, pituitary, pancreas, and the kidney. Oncocytic cells in the salivary glands can be categorized as oncocytic metaplasia, oncocytosis, and oncocytoma. Oncocytic metaplasia is a transformation of acinar and ductal cells to oncocytes. This is a phenomenon associated with aging and most often occurs after age 50. Oncocytic metaplasia occurs in oncocytomas, mixed tumors, and mucoepidermoid carcinoma (**Table 9–3**). Oncocytosis is the proliferation of oncocytes in the salivary glands either diffusely or in foci that produce microscopic or macroscopic nodules. An oncocytoma is a clinical entity, larger than focal oncocytosis with at least partial encapsulation.[15] In the multicellular theory, oncocytic tumors derive from striated duct cells.

TABLE 9–3 Where Oncocytic Cells, Epithelial Cells with Accumulations of Mitochondria, Are Found

1. Oncocytoma
2. Clear cell oncocytoma
3. Mixed tumor
4. Warthin's tumor
5. Malignant oncocytoma
6. Adenoid cystic carcinoma
7. Mucoepidermoid carcinoma
8. Adenocarcinoma
9. Distant metastasis from thyroid carcinoma or renal cell carcinoma
10. Oncocytic metaplasia
11. Oncocytosis

On fine-needle aspiration, a monotonous population of enlarged cells with abundant, granular cytoplasm is seen (**Fig. 9–16**). In surgical specimens, most oncocytoma are well circumscribed and encapsulated. Minor salivary gland oncocytomas, in contrast, are not encapsulated and have less defined borders. Oncocytomas are composed of sheets of oncocytes that are granular eosinophilic cells as a result of abundant mitochondria

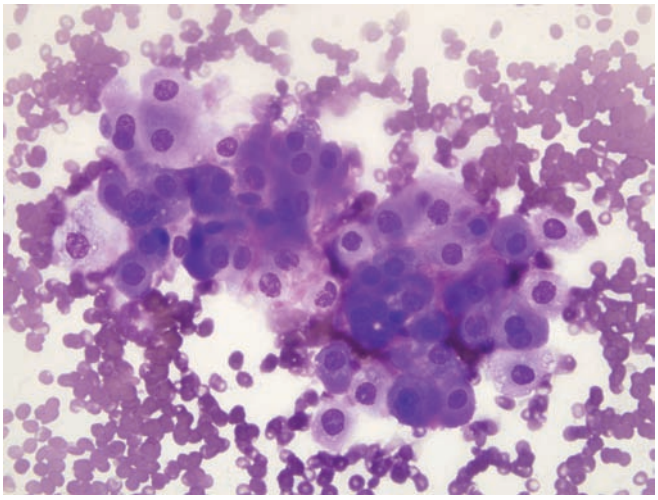


FIGURE 9–16 Fine-needle aspiration of oncocytoma. The smear shows a monotonous population of oncocytic cells with abundant granular cytoplasm (Diff-Quik, ×400).

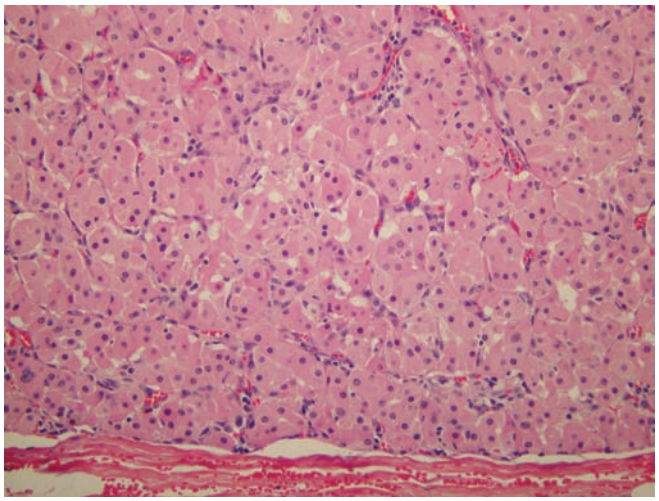


FIGURE 9–17 Histology of oncocytoma. These encapsulated tumors are usually solid and contain large cells with pink granular cytoplasm (H&E, ×200).

(**Fig. 9–17**). A true oncocyte has no lymphoid cells, differing therefore from the Warthin's tumor.[55] Other tumors with oncocytes must be excluded, including the benign mixed tumor, malignant oncocytoma, adenoid cystic carcinoma, mucoepidermoid carcinoma, and adenocarcinoma.[15] Benign oncocytoma has a lower K_i-67, a measure of proliferative activity determined by immunohistochemistry, than the K_i-67 of a malignant oncocytoma.[104] Metastatic renal cell tumor and thyroid tumors that contain a large number of oncocytes also must be differentiated from primary salivary gland oncocytoma.[15]

Radionucleatide scanning with technetium 99m pertechnetate results in uptake and retention. Most parotid and submandibular cases of oncocytoma are predictable and readily cured by surgery. Multifocal growth pattern and incomplete excision account for recurrent cases.

A variant of oncocytoma is clear cell oncocytoma, in which glycogen is also present in the cells, and the mitochondria are marginated to the edges.[105] The presence of glycogen imparts a clear appearance to the cells of hematoxylin-eosin (H&E) staining. The differential diagnosis of clear cell oncocytoma is different from traditional oncocytoma and includes other clear cell tumors, such as metastatic renal cell carcinoma, sebaceous neoplasms, and mucoepidermoid carcinoma.[106] The biologic behavior of clear cell oncocytoma is the same as for traditional oncocytoma.

Treatment of parotid and submandibular oncocytomas is complete surgical resection, and most follow a benign outcome. Oncocytic tumors of the minor salivary glands are distinctive from the major salivary gland tumors. Minor salivary gland oncocytomas are less predictable, grow in irregular patterns, and can be locally invasive to cartilage and bone. Most of these rare tumors arise from the minor salivary glands of the false vocal folds and ventricles. They may occur at any site in the laryngeal mucosa. They present as a painless mass in patients over 50 years of age, often in individuals with a smoking history. There is no gender predilection. Hoarseness, cough, and airway obstruction are possible when located in the larynx. On physical exam they appear as a polypoid laryngeal mass. The tumor can be multifocal with local destruction of laryngeal cartilage even when the neoplasm does not have any malignant features. CT imaging can be similar to a cyst of the laryngeal saccule. Grossly, they present as smooth and round cysts. They can have numerous small cysts with papillary projections and can have a similar histological appearance to a Warthin's tumor minus the lymphoid stroma. Classic Warthin's tumor can also present rarely in the larynx. They are part of a spectrum of clinically benign cystic and papillary lesions. They are derived from oncocytic metaplasia and hyperplasia of minor salivary gland ducts, referred to as papillary oncocytic cystadenoma.[15] There is debate as to whether these oncocytic lesions represent true neoplasms. Treatment is endoscopic surgical excision. They generally do not recur after excision. Because multifocal presentation is possible, close follow-up is recommended. Oral cavity oncocytomas can be oncocytic papillary cystadenomas[107] or more solid oncocytomas.[108] Sinonasal oncocytomas are locally aggressive and characterized by multiple recurrences.[109]

■ Cystadenoma

These unusual multicystic (and occasionally unicystic) neoplasms with papillary proliferations are more common in females, with presentation most commonly in the fifth decade of life. Half of these tumors occur in the minor salivary glands, mostly of the lips and buccal mucosa. Parotid masses make up most of the remaining neoplasms, with 5% occurring in the submandibular glands.[55] They are slow-growing asymptomatic masses. They are often encapsulated and are multicystic masses with papillary fronds covered by bland epithelium.[24] Treatment is excision with adequate margin.

■ Ductal Papilloma

These rare benign adenomas of ductal epithelium feature a papillary growth. The three ductal adenoma subtypes in order of frequency are: (1) intraductal papilloma, (2) sialadenoma papilliferum, and (3) inverted ductal papilloma. They derive from the excretory duct.

Intraductal papilloma is an asymptomatic papillary proliferation causing dilatation of the duct. These

asymptomatic, submucosal neoplasms occur in the fifth and sixth decade of life. They are unicystic (most cystadenomas are multicystic). They distend the duct wall with a papillary proliferation of duct epithelium. They mostly form near the mucosal surface of the excretory ducts of the oral minor salivary glands, with the lip and palate being the most common locations. They are often encapsulated. Their treatment is excision with rare recurrence.[110]

Sialadenoma papilliferum is a very rare tumor that can be clinically mistaken for a squamous papilloma. It occurs in adults, with a slight male predominance. Most of these neoplasms occur in the hard and soft palate, often at the junction, followed by the buccal mucosa.[111] These well-circumscribed, painless, submucosal tumors occur near or at the orifice of the excretory duct near the oral mucosa. The biphasic growth pattern consists of an outer portion with exophytic finger-like papillary projection and an inner endophytic component of glands and ducts.[112] The sialadenoma papilliferum is morphologically similar to the papillary syringoadenoma of the sweat gland.[113] It is treated with surgery. Recurrence rates of 10 to 15% assert a more significant biological behavior than inverted ductal papilloma and intraductal papilloma.[112]

Inverted ductal papilloma also is a luminal papillary proliferation that arises at the junction of the duct and oral mucosa. These minor salivary gland neoplasms present predominantly in the lip and buccal mucosa and have no gender predilection. They occur in adults in their fourth to sixth decade of life. They appear to arise from the excretory duct at a deeper level than the intraductal papilloma.[112] They are circumscribed, painless, submucosal masses that grow in an inverting pattern forming a broad-based mass. Histologically, they resemble the inverted papilloma of the nose and paranasal sinuses. They are treated with surgical resection and rarely recur. They are not associated with malignant degeneration.

Ductal papillomas must be distinguished from other neoplasms with papillary growth pattern, including Warthin's tumor, cystadenoma, mucoepidermoid carcinoma, acinic cell carcinoma, and cystadenocarcinomas.

■ Sebaceous Lymphadenoma and Sebaceous Adenoma

Intraoral sebaceous differentiation, mostly in the buccal mucosa and vermilion border of the upper lip, is expected in 80% of the population, where these glands are known as Fordyce's granules. Approximately 10% of parotid and submandibular glands have sebaceous differentiation.[114] Sebaceous glands are also occasionally found in periparotid lymph nodes. There are no morphologic differences between cutaneous sebaceous glands and the sebaceous glands in a salivary gland neoplasm. These sebaceous cell collections can be found in association with sebaceous neoplasms of the salivary glands.

The sebaceous lymphadenoma is a rare tumor presenting as a painless, slow-growing tumor mostly in the parotid, but occasionally in the minor salivary glands, and even more rarely in the submandibular gland. They occur mostly in patients in the fifth through seventh decade of life. They derive from sebaceous glands located at the blind ends of intralobular ducts. They can be encapsulated both in the parotid and minor salivary glands. Histological exam reveals islands of round-shaped, small, well-differentiated squamous epithelial cells, with focal sebaceous differentiation, lining the walls of cysts.[115] A background of lymphoid stroma with germinal centers is present, suggesting that these neoplasms arise from sebaceous glandular rests in a lymph node similar to what one observes in Warthin's tumor. Surgical excision is the treatment, and recurrence is not expected.

Sebaceous adenomas are very rare tumors presenting as a painless mass, most commonly in the fifth and sixth decade of life. There is a slight male predominance. About 50% occur in the parotid, with most of the rest presenting in the minor salivary glands and a few in the submandibular gland. They are encapsulated neoplasms composed of sebaceous cell rests with squamous differentiation, without lymphoid follicles. Surgical excision is the treatment, and recurrence is not expected.[55]

■ Mesenchymal Parapharyngeal Tumors

Tumors of the parapharyngeal space include deep lobe parotid tumors, neurogenic tumors, paragangliomas, and lymphoma.

Neurogenic Tumors: Schwannomas

The schwannoma is the most common parapharyngeal space neurogenic tumor, constituting 20 to 30% of tumors of the parapharyngeal space.[116] Schwannomas or neurilemmomas arise from the Schwann's cell of the nerve sheath. Only the optic and olfactory nerves lack Schwann's cells. Twenty-five to 45% of all schwannomas occur in the head and neck.[117] After the vestibular schwannoma (acoustic neuroma), the parapharyngeal space is the most common site of a nerve sheath tumor.[117] In the parapharyngeal space they may arise from CN IX, X, XI, and XII, the third division (mandibular) of CN V, the sympathetic nerve trunk, and the upper cervical nerves.[118] Most parapharyngeal schwannomas present in the poststyloid compartment

arising either from the sympathetic chain or vagus nerve, but also CN IX, XI, and XII.[116] Schwannomas arising from the lingual, inferior alveolar, and auriculotemporal nerve may occur in the prestyloid space.

Schwannomas are slow-growing, painless, well-encapsulated, solitary tumors associated with the peripheral nerve of origin. In comparison to intratemporal schwannomas with bony confines and limited space available for tumor extension and early neurological sequelae from nerve compression, parapharyngeal schwannomas can reach a large size before causing symptoms. The female to male gender ratio on presentation is about 2:1. They present commonly between 30 and 60 years of age. They can displace the pharynx and tonsil medially on intraoral exam or present as a cervical mass.[118] Because of stretching and compression of surrounding structures, the associated neurological deficit may not correlate with the nerve of origin.

Imaging is used to detect schwannomas, vascular tumors (paragangliomas), and parotid tumors and to detect if the carotid artery is at risk. CT or MRI studies can usually distinguish between a schwannoma and a paraganglioma[118] (**see Chapter 2, Fig. 2–14**). Both most often present in the poststyloid space. Schwannomas exhibit strong enhancement on gadolinium-enhanced T1-weighted imaging. On T2-weighted imaging with high spatial resolution, facial nerve schwannomas appear as hypointense, round masses.[119] Schwannomas enhance less than paragangliomas and lack the serpiginous flow voids (''salt and pepper'') enhancement pattern of a paraganglioma.[118] Most prestyloid parapharyngeal masses are deep lobe parotid tumors. MRI, CT, and arteriography cannot distinguish between a prestyloid schwannoma (arising from the lingual, inferior alveolar, or auriculotemporal nerve) and a deep lobe parotid tumor.[118]

Fine-needle aspiration may be performed for parapharyngeal tumors, usually to distinguish between a parotid epithelial neoplasm such as benign mixed tumor versus a neurogenic tumor. Although benign mixed tumor is usually a straightforward diagnosis, it is difficult to diagnose neurogenic tumors by fine-needle aspiration and to distinguish between benign and malignant neural tumors. In addition, fine-needle aspiration may cause significant bleeding if the tumor is a paraganglioma. For this reason, imaging prior to surgical resection without fine-needle aspiration is a recommended approach for a poststyloid parapharyngeal mass.

If fine-needle aspiration of schwannoma is performed, aspirates may yield spindle-shaped cells with wavy nuclei. Occasionally, nuclear palisading is seen.[120] Histologically, schwannomas contain Antoni type A tissue with a palisading array of nuclei around a central mass of cytoplasm (Verocay bodies) and/or Antoni type B with a loose surrounding stroma with no distinctive fiber and cell pattern (**Fig. 9–18**). Malignant degeneration is rare.

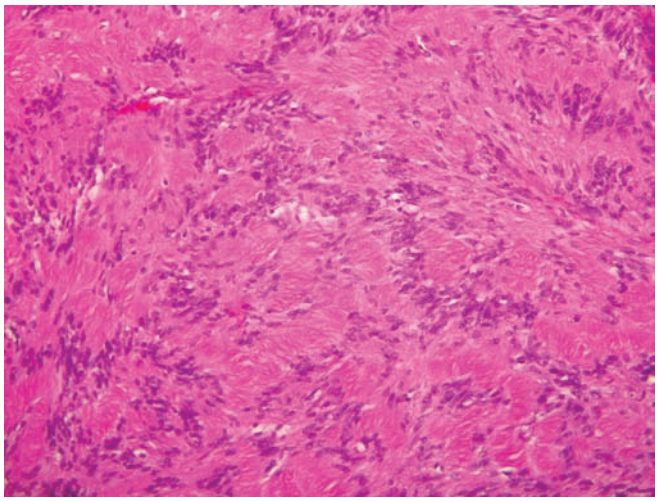


FIGURE 9–18 Histology of schwannoma. These benign neural tumors often show palisaded nuclei (Antoni A areas). (H&E, ×200).

Transcervical surgical approach with or without mandibulotomy (see Chapter 15) is preferred over a transoral approach.[118] A subplatysmal skin flap with preservation of the marginal mandibularis branch of the facial nerve is followed by ligation of the facial artery and vein. The submandibular gland is retracted anteriorly, and the posterior belly of the digastric is skeletonized or divided. The stylomandibular ligament is released, and access to the parapharyngeal space is achieved. Parotidectomy and removal of the styloid process can enhance exposure for superior extension.

Schwannomas arise eccentrically from the outer surface of the nerve sheath and can be dissected from the nerve of origin. This is an oversimplification, as the tumor can be intimately involved with the nerve. Dissection of most sympathetic chain schwannomas results in substantial injury to the nerve.[118] This clinically manifests as Horner's syndrome. Vagal schwannomas can extend into the jugular foramen and into the posterior cranial fossa, resulting in multiple cranial nerve dysfunctions. Arteriography and subsequent infratemporal, transmandibular, and transpterygoid approaches may be required.

Schwannomas of the peripheral facial nerve are rare, with most presenting in the intratemporal portion of the facial nerve. They can reach a large size prior to becoming symptomatic. Gradual onset facial paralysis occurs in 20% of cases.[121] Diagnosis may be suggested by strong enhancement on MRI on gadolinium-enhanced T1-weighted imaging and fine-needle aspiration. Nonetheless, preoperative diagnosis is not always established. Surgery of extratemporal facial neuromas will require a meticulous dissection of the facial nerve, frequently

resulting in nerve damage. This intraoperatively results in a dilemma for the surgeon treating the patient who has normal preoperative facial nerve function. In the patient with an established preoperative diagnosis of peripheral facial nerve schwannoma, the patient must be advised of the likely outcome of facial nerve grafting. Postponing surgery may delay nerve injury, but as the tumor enlarges, eventual excision will increase the likelihood of facial nerve dysfunction. Radiation therapy may have a potential role.

Paragangliomas

Paragangliomas or glomus tumors derive from islands of neural crest cells comprising part of the diffuse neuroendocrine system or amine precursor and uptake decarboxylase (APUD) system. The diffuse neuroendocrine system includes a group of cells throughout the body that produce and secrete neurotransmitters converting biologic amines such as dopa and dopamine to neurotransmitters, including norepinephrine and epinephrine. The conversion of norepinephrine to epinephrine is catalyzed by phenylethanolamine-*N*-methyltransferase that exists only in the adrenal medulla and in a few neurons in the central nervous system. Head and neck paragangliomas, therefore, do not secrete epinephrine, but do accumulate norepinephrine. All paragangliomas have neurosecretory granules seen by electron microscopy, but only 1 to 3% are functional.[122]

Approximately 90% of tumors arising from paraganglia are pheochromocytoma from the adrenal gland, where most chromaffin cells are located. Most extra-adrenal tumors are located in the abdomen, with a smaller number from the thorax. Three percent of extra-adrenal tumors are located in the head and neck. Eighty percent of head and neck paragangliomas concentrate in the carotid bifurcation (carotid body tumors).[123] In descending frequency, the adventitia of the jugular bulb (superior ganglion–glomus jugulare) and ganglion nodosum (inferior ganglion–glomus vagale) of the vagus nerve, followed by the middle ear (glomus tympanicum), are the other locations of head and neck paraganglioma. They present usually as solitary tumors. Ten percent of cases are multiple, presenting with paragangliomas of the neck, or neck combined with adrenal or extra-adrenal site.[124] They can be associated with multiple endocrine neoplasia type II (pheochromocytoma, medullary thyroid carcinoma, and hyperparathyroidism) and neurofibromatosis type I.[125] Ten percent of patients have a family history of paraganglioma, and in these patients one in four will have multiple paragangliomas.[126] Chronic hypoxic stimulation from living at high altitude is a contributing cause.

Paragangliomas often present in the fourth through sixth decades of life. They may be asymptomatic or present with hoarseness, dysphagia, aspiration from vocal cord paralysis, tongue hemiatrophy, palatal weakness, Horner's syndrome, and pain. The superior jugular ganglion paraganglioma (glomus jugulare) can extend beneath the skull base into the parapharyngeal space, having both an intracranial and extracranial component. The extracranial component is often intraluminal in the jugular vein. Vagal paraganglioma (glomus vagale) from the inferior ganglion are located between the skull base and hyoid bone, presenting commonly as a painless neck mass at the angle of the mandible. Paragangliomas only rarely secrete catecholamines. Therefore, preoperative 24-hour urine collection for norepinephrine and metabolites, including vanillymandelic acid, is not routinely performed for head and neck paraganglioma unless the patient has a suggestive history of palpitations, tachycardia, flushing, or excessive perspiration.

Parapharyngeal paragangliomas arise in the poststyloid compartment. CT and MRI have improved diagnosis of paragangliomas, with MRI venography and angiography adding to the definition of these tumors. Whereas carotid body paragangliomas are at the bifurcation of the internal and external carotid arteries, vagal paragangliomas displace the internal and external carotid arteries anteromedially and the internal jugular vein laterally. CT is best in determining bone involvement. MRI is superior in evaluating intracranial and vascular encroachment. Imaging in multiple planes is now possible with both CT and MRI. Paragangliomas exhibit a classic salt-and-pepper appearance on MRI because of hemorrhage and vascular flow voids, respectively.[118]

Paraganglia of the head and neck are neuroectoderm-derived chromaffin cells in extra-adrenal sites. Chromaffin cells secrete and store catecholamines. Paragangliomas have a high density of somatostatin type 2 receptors on the cell surface. Octreotide is a somatostatin analogue that when coupled to a radioisotope (indium 111) produces a scintigraphic image of these tumors both primary and recurrent.[127] Noninvasive studies have replaced angiography as the primary diagnostic tool; however, presurgical angiographic evaluation and percutaneous transcatheter arterial embolization continue to play an important role in the management of these tumors in selected cases.[128]

Paraganglioma recapitulate the architecture of normal paraganglia. Paragangliomas are grossly firm, brown tumors with a pseudocapsule. Microscopically, they exhibit clusters of chief cells (type I, epithelioid cells) separated by a vascular stroma. The clustering pattern is known as zellballen (from the German meaning ''cell balls'').[129] The sustentacular cells (type II supporting

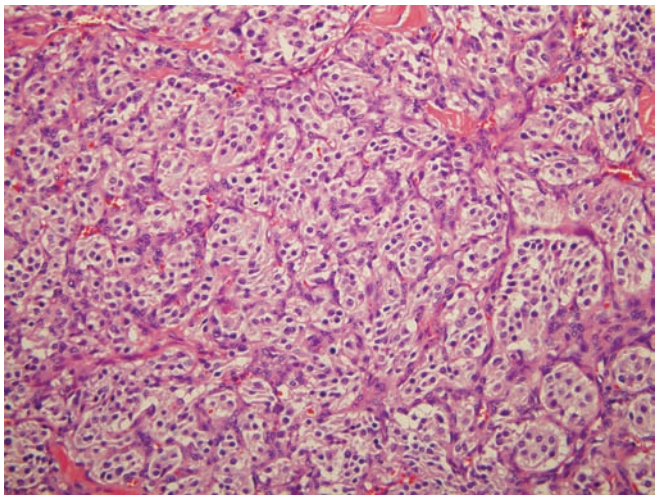


FIGURE 9–19 Histology of paraganglioma. These distinctive neoplasms contain nested neuroendocrine cells in balls (zellballen), surrounded by sustentacular cells (H&E, ×200).

cells) surround the edge of the cell balls (**Fig. 9–19**). Chief cells are immunoreactive to neuroendocrine markers, including synaptophysin, neuron-specific enolase, and chromogranin A.[130] Sustentacular cells are immunoreactive to S-100 protein. Paragangliomas are similar histologically to adrenal pheochromocytoma.

Five percent of jugulotympanic and 10 to 15% of vagal paragangliomas are malignant.[131] Malignant paragangliomas do not display nuclear and cellular pleomorphism and vascular or perineural invasion and are therefore not histologically distinguishable from benign paragangliomas.[132] They are distinguished from benign tumors clinically by invasion and metastasis. Because paragangliomas can be multiple, metastasis is suggested when lesions are present at sites where paraganglioma tissue is not expected, such as cervical lymph nodes.

The most common genetic defect is the *PGL1* gene at chromosome band 11q23. Genetic loci at *PGL1, PGL2,* and *PGL3* are involved with familial transmission.[133]

Surgical management of paraganglioma is very challenging because multiple cranial nerves are often involved, with invasion of the skull base and intracranial extension. Observation with serial imaging studies must be presented to the patient. Focused radiation therapy can be used for selected high-risk tumors with expected postoperative multiple lower cranial nerve dysfunctions, recurrent tumors, bilateral tumors, incompletely resected tumors, or metastatic tumors. Paragangliomas often show no signs of progression after radiation therapy.[134]

If surgery is elected, an active skull base team consisting of a head and neck surgeon, vascular surgeon, neuro-otologist, neurosurgeon, neuroradiologist, and speech pathologist is necessary. A lateral approach starts with a level 2 and 3 selective neck dissection to improve access and rule out metastasis. The internal carotid artery, jugular vein, and CN IX, X, XI, and XII are identified. A small vagal paraganglioma may be removed using only a cervical approach. The tumor may be adherent to the carotid artery, and a bypass procedure may be required. Preoperative balloon occlusion test should be considered if the carotid artery appears at risk near the skull base. If the tumor approaches the jugular foramen, the jugular foramen may need to be exposed from a transmastoid approach. Removing the styloid process and associated musculature improves the exposure to separate the tumor from the carotid artery. With intracranial extension, superior control of the internal carotid artery deep to the glenoid fossa is necessary. Treatment of a dural defect can be managed with a fat graft or a superficial temporoparietal fascia flap.

Resection of these tumors generally requires sacrifice of the vagus nerve, but multiple lower cranial nerves can be impaired. Type I medialization thyroplasty can be performed at the time of surgery or in a delayed fashion. Delayed treatment allows the addition of the arytenoids adduction suture under local anesthesia and sedation where the responsive patient allows fine-tuning of this delicate procedure. Unilateral palatal adhesion can rehabilitate the palate in patients with velopharyngeal insufficiency.

■ Neurofibromas

Neurofibromas can be asymptomatic and can rarely present in the parapharyngeal space as a solitary neck mass. They are also nerve sheath tumors (along with schwannomas) but in contrast to schwannomas are unencapsulated and grow between the nerve fibers of the parent nerve instead of pushing the nerve to one side. Histological exam reveals a spindle cell lesion with elongated, wavy nuclei. Solitary neurofibromas are best treated by complete surgical resection. In von Recklinghausen's disease (neurofibromatosis) neurofibromas can be multiple and surgical treatment is pursued for symptomatic lesions. Von Recklinghausen's disease is autosomal dominant with variable penetrance with half of patients having a family history and the other half resulting from spontaneous mutation. Initial clinical findings are café-au-lait spots and neurofibroma. Five or more brown cutaneous macules are diagnostic. Neurofibromas in von Recklinghausen's disease mostly involve CN VIII. They can have sarcomatous transformation in von Recklinghausen's disease in 10% of cases.[135]

■ Traumatic Neuromas

Traumatic neuromas may present as a small mass (< 2 cm) in the parotid or submandibular areas. They can be

asymptomatic or present with paresthesia or tingling. Although they are most common after radical neck dissection, they can occur after salivary gland surgery or from blunt trauma to the neck. Traumatic neuromas are an attempt of an injured nerve to regenerate. They are fibrous masses with a mix of neural axons, Schwann's cells, and perineural tissue. Excision is diagnostic, particularly in patients without a prior history of surgery.

■ Other Benign Mesenchymal Tumors: Lipomas

Lipomas are benign, often subcutaneous thinly encapsulated masses of adipose tissue. They occur infrequently in the salivary gland. They can occur in the superficial or deep lobe of the parotid as well as the parapharyngeal space. Lipomas have a wide age range, male predominance, slow growth rate, and are asymptomatic.[136] The ultrasound appearance is hypoechoic. CT and MRI have characteristic appearances with ill-defined margins.[137] Most lipomas of the parotid are composed of mature adipose tissue without myxoid, spindle cell, pleomorphic, or angiomatous features.[55] Lipomas rarely recur after excision.

Sialolipomas have been described as a distinct salivary gland lipoma occurring in major and minor salivary glands. These are lipomas with secondary entrapment of salivary gland elements. Histologically, the tumors have a fibrous capsule of glandular tissue and mature adipose elements without atypia. There is more adipose component in the parotid tumors compared with the minor salivary gland tumors. The glandular components include ductal, acinar, basal, and myoepithelial cells resembling normal salivary gland structures. Their cell proliferative activity measured by K_i67 immunohistochemical staining is low, suggesting glandular components become entrapped during lipomatous proliferation rather than representing true neoplastic elements.[136] Mixed tumors on rare occasion contain extensive fatty components and must be considered in the differential diagnosis. The fatty components in this type of mixed tumor may derive from pluripotential reserve cells of the mixed tumor.[138] The sharp separation of the epithelial component from the adipose element and the presence of normal-appearing acinar cells characterize the sialolipoma and distinguish it from a mixed tumor.[136] Superficial or partial superficial parotidectomy or resection of oral cavity tumor for the minor salivary gland sialolipoma is successful with rare recurrence.

Spindle cell lipomas are asymptomatic, slow-growing masses often 4 to 5 cm in size, occurring in males in their 60s and 70s. They must be distinguished from other spindle cell or mesenchymal tumors, including liposarcoma, schwannoma, leiomyoma, fibromatosis, melanoma, and malignant fibrous histiocytosis. They have mature fat cells, spindle cells in uniform arrangement, and areas of myxoid stromal change.[139] Spindle cell lipoma is cured by simple excision and must be differentiated from more ominous lesions.

Hibernomas are benign lipomatous tumors developing from vestigial remnants of brown adipose cell that have remained from embryonic life.[140] Other distinct microscopic variants of lipoma of the salivary glands include angiolipoma, fibrolipoma, and pleomorphic lipoma.[136] Atypical lipomas are well-differentiated lipomatous lesions that are benign tumors in superficial tissue locations that can recur locally but do not metastasize and are distinguished from liposarcoma.

■ Cysts of the Salivary Glands

About 5 to 10% of all salivary gland diseases are different types of salivary gland cysts (**Table 9–4**). Salivary gland cysts may be acquired or congenital. A true cyst has an epithelial lining in contrast to a pseudocyst as exemplified by a mucocele or a sialocele in the post-parotidectomy patient. Parotid cysts make up ~5% of parotid lesions. Pseudocysts are very common in minor salivary glands. Neoplasia with cystic changes must be excluded in salivary gland cystic lesions. Warthin's tumor is the neoplasm most commonly associated with a cystic component. Benign mixed tumor, mucoepidermoid carcinoma, and adenoid cystic carcinoma are also associated with cyst formation. If fine-needle aspiration of a salivary gland lesion shows only cyst contents, repeat aspiration of any residual mass is important to exclude a neoplasm.

TABLE 9–4 Cystic Salivary Gland Lesions

1. Retention cysts
2. Pseudocysts
   a. Traumatic-minor salivary gland
   b. Obstructive
   c. Ranula
3. Chronic sialadenitis
4. Benign lymphoepithelial cyst
   a. Non-HIV
   b. HIV
5. Type I branchial cleft cyst
6. Dermoid cyst
7. Congenital polycystic parotid gland
8. Lymphangioma
9. Warthin's tumor
10. Cystic mixed tumor
11. Cystadenoma
12. Low-grade mucoepidermoid
13. Adenoid cystic carcinoma
14. Lymphoma

HIV, human immunodeficiency virus

Acquired Cysts

A mucocele lacks an epithelial lining and is not a true cyst, and therefore is a pseudocyst. Mucoceles of the minor salivary gland are the most common salivary gland lesion. Mucoceles occur most commonly in the lips, particularly the lower lip, but also in the buccal mucosa and ventral tongue, during the first four decades of life. Mucoceles have a rapid onset, with fluctuation in size, bluish color, and fluid consistency. They have a preceding history of trauma (i.e., biting the lip) with rupture of the duct and mucous extravasation in the surrounding soft tissues and are surrounded by granulation tissue. Type IV collagenases and plasminogen activators are proteolytic enzymes thought to participate in the formation of mucoceles.[141] Mucoceles contain polymorphonuclear leukocytes and macrophages. Complete excision will prevent recurrence. Mucoceles of the anterior lingual salivary glands (glands of Blandin and Nuhn) can persist if glands of the deep tongue musculature are not excised.[142] Cryosurgery is an alternative management strategy for mucoceles.[143]

Minor salivary gland duct obstruction can result in a mucous retention cyst or sialocyst, a true cyst with an epithelial lining. Retention cysts are less common than mucoceles and do not often have an antecedent history of trauma. They may occur from a partial obstruction of the duct.[55] In the minor salivary glands, they most commonly occur in the lips, but also in the buccal mucosa and ventral tongue. Most patients with minor salivary gland retention cysts are in their fourth decade of life. Complete excision will prevent recurrence.

Retention cysts in major salivary glands are called salivary duct cysts or sialocysts. The cause of the duct obstruction in these epithelial-lined cysts is not always known. They are generally slow-growing, painless lesions. They are usually unilocular, but can be multilocular. Retention cysts are treated with complete excision to prevent recurrence.

Epithelial alterations in salivary duct cysts of the parotid gland and in mucous retention cysts of minor salivary glands include metaplasias (goblet cells, clear cells, squamous cells) and focal epithelial proliferations. These changes are comparable to similar alterations in odontogenic cysts. Retention cysts or salivary duct cysts may be the starting point of a salivary gland tumor such as a cystadenoma or mucoepidermoid carcinoma in rare cases.[144]

Benign Lymphoepithelial Cysts

Benign lymphoepithelial cysts in non-HIV patients form from epithelial ductular inclusions in lymph nodes that then become cystic.[145] They form mostly unilaterally, but occasionally bilaterally, predominantly in adults, in their fourth and fifth decade of life, as painless, asymptomatic masses. Prior to the AIDS epidemic, they were typically identified in the floor of the mouth and less commonly the parotid.

They have a similar histology whether from the major or minor salivary glands. Histological exam shows a squamous epithelial-lined unilocular cyst within or associated with lymph nodes. Multilocular presentation is rare. Fine-needle aspiration of the cyst contents show a population of lymphocytes, histiocytes, plasma cells, and metaplastic squamous cells in a proteinaceous background.[15] It is important to distinguish between lymphoepithelial cysts and various lymphoid lesions, including reactive lymph nodes and lymphoma. Other neoplastic processes with a significant lymphoid component include Warthin's tumor, sebaceous lymphadenoma, and lymphoepithelial carcinoma. Benign lymphoepithelial cysts associated with HIV and those seen in benign lymphoepithelial lesion (or myoepithelial sialadenitis) of Sjögren's are discussed in Chapter 5. Treatment of benign lymphoepithelial cysts depends on symptoms and the suspicion of malignancy.

Branchial Cleft Cysts and Ranulas

See Chapter 8

Sialadenosis

Sialadenosis or sialosis is a noninflammatory, nonneoplastic, mostly symmetric enlargement of the salivary glands, sometimes associated with pain. The parotid glands are most commonly involved, but structural and functional changes can occur in the submandibular and minor salivary glands.[146] The enlargement is gradual, bilateral, but not always symmetric. There is no gender predilection. The peak incidence is between 30 and 70 years of age.[147]

An underlying systemic cause for sialadenosis is almost always found. Three broad headings (**Table 9–5**) for the cause of sialadenosis are endocrine (diabetes mellitus, adrenal disorders), dystrophic-metabolic (alcoholism and malnutrition), and neurogenic (anticholinergic medications disrupting the autonomic nervous system).[148] In contrast, Mikulicz's disease is an historic term that describes patients with asymptomatic enlargement of the salivary glands or lacrimal glands without an underlying disease. Sialadenosis must be distinguished from other causes of bilateral parotid swelling including Sjögren's syndrome, sialadenitis, sarcoidosis, lymphoma, and tuberculosis.

Parotid enlargement has been described in nearly all endocrine disorders. Diabetes is the most common, but it is also observed in hyperthyroidism, hypothyroidism,

TABLE 9–5 Causes of Sialadenosis

Endocrine
1. Diabetes
2. Adrenal disorders
3. Hyperthyroidism
4. Hypothyroidism
5. Pancreatitis
6. Pregnancy
7. Lactation
8. Puberty
9. Menopause
10. Testicular and ovarian atrophy
Dystrophic-metabolic
1. Alcoholism
2. Kwashiorkor
3. Hypovitaminosis
4. Beriberi
5. Pellagra
6. Anorexia
7. Bulimia
8. Chagas' disease
9. Celiac disease
10. Bacillary dysentery
Neurogenic
1. Phenothiazine
2. Phenobarbitol
3. Iodine-containing products
4. Isoproterenol
5. Ethambutol
6. Heavy metals

pancreatitis, pregnancy, lactation, puberty, menopause, and testicular and ovarian atrophy.[55]

Alcoholic cirrhosis is associated with sialadenosis in up to 50% of cases. Sialadenosis is very rare in nonalcoholic cirrhosis. In chronic alcoholics, modification in acinar cells is noted; however, the most evident changes occur in the ductal system, where enlargement is present. Other findings include atrophy of epithelial cells and desquamated cells.[146]

Malnutrition leading to sialadenosis can occur in kwashiorkor, hypovitaminosis, beriberi, pellagra, anorexia, and bulimia. Any disease that interferes with absorption of nutrients can lead to sialadenosis, including Chagas' disease, celiac disease, and bacillary dysentery. Up to half of the patients with bulimia will exhibit sialadenosis. Malnutrition in bulimic patients results in acinar enlargement of the salivary glands with plump pyramidal cells containing prominent zymogen granules.[148]

Salivary gland hypertrophy is associated with medicines including phenothiazine, phenobarbitol, iodine-containing products, isoproterenol, ethambutol, and heavy metals, some that affect the autonomic nervous system.

Sialography in the later stages of the disease demonstrates compression of the proximal ducts by acinar swelling. Early stages of the disease may show no sialographic changes.[148]

Normal acinar cells are 30 to 40 μm, whereas in sialadenosis, the diameters are enlarged to 50 to 70 μm.[149] Acinar cell enlargement and disturbance of secretion in sialadenosis are pathologic findings hypothesized to occur from a peripheral autonomic neuropathy, a demyelinating polyneuropathy.[147] Ultrastuctural support for this notion comes from Donath and Seifert,[149] who have demonstrated degenerative changes both in myoepithelial cells and in the postganglionic sympathetic neurons of the autonomic nervous system, including loss of neurosecretory granules, destruction of mitochondria, hydropic swelling of the axoplasm, and a terminal axolysis. These cellular changes may result in a lengthening of the storage phase of the secretory granules and an arrest in protein synthesis by the acinar cells, both processes producing accumulation of granules and marked enlargement of acini.[150]

Three histological patterns of sialadenosis are recognized: granular, honeycomb or vacuolar transformation, and mixed.[149,150] Ultrastructural evidence reveals that acinar cells in sialadenosis are filled with zymogen granules of three parallel varieties. There is a dark granule type with densely packed protein-rich granules, but no evidence of increased protein secretion. A light granule type contains low optical–density secreting granules and increased synthesis of protein. A mixed granule type has light and dark acinar cells.[149] Fatty infiltration or lipomatosis and fibrosis of the interlobular septae are additional histological findings, along with naked nuclei. Inflammatory infiltrates are not seen.

Sialadenosis can be confused with a tumor, and a biopsy is diagnostic. This can often be accomplished with fine-needle aspiration where normal salivary gland acini and ducts are found. Careful correlation with radiology is essential to make sure that the finding of normal salivary gland tissue is representative of the process and is not merely a sampling error missing a discrete mass.[151] Amylase levels in the saliva and serum are commonly increased, assisting in the diagnosis. A careful history, however, may obviate the need for a biopsy.

Correction of the underlying systemic problem usually results in reduction in the size of the gland. Salivary substitutes, heat application to the swollen salivary glands, and sialagogues can be helpful. Pilocarpine, a cholinergic-mimetic medication, can reduce the parotid gland swelling in the bulimic patient.[152] The salivary gland swelling can be resistant to correction of the underlying problem. Refractory cases are often secondary to an endocrine and neurogenic basis.[148] Surgery is rarely indicated in refractory cases to improve unacceptable appearance.

Other Causes of Salivary Gland Enlargement

Bilateral parotid enlargement is seen in obesity because of fatty infiltration. Obesity is associated with diabetes mellitus and therefore may be caused by sialadenosis. Dehydration with salivary stasis and mucous plugging of salivary ducts result in swelling and pain. This enlargement is readily treated with rehydration, massage of the gland, and sialagogues. Pneumoparotitis can occur after intubation or endoscopy and can be seen in glass blowers.

Sclerosing polycystic adenosis is a rarely reported entity described as a pseudoneoplastic reactive inflammatory process of the major salivary glands similar to sclerosing adenosis of the breast.[153] Patients present at a mean age of 30 and have a female predominance. They develop a slow-growing unilateral mass in the parotid (less often in the submandibular gland) with pain or a tingling sensation. These lesions consist of incompletely encapsulated circumscribed masses characterized by hyalinized and sclerotic collagenous tissue with cystically dilated ducts and focal epithelial hyperplasia.[153,154] Treatment is excision with adequate margins. Recurrences are possible.

Enlargement of the minor salivary glands of the lips in adults with a clear, sticky mucous is called cheilitis glandularis. Excretory duct dilation results in eversion and enlargement of the lip. Three classifications based on clinical and histological findings have been described: simple, superficial, and deep.

Adenomatoid hyperplasia of the minor salivary glands is a rare idiopathic condition resulting in a painless, firm mass covered by intact oral mucosa usually of the hard and soft palate. They occur in the fourth to sixth decade more commonly in male patients. These well-circumscribed, unencapsulated lesions form lobules of normal-appearing mucinous acini within the lamina propria and submucosa. The treatment is excision.[155]

Accessory parotid gland tissue occurs anterior to the parotid in the distribution of the buccal nerve branches of the facial nerve. Heterotopic salivary gland tissue can be identified most commonly in periparotid and intraparotid lymph nodes. The neck at the anterior border of the sternocleidomastoid muscle in the area of the sternoclavicular joint is also an area of salivary gland heterotopia. More unusual locations include the pituitary, mandible, maxilla, lower neck, larynx, hypopharynx, middle ear, thyroglossal duct, mediastinum, prostrate, vulva, stomach, and rectum.[15] Their presumed origin is salivary gland rests. Generally, they are an asymptomatic incidental finding, although they can present as a mass or fistula. Heterotopic salivary gland tissue is treated with simple excision, and neoplasms of heterotopic salivary tissue are treated by the pathology of the tumor.

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10

Malignant Neoplasms of the Salivary Glands

F. CHRISTOPHER HOLSINGER, ADEL K. EL-NAGGAR, LEONARDO TORRES, DAVID I. ROSENTHAL, AND RANDAL S. WEBER

Malignant salivary gland tumors are uncommon and account for less than 1% of all malignancies and ~5% of head and neck cancers. There is an annual incidence of 1 to 2 per 100,000 worldwide.[1,2] These tumors comprise a wide spectrum of phenotypic and biological entities. Given their rarity and biological diversity, there is little evidence-based data to provide conclusive recommendations for treatment and outcome measures for these patients. This is compounded by the development of these tumors in a wide variety of anatomical sites, including both minor and major salivary glands. Unique among head and neck tumors, those of salivary origin may aptly fit the admonition of Hippocrates: ''Experience fallible, judgment difficult.'' Despite these difficulties, general guidelines for the management of these tumors can be drawn from the literature and are presented herein.

Overview

Epidemiology

The Surveillance, Epidemiology, and End Results (SEER) and American Cancer Society registries record salivary gland tumors (benign and malignant) in the anatomical site of origin (e.g., oral cavity and pharynx), rather than within a unique, organ-specific salivary gland category. This method of epidemiologic tabulation makes it difficult to determine the precise incidence of this rare disease. Nonetheless, a population-based study suggests the annual age-adjusted incidence for salivary malignancy is 0.9 per 100,000 (in US).[3]

Most salivary tumors (80%) arise in the parotid gland, and the majority of these (65%) are benign. Tumors of the submandibular gland account for 10 to 15%, with a higher incidence of malignancy, up to 50%. The remaining 5 to 10% arise in minor salivary glands, but almost 80% of these tumors are malignant. Very rarely, salivary gland malignancy may develop in heterotopic salivary tissue, primarily the lymph nodes and bones of the head and neck. For these heterotopic tumors, an adjacent or related primary tumor must be ruled out with careful examination and imaging.

There is no clear causative relationship between the development of salivary gland tumors and tobacco or ethanol use. However, ultraviolet radiation exposure has been suggested to play an etiologic role.[4–6] A review of the SEER epidemiological database from 1973 to 1981 demonstrated significantly higher rates of salivary malignancy for white males and females in the southern United States compared with the North, for all histological subtypes combined.[5]

Exposure to gamma radiation has also been suggested to play a role in salivary gland tumorigenesis. The rates of salivary malignancy among survivors of atomic bomb blasts and in patients treated with head and neck radiation for benign conditions are increased compared with controls.[7,8] Zheng et al have suggested a possible molecular mechanism for the putative association between gamma radiation and the development of salivary gland tumors.[9] Dental x-rays, nickel alloys, silica dust, kerosene, industrial rubber exposure, and hair dyes might have an association.

Embryology and Histogenesis of Salivary Gland Tumors

Salivary glands are ectodermally derived and develop from proliferations of oral epithelium that grow and invaginate into the underlying mesenchymal stroma. These solid, epithelial ingrowths canalize and then branch into tubules, which differentiate into the mature salivary gland structure (**Fig. 10–1**).

The functional unit of all major salivary gland tissue is the acinus. It is composed of mucinous, serous, and seromucinous cells that are surrounded by myoepithelial cells. Acini are linked to the intercalated ducts, then into mitochondria-rich striated ducts, and finally into the excretory ducts. The cellular composition varies according to the location and type of salivary gland. In the parotid, serous cells predominate, whereas the sublingual gland is mainly composed of mucinous cells. Submandibular glands are composed of both mucinous and serous elements.

The parotid gland, from an embryologic standpoint, develops early and represents the most complex structure, with the most pure acinus formation. The intercalated and striated ducts lead to excretory ducts that empty in Stensen's duct. The minor salivary glands lack a ductal network, and each secretory unit drains individually and varies in its cellular composition based on its location.

The histogenesis of salivary gland neoplasms has been the subject of great debate. The bicellular stem cell or reserve cell theory[10] proposed that salivary neoplasms are derived from unique stem cells with the capacity for self-renewal. In this hypothesis, two types of basal reserve cells (or stem cells) from the intercalated and excretory ducts provide the origin for most epithelial salivary neoplasms. Accordingly, epidermoid tumors, such as squamous cell carcinoma and mucoepidermoid carcinoma, are thought to arise from excretory duct reserve cells, whereas glandular tumors, such as adenocarcinomas, adenoid cystic carcinomas, and acinic cell carcinomas, arise from intercalated duct reserve cells.

An alternative hypothesis has recently been proposed. Known as the multicellular theory,[11] all cell types in the salivary gland unit (**Fig. 10–1**) are capable of replication and, therefore, of being involved in tumorigenic processes. Thus myoepithelial cells give rise to a remarkably heterogeneous range of tumors, including acinic cell carcinoma and adenoid cystic carcinoma. Terminal duct (also known as polymorphous low-grade) adenocarcinoma develops from the terminal intercalated duct and acini.[12,13] Tumors with oncocytic features because of increased cytoplasmic mitochondria may arise from striated ductal cells. Mucoepidermoid, salivary duct, and, rarely, primary squamous carcinomas arise from the excretory duct.

General Considerations

A slow-growing, painless mass is the presenting feature of most benign and malignant salivary gland neoplasm. This commonality may lead to a delay in diagnosis of malignant salivary gland tumors. The minority of tumors present with pain that is usually continuous, rather than

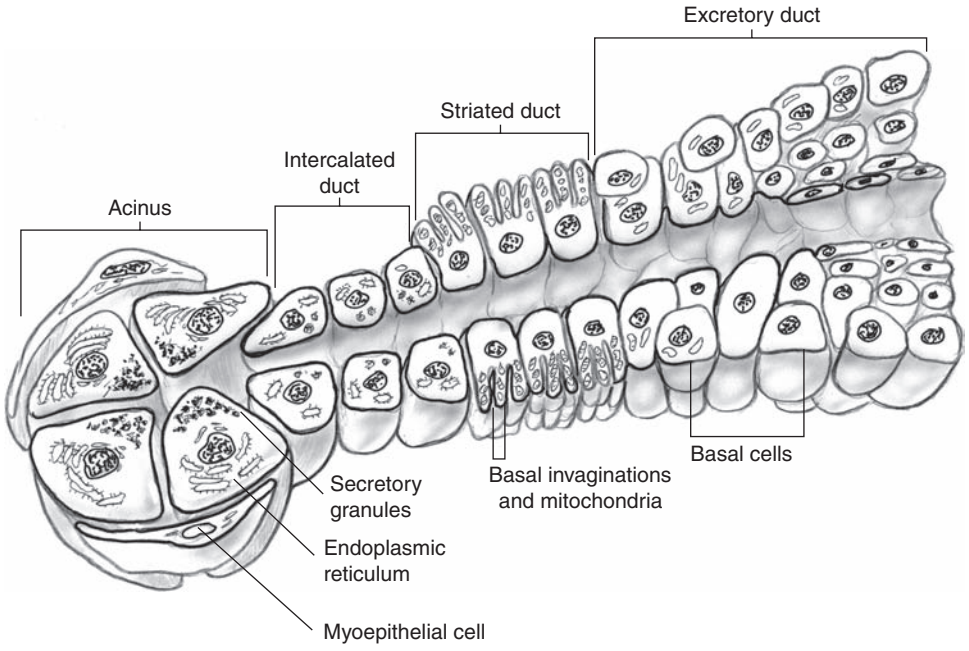

FIGURE 10–1 Salivary gland unit.

intermittent. Facial nerve dysfunction, adenopathy, trismus, numbness, fixation, loose dentition, and bleeding are strongly suggestive of malignancy. Imaging, in general, will not distinguish a malignant from benign neoplasm. Sialography has no significant role. Ultrasound may play a role in fine-needle aspiration of a neoplasm with solid and cystic features. Computed tomography (CT) and magnetic resonance imaging (MRI) will define the extent of tumor and are most important for large, deep lobe, and parapharyngeal space lesions (**see Chapter 2, Figs. 2–3, 2–4, 2–5, 2–13, 2–14, 2–15**). CT has the advantage of defining cortical bone involvement, whereas MRI provides superior soft tissue detail. Both provide surveillance of the neck. False-positive diagnosis of malignancy by fine-needle aspiration and frozen section can occur; these studies should not dictate sacrifice of the facial nerve.

Treatment of the Primary Tumor

Surgery is the primary treatment for malignant salivary gland tumors. The guiding surgical principal is wide excision of the tumor with an adequate margin of surrounding salivary gland or other tissue. However, different surgical approaches are generally indicated based on whether the neoplasm arises in the major (parotid, submandibular, or sublingual) or minor salivary glands.

The Parotid Gland

Because most parotid tumors arise in the superficial lobe, a superficial parotidectomy with a wide cuff of gland generally provides an adequate excision. Total parotidectomy is not indicated for all malignant parotid gland neoplasms unless the tumor arises within the deep lobe or there is direct extension from the superficial to deep lobe.

If the facial nerve functions preoperatively, every effort should be made to preserve it. Facial nerve dissection and preservation may leave disease at the tumor nerve interface, but the nerve should not be sacrificed for microscopic control of tumor. Postoperative radiation therapy is often effective in this situation for controlling microscopic disease in the parotid bed. Occasionally, in advanced tumors, resection of adjacent structures is indicated when there is intraoperative evidence of invasion. In this setting, the nerve may require resection. If necessary, frozen section margins are obtained from the proximal and distal nerve endings.

The Submandibular Gland

Preoperative fine-needle aspiration biopsy is mandatory for surgical treatment of submandibular lesions. Because the surgical approach differs significantly for inflammatory versus neoplastic lesions, the fine-needle aspiration result can prepare both the surgeon and patient for the anticipated surgical resection. However, intraoperative frozen section confirmation must ultimately guide the final surgical approach because extensive surgery should not be planned on the basis of fine-needle aspiration results alone.

If malignancy is known or suspected, a limited excision of the gland alone should be avoided. Therefore, a wide excision with planned level Ia–Ib neck dissection is necessary to obtain an appropriate soft tissue margin and to remove the primary echelon lymphatics. The hypoglossal and lingual nerves should always be preserved unless directly invaded or if their function is abnormal preoperatively. During a planned submandibular resection for malignancy, sampling of both the submandibular ganglion and the nerve to mylohyoid should be routinely performed to determine the presence of perineural invasion.

The Sublingual Gland

Tumors of the sublingual gland are quite rare, but they should always be considered during the evaluation of a submucosal anterolateral floor of the mouth lesion. Fine-needle aspiration biopsy is difficult, and an initial limited incisional biopsy is therefore indicated. Once confirmed, the surgical approach should encompass a wide resection, with a margin of overlying mucosa and a formal floor of the mouth resection. Preoperative counseling must include a discussion of the needed reconstruction and the possible need for temporary tracheotomy. Sampling of the adjacent nerve branches should be performed to determine perineural involvement, but again the lingual and hypoglossal nerves should be preserved unless directly involved or encased.

Minor Salivary Glands

Because of the diverse distribution of minor salivary glands within the head and neck, designing treatment can be difficult. There may be between 500 and 750 minor salivary glands within the submucosa of the upper aerodigestive tract. For optimal local and regional control, surgical resection is recommended. Although it is tempting to consider alternative treatments because of the associated morbidity of surgical resection, especially in the base of tongue (BOT) and larynx, disease control is often compromised.

Because the minor salivary glands are found in the highest density within the oral cavity, in particular the hard palate, minor salivary malignancy presents here most often. Fortunately, resection and functional reconstruction with minimal morbidity are often possible for patients with these tumors. In the oropharynx, wide resection and reconstruction are often most appropriate, but postoperative radiotherapy is often

required. For the larynx, tumors commonly arise in the supraglottic and subglottic larynx. When appropriate, a conservation approach should be considered, but in practice indications are rare.

The Neck

Neck dissection should be performed when there is clinical or radiographic evidence of regional metastasis. Although some have advocated routine prophylactic lymphadenectomy, there are no evidence-based data to support this approach, especially for patients who would receive radiotherapy for perineural invasion. However, when the tumor arises close to the primary draining nodal echelons in an N0 neck, a selective, function-sparing lymphadenectomy (zones 1, 2, and 3) can be performed to guide postoperative therapy. For instance, it is our practice to perform an elective neck dissection in patients with high-grade mucoepidermoid carcinoma (MEC) of the parotid and submandibular glands because there is a well-documented increased incidence of occult positive nodes.[14] In general, unless there are compelling pre- or intraoperative indications, neck dissection should not be routinely performed. Tumors at risk for occult metastasis include high-grade tumors (squamous cell carcinoma, high-grade adenocarcinoma, high-grade mucoepidermoid carcinoma, and undifferentiated carcinoma), size greater than 4 cm, tumors presenting with facial nerve dysfunction, extraglandular involvement, advanced age, recurrent tumors, and submandibular tumors.

Surgical Management of Cranial Nerves

Cranial Nerve VII

Occasionally, salivary tumors must be sharply dissected from the facial nerve, leaving microscopic disease behind. This should only be done when no gross tumor is left behind. For these patients, postoperative radiotherapy is necessary.

If the facial nerve functioned preoperatively but was sacrificed during surgery, nerve grafting should be performed. Reconstruction can be achieved with either direct neurorrhaphy (if the defect is small and the nerve edges mobile) or an interposition nerve graft or cable graft, depending on the length of the resected segment.

If the facial nerve was paralyzed preoperatively, reanimation of the face should be considered. For curative resections, a temporalis muscle transfer, fascial sling, or similar technique is appropriate. Because postoperative radiation is necessary, any reanimation approach utilizing foreign material or implants must be avoided. Gold weight implantation into the upper eyelid also should be considered in either case.

A mastoidectomy is occasionally necessary to achieve negative margins on the proximal stump of the facial nerve. When the main trunk of the facial nerve is sacrificed at the stylomastoid foramen, a mastoidectomy provides access and nerve mobility to perform an interposition nerve graft. Finally, in the setting of extensive scarring from previous surgery or with recurrent disease, a mastoidectomy may facilitate the identification of the main trunk of the facial nerve.

For advanced salivary tumors extending beyond the confines of the parotid gland, preoperative imaging allows for better delineation of the extent of the resection of surrounding structures. Preoperative planning and postoperative reconstruction must consider the need to resect skin, mandibular ramus, and masseter muscle; infratemporal fossa dissection; or subtotal petrosectomy. A lateral temporal bone resection is indicated when the tumor involves the external auditory canal or the temporomandibular joint.

Cranial Nerve V

If the lingual nerve is involved by submandibular or sublingual tumors, all gross tumor should be resected and the nerve dissected toward its ganglion. A microscopically negative margin should be obtained when possible. If multiple margins remain positive to the foramen ovale, the nerve stump should be marked with a metal clip, to assist in planning the radiation field.

For minor salivary gland tumors arising in the hard palate, infrastructure maxillectomy with split-thickness skin graft and prosthetic reconstruction is often necessary. For these patients, resection of the inferior turbinate facilitates obturation. Branches of the maxillary division of the trigeminal nerve (infraorbital and greater palatine nerves) should be biopsied if perineural invasion is suspected. For larger tumors requiring total maxillectomy, the branches of the second (V_2) and third (V_3) divisions of the trigeminal nerve are at high risk for perineural spread and should be sampled. Although these nerves may provide an avenue for early skull base and intracranial disease, a balanced approach must be selected because, regardless of the extent of surgery, postoperative radiation therapy will be necessary.

Adjuvant Radiation Therapy

Postoperative Radiation Therapy

Indications for postoperative x-ray therapy are listed in **Table 10–1** (see Chapter 13 for an expanded discussion). The typical recommended dose is ~60 Gy. Treatment volumes depend on the tumor histology, location of the primary tumor, and the risk of tumor involvement in the neck and to neural pathways.

Adjuvant postoperative x-ray therapy leads to improved local control especially for T3–4 and high-grade tumors.[15–18] In an older series, postoperative radiotherapy has been shown to reduce local recurrence

TABLE 10–1 Indications for Postoperative Radiotherapy

1. Compromised margins of resection, including tumor enucleation
2. Extraglandular extension
3. Facial nerve preservation with close margins (tumor peeled away)
4. Perineural invasion
5. Metastatic lymphadenopathy
6. High-grade tumors
7. Recurrent low-grade tumors with no good salvage option on future recurrence

from ~30 to 10%.[19] Skip metastases may occur in levels III and IV with negative level II nodes in up to 25% of patients undergoing elective neck dissections.[20]

It is hard to demonstrate an objective improvement in survival by any modality of adjuvant radiation therapy; however, a matched-pair retrospective analysis at Memorial Sloan Kettering Cancer Center suggested improved local control and survival for adjuvant radiotherapy for all patients with positive nodes and stage III and IV disease.[20] The salvage rates are nil for many patients who subsequently develop recurrences.

Data from the MD Anderson Cancer Center indicate excellent locoregional control and modest complication rates for patients with parotid cancers treated with ipsilateral electron fields directed at the parotid bed.[17] The electron beam was often mixed with a small proportion of photons to improve skin sparing. Alternative treatment techniques evaluated included the ipsilateral ''wedge-pair'' technique using photons. The electron-based technique was appropriate for all but deeply seated tumors, and overall had a lower complication rate as compared with the wedge-pair technique. The locoregional control rate was 84%, and there was a 22% risk for chronic complications (hearing loss 7%, soft tissue necrosis 9%, temporal lobe necrosis 1%, or soft tissue/bone exposure/necrosis 9%).

Postoperative radiation therapy also using ipsilateral primarily electron or mixed beam technique for submandibular gland cancer has led to local control in ~90% of patients.[18] There was no salvage for patients with locoregional recurrence, underscoring the utility for postoperative radiation therapy. In this series of 94 patients, failure along nerves was rare. The authors recommend treatment of the nerve pathway to the skull base foramen only for patients with involvement of a named nerve, but covering the nerve's pathway through the mandible and neck for patients with focal and microscopic perineural invasion. This limits the morbidity of unnecessarily large radiation therapy fields. Thus the risk for serious complications was lower than with the larger fields used for parotid cancers that also cover more complex and costly areas of anatomical function. There was a 5% incidence of osteoradionecrosis of the mandible.

Low-grade mucoepidermoid carcinomas have near uniform control with complete surgical excision. If there is compromised resection without a good option for reoperation to achieve that complete resection, or if observation and salvage are not a good option, then the results are improved with postoperative radiotherapy.[19,21]

Previous surgical series have reported local recurrence rates approximating 50%. This is not surprising because many patients have disease originating in paranasal sinus and palate sites. Postoperative radiation therapy has led to local control rates of 88%, and overall survival rates of 81%, 65%, and 43% at 5, 10, and 15 years, respectively.[16] This decrement in survival reflects the preponderance (71%) of patients with adenoid cystic carcinomas, for whom the dominant pattern of failure was distant metastases. Failures in the neck were rare (<5%), so the authors recommend neck treatment only for the minority with nodal involvement, for tongue primaries, and for those whose neck was entered for resection of the primary, thus becoming a part of the operative bed. However, because of the unique natural history of adenoid cystic carcinoma and proclivity for perineural invasion, radiotherapy should be applied postoperatively. When involved, the facial nerve should be treated up to its point of entry into the base of the skull for parotid tumors.[22,23] The microscopic involvement of unnamed nerves, however, does not require treatment to the skull base, but for a generous portion of the nerve path in the neck.

The involvement of one side of the neck does not place the other side at risk in salivary cancer, as is the case for many occurrences of squamous carcinoma of the head and neck. Two studies have shown that contralateral elective neck radiation is not indicated.[24,25] This decreases the incidence/severity of xerostomia, and other potential risks and complications for the irradiation of unnecessary large volumes.

Gross Disease

There are data on the treatment of patients with gross residual salivary gland cancers following surgical resection. Conventional once-a-day photon radiation therapy has been associated with a local control rate of 20 to 25% for patients with inoperable or recurrent tumors (**Table 10–2**). Data on twice a day fractionation for photon radiation therapy are limited. One report, however, describes a 5-year actuarial local control of 100% for 9 parotid and 78% control for 15 minor salivary tumors.[26] As twice-a-day radiotherapy has led to improved local control for other head and neck sites, it is reasonable to accept that it might lead to some improvement for salivary cancers, but the results of this trial have yet to be confirmed, and a more

TABLE 10–2 Local Control for Gross Tumor with Low Linear Energy Transfer, Once Daily

Series	Numbers of patients	Control rate (%)
Fitzpatrick	50	12
Vikram	49	4
Borthne	35	23
Rafla	25	36
Fu	19	32
Stewart	19	47
Ellis	17	29
Dobrowsky	17	41
Shidnia	16	38
Elkon	13	15
Ravasz	12	25
Rossman	11	54
Overall	283	24

comprehensive evaluation of efficacy would require at least larger numbers (see Chapter 13).

A prospective clinical trial comparing photon radiation therapy to neutrons was undertaken by radiation therapy oncology group/medical research council (RTOG/MRC) for inoperable or recurrent salivary cancers. This demonstrated a greater than threefold improvement in the local control rate and a greater than twofold survival advantage at 2 years favoring neutrons. There was early closure of this trial at interim analysis for ethical reasons.[26a] A retrospective review of 263 patients treated with fast neutron radiotherapy for gross disease revealed a 6-year locoregional control rate of 59%.[27]

Photon radiation therapy should be used definitively for those patients with gross disease who cannot undergo surgery and for whom neutron beam therapy is not available or appropriate. In those circumstances, accelerated radiotherapy should be considered. The use of neutrons is not presently indicated in the setting of postoperative radiation therapy without gross disease.

Palliative Treatment

Neutron radiation may be a treatment option for inoperable locoregional disease or patients with comorbidities that preclude surgery. There are only two centers in the United States that can deliver this therapy, but this approach has been more widely used and studied in Europe.[28] In 1988, a multicenter randomized study of 25 patients showed initially promising results in the locoregional control of unresectable salivary gland tumors, when neutron beam versus photon irradiation was compared. However, no survival difference could be demonstrated.[26a,29]

Chemotherapy

No single chemotherapeutic agent or combination regimen has shown any sustained efficacy for salivary tumors. Thus chemotherapy is indicated only for palliation of symptomatic patients with recurrent and/or unresectable cancers.[30]

Although unproven, it is widely supposed that there are differences in response to chemotherapy depending on the histogenic origin of the tumors.[31] In general, tumors putatively arising from intercalated duct origin (adenoid cystic carcinoma, adenocarcinoma not otherwise specified, acinic cell carcinoma, terminal duct/polymorphous low-grade adenocarcinoma, and myoepithelial carcinoma) are low grade and biologically more indolent compared with those derived from the excretory duct, such as salivary duct, mucoepidermoid, and squamous carcinomas.

Accordingly, for tumors of intercalated duct origin, cyclophosphamide, doxorubicin, and cisplatin[32,33] may offer the best response. Patients with mucoepidermoid, salivary duct, and undifferentiated carcinomas, however, appear to respond better to those drugs active against squamous cell carcinomas (e.g., cisplatin, 5-fluorouracil, and methotrexate). Unfortunately, for both groups, despite an occasional complete response, there has been no demonstrated survival benefit (see Chapter 12).

Molecular Targeted Therapy

HER2/neu (or *c-erbB2*) is a member of the epidermal growth factor receptor family. As a proto-oncogene, *HER2* can dimerize with other c-ERB family members, and can initiate a cascade of downstream effects, leading to cell proliferation, angiogenesis, and resistance to programmed cell death, or apoptosis.[34] In breast cancer, resistance to chemotherapy (and its attendant poorer prognosis) has been correlated with *HER2* overexpression.[35] Trastuzumab is a monoclonal antibody that selectively blocks the *HER2* receptor and alone has single-agent activity with minimal side effects. This molecular targeted compound has shown promise in prospective clinical trials for patients with breast cancer, improving their response to standard cytotoxic therapy.[36]

In a multi-institutional study of patients with any histological type of salivary malignancy, *HER2* overexpression was found in 10 of 12 (83%) patients with salivary duct carcinoma.[31] For patients with salivary carcinoma, the vast majority of patients with *HER2* overexpression had tumors arising from the excretory duct (**Fig. 10–1**): mucoepidermoid, squamous, and salivary duct carcinoma. Although these tumors represented a minority (22%) of the tumors in the study, there were striking responses in this group. In particular, two patients with salivary duct carcinoma had stable disease for 24 and 40 months. Unfortunately, with the small number of patients in the study, no conclusions could be drawn. But for patients with excretory

duct-derived carcinomas, trastuzumab may provide hope for systemic therapy.

■ Epithelial-derived Salivary Gland Malignancies

Mucoepidermoid Carcinoma

Clinical Presentation

Mucoepidermoid carcinoma (MEC) is the most common malignant tumor of the salivary glands, making up more than one third of salivary malignant neoplasms. It is the most common malignant tumor of the parotid gland and the second most common tumor arising in the submandibular and sublingual glands. In children, MEC is the most common malignant tumor of salivary gland origin. The majority of patients present with a painless swelling of the area affected. Pain may occur, but it is usually preceded by the appearance of a mass. Cervical node involvement can be seen in one third of the patients. Primary lesions can be found mostly in the body and tail of the parotid gland, and presentation with facial palsy is not uncommon. High-grade MEC is associated with rapid growth at presentation. Minor salivary gland mucoepidermoid carcinoma presents most commonly in the buccal mucosa and palate.

Histology

The histological grading of mucoepidermoid carcinoma serves as a crucial prognostic factor and strongly correlates with clinical behavior. Its first histological description was made by Volkmann in 1895.[37] Some 50 years later, Stewart et al coined the term *mucoepidermoid carcinoma*.[38]

Since then, a grading system has been developed based on the histological findings in which low-grade or well differentiated lesions show a better prognosis than high-grade or poorly differentiated tumors.[39,40] The cardinal histological features include mucinous, intermediate, and epidermoid cellular elements, forming glandular, cystic, and solid arrangements.

Low-grade-type tumors show glandular or microcystic structures lined with a cell layer of mucus-producing cells (**Fig. 10–2**). The cystic structures can also have papillary infoldings with the presence of intermediate cells that may differentiate into epidermal and mucous cells. As some of these microcystic formations coalesce into larger cysts, some mucinous material may extrude and elicit an intense inflammatory reaction. Intermediate-grade tumors are characterized by areas of mostly squamous or intermediate basaloid-type elements (**Fig. 10–3**). High-grade forms show a greater percentage of solid sheets of tumor, with few glandular or cystic

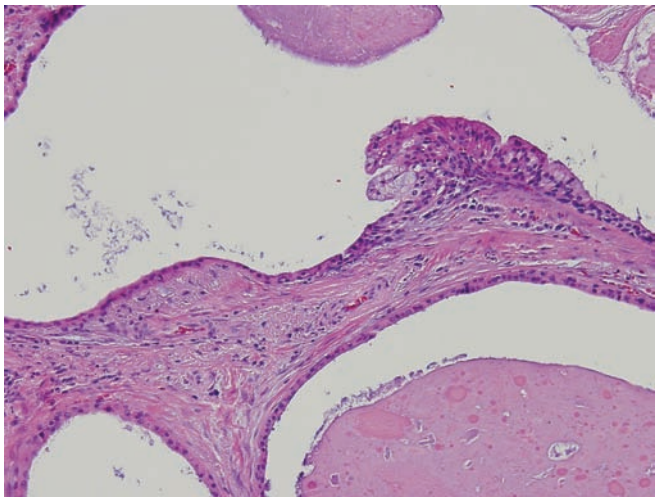

FIGURE 10–2 Low-grade mucoepidermoid carcinoma: largely cystic with small tumor nests (cystic) (H&E, ×20).

formations (**Fig. 10–4**). Intermediate basal and epidermoid cells are more predominant than mucus-producing cells in this aggressive form of MEC. Sclerosing mucoepidermoid carcinoma is characterized by an intense central sclerosis, frequently with dense collagenous depositions, ductal proliferations of mucinous and/or epidermoid cells, surrounded by plasma cells, eosinophils, or lymphocytes at the periphery.[41,42]

Histological grading of mucoepidermoid carcinomas of major salivary glands, using the modified Healey three-tiered system, correlates well with several important clinical prognostic features. In a study of 48 patients from the MD Anderson Cancer Center, the presence of lymphatic spread was closely correlated with increasing histological grade: 0% for low-, 22% for intermediate-, and 72% for high-grade tumors. ($p < .001$). Furthermore,

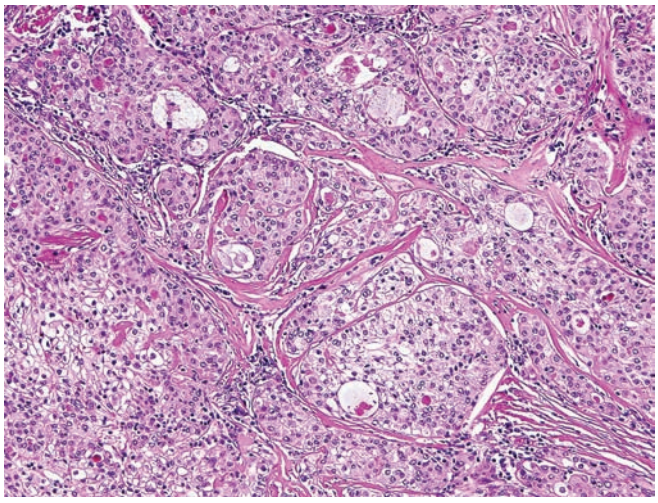

FIGURE 10–3 Intermediate grade mucoepidermoid carcinoma: predominately solid tumor nests with minor cystic formation (H&E, ×40).

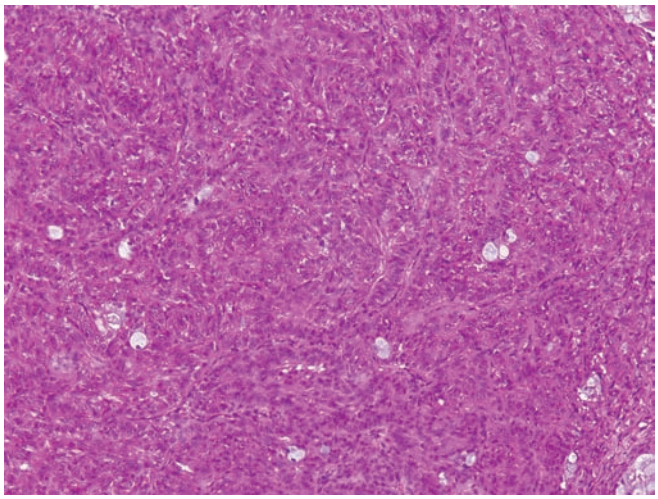

FIGURE 10–4 High-grade mucoepidermoid carcinoma: solid nests of poorly differentiated tumor cells (H&E, ×20).

survival was decreased significantly ($p < .0001$) with increasing tumor grade: 100% for low-, 70% for intermediate-, and 22% for high-grade tumors. Finally, perineural and lymphovascular invasion are not uncommon findings in MEC. Regional metastases can show cellular elements of all types not necessarily correlated to the primary lesion.

Treatment

Comprehensive surgical resection is the treatment of choice for MEC, depending on the location of the lesion. A complete superficial lobe parotidectomy with a wide cuff of gland around the tumor should provide an oncologically appropriate margin. Deep lobe parotidectomy should not be performed routinely but rather when tumor spread dictates. During resection of the primary, the facial nerve should be preserved whenever possible.

Neck dissection should be performed when there is clinical evidence of regional metastasis, either radiographically or clinically. Although some have advocated prophylactic lymphadenectomy for high-grade histology, there are no evidence-based data to support this approach, especially for patients who are scheduled to receive radiotherapy. Another relative indication for selective lymphadenectomy is the proximity of tumor to regional lymph nodes.

Postoperative radiotherapy is indicated in patients with perineural involvement, positive margins, high-grade tumors, and tumors with cervical lymphadenopathy.

Adenoid Cystic Carcinoma

Adenoid cystic carcinoma (ACC) is a relatively rare and indolently malignant salivary gland tumor with predilection for perineural invasion. It is well known, despite its infrequency, for the perplexing dilemmas it poses to patients and their treating head and neck oncologists.

The first recognition of ACC probably dates back to 1853[43] and 1854.[44] Robin and colleagues first described these *tumeurs hétéradéniques*.[43,44] Two years later, writing in a monograph from the University of Berlin, Billroth coined the term *cylindroma* to describe its gross clinicopathologic characteristics, but its true malignant potential was probably underappreciated.[45] Although in 1930, Spies first used the term *adenoid cystic carcinoma*,[46] the term *cylindroma* persisted until 1942, when Dockery and Mayo suggested *cylindroma-type adenocarcinoma*. By then, the malignant, albeit indolent, behavior of this tumor was more widely appreciated. In fact, in their 1942 description, the propensity of ACC for ''spread along nerve sheaths'' is first mentioned.[47] Finally, Foote and Frazell wrote the first definitive review, detailing its classic histopathologic features.[48]

Clinical Presentation

It has been estimated that adenoid cystic carcinoma constitutes up to 10% of all salivary neoplasms. Although ACC is thought to be the second-most common malignant tumor of the salivary glands, it is the most common malignancy found in the minor salivary, submandibular, and sublingual glands. In two large reviews, the most common site of origin is the oral cavity, followed by the sinonasal tract.[49,50] The palate is the most common location in the oral cavity (**Fig. 10–5**).

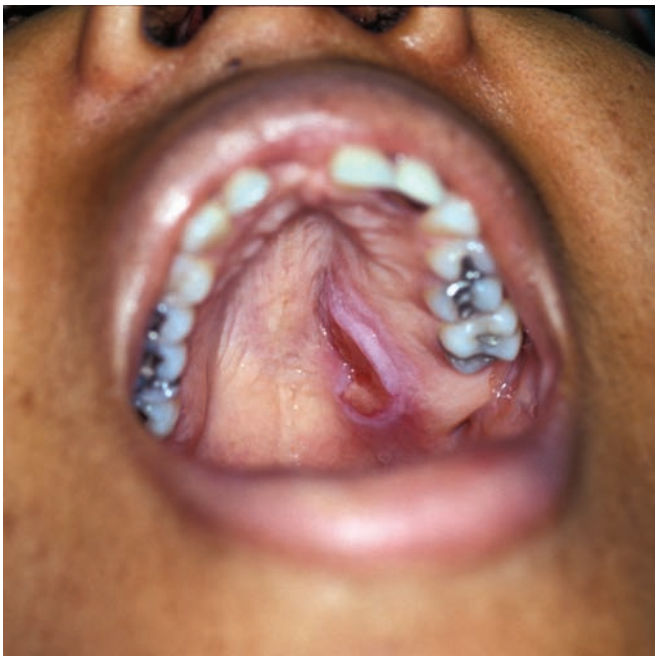

FIGURE 10–5 Adenoid cystic carcinoma presenting on the hard palate.

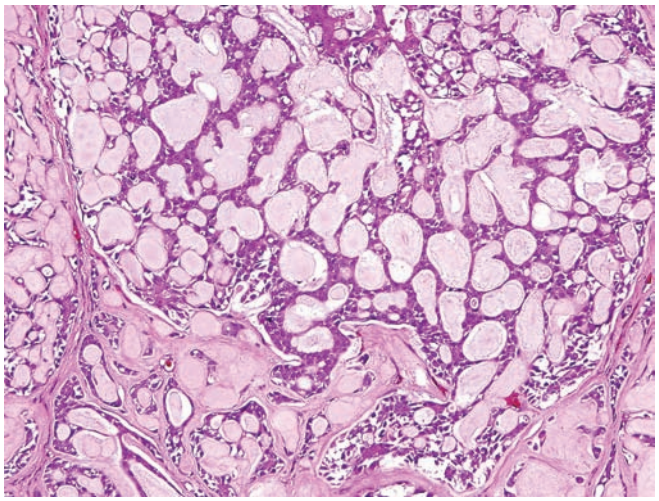

FIGURE 10–6 Adenoid cystic carcinoma: cribriform form (H&E, ×20).

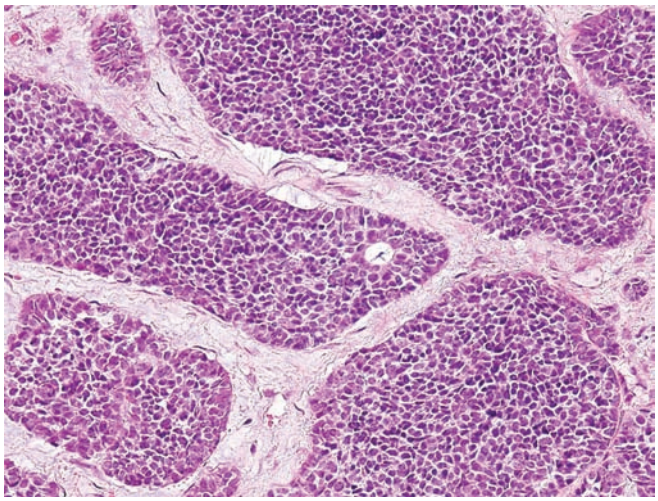

FIGURE 10–7 Adenoid cystic carcinoma: solid form (H&E, ×20).

ACC often presents as a slowly growing and infiltrative mass. Due to the propensity for perineural invasion, patients with ACC should be specifically questioned about the function of regional and motor nerves. Formication, paresthesias, and numbness should always be recorded. Muscle fasciculation or atrophy and facial paresis are clear signs of facial nerve involvement. Regional lymphatic metastasis in ACC is not common. For major and minor salivary glands, less than 20% of patients with ACC developed metastasis.[49,50] But in a review of submandibular ACC, 24% of patients were found to have regional lymphatic spread.[51]

Imaging

Abnormal attenuation within the pterygopalatine fossa on soft tissue CT windows[52] or abnormal signal intensity/enhancement on postcontrast T1-weighted fat-suppressed MRI is strong evidence of perineural tumor spread.[53] The foramen ovale and rotundum, the cavernous sinus, and Meckel's cave should also be carefully examined with high-resolution MRI to exclude perineural dissemination.

Pathogenesis

ACC is divided based on tumor architecture into cribriform, tubular, and solid patterns. The cribriform type is most similar and best known because of its classic ''Swiss cheese'' morphology (**Fig. 10–6**). In this form, circular tumor nests are seen within pseudoglandular spaces filled with hyaline-like connective tissue. The solid pattern (**Fig. 10–7**) represents a high-grade tumor and is characterized by sheets of basaloid cells with minor tubular or cribriform components. The tubular pattern is considered generally a lower grade ACC (**Fig. 10–8**) and is composed of ductal structures formed of outer myoepithelial and inner epithelial cells. The cribriform pattern has the best prognosis, with the tubular having a prognosis intermediate to the cribriform (glandular architecture) and solid (epithelial architecture) patterns.[50] Others have found prognosis more closely correlated with staging than histology. Tubular and solid patterns have been reported to have more early local recurrence than cribriform with survival rate determined more by stage.

For the diagnosis of ACC, most tumors demonstrate mixed architecture, and the predominant subtype determines the diagnosis. ACC can be easily confused with basosquamous carcinoma of the upper aerodigestive tract because of the pseudocribriform pattern. This should always be considered when the diagnosis of adenoid cystic carcinoma is found within lymph node(s), especially if the primary is unknown.

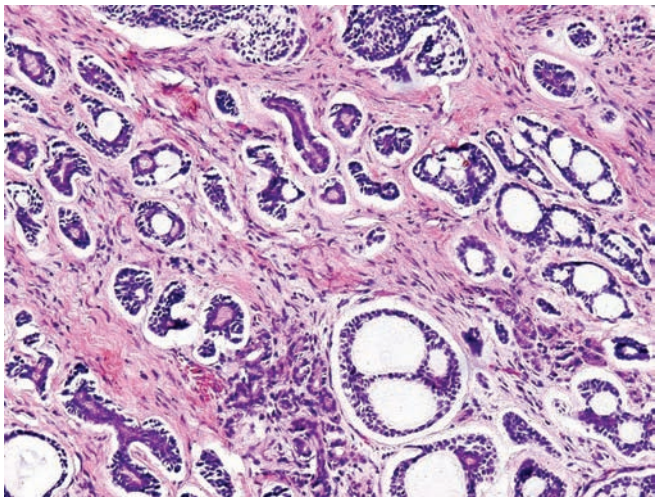

FIGURE 10–8 Adenoid cystic carcinoma (predominantly tubular form with focal cribriform areas) (H&E, ×20).

The most remarkable feature of ACC is its predilection for perineural invasion. Because most ACC of the minor salivary glands arise from sites in the oral, oropharyngeal, and paranasal mucosa, the maxillary (V_2) and the mandibular (V_3) branches of the trigeminal nerve are most commonly involved by tumor. The facial nerve is typically involved by tumors arising in the parotid gland. For submandibular or sublingual tumors, the lingual, hypoglossal, and marginal mandibular nerves are at risk.

Perineural involvement is found often in patients with advanced or high-grade tumors and with recurrence, yet its pathogenesis remains poorly understood. Perineural invasion (PNI) is the process by which cancer cells penetrate the perineural space and permeate along the peripheral nerves. Tumor can spread along the nerve following a path of least resistance through connective tissue.

Although described by Cruveilhier in 1835,[54] Ernst published the first rigorous review in 1905.[55] Adenoid cystic and other salivary malignancies are not the only ''neurotropic'' cancers. PNI is also commonly encountered in prostate, biliary tree, and pancreatic carcinomas, as well as head and neck cutaneous and mucosal cancers. Although Ernst proposed that PNI resulted from tumoral transit through lymphatic vessels within the perineural space, Rodin et al demonstrated in prostate cancer that the perineurium was devoid of lymphatics.[56] These authors proposed that tumor cells infiltrate nerves as a path of ''least resistance'' into the perineural space. More recently, tumor deposition of laminin-5[57] and nerve cell adhesion molecule expression[58] have been implicated in the pathogenesis of PNI.

In the MD Anderson Cancer Center review,[50] half of the patients (79 of 160) presented with perineural invasion. Major (or named) nerves were involved in 36 patients, and minor or unnamed nerves displayed evidence of perineural invasion in 43 patients. In the largest major review using current treatment approaches, major nerve involvement was clearly associated with both increased locoregional failure and diminished survival.[50] Now in most centers, assessment for perineural spread is routinely performed for patients with ACC. Even so, its identification in ACC depends on the fastidiousness of histopathologic examination of tumor specimens.

Genetics

The molecular alterations that underlie the development and progression of ACC remain unknown. A recent study using oligonucleotide microarray analysis[59] identified several genes that were associated with ACC. These genes included casein *kinase 1*, transcription factors *SOX4* and *AP-2* gamma, as well as members of the *Wnt/β-catenin* signaling pathway: *epsilon* and *frizzled-7*. Future study with genomic and proteomic assessment of expression patterns in patient tumor samples and serum will be needed to elucidate the mechanism of ACC pathogenesis.

Treatment

Adenoid cystic carcinoma is characterized by a protracted and variable clinical course. Even after successful local and regional treatment, there remains a great tendency for delayed local and distant spread.

The mainstay of treatment is surgery and postoperative radiation therapy.[22] Appropriate resection of the affected salivary gland (submandibular and/or sublingual resection, parotidectomy, or wide resection of minor salivary tumor) should be performed whenever possible. Elective neck dissection is not used routinely. The surgical management of perineural invasion is discussed earlier.

Given the high incidence of PNI, patients will often require postoperative radiation therapy (see Chapter 13). Thus preoperative dental consultation is required. For tumors of the base of the tongue and other minor salivary gland tumors, postoperative radiation therapy is important in achieving final local control after gross total excision. A postoperative dose of 60 Gy in 30 fractions to the operative bed is recommended. When a major, named nerve is invaded, the path of the nerve is treated electively to its ganglion.[16] The largest panoramic view of the natural history of adenoid cystic carcinoma was presented in Conley et al's 1991 textbook.[60] This review of 406 patients demonstrated that at 10 years, roughly one third of patients were free of disease, one third were dead of disease, and one third were alive with disease. Thus true incidence of locoregional control and/or distant metastasis depends on the duration of follow-up for these patients. Conley et al[60] postulated that with 30-year follow-up as many as 80% of patients would succumb to their disease. In the MD Anderson series, disease-specific survival rates later confirmed this trend. At 5 and 7 years, disease-specific survival was 89.0 and 74.8%, which dropped to 67.4% and 39.6% at 10 and 15 years, respectively.[50,61]

Compared with carcinomas of the upper aerodigestive tract, the survival of patients with ACC does not stabilize at 5 years, and the survival rate continues to decline even after 15 years. Depending on the number and location of the sites of distant failure, prolonged survival with the disease is possible. Accordingly, patients should be counseled that even after local and regional control is achieved, adenoid cystic carcinoma remains a chronic disease, and that yearly lifetime follow-up is required for adequate surveillance.

With appropriate local and regional treatment, the most common mode of failure is now distant metastasis. The most common sites are lung (67%), liver (12%),

and bone. Although predictive indicators for distant metastasis remain elusive, clinical stage and locoregional failure are most important.[50,61] Although anecdotal, numerous reports suggest an increased rate of distant failure for patients with ACC of the submandibular gland.[62]

There is no effective treatment for the development of distant metastasis from ACC. Half of patients have distant metastasis 3 years after diagnosis of their tumors.[62] The most studied regimen for ACC is cyclophosphamide, doxorubicin, and cisplatin (CAP).[32,33] Unfortunately, despite an occasional complete response, there has been no demonstrated survival benefit. Surgical resection, especially for pulmonary metastases, may be considered for isolated lesions, although no survival benefit has been shown.[63,64] Almost half of patients have more than one site of failure, with distant metastasis associated with locoregional failure in two thirds of patients.[64] Patients may have subclinical metastasis at the time of diagnosis of the primary tumor. Thus such palliative therapies should be reserved for symptomatic patients, with adequate performance status and with an understanding of the inexorable course of this disease.

Acinic Cell Carcinoma

Clinical Presentation

Acinic cell carcinoma accounts for ~1 to 6% of all salivary tumors. The parotid gland is the most often involved site, and occasionally it can present bilaterally. The most common presentation is a solid or cystic mass in the parotid gland with a slow-growing behavior. The mass can be associated with regional pain and facial dysfunction or paralysis. In adults it presents most commonly during the fourth or fifth decade of life and shows a female predominance. Acinic cell carcinoma is the second most common malignant salivary gland tumor in children.[65]

Imaging

CT and MRI findings are nonspecific for the disease and usually of a benign appearance. On CT, acinic cell carcinoma may show contrast enhancement with single or multiple lobules with or without calcifications. MRI is nonspecific, although if surrounding fat is displaced or obliterated, invasion is suggested.[66]

Histology

The classic histological appearance of acinic cell carcinoma (**Fig. 10–9**) displays large, polygonal serous cells with basophilic cytoplasm with coarse granules and small, centralized nuclei. These granules can be demonstrated with periodic acid-Schiff (PAS) diastase staining. Several patterns have been observed, including tubular, ductoglandular, medullary, acinar, follicular, microcystic/macrocystic, papillary cystic, and solid, with the solid and microcystic being the most common patterns.[67,68] No significant prognostic predictive value is associated with subtypes,[68] although some have proposed that a solid architecture is associated with a poorer prognosis.[69] The supporting stroma, although small, can contain a lymphocytic spread with formation of germinal centers in this tumor type. Acinic cell carcinoma may not uncommonly develop in intraparotid lymph nodes and should be differentiated from metastatic disease.

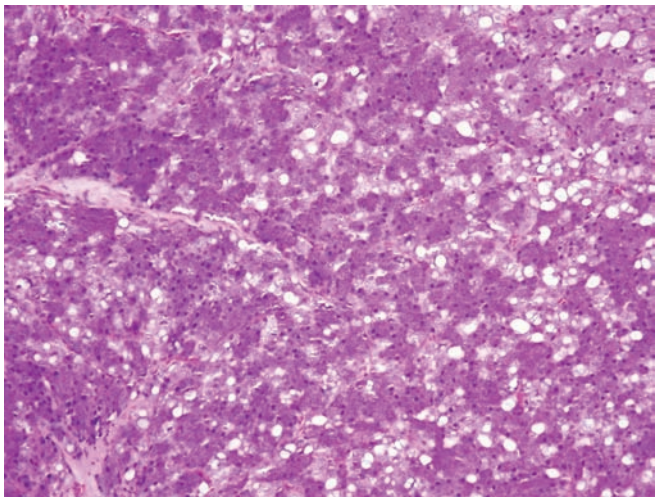

FIGURE 10–9 Acinic cell carcinoma (H&E, ×20).

Genetics

Genetic alterations at certain chromosomal loci in 25 primary parotid acinic cell carcinomas have been identified. In one study, 84% of the tumors had alteration in at least one of the chromosomal loci: *4p*, *5q*, *6p*, and *17p* predominated over *1p* and *1q*, *4q*, *5p*, and *6q*. Loss of heterozygosity (LOH) at *4p15–16*, *6p25-qter*, and *17p11* suggests the possibility of tumor suppressor genes involved in tumorigenesis of acinic cell carcinoma. In addition, LOH was significantly associated with tumor grade.[70]

Treatment

In most cases, acinic cell carcinoma behaves as a relatively low-grade malignancy. As such, adequate surgical resection will yield acceptable rates of local control and overall survival.[65,71] Despite reports of associated adjacent microscopic, lymphocytic infiltration, these tumors metastasize in only 10 to 20% of cases.[71] Thus adequate surgical margins are paramount, as local recurrence is common with incomplete or close excisions. Postoperative radiation seems to be effective in treating microscopic disease remaining after surgery.[72] Local recurrence occurs in one third of patients.[71] Distant failure, though rare, has

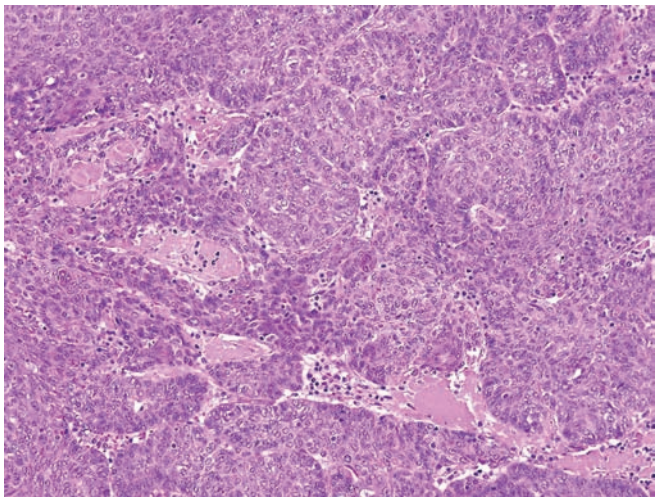

FIGURE 10–10 Basal cell salivary adenocarcinoma: nests of uniform basal cells with peripheral palisading (H&E, ×20).

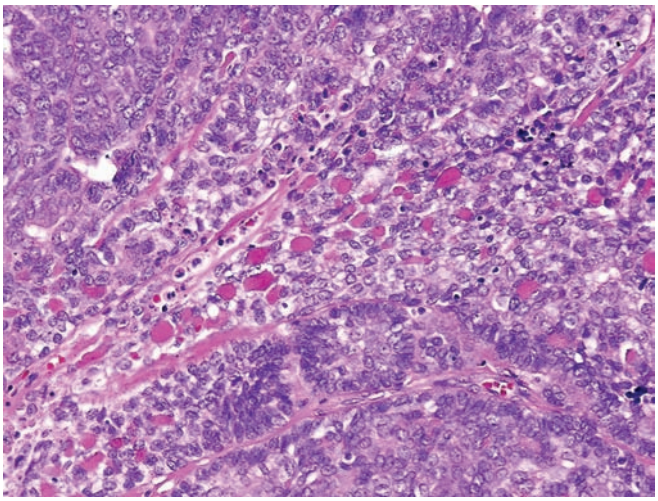

FIGURE 10–11 Basal cell salivary adenocarcinoma (H&E, ×40).

been reported many years after initial treatment, most commonly to the lungs and bone.[65] Negative prognostic factors, pain, and facial nerve dysfunction occur in 5 to 10% of patients. Other negative prognosticators include deep lobe tumors, multiple nodules, and distant metastasis.[71]

Basal Cell Salivary Adenocarcinoma

Clinical Presentation

Even among salivary gland neoplasms, basal cell adenocarcinoma is quite rare. Among the reported cases, 90% are found in the parotid salivary gland, although they may present in the submandibular and minor salivary glands.[73] These tumors typically present in the sixth decade[74] as a long-standing, asymptomatic mass, with sudden growth and associated pain.

Histology

Basal cell salivary adenocarcinoma should be differentiated from solid-pattern adenoid cystic carcinoma and metastatic basal cell carcinoma of skin. It is comprised of small ovoid cells with dark hyperchromatic nuclei with scant cytoplasm (**Fig. 10–10**) and occasionally polygonal cells with eosinophilic cytoplasm. Peripheral palisading can be seen as well (**Fig. 10–11**). Solid, membranous, tubular, and trabecular forms have been reported.

Basal cell salivary adenocarcinoma may arise de novo or as a carcinoma ex-basal cell adenoma (**Fig. 10–12**). An infiltrative pattern of growth distinguishes this neoplasm from basal cell adenoma. However, invasion must be carefully defined and distinguished from both multinodular and multifocal disease, both of which are features of basal cell adenoma.[75] Both perineural and lymphovascular invasion are not uncommon, especially in tumors arising from the minor salivary glands.

The differential diagnosis includes an impressive array of similar histological species. Basal cell adenocarcinoma must be distinguished from basal cell adenoma on the basis of extraglandular extension and the infiltrative nature of the adenocarcinoma. Basal cell adenocarcinoma can closely resemble solid pattern adenoid cystic carcinoma in the homogeneity of dark tumor cells, though without the variegation typically seen in adenoid cystic carcinoma. In addition, a higher mitotic rate and more necrosis are more often seen in ACC. Basal cell adenocarcinoma can be distinguished from terminal duct/polymorphous low-grade adenocarcinoma by the basaloid, uniform architecture and cellular composition, in contrast to the greater cellular variability typically seen in terminal duct adenocarcinoma. Undifferentiated small cell or neuroendocrine carcinomas and

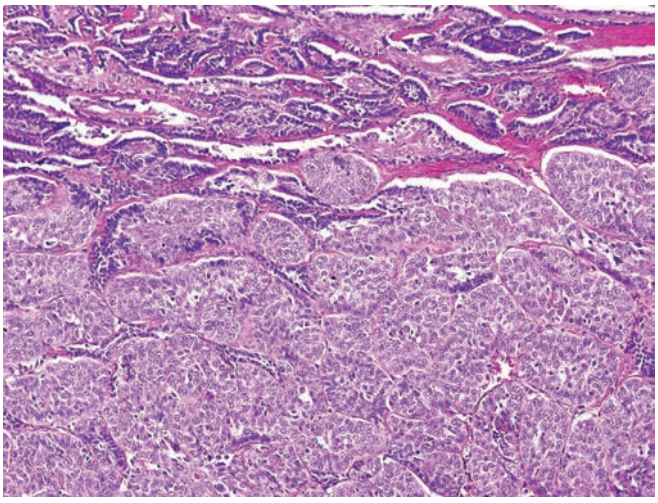

FIGURE 10–12 Basaloid salivary adenocarcinoma (lower two thirds) ex-monomorphic adenoma (upper one third) (H&E, ×20).

basaloid-squamous cell carcinoma can also be included in the differential diagnosis.

Basal cell adenocarcinoma tends to act as a lower-grade malignancy. In the parotid and submandibular glands, with proper surgical resection and appropriate margins, local recurrence, as well as regional and distant spread, is rare. However, for tumors arising in minor salivary glands, radiotherapy may be required when there is evidence of an infiltrative growth pattern, or with evidence of perineural and vascular invasion. As with any malignancy with a low mitotic rate, patients with basal cell adenocarcinoma should be followed on a long-term basis, as delayed occult recurrence remains a possibility.[74,75]

Myoepithelial Carcinomas

The myoepithelial cell is believed to arise from the ectodermal precursor of the intercalated duct and was first described by Zimmerman in 1898.[76] As such, it is an integral component of several salivary tumors with both mesenchymal and epithelial features.[77] Yet myoepithelial carcinoma is exceedingly rare.

Clinical Features

Myoepithelial carcinomas are unencapsulated, infiltrative tumors predominantly found in the parotid gland. Myoepithelial carcinoma may arise de novo or within a long-standing pleomorphic adenoma. Di Palma and Guzzo[78] considered myoepithelial carcinoma to be low grade when it arises in a pleomorphic adenoma, and high grade when it arises de novo. However, a larger and more recent review did not find this to be the case.[79] Comprehensive surgical resection with wide margin is necessary for adequate local control. Regional metastasis is uncommon, but distant failure is well documented in the few large reviews available.[78,79]

Histology

The tumor is composed of myoepithelial cells lacking any ductal or acinar differentiation[80,81] and should be distinguished from the benign monomorphic ''myoepithelioma'' and myoepithelial-predominant pleomorphic adenoma. Myoepithelial carcinoma may present as pure spindle cell, pure plasmacytoid, and a mixture of the two. Both spindled and plasmacytoid forms (**Fig. 10–13**) manifest malignant cellular features, including pleomorphism, high rates of mitosis, and necrosis. Immunohistochemical staining for smooth muscle actin and S-100 (**Fig. 10–14**) is typically positive. Also, strong epithelial membrane antigen (EMA) and/or cytokeratin staining confirm the epithelial nature of this lesion. Based on careful immunohistochemical assessment (**Table 10–3**), the diagnosis of myoepithelial carcinoma can be established by their characteristic positivity for cytokeratin, S-100, and smooth muscle actin.

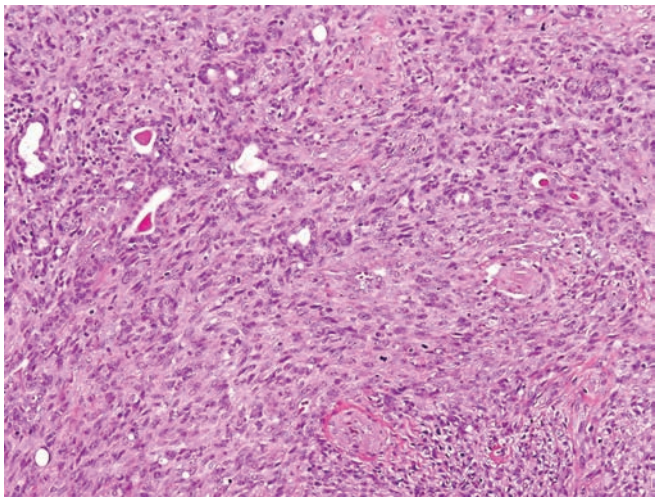

FIGURE 10–13 Myoepithelial carcinoma: spindle cell form (H&E, ×20).

The tumor should also be distinguished from leiomyosarcoma, nerve sheath tumor, synovial sarcoma (which has distinctive biphasic features), and spindle cell melanoma. Clear cell and epithelial (**Fig. 10–15**) variants are described but should be distinguished from epithelial-myoepithelial carcinoma (see below).

Salivary Clear Cell Carcinomas

Primary clear cell tumors represent a richly diverse category of salivary gland malignancy.[82] Primary salivary carcinomas with clear cell features include epithelial-myoepithelial carcinoma (EMEC) and clear cell carcinoma (CCC).[83] As discussed above, myoepithelial carcinoma has features of clear cell carcinoma as well. However, there are also clear cell variants of other salivary tumors, including acinic cell carcinoma,

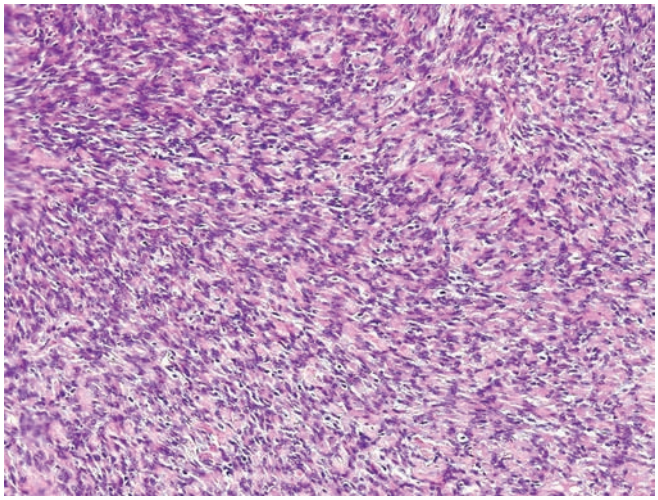

FIGURE 10–14 Myoepithelial carcinoma: spindle cells with palisading features) (H&E, ×20).

TABLE 10–3 Comparative Histopathologic Criteria for Myoepithelial Carcinoma

	Characteristic					
	H&E	Immunhistochemical stains				
Tumor type		EMA	CytoKer	S-100	HMB45	SMA
Epithelial-myoepithelial carcinoma	Dual population	+	+			
Leiomyosarcoma		−	−			+
Malignant melanoma				+	+	
Myoepithelial carcinoma (clear, epithelial, or spindle variant)	Single population	+	+			
Nerve sheath tumor			−	+		
Synovial sarcoma	Biphasic		−			

CytoKer, cytokeratin; EMA, epithelial membrane antigen; H&E, hematoxylin-eosin; SMA, smooth muscle actin

oncocytoma, and mucoepidermoid carcinoma, which must always be considered. Finally, within the head and neck, metastatic tumors, such as renal cell carcinoma and balloon cell melanoma, should also be considered.

Epithelial-Myoepithelial Carcinoma

Epithelial-myoepithelial carcinoma was first proposed by Donath et al[84] in 1972, although similar tumors had been described previously as clear cell carcinoma, clear cell adenoma, glycogen-rich adenoma, and glycogen-rich adenocarcinoma. Corio et al[85] translated the term and introduced this neoplasm into the English-language medical literature.

Epithelial-myoepithelial carcinomas are most commonly found within the parotid glands (75%),[83,85–88] and the rest occur about evenly in the submandibular and sublingual glands and the minor salivary glands. It has predilection to occur in women, by a ratio of nearly 2:1. Because of their infiltrative pattern of growth, EMEC displays a particularly decided locoregional aggressiveness, but, when appropriately treated with complete surgical resection, it has a relatively low mortality.

The distinguishing histological feature of EMEC is classically described as sheets of well-delineated tubules lined by two layers; the internal layer with prominently eosinophilic ductal cells, and the outer layer with pale clear cells of myoepithelial origin with abundant cells overlying a basement membrane (**Fig. 10–16**). Both cell types vary in their distribution and phenotypic expression, not only from patient to patient, but also within the same tumor. However, typically the clear cells of the outer tubular layer are polyhedral (**Fig. 10–17**) and contain abundant diastase-digestible PAS-positive cytoplasmic granules, which stain negative for mucicarmine. Often, there is minimal nuclear pleomorphism and low rates of mitotic figures. Though rare, EMEC has such a distinctive histological appearance that it should be considered in the differential cytological diagnosis of any biphasic tumor.[82]

Clear Cell Carcinoma

Clear cell carcinoma is characterized by a predominant distribution of tumor cells with clear, PAS-positive

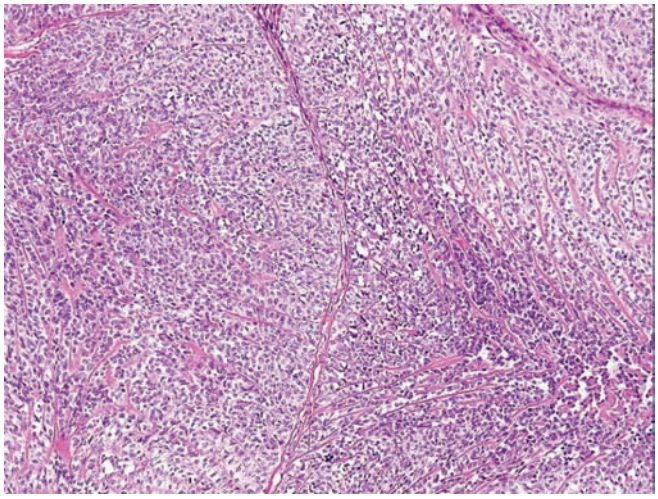

FIGURE 10–15 Myoepithelial carcinoma: epitheloid cellular features (H&E, ×20).

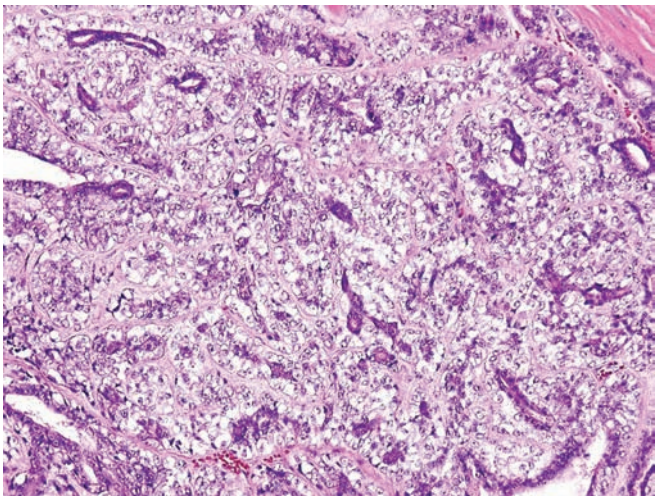

FIGURE 10–16 Epimyoepithelial carcinoma: low power (H&E, ×20). (Note: dark duct epithelial and clear periductal myoepithelial cells.)

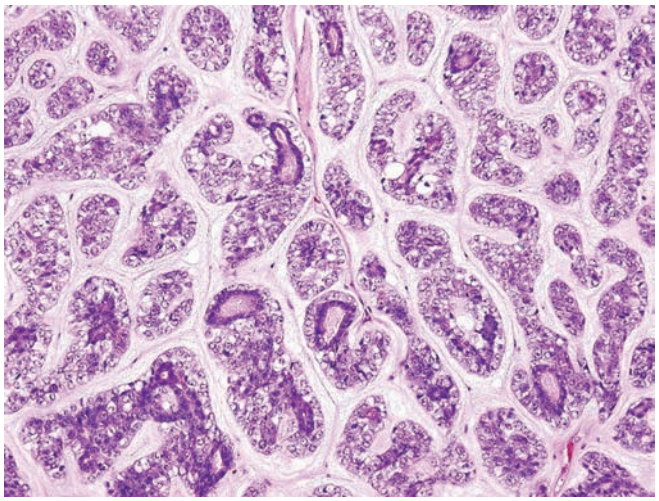

FIGURE 10–17 Epimyoepithelial carcinoma: high power (H&E, ×40).

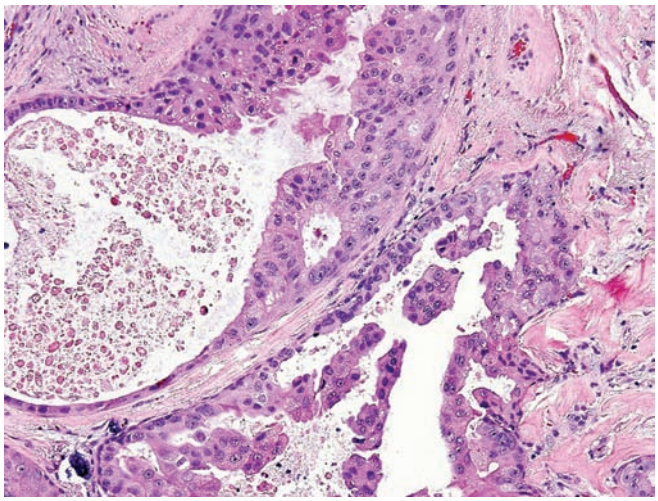

FIGURE 10–18 Salivary duct carcinoma: papillary formation (H&E, ×40).

cytoplasm. The tumor cells are cuboidal to polygonal with high nuclear-cytoplasmic ratios. CCC appears more homogenous when compared with EMEC with more cellular uniformity. Focal areas of eosinophilic cytoplasm and/or squamous differentiation can also be found. Glandular ductal formations are not typically seen.[82]

Salivary Duct Carcinoma

Clinical Presentation

Salivary duct carcinoma (SCD) is a rare, high-grade epithelial malignancy with a remarkable resemblance to mammary ductal carcinoma. The most commonly involved sites are the parotid gland in more than 85% of the cases, followed by the submandibular gland. The clinical presentation of patients with SDC is either a painless or pain-associated swelling of the parotid gland. Concurrent symptoms may include facial nerve dysfunction or paralysis in as many as a third of patients. There is a clear male predominance, and the age range is usually greater than 50 years old.

Histology

''Speichelgangcarcinoma'' was first described in 1968 by Kleinsasser et al[89] and later translated into salivary duct carcinoma.[90,91] Cells are cuboidal or polygonal with ductal formations and comedonecrosis. They contain amphophilic and eosinophilic cytoplasm with a granular or powder-like interior. Nuclear pleomorphism as well as cellular variability can be seen with the presence of mitotic figures. Salivary duct carcinoma typically displays intraductal and infiltrative ductal features (**Figs. 10–18, 10–19**). They are often associated with desmoplastic reaction in the surrounding soft tissues. They may present as de novo or most commonly in the setting of carcinoma ex-pleomorphic adenoma.

Although solid areas may be seen, the most common histological patterns include the comedonecrotic, cystic (**Fig. 10–20**), papillary, and cribriform subtypes. Goblet cell metaplasia, basal cell hyperplasic, and background necrosis can be seen adjacent to the area of the neoplasia. Perivascular and perineural invasion commonly occurs. Extensive perineural invasion and lymphovascular invasion are common.

Treatment

SCD is a high-grade malignancy with high rates of early metastasis and death. Parotidectomy with appropriate neck dissection is the mainstay of surgical treatment. Because ~60% of patients will have regional lymphatic spread, an appropriate cervical lymphadenectomy should always be considered. Postoperative radiation is advocated for this aggressive malignancy.

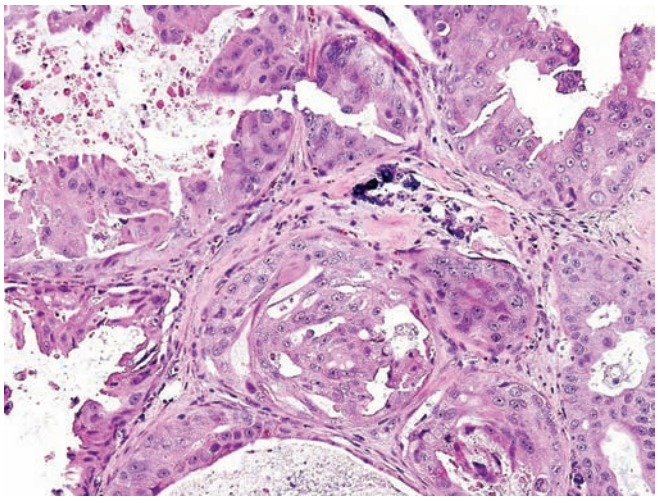

FIGURE 10–19 Salivary duct carcinoma (H&E, ×40).

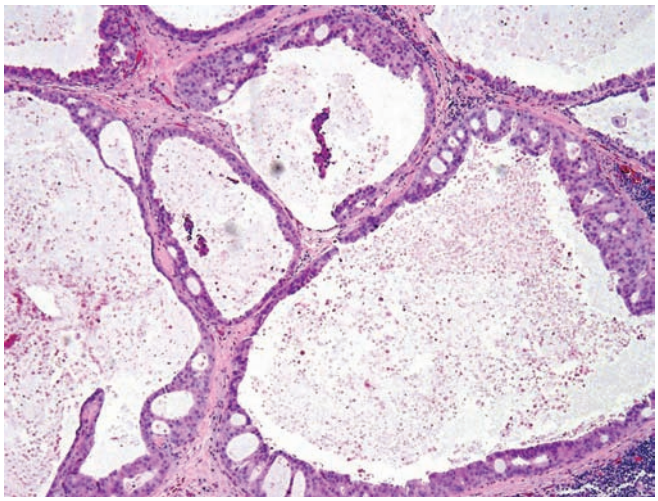

FIGURE 10–20 Salivary duct carcinoma (cystic) (H&E, ×20).

Despite appropriate surgery and postoperative radiation therapy, many patients succumb to distant disease. In fact, distant metastasis is common, even at primary presentation, to the lungs, bone, liver, and brain. In the three largest clinical reviews of the disease, the rate of distant metastasis varied from 46 to 62% and was often the cause of death. Therefore, a thorough preoperative workup should be undertaken. Although no proven systemic therapy is available for patients with salivary duct carcinoma, transtuzumab may provide hope for systemic therapy for patients with SDC (see previous discussion).[31]

Terminal Duct (or Polymorphous Low-Grade) Adenocarcinoma

Clinical Presentation

Terminal duct adenocarcinoma (TDC) or polymorphous low-grade adenocarcinoma is the second most common malignant salivary tumor in the oral cavity. The most common sites are the buccal mucosa and at the junction of the soft and hard palate, usually in elderly individuals. Other sites include lip and retromolar trigone. Patients typically present with a painless, elevated, and firm mass, usually with an intact mucosa around it. The occasional patient presents with pain or a poor fitting denture. Because of the overall good prognosis, pain is not a negative prognostic factor, as can be seen with other salivary gland malignancies. Some clinicopathological reports have shown a slight predominance in females.[92]

Although TDC is well known for its predilection to arise from minor salivary glands, these tumors are also diagnosed in the parotid gland. One review of 22 TDCs of parotid gland confirmed the low-grade nature of these tumors, regardless of the site of origin.[93] TDC shares with adenoid cystic carcinoma a similar histogenesis (intercalated duct origin) and cellular composition. Not surprisingly, the same pattern of local and perineural invasion is seen in both tumors.[94] In the past, it has been called lobular carcinoma or trabecular carcinoma of the salivary glands.

Histology

TDC is characterized by cuboidal or columnar cells of small to medium size, with an ovoid to spindle nucleus with fine chromatin and small nucleoli. The scant eosinophilic cytoplasm is mostly clear, although at times it may present with a granular or mucoid appearance. Mitotic figures, nuclear atypia, and necrosis are absent features. The benign morphology of the cells may confuse them with a monomorphic adenoma.

There are four typical growth patterns: solid (**Fig. 10–21**), cribriform, cystic, and tubular, and combinations thereof (**Fig. 10–22**). The tumor may be circumscribed but unencapsulated. The stroma may be mucoid, hyaline, or mucohyaline and loosely vascular. Invasion into the surrounding tissues typically presents either by single or multiple ducts and by solid epithelial nodules. Extension to the adjacent bone (hard palate) may also be observed. Some of the cells show a spindle cell appearance that could be suggestive of myoepithelial differentiation.[94]

Treatment

Complete surgical excision is the preferred mode of treatment.[92,93] Neck dissection is rarely indicated, as involvement of regional nodes is well below 10%. With appropriate surgical margins, local recurrence is low, but it has been reported to be as high as 17%.[95] Mortality occurs in 5 to 10% of cases. Due to the high incidence of PNI, these patients may be candidates for

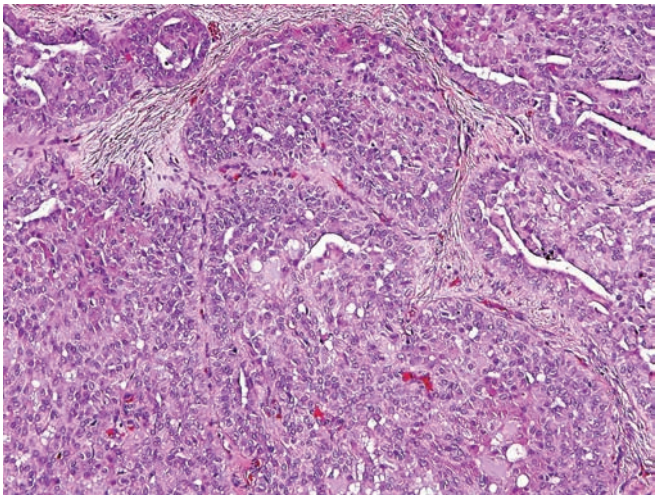

FIGURE 10–21 Terminal duct carcinoma solid component (H&E, ×40).

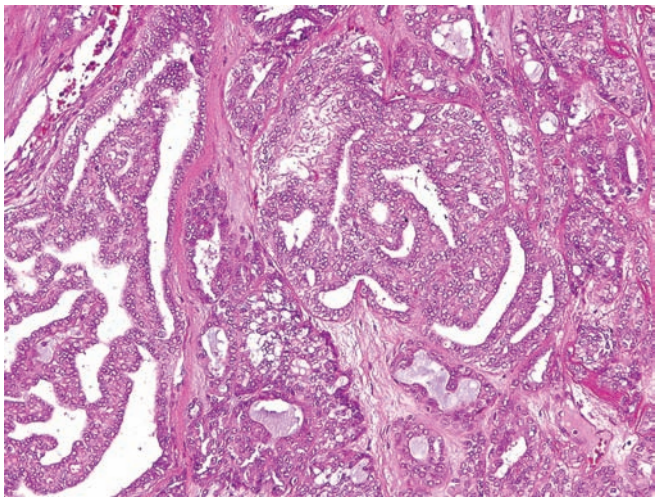

FIGURE 10–22 Terminal duct carcinoma (cystic and tubular components) (H&E, ×40).

adjuvant postoperative radiotherapy; however, no survival advantage has been proven.

Unclassified Adenocarcinoma

Adenocarcinoma not otherwise specified (NOS) of salivary tissue is a category used with diminishing frequency and now is most often used as a diagnosis of exclusion. Clinicopathological entities such as salivary duct carcinoma, terminal duct carcinoma, and epimyoepithelial carcinoma, formerly in the NOS category, are examples of this process. There remain, however, adenocarcinomas of salivary tissues that cannot be accommodated in conventional classifications.[96] They are the least common of salivary carcinomas (1–2% of tumors) and manifest a cytoarchitecture ranging from a well-differentiated, low-grade appearance to high-grade, invasive lesions (**Fig. 10–23**).

■ Epithelial-Mesenchymal-derived Salivary Gland Malignancies

These tumors conceptually derive from both epithelial and mesenchymal salivary gland tissues and include carcinoma ex-pleomorphic adenoma, carcinosarcoma, and metastasizing pleomorphic adenoma.

Carcinoma Ex-Pleomorphic Adenoma

Carcinoma ex-pleomorphic adenoma (CXPA) is the most common ''malignant mixed'' tumor. It has been estimated that CXPA may account for as much as 10% of all salivary gland malignancy. It arises from long-standing benign pleomorphic adenoma (mixed tumor) or in the setting of recurrent disease, mostly in the parotid gland. A typical presentation is the rapid growth of tumor in a long-standing salivary mass. The risk of malignant transformation increases with time and age of the patient. Among younger patients with pleomorphic adenoma, their lifetime risk may be higher for malignant transformation. Thackray and Lucas[97] estimated that malignant transformation eventually occurred in up to 25% of untreated mixed tumors. In an epidemiological study of 498 patients, Spitz et al[4] estimated at least a 3 to 10% rate of conversion from benign to malignant disease tumors. From a classic 1974 study, it has been estimated that 1 to 2% of adenomas of less than 5 years' duration, and 9.4% of adenomas present for more than 15 years, can transform into CXPA.[98]

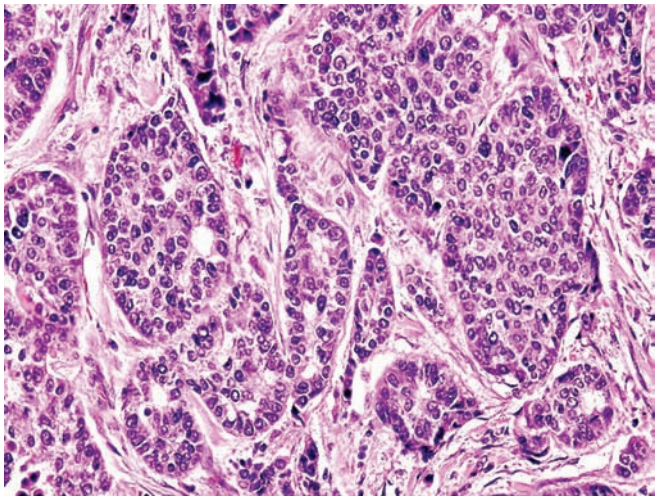

FIGURE 10–23 Adenocarcinoma not otherwise classified (H&E, ×40).

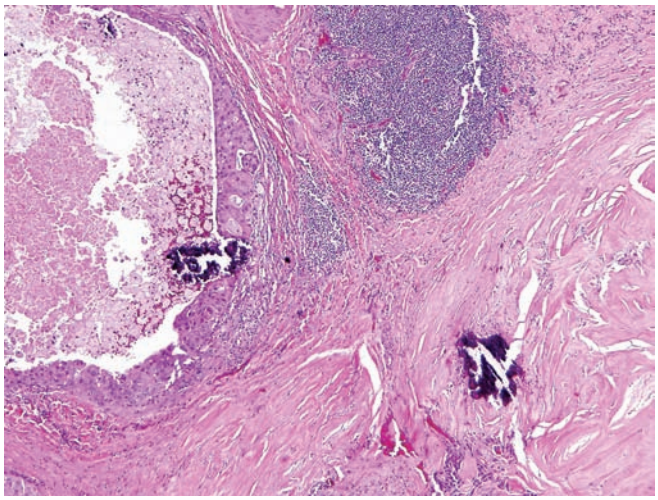

FIGURE 10–24 Carcinoma ex-pleomorphic adenoma: hyalinized and fibrotic remnants of pleomorphic adenoma: lower right (H&E, ×20).

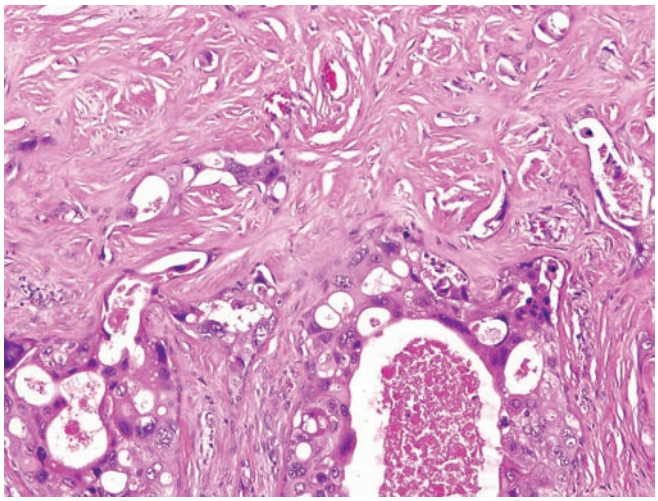

FIGURE 10–25 Salivary duct carcinoma ex-pleomorphic adenoma (H&E, ×40).

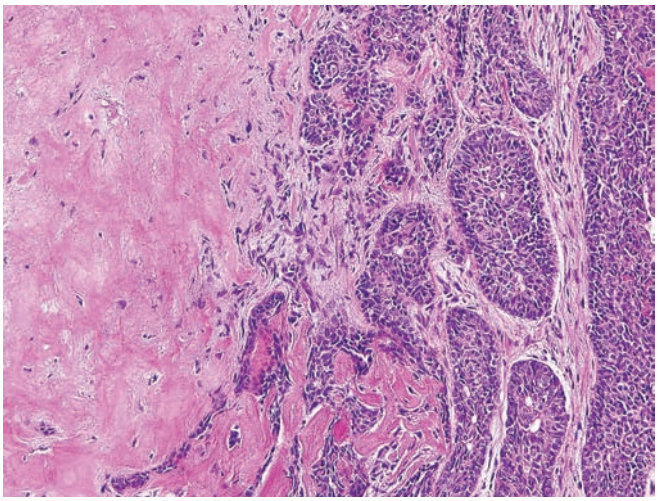

FIGURE 10–26 Poorly differentiated carcinoma (right) ex-pleomorphic adenoma (left) (H&E, ×20).

Histology

These tumors are comprised only of epithelial-derived carcinoma arising within the mixed tumor tissue types. CXPA often displays carcinoma within residual foci of benign mixed tumor (**Fig. 10–24**). If metastasis is present, only the carcinomatous element is present. In order of descending frequency, the carcinomatous histological subtypes seen within CXPA are salivary duct (**Fig. 10–25**), poorly or undifferentiated (**Fig. 10–26**) carcinoma, terminal duct carcinoma, myoepithelial carcinoma, and adenocarcinoma NOS. However, a thorough sampling of the entire tumor specimen is necessary to identify the preexisting benign component. Occasionally, the pleomorphic adenoma can be entirely replaced by a hyalinized round nodule, confounding diagnosis. An infiltrative growth pattern, hyalinization, hemorrhage, and calcification are often seen. Because the residual mixed tumor may be small, misdiagnosis is possible.

Immunohistochemical evidence suggests the antigens laminin and collagen IV, the main constituents of the basement membrane, may be involved in the malignant transformation of mixed tumors. The basement membrane is involved in cell differentiation and proliferation. Disruption of the basement membrane has been associated with the invasive properties of neoplasms. The discovery of significantly greater collagen IV deposits around tumor cell aggregates from metastasizing as opposed to nonmetastasizing carcinoma ex-pleomorphic adenoma suggests a role of collagen IV in the biological progression of the disease.[99] Carcinoembryonic antigen expression and high proliferative activity are associated with malignant transformation of the mixed tumor.[100]

Treatment

These aggressive tumors are generally treated with surgery and radiation therapy. The 42% rate of local recurrence in the rare submandibular and minor salivary gland CXPA is twice the rate of local recurrence in the parotid. Cervical metastasis occurs in 10 to 20% of CXPA cases. Distant metastasis occurs in 30% of patients, with the lung and bone most commonly involved. Long-term survival rates of frankly invasive CXPA are 30 to 40%. This drops to 3% in patients with nodal disease.[101] A subset of CXPA patients with microscopic invasion of less than 8 mm has a potentially favorable prognosis.[102]

Carcinosarcoma

For the diagnosis of carcinosarcoma, both the primary tumor and any metastasis must display evidence of both malignant epithelial and malignant mesenchymal components. As such, this tumor is exceedingly rare and poorly understood. Typically, carcinosarcoma presents suddenly within a long-standing mixed tumor of the major salivary glands, particularly the parotid. Its natural history is fulminant, aggressive, and often rapidly fatal.

Histology

A biphasic microscopic morphology must be identified to establish the diagnosis of carcinosarcoma. The spectrum of sarcomas includes chondro-, fibro-, leio-, myxo-, and osteosarcoma, as well as malignant fibrous histiocytoma, most often in association with a salivary ductal carcinoma (**Fig. 10–27**). Immunohistochemical analysis has suggested that both elements are derived from a common precursor cell, possibly of myoepithelial origin.[103]

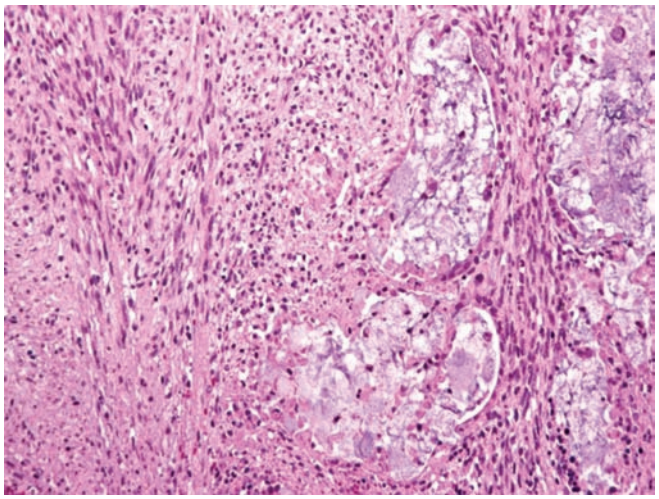

FIGURE 10–27 Carcinosarcoma: carcinoma component (right): sarcoma component (left) (H&E, ×40).

Metastasizing Pleomorphic Adenoma

Though benign on histology, metastasizing pleomorphic adenoma (mPA) is a salivary gland tumor that behaves with unequivocally malignant features, primarily in its capacity for distant metastasis. By histology and cytology, mPA cannot be distinguished from typical pleomorphic adenoma. The diagnosis can only be made after the histologically bland pleomorphic adenoma has spread to a distant site.[104]

Although initially referred to as a ''benign'' metastasizing mixed tumor in the 1940s,[105,106] subsequent reports have confirmed its functionally morbid, sometimes protracted, and even lethal[107] natural history. However, this tumor must be distinguished from carcinoma ex-pleomorphic adenoma and carcinosarcoma by the lack of malignant epithelial and/or mesenchymal components, respectively.[108]

Many reports clearly suggest an association with previous surgical exploration. It may be that repeated surgical treatment provides an opportunity for hematogenous dissemination of an otherwise benign, and if properly treated, indolent neoplasm.[109] However, this is clearly a spectrum of behavior, and these lesions must be distinguished from locally recurrent pleomorphic adenoma.[110,111] With proper initial surgical treatment, rates of local recurrence should be quite low.[112]

The underlying mechanism for the metastatic behavior of this histologically benign tumor remains unclear. El-Naggar et al[113] have suggested that metastasizing pleomorphic adenomas may represent unrecognized true malignancy. Further evidence of the clinical malignancy of some of these cases can also be drawn from previously documented cases in which ~50% of patients had died of their disease with documented metastases in bones, lungs, lymph nodes, or deep organs. The lack of recognized histological parameters of malignancy in these cases raises the possibility that a small subset of pleomorphic adenomas with submicroscopic alterations may pursue a malignant course. To date, no correlation has been found in any study between the presence or deletion of specific chromosomal alterations and subsequent tumor recurrence or malignant transformation.

Staging

The American Joint Committee on Cancer (AJCC) and the World Health Organization (WHO) provide a staging system for major salivary gland malignancy (**Tables 10–4, 10–5**).[114] A staging system for minor salivary gland tumors does not exist.

■ Mesenchymal-derived Salivary Malignancies

Primary salivary gland sarcomas represent less than 1% of salivary malignancies. They present in an older population and less commonly than benign mesenchymal-derived salivary tumors. Eighty percent of mesenchymal-derived salivary malignancies occur in the parotid as a nodule or swelling. Primary origin must be supported with sarcoma in no other site, exclusion of sarcoma invading from adjacent soft tissue, and exclusion of carcinosarcoma. Anaplastic carcinoma and neurotropic melanomas must be distinguished.[115] Immunohistochemistry has an important role in histopathologic classification.

The most common are hemangiopericytoma (16% of cases), not surprising given the propensity for parotid involvement by benign vascular tumors. Malignant schwannomas (mostly spindle cell) make up 15% of cases. The abundant peripheral nerve supply in

TABLE 10–4 2002 AJCC TNM Definitions for Staging of Major Salivary Malignancies

Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 2 cm or less
T2	Tumor 2 cm
T3	Tumor more than 4 cm or extraparenchymal extension
T4a	Tumor invades skin, mandible, ear canal, or facial nerve
T4b	Tumor invades skull base, pterygoid plated, or encases carotid artery
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node 3 cm or less
N2a	Metastasis in single ipsilateral lymph node 3 to 6 cm
N2b	Metastasis in multiple ipsilateral lymph nodes <6 cm
N2c	Metastasis in bilateral or contralateral lymph nodes <6 cm
N3	Metastasis in lymph node >6 cm
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

AJCC, American Joint Committee on Cancer

TABLE 10–5 2002 AJCC Stage Groupings for Major Salivary Malignancies

Stage 1	T1N0M0
Stage 2	T2N0M0
Stage 3	T3N0M0, T1N1M0, T2N1M0, T3N1M0
Stage 4a	T4aN0M0, T4aN1M0, T1N2M0, T2N2M0, T3N2M0, T4aN2M0
Stage 4b	T4b any N M0, any TN3M0
Stage 4c	Any T, any N M1

AJCC, American Joint Committee on Cancer

salivary glands accounts for the relatively high frequency of both benign and malignant neural tumors. Fibrosarcoma and malignant fibrous histiocytoma represent 14% and 11% of reported sarcomas, respectively.[115] Nearly all forms of sarcoma present in salivary glands.

The treatment is aggressive surgical resection and postoperative radiation therapy. Recurrences manifest in 40 to 64% of patients, with metastases (usually hematogenous) in 38 to 64%. Metastasis is most common to the lung, followed by cervical lymph nodes. A rate under 10% for cervical metastasis suggests elective neck dissection is not necessary. Mortality is 36 to 64% within 3 years of diagnosis, with the average time from treatment to death being 2.4 years.[115,116] Tumors arising within the gland have fewer recurrences and metastases than in patients with secondary salivary gland involvement. This may well be more related to the stage of the disease rather than the site of location.[115] Salivary gland sarcomas behave like their soft tissue counterparts with prognosis related to tumor size, sarcoma type, and histological grade.[116] Kaposi's sarcoma presents in acquired immunodeficiency syndrome (AIDS) patients usually in intraparotid nodes.

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11

Metastasis to Major Salivary Glands

PAUL SABINI AND ROBERT L. WITT

Skin Cancer and the Salivary Glands

Despite its prevalence, nonmelanoma skin cancer often manages to surprise both patients and clinicians with its destructive and sometimes lethal ability. The annual mortality rate from nonmelanotic cutaneous carcinoma approaches that for the more lethal but less common melanoma.[1] As disfiguring as both forms of skin cancer can be, the mortality rates are mostly related to metastatic rather than local disease. Surgeons need to consider the pathways for metastases in melanoma and squamous cell skin cancer patients. Furthermore, only when the tumor is reliably extirpated should the surgeon focus on the reconstructive effort.

Skin cancer is the most common cancer in the world, and 80% of all skin cancers occur in the head and neck region.[2] The incidence of these lesions by most accounts has doubled and tripled in the past several decades. Assessing and managing metastatic disease is complicated by the cranial nerves, particularly the facial nerve as it courses through the lymphatic-laden parotid gland.

Squamous cell carcinomas and melanomas comprise the overwhelming majority of head and neck malignant neoplasms that metastasize to the parotid;[3] however, other tumors such as Merkel cell carcinoma, eccrine carcinomas, sebaceous carcinoma, olfactory neuroblastoma, retinoblastoma, thyroid, and intracranial neoplasms may be encountered. Merkel cell carcinoma and desmoplastic squamous cell carcinomas are of particular note for their metastatic potential. In patients with aggressive cutaneous carcinomas, the parotid gland will need to be addressed in the absence of clinically evident metastases.

Anatomy

The skin is an ectodermally derived three-layered structure consisting of the epidermis, the papillary dermis, and the reticular dermis. The latter rests upon a layer of fat that incorporates the deepest extension of hair follicles and eccrine sweat glands. Superficial skin cancers (those within the epidermis) can track unimpeded along hair follicles and sweat glands and persist after treatment if the treatment does not extend beneath the root of the follicle or sweat gland. Keratinocytes comprise the majority of the cells within the epidermis and give rise to basal and squamous cell carcinomas; however, the epidermis also contains melanocytes, Merkel cells, and Langerhans' cells. Separating the keratinocytes from the papillary dermis is the basement membrane. Once a cancer cell violates the basement membrane, it has access to the lymphatic channels and the superficial vascular plexus, both of which reach into the papillary dermis. A fascial cover separates the parotid gland from the surrounding tissue. Extraglandular nodes are located in pretragal and supratragal tissues superficial to the posterior portion of the parotid and in the infra-auricular tissues superficial to the tail of the parotid. Metastatic involvement of these superficial nodes can lead to direct penetration of the parotid fascia, a particular potential for preauricular and auricular cutaneous carcinoma. A glandular infiltration of neoplasm has free reign of the gland and will simply push nerves, vessels, and nodes away as it expands. The facial nerve itself is often only infiltrated by an aggressive malignancy or an exceptionally large growth. Otherwise, the seventh nerve is ''pushed'' away from a growth;

therefore, the nerve's position cannot be protected without a dissection.

The parotid lymph nodes drain the face lateral to the nose and anterior to the ear. The scalp can be divided in a coronal plane through the external auditory canal with areas anterior to the plane draining into the parotid and submandibular nodes and areas posterior draining into the occipital nodes and posterior cervical nodes. The eyelids, conjunctiva, lacrimal gland, posterior cheek, upper neck, anterior ear, external auditory meatus, and eustachian tube drain to the parotid gland. The postauricular sulcus drains predominantly to the posterior neck (**Fig. 11–1**). The lymph nodes surrounding the submandibular gland are the focus of metastatic disease from the skin and mucous membranes of the anterior face, nose, lips, buccal mucosa, gingiva, mobile tongue, floor of the mouth, and palatoglossal folds.

Epidemiology of Skin Cancer

Each year approximately 500,000 people in the United States will be diagnosed with nonmelanoma skin cancer. Squamous cell carcinoma, comprising 20 to 30% of cutaneous malignancies, is second in incidence to basal cell carcinoma. Approximately 32,000 new cases of melanoma will be diagnosed each year. Ultraviolet radiation is the principal etiology[4] of these cancers brought on by lifestyle choices and possibly ozone depletion.

Recent epidemiologic studies are revealing that skin cancer can be more than a disease unto itself; it can also be the harbinger of other cancers. Like the skin, the parotid gland is of ectodermal origin. Epidemiologic data have shown an increase in primary, nonmetastatic parotid cancer in patients with a prior history of skin cancer, suggesting an inherent susceptibility to ectodermal carcinogenesis in those individuals.[5] In Switzerland, Levi et al[5] found a threefold increase in the incidence of salivary gland cancers among patients with a history of basal cell carcinoma. They noted an even stronger association between squamous cell skin cancer and subsequent salivary gland cancers.[6] In the United States, Kahn et al[7] reported similar results and also looked at cancer mortality following a history of nonmelanoma skin cancer. Among the cancers contributing to an

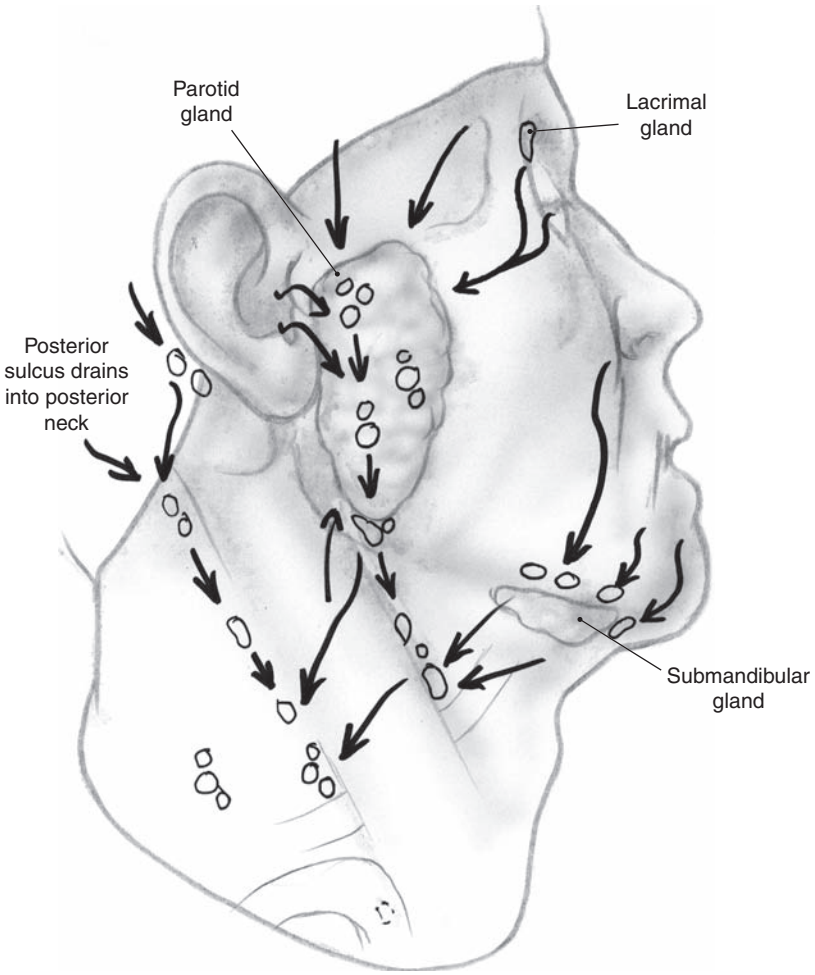

FIGURE 11–1 Lymphatic drainage to the salivary glands.

increased mortality in these patients were salivary gland carcinomas. The preceding three studies defined their cancers as second primaries and not metastatic lesions to the parotid. Speculation on the observed associations between nonmelanoma skin cancers and subsequent primary parotid neoplasms range from a common genetic susceptibility or environmental agent to a simple increase in encounters with the health care profession brought on by a disease (skin cancer) that the patient could not ignore.[8]

Evaluation and Treatment of the Skin Cancer Patient

A history and physical examination followed by a biopsy will initiate the evaluation of a skin cancer patient. Basal cell carcinomas and squamous cell carcinomas may present as nonhealing or flaking lesions. Physical examination should define the suspected size of the growth. The visible and microscopic extent of a nodular basal cell carcinoma rarely differs. However, poorly differentiated squamous cell carcinomas and morpheaform basal cell carcinomas are notorious for diving into tissue and extending beyond the reaches of the physician's eye. Mohs micrographic surgery is the treatment of choice for the latter two types of skin cancers. Mohs could be considered for any nonmelanoma facial skin cancer. No published technique approaches the control offered by Mohs micrographic surgery for basal and squamous cell carcinomas. Many surgeons, including some Mohs surgeons, are reluctant to advocate Mohs surgery for all nonmelanoma head and neck skin cancers. Lack of access to a Mohs surgeon is a valid and frequently cited reason; however, the other frequently cited issue pertains to cost control and stems from a failure to recognize all of the health care costs involved in the care of a skin cancer patient when Mohs is not utilized. Cook and Zitelli[9] effectively refute the notion that Mohs micrographic surgery is not cost-effective. They compared Mohs surgery to traditional excision with vertical section analysis and reviewed the costs to the health care system. Mohs did not increase costs, yet it indisputably increases local control. The increased use of Mohs surgery may diminish the incidence of recurrent and metastatic nonmelanotic cutaneous cancer. The use of Mohs surgery for melanoma remains more controversial, and few surgeons advocate it in the setting of invasive melanoma.[10]

■ Evaluating Metastatic Disease

Involvement of the major salivary glands can occur by direct invasion, lymphatic metastasis from a nonsalivary gland primary, and hematogenous spread from a distant primary. Direct invasion of the parotid gland is expedited by an interconnected plexus of periglandular and intraglandular lymph nodes. Submandibular lymph nodes lie outside the capsule of the gland, and parenchymal involvement would be by direct extension from these lymph nodes. Greater direct sun exposure to the preauricular region in comparison to the submandibular region leads to more direct invasion of the parotid gland by skin cancer (see Chapter 2, **Fig. 2–1**).

Ten to 15% of malignant neoplasms in the major salivary glands are from cancer metastases. Higher rates occur in Australia, where an elevated incidence of cutaneous malignancy pervades. Head and neck cutaneous squamous cell carcinoma and malignant melanoma make up 80 to 85% of metastatic tumors to the major salivary glands.[3] Cutaneous squamous cell carcinoma with metastasis to the parotid is more common than melanoma. Its spread is via the lymphatic system. Ninety percent of such carcinoma is to the parotid. The balance is to the lymph nodes surrounding the submandibular gland. Metastasis to the sublingual gland has not yet been reported. The nasopharynx is the most common upper aerodigestive primary site that metastasizes to the parotid.

Metastatic disease to the salivary glands occurs later in life, with peak incidences in the sixth and seventh decade of life, predominantly in males. In melanoma and infraclavicular metastasis to the salivary glands, the first manifestation of disease may be the salivary gland mass. Kidney, lung, and breast are the most common sites of distant metastasis to the salivary glands. Prostate, colon, pancreas, stomach, bladder, uterus, and ovary are other sites. Careful evaluation usually results in identification of widespread metastasis once the salivary glands are involved with infraclavicular metastasis. Local control with a solitary metastasis to the salivary gland is possible.

■ Basal Cell Carcinoma

Basal cell carcinoma involving the parotid is usually from direct extension. Fewer than 200 cases of metastatic basal cell carcinoma have been reported. Metastatic basal cell carcinoma tends to occur in a younger population than nonmetastatic basal cell carcinoma, with an average age of 45.[11] The time period between diagnosis of the initial lesion and metastasis is on average 6 to 9 years, sharply contrasting to the early appearance of metastatic squamous cell carcinoma.[12] The risk factors that have been identified include recurrent tumors, tumors in patients with a history of radiation therapy, tumors greater than 10 cm^2, and tumors of the scalp and face. The rare basal cell

carcinoma meeting all four criteria may have up to a 50% chance of metastasis. Metastatic basal cell carcinoma occurs most notably in the setting of the morpheaform subtype.[13] Unfortunately, the limited number of reports of metastatic basal cell carcinoma does not offer a common approach to this rare entity. Up to two thirds of the cases appear to have lymphatic spread; therefore, sentinel node biopsy may have a future role in the evaluation of the high-risk patient.[13] Regional metastases have been noted mostly in the parotid and periparotid nodes. When metastatic basal cell carcinoma to the parotid is present, a total parotidectomy with preservation of the facial nerve (when not grossly involved) and a selective neck dissection (for the otherwise N0 neck) are recommended. A careful search for distant metastasis should precede surgery. In the patient with comorbidities, radiation therapy should be considered. The prognosis for basal cell carcinoma metastatic to the parotid is poor, with 6-month and 1-year survival at 50% and 20%, respectively.[12]

■ Cutaneous Squamous Cell Carcinoma

Five percent of cutaneous squamous cell carcinoma patients have metastatic disease to the parotid or neck, occurring usually within 1 year of the index cancer.[14] Metastatic disease to the parotid or neck may potentially not present for 2 or 3 years after resection of the primary lesion. These must be distinguished from the more unusual squamous cell carcinoma from a distant primary site and a primary parotid squamous cell carcinoma (a diagnosis of exclusion). Histological evaluation will not distinguish between these entities.[15]

The following risk factors are associated with metastases: tumor diameter greater than 2 cm, thickness greater than 4 mm, local recurrence, poorly differentiated tumors, rapid growth, perineural or perivascular invasion, location on the preauricular skin, external ear (with cartilage invasion), lip (with diameter greater than 1.5 cm), upper lip, within a scar or a non-sun-exposed area, and in patients who are immunocompomised.[14] The occurrence of metastatic disease from cutaneous squamous cell carcinoma to the parotid gland correlates with the local control rate. The majority of parotid metastases occur within 1 year of treatment of the primary tumor and often occur simultaneously with local recurrence.[16] Preauricular lesions have a high rate of recurrence and have the highest propensity for secondary involvement of the parotid (10% rate). Superficial parotidectomy should be considered in the primary treatment in selected preauricular skin squamous cell carcinomas. External ear and periauricular carcinoma have a propensity to invade the parotid, postauricular, and/or upper jugular nodes. Additional associated adverse prognostic factors would warrant strong consideration for elective parotidectomy with supraomohyoid and postauricular dissection for external ear and periauricular squamous cell carcinoma.[17] In patients who developed external ear squamous cell carcinoma and regional metastases, 100% had parotid involvement, and 57% had cervical nodal spread.[18]

Lesions on the lip are associated with higher metastatic potential than other cutaneous sites.[19] The lateral lip drains to the submandibular nodes. The middle third of the lip drains to the submental nodes, either submandibular nodes or bilateral submandibular nodes. Upper lip cancers drain primarily to the submandibular nodes, but also to the preauricular, parotid, and submental nodes. A squamous cell carcinoma of the lip must be distinguished from mucoepidermoid carcinoma of a minor salivary gland origin. Poorly differentiated mucoepidermoid carcinomas will contain a relatively high number of squamous cells,[20] and a biopsy may only reveal this component to the pathologist. The high-grade mucoepidermoid carcinoma is an even more aggressive tumor with a greater metastatic potential.

Periparotid lymph node involvement carries a better prognosis than parenchymal metastatic parotid disease. Parotid parenchymal metastasis from a cutaneous squamous cell carcinoma primary has a reported 50% rate of recurrence and 20% mortality rate despite aggressive surgery and postoperative radiation therapy. Facial nerve weakness has been reported on initial presentation in 30% of cases, requiring nerve sacrifice in close to half of all cases.[2]

Metastatic cutaneous squamous cell carcinoma to the parotid is associated with a high incidence of clinical and occult neck metastases. A 25% rate of clinical neck metastasis can be expected in a patient with a parotid metastasis from a cutaneous primary. A 35% rate of positive neck lymph nodes with selective neck dissection has been reported in patients with parotid metastasis from a cutaneous primary and an N0 neck.[21] The N0 neck with a metastasis to the parotid from a skin cutaneous primary from the anterior scalp, face, ear, and anterior neck should be treated with an anterolateral selective neck dissection (levels I, II, III, and IV) or radiation therapy. Posterior lesions would be treated with a posterolateral selective neck dissection (levels I, II, III, and V) or radiation.[22]

As the parotid gland develops, 20 to 30 lymph nodes are encased within it[23] (accounting for the fact that the parotid is the salivary gland most involved with metastatic disease). Pathologic and clinical evidence suggests between one and five deep parotid lymph nodes exist in 90% of patients.[24] Computed tomography (CT) or magnetic resonance imaging (MRI) may help determine if deep parotid or parapharyngeal nodes are present. In the presence of palpable intraparotid metastasis, a

total parotidectomy with preservation of the facial nerve, when not grossly involved with tumor, offers the patient an anatomically appropriate operation.[24,25] However, many surgeons favor a lateral lobectomy without clinical evidence of deep lobe involvement. Tumor control has not been proven higher with total parotidectomy or sacrifice of the facial nerve when the nerve was not grossly involved.[1] Local recurrence in the parotid bed is the most common site of failure in cutaneous squamous cell carcinoma metastatic to the parotid.[2] A 75% rate of recurrence with surgery alone[16] has led to combined modality treatment with radiation therapy. Dona et al[26] reported an improved 24% locoregional recurrence rate after parotidectomy and postoperative radiation, with recurrence occurring in a median time of less than 8 months. Radiation therapy should include the deep lobe if not resected (see Chapter 13).

Metastatic disease to the parotid carries a significant adverse clinical prognosis. The size of the parotid metastasis (<3 cm vs >3 cm) carries a significant adverse clinical prognosis. Metastatic cutaneous squamous cell carcinoma in both the parotid gland and cervical lymph nodes carries a worse prognosis than those with disease in the parotid alone. A TNM staging that separates parotid and neck stage may be valid.[27]

■ Management of the Parotid Gland in the Presence of Cervical Metastatic Disease

Skin cancer patients may present with clinically positive neck disease without obvious parotid metastasis. In these individuals, the parotid nodes should be evaluated if they are within the path of spread. Cancers occurring lateral to the nasal sidewall and anterior to the coronal plane of the external auditory canal place the parotid in the path of spread. Most clinicians favor lateral lobectomy in the absence of palpable intraparotid nodes. In those patient, postoperative radiation therapy should include the remaining portion of the parotid gland. Neck metastases from skin cancers occurring posterior to the coronal plane of the external auditory canal do not warrant a parotidectomy.

Melanoma

The majority of melanomas involving the parotid gland result from metastasis from a head and neck cutaneous primary. Melanocytes within the parotid gland acinar and ductal cells support the remote possibility of primary melanoma of the parotid.[28] To support a diagnosis of primary melanoma, the tumor epicenter should be in the parotid with no lymph node tissue in the mass. Unknown primary is a more likely scenario than primary melanoma of the parotid. Primary melanomas are known to occasionally undergo regression. Patients with unknown primary melanomas may have a survival advantage over patients with known primary.[29]

In patients with cutaneous malignant melanoma (CMM) of the head and neck, regional metastatic rates correlate with tumor thickness. Occult regional metastasis is 5% in tumors less than 1 mm, 20% for tumors between 1 and 4 mm, and up to 50% for tumors greater than 4 mm. However, no prospective trial has shown a survival advantage with elective lymphadenectomy partly because only 10 to 20% of patients present with occult nodal disease. Sentinel node biopsy (SNB) may spare a more radical procedure in most patients. SNB provides prognostic information and identifies patients who need lymphadenectomy and may benefit from adjuvant therapy or who may qualify for clinical trials. It is appropriate for T2N0M0, T3N0M0, and T4N0M0 CMM lesions.

Head and neck lymphatic drainage from the skin has unexpected drainage patterns with occasional bilateral or contralateral drainage. Skin metastasis to the neck without parotid involvement has been reported in 36% of patients.[30] Most large series show a 95% success rate in localizing the sentinel node when preoperative lymphoscintigraphy and a handheld gamma probe are combined with blue dye injection.[31,32] The two techniques are complementary because the sentinel lymph node containing micrometastasis may stain blue but not be radioactive or be radioactive and not stain blue. A sentinel lymph node found to be positive for micrometastasis is frequently the only node with metastatic disease.

Lymphoscintigraphy using technetium Tc 99m sulfur colloid has a low exposure to radiation for patients and physicians. For CMM, 0.5 mCi Tc 99m-labeled sulfur colloid is injected intradermally around the primary tumor. Imaging can occur 20 minutes after injection to determine likely sentinel nodes. The patient is taken to the operating room. Before skin incision, the gamma probe can identify a sentinel node within 1 cm, and the skin is marked in this location. The gamma probe can visualize a lymph node smaller than 5 mm. The gamma probe must be pointed away from the primary lesion because the primary lesion causes high background noise. Because the probe is held against the tissue during dissection, nodes in close proximity can be distinguished. Nodes that are more than 10% as hot as the hottest node are removed. Isosulfan blue dye, 1.0 mL, is injected intradermally around the primary tumor in the operating room prior to skin incision. Extravasation of dye staining the surgical field and obscuring tissue planes is a risk.

SNB reduces the number of nodes harvested and allows meticulous testing on the most important nodes. This cannot be done at frozen section. In addition to

hemaoxylin and eosin staining, immunohistochemistry staining with HMB-45 and S-100 is performed. Reverse transcriptase polymerase chain reaction technology is also utilized. A differentiation must be made between melanoma and poorly differentiated carcinoma, adenocarcinoma, and anaplastic carcinoma. Desmoplastic melanoma, a spindle-shaped tumor mimicking other spindle cell tumors, including malignant myoepithelioma, sarcomatoid carcinoma, and malignant schwannoma, involves the parotid by neurotropic spread.[33]

Sentinel node biopsies are in their infancy, and the long-term utility will come to light when patients with negative sentinel nodes are followed over many years. To date there is no evidence of improved survival with SNB for cutaneous malignant melanoma.

Thirty-eight percent of patients with parotid metastasis from a CMM have been reported to have clinical cervical lymph node metastasis. In addition, 27% of patients with parotid metastasis from CMM will have occult cervical neck metastasis in the N0 neck.[21] Patients with parotid metastasis and N0 neck should be considered for elective neck dissection. Radiotherapy improves regional control but not overall survival. Metastatic melanoma to the parotid carries a grim prognosis with a high rate of distant metastasis.

Surgical Technique in Sentinel Lymph Node Biopsy of the Parotid Gland

Up to 50% of head and neck melanomas drain to the periparotid region. Many reports describe SNB in the parotid without identification of the facial nerve. As the utility of and familiarity with SNB increases among surgeons, this trend of ''berry picking'' may continue. The incidence of iatrogenic facial nerve paralysis will climb if that method gains a foothold. Reports that describe a lack of facial nerve dissection come in two varieties: Either the authors fail to appreciate the danger to the facial nerve, or the authors do appreciate the risk but feel that blunt dissection will spare the nerve.[34,35]

Blunt dissection through the parotid gland in search of a potential malignancy risks not only the nerve during that procedure. If an intraparotid sentinel node contains cancer, then the nerve will need a formal dissection anyway to remove the gland. If the surgeon has not done a dissection to find the node and finds cancer in that node, then the subsequent nerve dissection is inevitably more treacherous. The TNM staging system for melanoma is shown in **Table 11–1**.[36]

TABLE 11–1 TNM Classification for Malignant Melanoma

pTNM Pathological classification
pT1a 1 mm or less in thickness, no ulceration
pT1b 1 mm or less in thickness, with ulceration
pT2a >1–2 mm, no ulceration
pT2b >1–2 mm, ulceration
pT3a >2–4 mm, no ulceration
pT3b >2–4 mm, with ulceration
pT4a >4 mm, no ulceration
pT4b >4 mm, with ulceration
N1a 1 node, microscopic
N1b 1 node, macroscopic
N2a 2–3 nodes microscopic
N2b 2–3 nodes macroscopic
N2c satellite or in transit without nodes
N3 4 or more nodes; matted
Stage grouping
Stage I and II: N0
Stage III: Any pT, N1, N2, N3
Stage IV: Any pT, any N, M1

pT, primary tumor

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12

Treatment of Salivary Lymphoma and Advanced Nonlymphoid Malignant Salivary Gland Neoplasms

CHARLES J. SCHNEIDER

The majority of lymphomas involving head and neck sites are secondary ''nodal'' lymphomas, which most commonly involve cervical lymph nodes as a manifestation of systemic disease. Approximately 10% of all patients with non-Hodgkin's lymphoma have primary ''extranodal'' disease originating in the head and neck. The most common sites of primary lymphoma arising in the head and neck include Waldeyer's ring, the salivary glands, the nasal cavity, the paranasal sinuses, the thyroid gland, and the orbit. More than half of these head and neck lymphomas occur in Waldeyer's ring, and approximately one third occur in the paranasal sinuses, the nasal cavity, the oral cavity, and the orbit. The remaining 5 to 10% have their origins in the salivary glands. Salivary gland lymphomas are rare, representing only 1.7 to 5% of all neoplastic disorders of the salivary glands, and ~4.7% of lymphomas from all body sites.[1–5]

The parotid gland is the most common major salivary gland to be involved with malignant lymphoma. This is not unexpected due to the large number of lymph nodes situated within and near the parotid gland, as well as the presence of lymphoid aggregates within the gland itself. Although the overall incidence of primary parotid lymphoma is only 1 to 4%, this entity represents anywhere from 64 to 93% of all cases of primary salivary gland lymphoma.[3,6] A report from the British Salivary Tumor Panel in 1986 estimated that 61% of salivary gland lymphomas arise in the parotid gland, 18% in the submandibular gland, and the remaining 21% in minor salivary glands.[7] In a retrospective study of 26 patients with salivary gland lymphoma, 76.9% of cases involved the parotid gland, and 23.1% of cases involved the submandibular gland.[1]

Patients with primary salivary gland lymphoma usually present with an enlarging painless mass within the salivary gland. Facial nerve involvement is rare.[5,6] Whereas non-Hodgkin's lymphomas occurring in the head and neck region are most common between the ages of 50 and 60 years, the mean age of diagnosis for patients with primary salivary gland lymphomas is ~65.5 years.[1,5] The male to female ratio is 1.6:1 for all extranodal head and neck lymphomas. In contrast, lymphomas arising in the salivary glands, as well as in the orbit and thyroid gland, occur equally or more frequently in women.[5] In a retrospective study of patients with salivary gland lymphomas, the female to male ratio was 3.3:1.[1]

Salivary gland lymphomas are staged as either extranodal or nodal.[8] Nodal, or secondary, salivary gland lymphoma is an occasional manifestation of systemic non-Hodgkin's lymphoma, most commonly follicular histology. Extranodal, or primary, salivary gland lymphoma arises from lymphocytes within the salivary gland parenchyma itself. The most common extranodal histology is the marginal zone mucosa-associated lymphoid tissue (MALT) lymphoma. Because all of the salivary glands, with the exception of the parotid gland, are normally devoid of lymphoid tissue, lymphomas arising within the parenchyma of the salivary gland itself are usually derived from infiltration of reactive lymphocytes into the gland, which is seen in certain autoimmune diseases such as Sjögren's syndrome. Extranodal primary lymphomas arising within salivary glands are thus fairly rare.[6] To satisfy the criteria defining primary extranodal salivary gland lymphoma, the first clinical manifestation of lymphoma must involve a salivary gland, and there

must be histological proof that the lymphoma involves the salivary gland parenchyma. In addition, the lymphoid infiltrate must be a monoclonal malignant process, rather than a polyclonal reactive process. Until 1975, only 64 cases of primary salivary gland lymphoma were reported in the literature.[9]

Defining primary extranodal lymphoma arising in the parotid gland is more difficult than doing so for the other salivary glands (**Table 12–1**). Small lymph nodes are embedded within the parotid gland but not in the other salivary glands. These intraparotid nodes are complex. They can contain salivary ducts and acini, a phenomenon that reflects the close relationship between the salivary gland and this lymphoid tissue during embryonic development. Given this intimate relationship, it is often difficult for the pathologist to discriminate between primary and secondary parotid lymphoma. Numerous conflicting criteria have been described in the literature to define primary parotid gland lymphoma. Some authorities indicate that any lymphoma originating in the parotid gland represents a primary parotid lymphoma, even if the lymphoma originates from intraglandular lymph nodes, as long as the parotid tumor is the only clinical manifestation of lymphoma. Other authors strictly define a parotid lymphoma as a lymphoma that must originate in glandular parenchyma.[8] Most experts use this latter definition and reserve the diagnosis of primary parotid salivary gland lymphoma for a lesion that contains no discernible lymph nodes or visible lymph node capsule surrounding the lymphoid infiltrate.[10]

■ Pathogenesis and Risk Factors

Sjögren's Syndrome

A reactive salivary gland inflammatory process known as myoepithelial (lymphoepithelial) sialadenitis (MESA or LESA) occurs in patients with Sjögren's syndrome. MESA has also been called Mikulicz's disease.[4,11] MESA is a benign lymphoid infiltration of the salivary gland resulting in destruction and atrophy of the acinar ducts, in conjunction with proliferation of basal epithelial cells that form ''epimyoepithelial islands.'' The lymphocytes of MESA are reactive B cells that have infiltrated into the organ, due to autoimmune stimulation. MESA is found in virtually all patients with Sjögren's syndrome (see **Figs. 5–11, 5–12**).[5,11]

The lymphoepithelial lesion of MESA may undergo clonal expansion in a multistep process, resulting in evolution to lymphoma in ~4 to 7% of patients with Sjögren's syndrome[12] (**Table 12–2**). A chronic inflammatory stimulus represents the initial event, and subsequent sequential proto-oncogene activation may eventually lead to lymphoma. An evolution of histopathologic findings begins with early myoepithelial sialadenitis, which is characterized by focal and organized lymphoid infiltration into Peyer's patchlike structures surrounding dilated epithelial ducts. (Mucosa-associated lymphoid tissue is normally found in intestinal mucosa, and in this location the lymphoid aggregates are known as Peyer's patches.) In established MESA, the polyclonal lymphoid infiltrate becomes dense and confluent, and the epimyoepithelial islands proliferate. Transformation of established MESA into lymphoma occurs when the lymphoid infiltrate around the epimyoepithelial islands becomes monoclonal. In frank lymphoma, monomorphic monoclonal lymphocytes that demonstrate immunoglobulin light chain restriction infiltrate the entire salivary gland.[3,13]

Molecular studies have shown that in both MESA lymphoid cells and MALT lymphoma monoclonal B cells, a B-cell receptor derived from a restricted subset of both B-region and D-region immunoglobulin genes is expressed, consistent with B-cell stimulation by a common or restricted antigen group. This finding supports the hypothesis that chronic stimulation by

TABLE 12–1 Criteria for Extranodal or Primary Salivary Gland Lymphoma

The first clinical manifestation of lymphoma must involve a salivary gland.
It must arise from lymphocytes within the salivary gland parenchyma itself.
There must be histological proof that the lymphoma involves the salivary gland parenchyma.
The lymphoid infiltrate must be a monoclonal malignant process.
It contains no discernible lymph nodes or visible lymph node capsule surrounding the lymphoid infiltrate.

TABLE 12–2 Multistep Clonal Expansion of the Lymphoepithelial Lesion of MESA

1. MESA is a benign lymphoid infiltration of the salivary gland resulting in destruction and atrophy of the acinar ducts, in conjunction with proliferation of basal epithelial cells that form "epimyoepithelial islands."
2. The lymphocytes of MESA are reactive B cells that have infiltrated into the organ, due to autoimmune stimulation (i.e., Sjögren's syndrome).
3. A chronic inflammatory stimulus represents the initial event.
4. Focal and organized lymphoid infiltration into Peyer's patch-like structures surround dilated epithelial ducts.
5. The polyclonal lymphoid infiltrate becomes dense and confluent, and epimyoepithelial islands proliferate.
6. Proto-oncogene activation transforms established MESA into lymphoma when the lymphoid infiltrate around the epimyoepithelial islands becomes monoclonal.
7. In frank lymphoma, monomorphic monoclonal lymphocytes that demonstrate immunoglobulin light chain restriction infiltrate the entire salivary gland.

MESA, myoepithelial sialadenitis

autoantibodies, which are presumably produced by exposure to exogenous antigens with similarities to self-antigens, plays a role in the lymphoproliferative process by selecting out a specific B-cell subset. B-cell clones are detected in over 50% of patients with MESA when molecular genetic methods are utilized. Finding these B-cell clones does not necessarily correlate with immediate transformation to frank lymphoma. In patients with Sjögren's syndrome who undergo salivary gland biopsies revealing MESA, ~25 to 80% of patients also have immunophenotypic evidence of low-grade MALT lymphoma, which was not clinically apparent. Of these patients, between 10 to 45% eventually develop frank salivary gland lymphoma, often after very long time intervals.[4,14]

Patients with Sjögren's syndrome have a 43.8-fold higher incidence of lymphoma compared with age-matched controls, and ~20% of all salivary gland lymphomas are associated with Sjögren's syndrome. The lymphomas that arise in the context of Sjögren's syndrome are primarily low-grade B-cell lymphomas, including extranodal marginal zone MALT lymphoma, small lymphocytic lymphoma, and follicular center cell lymphoma. MALT lymphoma accounts for 75 to 80% of lymphomas that develop in patients with Sjögren's syndrome. Fifteen to 25% are intermediate-grade or high-grade B-cell lymphomas, which were likely MALT lymphomas that subsequently transformed to high-grade entities.[4,6,14]

Helicobacter pylori

Helicobacter pylori has been implicated as the main agent responsible for the development of MALT lymphomas in the stomach. Thus it has been postulated that *H. pylori* might also play a role in the pathogenesis of salivary gland MALT lymphomas.[15] Although *H. pylori* organisms can be demonstrated in the saliva of patients with gastric *H. pylori* infection 75% of the time, reports of direct infection of salivary gland tissue itself are sparse.[16] If *H. pylori* does play a direct role in the development of some MALT lymphomas, it would seem to be a relatively unusual occurrence. Jordan et al[17] analyzed 20 biopsies obtained from patients with MESA. All biopsies had histological features of organized MALT, and 14 cases showed immunoglobulin heavy chain gene monoclonality consistent with MALT lymphoma. None of these biopsies contained *H. pylori* deoxyribonucleic acid (DNA). These authors concluded that *H. pylori* does not play a significant role in the pathogenesis of most MALT lymphomas of the salivary gland.[17]

There have been reports of salivary gland lymphomas regressing after antibiotic therapy appropriate for *Helicobacter pylori*, even if no *H. pylori* organisms were identified within the gland.[18] Recirculation of organism-associated antigens from another site of *H. pylori* infection may lead to antibody production with cross-reactivity to the salivary gland, leading to inflammation and subsequent lymphoma. This hypothesis would explain the favorable effect of antibiotics on the malignant salivary gland process, despite the absence of *H. pylori* directly involving salivary gland tissue.[15,18]

Epstein-Barr Virus

Epstein-Barr virus (EBV) is a DNA gamma herpes virus that infects epithelial cells of the oropharynx and a subset of B lymphocytes. Epstein-Barr virus infection has been linked to several malignancies, including nasopharyngeal carcinoma, Burkitt's lymphoma, T-cell non-Hodgkin's lymphoma, Hodgkin's disease, and other lymphoproliferative disorders in immunodeficient individuals. Most EBV-associated malignancies occur in the head and neck region.[19]

It has been postulated that EBV may be implicated in the pathogenesis of salivary gland lymphomas. In a study of 50 patients with primary non-Hodgkin's lymphomas arising in the salivary gland and oral cavity, none of these lymphomas were Epstein-Barr virus positive. These results would seem to indicate that EBV is not involved in the pathogenesis of oral and salivary gland lymphomas, at least in immunocompetent patients.[19] In contrast, a prospective pathologic study of tissue samples from 19 consecutive patients with salivary gland lymphomas identified Epstein-Barr virus DNA in one sample from a patient with parotid gland lymphoma.[20] In another study of 45 patients with MESA, EBV DNA was detected in 3 of 36 samples from patients with salivary gland lymphoma, which represents an 8% incidence of EBV infection. This correlation statistic is similar to figures published for other lymphoma types.[21] Finally, the incidence of EBV involving salivary gland tissue is higher for T-cell lymphomas, compared with B-cell lymphomas. It has been estimated that ~50% of T-cell salivary gland lymphomas may be caused by EBV infection of lymphocytes.[22]

Post-transplantation Lymphoproliferative Disorder

Post-transplantation lymphoproliferative disorders (PTLDs) occur in 2 to 10% of patients who have received prolonged immunosuppression in the context of both solid organ and bone marrow transplantation. The spectrum of PTLDs includes benign disorders such as plasma cell hyperplasia and polymorphic B-cell hyperplasia, and malignant entities such as B-cell lymphoma and multiple myeloma. PTLD B-cell

lymphomas are usually low-grade non-Hodgkin's lymphomas that are associated with Epstein-Barr virus infection.[23] Salivary gland lymphomas are rarely described in the post-transplant setting. In one report, two cases of parotid gland MALT lymphoma arising in the post-transplant setting had no evidence of EBV involving lymphoid tissue by in situ hybridization.[23]

Human Immunodeficiency Virus

Salivary gland enlargement, due to infiltration of reactive lymphocytes, has been described in patients infected with human immunodeficiency virus (HIV). The pathologic characteristics of these salivary gland infiltrates include glandular atrophy, follicular hyperplasia, cystic dilation of ducts with squamous metaplasia, and the presence of epimyoepithelial islands. These pathologic findings have been described by a variety of terms, including benign lymphoepithelial lesion (BLL), lymphoid hyperplasia, and HIV-associated salivary gland disease. HIV-1 major core protein, P-24, as well as HIV-1 ribonucleic acid (RNA) sequences have been found within follicular dendritic cells of salivary glands containing HIV-associated BLL. Epstein-Barr virus DNA has also been reported in salivary gland tissue of some patients with HIV-associated BLL. HIV-associated BLL is considered a risk factor for salivary gland lymphoma.[24]

In a study of six cases of primary salivary gland lymphoma occurring in patients with HIV infection, one patient had small noncleaved cell Burkitt's lymphoma, two patients had large cell immunoblastic lymphoma, and the remaining three had large cell intermediate-grade non-Hodgkin's lymphoma. Epstein-Barr antigens were detected by in situ hybridization for EBV RNA in three of the six HIV-related lymphomas. In all cases, the HIV p24 antigen was selectively deposited in the germinal centers and follicular dendritic cells of salivary gland tissue.[25]

The salivary gland lymphomas arising in patients with HIV disease are rarely MALT lymphomas. Some cases of MALT lymphoma have been reported in pediatric patients with HIV disease. In one report, four HIV-1 positive pediatric patients were found to have MALT salivary gland lymphoma. The pathogenesis of the MALT lesions that occur in patients who are positive for HIV infection is unclear. The HIV retrovirus may play a direct role. Alternatively, EBV may be involved in the pathogenesis of these lesions.[26]

Hepatitis C

There is a correlation between hepatitis C virus infection and extranodal MALT lymphomas, including salivary gland MALT lymphomas.[27] Hepatitis C virus antigen has been found within the salivary gland epithelial cells from patients with parotid MALT lymphomas. Hepatitis C virus may act as an exogenous antigenic stimulus that leads to B-cell proliferation. Alternatively, the virus may contribute to the development of the multistep process of lymphomagenesis.[3]

Hepatitis C virus has also been implicated in the pathogenesis of lymphomas occurring in patients with the autoimmune disease known as mixed cryoglobulinemia. Homologies have been demonstrated between the antigen combinatory regions of the antigen receptor variable region genes expressed in both hepatitis C virus–associated non-Hodgkin's lymphoma tissue in patients with mixed cryoglobulinemia, and non-neoplastic salivary gland MESA arising in the context of Sjögren's syndrome. Given the similarities, an immunologic cross-reactivity may exist between hepatitis C virus and the unknown stimulating agent that underlies both of these disorders.[28]

Küttner's Tumor (Chronic Sclerosing Sialadenitis)

In 1896, Küttner described a series of patients with a unilateral hard tumor-like mass involving the submandibular gland. Histologically, this entity showed evidence of chronic sclerosing sialadenitis. Küttner's tumor is not associated with Sjögren's syndrome or any other autoimmune disease. The pathogenesis of chronic sclerosing sialadenitis is duct obstruction by abnormal secretions. The salivary gland epithelial ducts are typically dilated and filled with secretions, and sialoliths are found in 50 to 80% of the cases. Periductal fibrosis, lobular fibrosis, and acinar atrophy are seen and associated with a lymphoplasmacytic infiltrate. The presence of marked fibrosis and the lack of epithelial proliferation distinguish sclerosing sialadenitis from MALT.[11] MALT lymphoma has been described in association with chronic sclerosing sialadenitis. Several case reports suggest that chronic sclerosing sialadenitis is a risk factor for low-grade MALT salivary gland lymphoma.[11]

Human Herpes Virus-8

Human herpes virus-8 (HHV-8) may rarely be involved in Sjögren's syndrome–associated MALT lymphomas. HHV-8 DNA sequences have been detected in tissue from one patient with a parotid gland MALT lymphoma. This patient was an HHV-8 seropositive woman with Sjögren's syndrome. Although HHV-8 may trigger MALT lymphomas in patients with Sjögren's syndrome, HHV-8 does not usually infect salivary gland epithelium and probably plays a minimal role in the etiology of epithelial salivary gland neoplasms.[29,30]

Pathology

Histological Classification

Most salivary gland lymphomas are non-Hodgkin's lymphomas of the B-cell type. T-cell non-Hodgkin's lymphoma and Hodgkin's disease involving the salivary glands are very rare.[3] Fifty-five to 70% of salivary lymphomas are low-grade lymphomas, such as extranodal marginal zone mucosa-associated lymphoid tissue lymphoma, small lymphocytic lymphoma, and follicular lymphoma. The majority of low-grade salivary gland lymphomas are MALT lymphomas, which are described in more detail below.[6] Approximately 31 to 36% of salivary gland lymphomas have an intermediate- or high-grade histology.[6] Some intermediate- and high-grade salivary gland lymphomas are originally derived from MALT or follicular lymphomas and become more aggressive lymphomas by the process of transformation.[3] Most high-grade lymphomas in the salivary glands are diffuse large B-cell lymphomas. Rare cases of lymphoblastic lymphoma and Burkitt-like lymphoma have been reported.[4] Cytological diagnosis is possible with fine-needle aspiration and flow cytometry, but often tissue diagnosis with histology is necessary.

Forty cases of primary salivary gland lymphoma were reported to the British Salivary Gland Tumor Panel between 1971 and 1984. This number represents 1.7% of the total collection of 2340 salivary gland tumors referred to the panel during this time frame. There were two cases of nodular sclerosing Hodgkin's disease, both arising in the parotid gland. The remaining cases were all non-Hodgkin's lymphomas, 64% of which were low-grade and 36% intermediate-grade by the working formulation histological classification.[7]

Mucosa-associated Lymphoid Tissue Lymphomas

Mucosa-associated lymphoid tissue lymphomas were first described by Isaacson and Wright in 1983,[7a] when they described a small series of patients with low-grade B-cell lymphomas arising in gastrointestinal tract mucosa. Although MALT lymphomas occur most frequently in the stomach, they can also occur in various nongastrointestinal sites that are embryologically derived from the foregut, such as the thyroid, lung, breast, orbit, conjunctiva, and salivary gland. Nongastrointestinal locations represent ~30 to 40% of all low-grade MALT lymphomas.[27,31]

Mucosa-associated lymphoid tissue is normally found in intestinal mucosa, known as Peyer's patches. MALT lymphomas arise in sites that normally contain no mucosa-associated lymphoid tissue, such as the salivary gland and stomach. Because salivary glands do not normally contain mucosa-associated lymphoid tissue, the histological organization of MALT lymphoma is acquired in these organs as a result of chronic antigenic stimulation, either in the context of infection or autoimmune disease. Some examples include *Helicobacter pylori* colonization in the stomach, bronchiectasis in the lung, myoepithelial sialadenitis in Sjögren's syndrome, and Hashimoto's thyroiditis in the thyroid gland. The histological features of mucosa-associated lymphoid tissue are retained in these organs after lymphoid transformation from reactive tissue to MALT lymphoma.[18,24,27,31,32]

In the Revised European-American Lymphoma (REAL) classification system for lymphomas, published in 1994, the MALT lymphomas are classified among the marginal zone B-cell lymphomas.[27] The marginal zone lymphomas are monoclonal B-cell proliferations, which represent neoplasms derived from lymphocytes that reside in the B-cell-rich marginal zone located external to the mantle zone within lymph nodes (**Fig. 12–1**). The marginal zone is well defined in the spleen and in intestinal Peyer's patches, but it is very poorly demarcated in peripheral lymph nodes. Subtype entities of marginal zone lymphoma include the extranodal mucosa-associated lymphoid tissue lymphomas, the nodal monocytoid B-cell lymphomas, and the splenic marginal zone lymphomas.[32]

The central feature of MALT lymphomas is the lymphoepithelial lesion. Aggregates of neoplastic centrocyte-like cells arise in the marginal zone and subsequently infiltrate glandular epithelium in a destructive fashion.[27] Findings from immunohistochemistry for salivary gland lymphomas are similar to immunohistochemistry profiles of non–salivary gland lymphomas. MALT lymphomas may have a similar histological

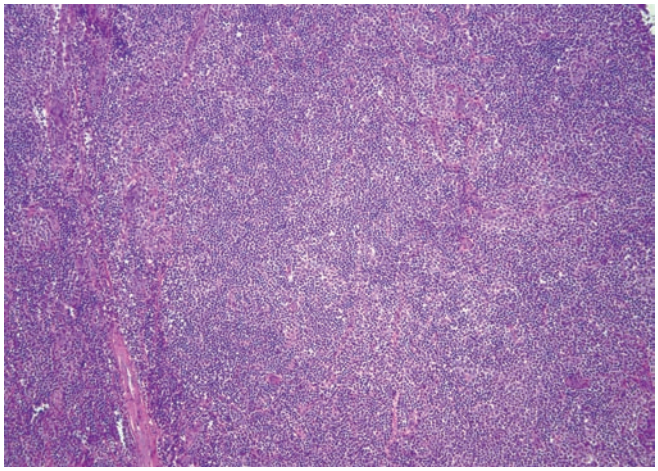

FIGURE 12–1 Mucosa-associated lymphoid tissue (MALT) lymphoma comprised of predominantly small, mature-appearing lymphocytes with scattered monocytoid and plasmacytoid cells in the background (H&E, ×40).

appearance to other low-grade lymphomas, such as B-cell small lymphocytic lymphoma and mantle cell lymphoma, but immunohistochemistry can discriminate MALT lymphomas from the other low-grade B-cell lymphomas. Marginal zone lymphomas including MALT lymphomas are positive for the B-cell antigens CD-19, CD-20, and CD-22. They are also positive for CD-79A. In contrast to small lymphocytic lymphoma, they are negative for CD-5, CD-10, and cyclin D-1 (BCL-1).[12] Expression of CD-43 and CD-23 is variable. MALT lymphomas arising in salivary glands express monoclonal surface immunoglobulin, including IgM, IgG, and IgA, but not IgD.[32,33] The variable (V) regions of the immunoglobulin gene in these lymphomas show evidence of somatic mutation, indicating a post-germinal center memory cell stage of differentiation.[4,34]

Follicular center cell salivary gland lymphomas are positive for CD-10 and BCL-2.[34] Kojima et al[10] examined 20 cases of primary salivary gland lymphoma. Of these they identified six patients with follicular lymphoma. Immunohistochemistry showed that all six cases were CD-10 positive, CD-79A positive, BCL-6 positive, CD-3 negative, CD-5 negative, CD-21 negative, CD-23 negative, and cyclin D-1 (BCL-1) negative. The tumor cells expressed BCL-2 in three cases and P-53 onco-protein in four cases.[10]

T-Cell Lymphoma

Primary T-cell lymphoma of the salivary gland is rare. A recent literature review found only 14 cases of primary T-cell lymphoma of the salivary gland, with all but two of these cases occurring in patients in the East. Parotid and submandibular glands are the most frequently involved, and the most frequent histological type is peripheral T-cell lymphoma of low-grade morphology. T-cell lymphomas of the salivary gland can mimic a low-grade extranodal marginal zone B-cell lymphoma, but they are usually not associated with preexisting sialadenitis or evidence of an underlying autoimmune disease.[22] Other T-cell salivary gland lymphomas identified in the literature include angiocentric T-cell/NK-cell lymphoma and T-cell anaplastic large cell lymphoma. Angiocentric lymphoma is a high-grade lymphoma, with a poor prognosis.[35]

Hodgkin's Disease

The vast majority of parotid gland lymphomas are of the non-Hodgkin's type. Hodgkin's lymphoma involving the salivary glands has been described but is exceedingly rare. Only 32 cases of Hodgkin's lymphoma arising in the parotid gland have been reported in the English-language literature. Lymphocyte predominant histology seems to be the most common subtype affecting the parotid gland. This is in contrast to the classic presentation of nodal Hodgkin's disease, which is most commonly the nodular sclerosing histological subtype.[36]

Plasma Cell Neoplasm

Primary extramedullary plasmacytomas are uncommon tumors that can occur in the head and neck region. These lymphoid malignancies usually involve the submucosal tissue of the upper airway, such as the nasal passages, sinuses, and nasopharynx. Primary extramedullary plasmacytoma involving the salivary glands is rare, and thus usually appears in the literature as single case reports. Amyloid deposition is noted in ~25% of cases of extramedullary salivary gland plasmacytoma. Treatment consists of surgical resection or more commonly radiation therapy. The prognosis is good.[37,38]

■ Genetics

Trisomy 3

The single most common cytogenetic abnormality in salivary gland and extrasalivary gland MALT lymphomas is trisomy 3. In situ hybridization studies with chromosome-specific probes have found trisomy 3 in the interphase nuclei of ~60 to 70% of cases of low-grade MALT lymphomas. Up to 80% of salivary gland MALT lymphomas contain the trisomy 3 abnormality.[24,32]

Translocation t(11,18)

The t(11,18) translocation is associated exclusively with low-grade extranodal MALT lymphoma. This translocation is observed in up to 50% of extranodal MALT lymphoma cases but it is not observed in other marginal zone lymphomas or in extranodal large B-cell lymphoma. The translocation can be found in tumors of the salivary gland and lacrimal gland, as well as other MALT-associated sites.[4,12] Ott et al[39] analyzed the cytogenetics of 44 MALT lymphomas arising in the stomach, parotid gland, thyroid gland, lung, breast, and conjunctiva. Fifty-three percent of the low-grade lymphomas displayed the t(11,18) translocation. In contrast, this same translocation was not found in a single case of high-grade lymphomas arising from MALT.[39]

The genes involved in the t(11,18) translocation are not entirely clear. Some candidate genes include the *DCC* gene, the *YES* proto-oncogene, the *ITF2* gene, the *SSAV*-related endogenous retroviral element, and the *DPC4* gene. Kalla et al[40] identified a fusion transcript consisting of the *AP12* gene, which is an inhibitor of apoptosis located on chromosome 11, and the *MALT-1* gene located on 18 (q-21), in 18 out of 24

gastric and extragastric MALT lymphomas. This fusion protein may interfere with the regulation of apoptosis, which is normally performed by the antiapoptotic function of the *AP12* gene product.[39,40]

Translocation t(14,18) (BCL-2)

There is usually molecular genetic evidence of the t(14,18) BCL-2 translocation in follicular center cell low-grade non-Hodgkin's lymphoma arising in the salivary gland.[34] Kerrigan et al[41] investigated the presence or absence of the BCL-2 chromosome translocation using molecular techniques in a series of patients with non-Hodgkin's lymphoma involving the salivary glands. Of the seven cases examined, three had molecular evidence of a t(14,18) translocation. The four cases lacking BCL-2 rearrangement had diffuse growth patterns. All three cases with BCL-2 rearrangements were nodular lymphomas that arose in patients without Sjögren's syndrome or other autoimmune disease. These cases lacked histological evidence of MESA, and thus did not represent MALT-derived lymphomas. These BCL-2-positive salivary gland lymphomas were likely non-MALT-derived follicular lymphomas, which appeared to arise in lymph nodes adjacent to the salivary glands rather than arising in the salivary gland itself.[41] In contrast, other authors have described the BCL-2 translocation in MALT lymphomas.[24] Pisa et al[42] observed the t(14,18) BCL-2 proto-oncogene translocation in five of seven Sjögren syndrome–associated MALT lymphomas using Southern blot analysis.

Treatment for Salivary Gland Lymphoma

Natural history and prognosis depend not only on the histological subtype of lymphoma but also on the classification of the salivary gland lymphoma as either secondary (nodal) or primary (extranodal). Many patients with secondary nodal salivary gland lymphoma have evidence of systemic disease, whereas patients with primary extranodal salivary gland lymphomas arising from lymphocytes involved in a chronic inflammatory process such as MESA are more likely to have localized disease. A retrospective study showed that patients with primary extranodal salivary gland lymphoma have a favorable prognosis, with more than double the median time to disease progression compared with patients with secondary nodal lymphomas (27.6 months vs 13.3 months). Only 7.7% of patients with primary extranodal lymphomas developed disseminated disease, compared with 46.1% of patients with secondary nodal lymphomas. Lymphoma-related death occurred in 53.8% of the patients with secondary nodal lymphoma, and only 7.7% of patients with primary extranodal lymphoma.[1]

The median survival for all lymphomas originating within the major salivary glands is ~49 months.[6] Intermediate and high-grade lymphomas have a shorter natural history than do low-grade indolent lymphomas, as expected. Low-grade lymphomas, especially those with MALT histology, tend to remain localized to the primary site for long periods of time. They have a very long natural history and a favorable prognosis.[27] Follicular lymphomas arising from the salivary glands appear to have many of the prognostic characteristics of MALT lymphoma arising in the salivary glands, perhaps because they often arise in the context of MESA, as do the MALT lymphomas. They have an indolent natural history and a favorable prognosis.[10]

Localized treatment approaches, such as resection and/or irradiation, are adequate and often curative for patients with localized primary salivary gland lymphoma. A systemic approach to disease is required in patients with secondary nodal salivary gland lymphoma or in patients with primary extranodal lymphoma with spread to extrasalivary sites.[1] The most appropriate treatment approach naturally depends not only on the stage of disease but also on the histological identity of the lymphoma in question.

Treatment for Localized MALT Lymphoma

In a retrospective analysis of 75 patients with nongastrointestinal MALT lymphoma, patients were treated according to both disease stage and site. Patients with localized MALT lymphoma were generally treated with surgery or involved field radiation therapy, and some patients received adjuvant chemotherapy. Most advanced-stage patients received chemotherapy, either consisting of a single agent such as chlorambucil, cyclophosphamide, or fludarabine or a multiagent chemotherapy regimen such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone). Of these 75 patients, only 6 had salivary gland lymphomas. All of the patients with salivary gland lymphoma received chemotherapy, and two of them received involved field radiation therapy as well. Four of the patients (67%) achieved a complete remission, and two of the patients (33%) achieved a partial remission. No firm conclusions can be drawn regarding salivary gland lymphomas from this study because the sample size in this analysis was small.[27]

Tsang et al[43] reviewed the records of 75 patients with biopsy-proven MALT lymphomas arising in extralymphatic organs that were all diagnosed and treated from 1989 to 1998 at Princess Margaret Hospital. Of these patients, 15 (21.4%) had MALT lymphomas arising in a salivary gland, 13 of which were located in the parotid

gland. Of the 13 patients with parotid gland lymphoma, 3 patients eventually relapsed after receiving radiotherapy. These MALT lymphomas respond extremely well to moderate-dose-involved field radiation, with dose ranges from 17.5 to 40 Gy.[43] Lower doses are used for conjunctival and orbital adnexal salivary gland disease. A median of 33.3 Gy has been reported for use in parotid salivary gland lymphomas.[44]

A small randomized study of 39 patients with early-stage low-grade marginal zone MALT B-cell lymphomas compared radiotherapy alone to chemo-irradiation for patients with salivary gland MALT lymphomas. Overall, survival and failure-free survival were 90% at 5 years. There was no significant difference between the treatment groups. Thus radiation without chemotherapy would seem most appropriate in this setting.[45]

Treatment for Advanced-Stage Extranodal MALT Lymphoma

Patients with advanced-stage extranodal MALT lymphomas involving multiple sites of disease should be treated with chemotherapy. Options include cladribine (2-CDA), single-agent oral alkylating agent chemotherapy (cyclophosphamide or chlorambucil), multiagent chemotherapy utilizing CVP (cyclophosphamide, vincristine, and prednisone) or CHOP for six cycles, immunotherapy (anti-CD20 monoclonal antibody therapy utilizing rituximab), or chemoimmunotherapy (R-CHOP).[44]

Purine Analogues in MALT Lymphoma

The purine analogues are cytotoxic agents that are specific for lymphoid cells, inducing apoptosis in both resting and dividing cells. Because they target cells that are not in the process of dividing, they are promising therapeutic agents for use in indolent lymphomas that have a low proliferative index. The purine analogues 2-CDA and fludarabine have single-agent efficacy in previously treated and untreated indolent non-Hodgkin's lymphomas. The purine analogues are considered appropriate as first- or second-line therapy for low-grade MALT lymphomas, including those arising in the salivary glands.[32]

Several studies have demonstrated promising results with the purine analogues in patients with low-grade salivary gland lymphomas. Jager et al[46] treated 19 patients with gastric MALT lymphoma and 7 patients with extragastric MALT lymphoma who were chemotherapy naive with 2-CDA. Three patients in this study had MALT lymphoma arising in the parotid gland, and two in the lacrimal gland. Eighty-four percent of patients overall achieved a complete response. One hundred percent of patients with gastric presentation achieved a complete response, and 43% of patients with extragastric presentation achieved a complete response. 2-CDA thus appears to be an active agent in MALT lymphoma involving the salivary glands.[46]

Treatment for Follicular Lymphoma

Patients with stage III or IV low-grade follicular salivary gland lymphomas should receive chemotherapy or chemoimmunotherapy. Options include CVP, CHOP, oral alkylating agents such as chlorambucil and cyclophosphamide, or anti-CD-20 monoclonal antibody therapy utilizing rituximab.[5]

Treatment for Diffuse Large Cell Lymphoma

Recommendations for grade I or II intermediate-grade diffuse large cell salivary gland lymphomas include three cycles of CHOP followed by radiation therapy, versus three cycles of R-CHOP followed by involved field radiation therapy. Stage III or IV large cell lymphoma should be treated with standard R-CHOP or CHOP chemotherapy for six to eight cycles and no radiation therapy.[5]

Treatment for Salivary Gland Plasmacytomas

The treatment of choice for salivary gland plasmacytoma is radiotherapy. Local control is achieved in $> 75\%$ of patients. The regional lymphatics should be electively irradiated as well. Even if the salivary gland has been excised, postoperative radiation therapy should be considered. In the absence of radiation therapy, 29% of patients who are status postresection develop lymph node metastases, and 21% of patients develop systemic disease.[38]

■ Treatment for Nonlymphoid Salivary Gland Malignant Tumors

Surgery and Radiation for Localized Disease

The majority of salivary gland carcinomas are initially treated with surgical resection. After complete excision, adjuvant radiation is considered for select histological subtypes of salivary gland carcinoma. Patients with small, mobile primary tumors with low-grade histology are managed with surgical resection alone.[47–50]

Chemotherapy for Recurrent and Advanced Disease

The overall incidence of distant metastases for patients with malignant salivary gland tumors is $\sim 25\%$.[49] These patients will eventually succumb to their disease.

Chemotherapy can often palliate symptoms and in some cases prolong survival. In general, the most active agents in metastatic salivary gland carcinomas include cisplatin, doxorubicin, and 5-fluorouracil (5-FU).[47] Other agents with activity include chlorambucil, hydroxyurea, hexamethylmelamine, daunorubicin, cyclophosphamide, mitomycin C, methotrexate, bleomycin, and vincristine.[51] Newer agents with promise include the taxanes and vinorelbine.[47]

The most widely used three-drug chemotherapy combination for patients with advanced salivary gland carcinomas is the CAP (cyclophosphamide, doxorubicin, and cisplatin) regimen. In one study of 22 patients with a variety of tumor histology including adenoid cystic carcinoma, salivary duct carcinoma, adenocarcinoma, mucoepidermoid carcinoma, nonkeratinizing undifferentiated carcinoma, and neuroendocrine small cell cancer, the CAP regimen provided an overall response rate of 27%. CAP thus appears to be a moderately active combination chemotherapy program for all patients with advanced salivary gland cancer, regardless of tumor histology.[52]

Suen and Johns[53] evaluated 85 cases of salivary gland cancers treated with chemotherapy and assessed the most active drugs for each histological class of tumors. The overall response rate to chemotherapy was 42%. Chemosensitivity seemed to depend on tumor histology. The adenocarcinoma-like cancers (adenoid cystic carcinoma, adenocarcinoma, malignant mixed tumor, and acinous cell tumors) had the highest response rates to doxorubicin, cisplatin, and 5-FU. The squamous-like cancers (squamous cell carcinoma and mucoepidermoid carcinoma) responded well to methotrexate and cisplatin.[53] Other authors have also commented on this chemosensitivity pattern. Kaplan et al[54] reviewed the results of 15 chemotherapy trials containing a total of 116 patients with advanced salivary gland cancers. Adenoid cystic carcinoma, adenocarcinoma, malignant mixed tumor, and acinic cell carcinoma had similar chemotherapy sensitivities. For this ''adenocarcinoma-like'' group of tumors, the most active agents included cisplatin, 5-FU, and doxorubicin, and an enhancing effect was seen between cisplatin and doxorubicin. Cyclophosphamide and methotrexate were ineffective. In this pooled analysis, high-grade mucoepidermoid carcinoma appeared to share a similar chemosensitivity spectrum with squamous cell carcinoma of the head and neck. Both histological types demonstrated a 36% response to methotrexate, and both were responsive to cisplatin-containing regimens. In contrast to the adenocarcinoma-like histological types, the squamous-like histological types did not respond as well to the anthracyclines.[54] Overall response rates as high as 38% have been seen in mucoepidermoid carcinoma using non-anthracycline-containing chemotherapy combinations.[55]

Some newer agents hold promise for treating patients with advanced salivary gland carcinomas. In a small study of nine patients with adenocarcinoma-like tumor histological type, epirubicin combined with cisplatin and 5-FU demonstrated an overall response rate of 44.4%.[48] Vinorelbine (Navelbine) appears to have single response rate activity in adenocarcinoma-like histological types, showing an overall response rate of 20% in a small study of 20 patients.[56] Another study randomized 36 patients with predominantly adenocarcinoma-like tumor histological type to receive single-agent vinorelbine versus vinorelbine combined with cisplatin. The combination arm was superior, showing an overall response rate of 44% compared with 20% with the single agent.[57] Finally, the taxanes appear to have activity in salivary gland carcinomas. A small study of 14 patients with advanced salivary gland carcinoma showed a response rate of 14% to carboplatin and paclitaxel.[58] Other authors have reported success with this combination in patients with heavily pretreated metastatic disease.[47]

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13

Advances in Radiation Therapy for Salivary Gland Neoplasms

ADAM RABEN

Several chapters on the management of major and minor salivary gland cancers have been written over the last decade, providing the surgeon and radiation oncologist with guidelines to treating these neoplasms. What has changed, then, that would require additional insight? The vast experience published in treating these neoplasms is retrospective in nature, and few prospective trials have been conducted. As a result, drawing firm conclusions from the literature should be made with caution because of the heterogeneity of the patient population, tumor sites, histologies, stages, and reasons for choosing one therapy over another.

The major changes in management have been the adoption, albeit slow, in both academic and community cancer centers across the United States of a new philosophy toward a multidisciplinary team approach. In the field of radiation oncology, rapid advancements in imaging technology—magnetic resonance imaging (MRI), spiral computed tomography (CT) scans, and positron emission tomography (PET) scans—fusion and computer planning software, and treatment delivery technology have been remarkable. Highly complex, conformal radiotherapy plans such as intensity modulated radiation therapy (IMRT) selectively distribute high doses to the intended target while limiting doses to critical normal structures. More complex radiotherapy is now being investigated, where biologic imaging information from PET and radiobiologic principles of tumor and normal tissue responses are being incorporated into the algorithms that determine differential beam intensity depending on the type of tumor, its unique biologic growth rate, and its position in the body relative to other normal tissues. This has significant implications for improving the therapeutic ratio. For unresectable tumors, the introduction of newer chemotherapy agents that have activity against salivary tumors provides a chance to improve local control rates for tumors that typically have had a poor prognosis by combining with conventional radiotherapy in a concurrent fashion. Alternative forms of ionizing radiation that differ from conventional photon radiation (e.g., charged particle therapy) have been and are currently under investigation that have both radiobiologic and physical characteristics that may be advantageous in improving local control. As the intensity of the therapy is increased, the potential for more acute and late side effects increases. The introduction of radioprotectors in the last 5 years during radiotherapy may reduce xerostomia and mucositis during treatment and prevent late side effects that affect the patient's quality of life.

General Radiation Therapy Management

Indications for Primary Radiation Therapy: Major Salivary Glands

The major salivary glands are paired glands, have orderly lymphatic drainage patterns, and almost never require management of the opposite side or contralateral neck. The reasons to treat malignant salivary glands with radiotherapy in the absence of surgery include the following: (1) when the surgeon determines the tumor to be unresectable, (2) if surgery is technically feasible but medically prohibitive as a result of patient

comorbidities or poor functional status, (3) in the setting of unresectable recurrent disease, and (4) if surgery is technically feasible but would result in unacceptable functional and/or cosmetic outcome.

The perception in the head and neck surgical community that partially resected or unresected parotid neoplasms are radioresistant is unfounded and is not supported in the available literature. The majority of reported data, however, is from small, single institutional experiences that often lump different histologies, stages, and sites (major vs minor salivary) and recurrent versus primary unresectable disease into their outcome analysis. Alternative strategies and outcomes to improve local control over conventional radiotherapy will be highlighted in this chapter.

Indications for Adjuvant Radiation Therapy: Major Salivary Glands

The indications for adjuvant radiation therapy are multifactorial and include (1) positive microscopic margins, (2) deeply infiltrative tumors beyond the parotid bed, (3) perineural invasion, (4) high grade or poorly differentiated tumors, (5) recurrent disease, (6) piecemeal resection despite negative margins, and (7) when the surgeon feels uncomfortable about the gross surgical findings despite negative margins. Failure to at least consider adjuvant radiotherapy for the above reasons increases the risk of local recurrence and reduces the ability to gain local control in the future should a recurrence occur. It further jeopardizes the preservation of the facial nerve and its branches, which in turn can lead to devastating functional and cosmetic consequences.

Indications for Elective Treatment of the Neck: Major Salivary Glands

The indications for elective treatment of the neck have been defined through retrospective patterns of failure after large surgical series.[1,2] In general, high-grade, poorly differentiated tumors, regardless of histology, and large tumors (>4 cm) have a high rate of occult ipsilateral neck metastases and require consideration for adjuvant treatment. The risk of contralateral occult neck metastases is too low to warrant treatment even in the setting of multiple ipsilateral nodal metastases.

Advances in Radiation Treatment Planning

Recent publications for major and minor salivary gland neoplasms have incorporated complex treatment-planning methods such as CT-based image acquisition with advanced contouring tools, sophisticated computer software for treatment planning, three-dimensional conformal radiotherapy (3D-CRT), and, most recently, intensity modulated radiation therapy, which provide tight dose gradients that spare surrounding normal structures, and the use of sophisticated automated beam shaping devices such as multileaf collimators (MLCs) to deliver multiple beams in rapid succession.

Advances in Target Delineation

A more comprehensive understanding by the radiation oncologist of head and neck anatomy, as well as careful understanding of nodal sites at risk, is required now that a majority of treatment planning is based on anatomical information obtained from CT scans. In other words, we have to think like surgeons. The selection of nodal sites at risk has for the most part been an arbitrary exercise based on the individual radiation oncologist's perception of risk. Primary site, involved nodal, and high-risk elective nodal target volumes can now be delineated with the help of published reference guides to assist in the location of lymph node levels, in relation to CT-based anatomical landmarks.[3–5] In 2004, a consensus was achieved by a joint surgical-radiation oncology group to arrive at an agreement of anatomical nodal groups, their percent risk of harboring microscopic disease, and their locations using recognizable anatomical reference points on CT.[6]

Advances in Simulation and Image Acquisition

Prior to the introduction of CT simulators, treatment planning for parotid tumors was performed with the use of a conventional fluoroscopic simulator. Treatment was commonly delivered with a two-dimensional approach using either a wedged pair of ipsilateral photons fields or mixed photon electron fields in an enface technique. Current spiral CT simulators allow for the rapid acquisition of selected head and neck anatomy and provide a platform for three-dimensional reconstruction. Initial CT image acquisition for parotid neoplasms is generally performed with the patient's head in the supine position in a rigid immobilization mask to prevent motion and limit treatment setup error (**Fig. 13–1**). Intravenous (IV) contrast is not always necessary if a good contrast diagnostic scan was performed at the time of diagnosis. However, if surgery was performed and a delay longer than 6 weeks occurs from the completion of surgery until treatment planning, then IV contrast is encouraged to reduce the risk of missing a new lymph node metastasis. One advantage of CT simulation is the ability to produce digitally reconstructed radiographs (DRRs) after the patient has left the simulation suite (**Fig. 13–2**). This leads to an expedited, convenient experience for the patient

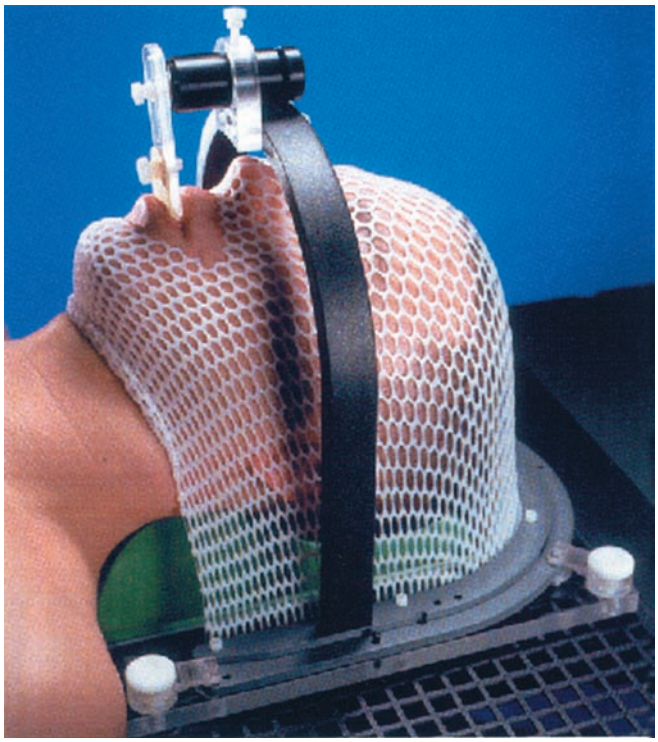

FIGURE 13–1 Example of rigid head and neck immobilization for three-dimensional conformal radiotherapy (CRT) or intensity modulated radiation therapy (IMRT).

because DRRs of any field angle can be generated after image acquisition and 3D reconstruction and later viewed and compared for setup accuracy with on-treatment digital port films. No longer does the patient have to endure a prolonged simulation waiting for hard copy films to be produced.

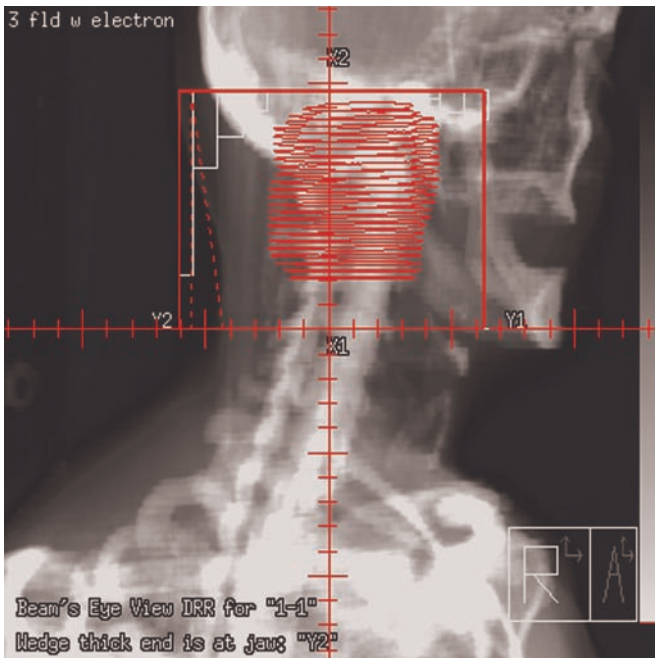

FIGURE 13–2 Digitally reconstructed radiograph (DRR) of target and normal anatomy with multileaf collimator (MLC) automatic blocking.

Advances in Computer Treatment Planning

Anatomical data acquired in the CT simulator are downloaded into a treatment-planning computer system. At this point, a decision is made to treat with 3D-CRT or IMRT. The physician locates and contours the primary and nodal target volumes for treatment, and normal structures to avoid. Gross tumor and gross nodal disease are delineated on the computer and then expanded to include regions of high-risk microscopic spread. This clinical target volume (CTV) includes both regions adjacent to the primary tumor, as well as nodal regions felt to be at high risk for metastatic spread (**Fig. 13–3**). The CTV is often not a spherical or symmetrical expansion, and it generally requires a more individualized approach when the CTV overlaps with critical normal structures such as the spinal cord. The critical structures designated by the radiation oncologist take priority over the CTV and cannot be compromised. A final margin is then added to account for potential setup error and either patient or primary target motion called the planning target volume (PTV). Target delineation is performed on the computer planning station with access to 3D-reconstructed images in the axial, coronal, and sagittal planes. Significant advances in fusion software allow other diagnostic imaging modalities such as MRI and more recently PET (**Fig. 13–4**) to be imported and then overlaid onto to the planning CT for additional anatomical and biologic information. The incorporation of PET scanning for major salivary gland cancers is controversial, given the typical slow tumor growth associated with these neoplasms. However, for more aggressive cancers, they may demonstrate regional or distant sites of metastases that would alter radiotherapy fields or overall management. In case of adenoid cystic cancers or other advanced cases requiring base of skull coverage, MRI fusion can be invaluable. Normal structures are contoured either adjacent or in close proximity to the parotid gland or structures of critical value, such as the spinal cord, temporal lobe, cochlea, lens, and orbit. Organs at risk (OARs) are contoured to differentiate them from the target volume. Normal structures that are critical to life cannot be overdosed and take priority over the PTV. Other important normal structures that are necessary to maintain a reasonable quality of life are contoured, such as the contralateral parotid. One of the most significant side effects of head and neck radiotherapy is xerostomia. Several investigators have studied the tolerance of the parotid and the radiation threshold dose leading to the development of xerostomia. Meaningful parotid sparing

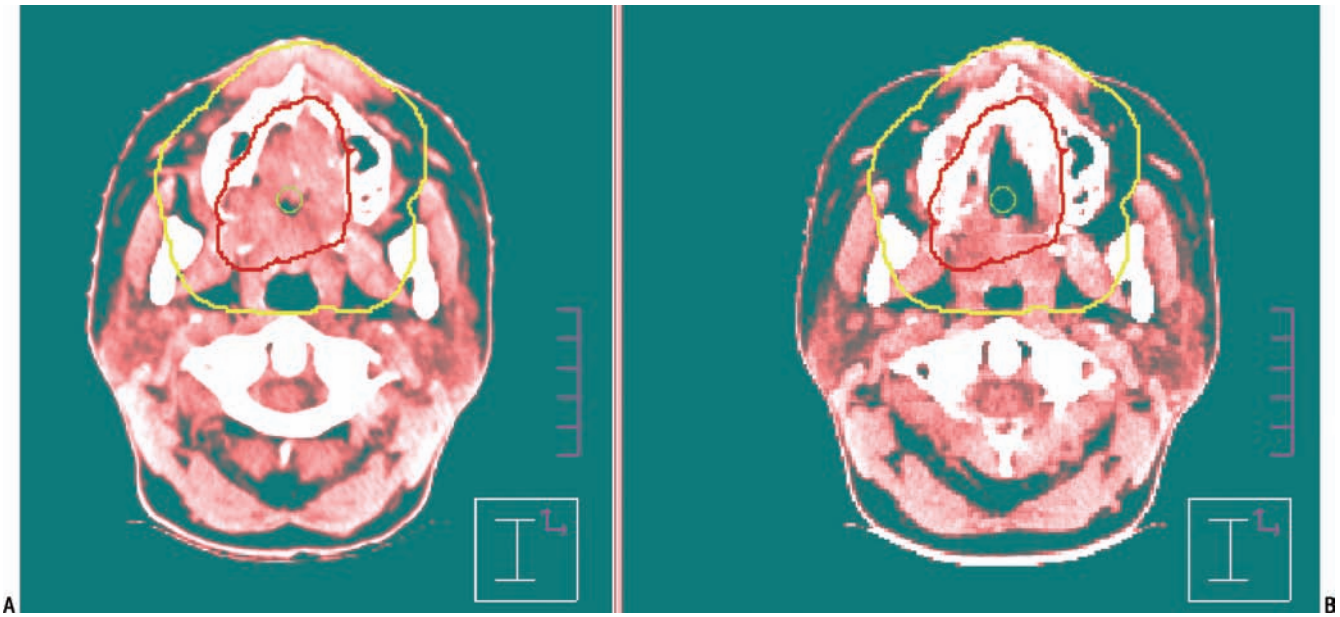

FIGURE 13–3 Example of an outline of **(A)** gross (GTV) and **(B)** clinical (CTV) target volumes for IMRT. This is a 27-year-old female patient who presented with unresectable T4 adenoid cystic carcinoma of the hard palate. She received two cycles of neoadjuvant chemotherapy (carboplatin and a taxane) at the beginning of treatment, began IMRT, and was rescanned at 30 Gy. Significant tumor regression occurred, allowing generation of a second IMRT plan to avoid exceeding tolerance of the optic nerves and chiasm. The base of the skull was included.

should be a goal of any IMRT plan, but not at the expense of PTV coverage. Although estimates of the threshold dose vary, the mean dose delivered to the parotid is predictive of sustained xerostomia. Thus meaningful parotid sparing is achieved when the mean dose does not exceed 26 Gy.[7] Other excellent references are available that describe the respective tolerance doses of normal head and neck OARs to irradiation.[8]

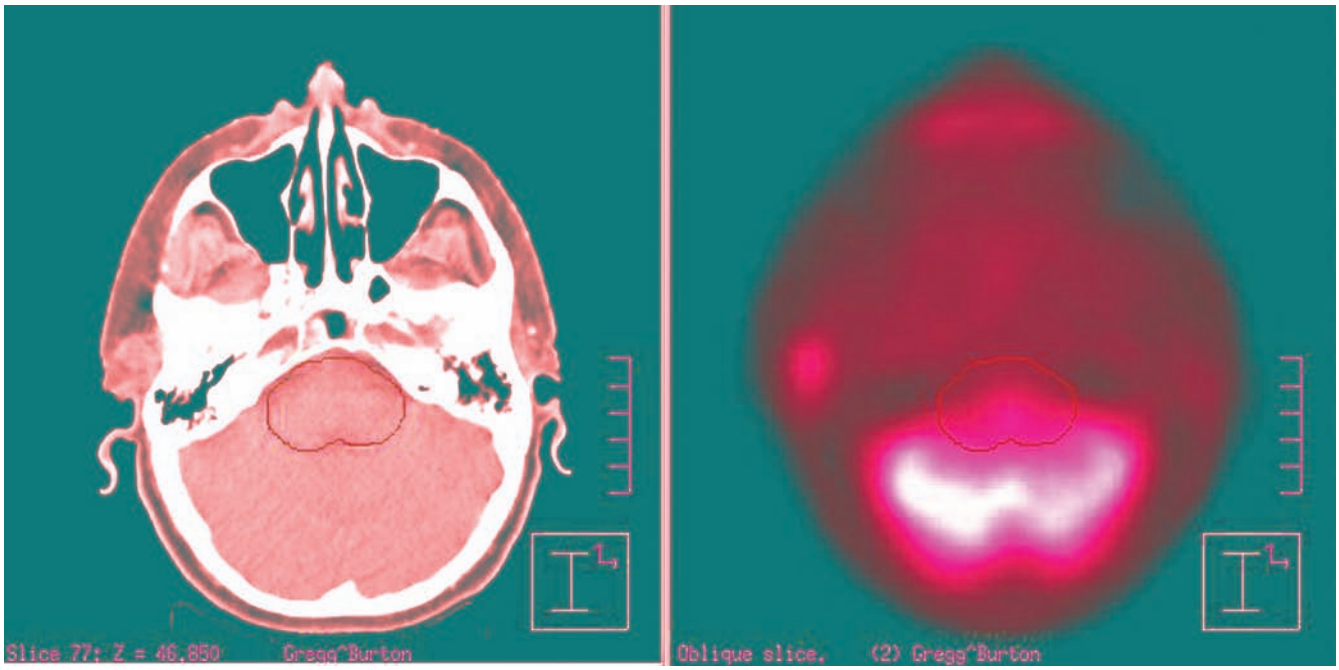

FIGURE 13–4 Example of the incorporation of positron emission tomography–computed tomography (PET-CT) fusion software for 3D-CRT planning of a parotid mass. The mass can be seen just anterior to the patient's right ear. The brainstem is outlined to evaluate the dose to that structure.

Intensity Modulated Radiation Therapy

With so many critical normal structures in proximity to the parotid gland, delivering a homogeneous tumoricidal dose to the parotid and nodal levels at risk is a challenge. Additionally, the internal inhomogeneity of the head and neck combined with changes in external contour from vertex to clavicle provides a significant challenge in treatment planning. The development of sophisticated computer planning in the early 1990s led to refinements in conformal beam shaping and delivery, which in turn improved tumor coverage and dose conformality.[9] Selection of beam directions and beam shaping was based on 3D images of the target and normal tissues acquired from CT simulation. Three-dimensional conformal radiotherapy, once considered state of the art, is now a standard and mandatory approach to treatment of parotid tumors. The recent development of intensity modulated radiation therapy has brought excitement and promise for even greater target conformality and normal tissue avoidance. IMRT goes beyond 3D-CRT by enabling variations of the radiation intensity within each beam.[10] New complex computer algorithms provide a means of producing multiple non-cross-firing, coplanar, and noncoplanar beam arrangements that deliver complicated convex dose distributions and steep dose gradients that are ideally suited for parotid neoplasms (**Fig. 13–5**).

Within individual treatment field angles, multiple beam segments are delivered sequentially to build an intensity map generated by the computer plan that modulates dose around normal adjacent structures.[11] For 3D-CRT, optimization of the beam weighting, use of tissue compensators, and determination of beam angles are performed through a series of manual iterations that can be time consuming and require multiple trials if the dose distribution does not meet the physician's requirements or goals. This approach is called forward planning and is often limited due to the human factor. IMRT employs more sophisticated computer software that can generate IMRT plans through an iterative process called inverse planning, in which beam optimization is performed by the computer rather than manual adjustment. Multiple iterations can be produced and evaluated faster than a manual human approach.[10] Inverse computer planning requires the physician to preset dose objectives and constraints prior to beam intensity calculation. The final plan must be accepted by the physician, dosimetrist, and physicist before treatment can begin. Dose volume histograms (DVHs) (**Fig. 13–5**) are produced that represent graphical

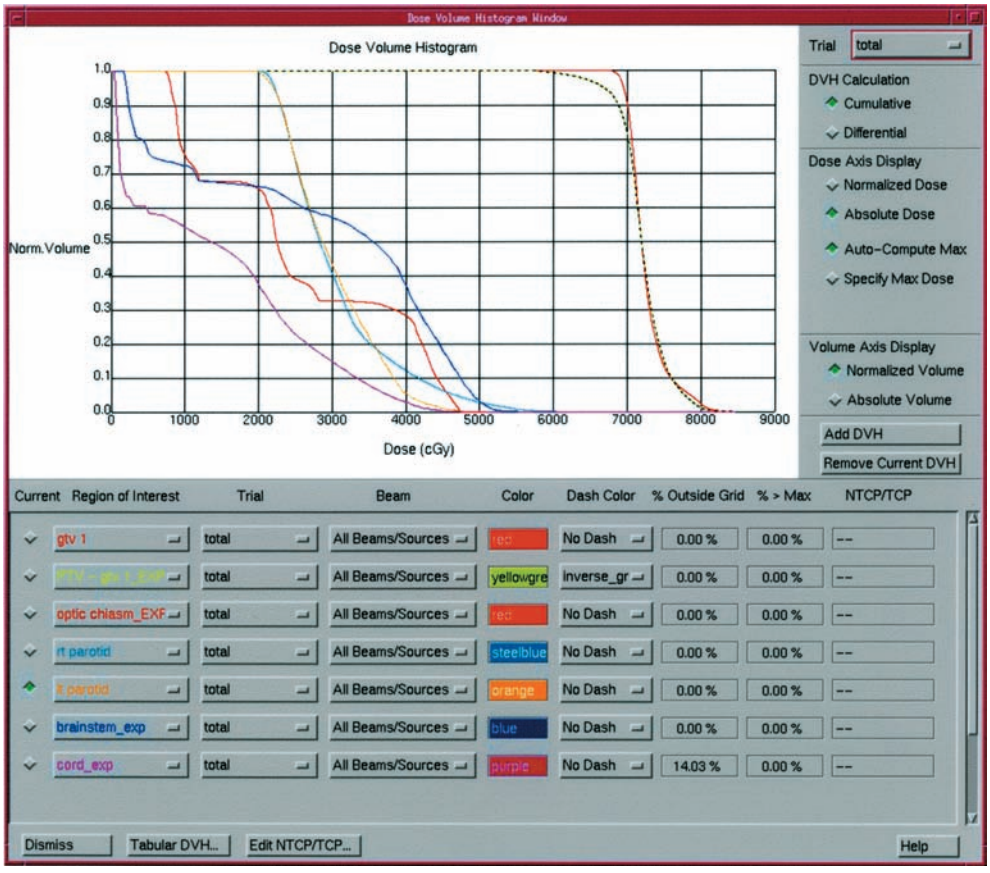

FIGURE 13–5 Example of a dose volume histogram used to evaluate the dose to the target and normal structures during planning for IMRT.

illustrations of the IMRT plan and display differential dose distributions to the tumor and normal tissues. Once the IMRT plan is accepted, the data can be automatically transferred to the linear accelerator for future treatment.

Treatment, as mentioned earlier, is delivered with automatic blocking devices built in to the head of the machine known as multileaf collimators. The MLCs then form the blocking arrangements in a series of dynamic or static movements to achieve the dose intensity map from the original plan. The decision to use IMRT over 3D-CRT should be made with the input of an IMRT team that includes the physician, physicist, and dosimetrist and should be based on predetermined rationales for IMRT rather than on an ad hoc basis. The design of a departmental treatment algorithm that defines specifically why IMRT would offer advantages in a clinical situation is extremely helpful. The primary reason to employ IMRT for parotid neoplasms is to improve target conformality that delivers an appropriate tumoricidal dose while limiting the dose to adjacent critical structures. A secondary end point is to limit the dose to the contralateral parotid and ipsilateral and/or contralateral submandibular and sublingual glands to preserve remaining salivary function. An example of a situation where IMRT might be beneficial would be in the setting of adenoid cystic cancers where base of skull coverage may be required.

Recent investigations have compared standard 3D-CRT to IMRT to evaluate the role of IMRT for parotid tumors. Bragg et al[12] compared IMRT treatment plans with 3D-CRT plans for parotid tumors. For a nine-patient dataset, one 3D-CRT plan was generated for each of nine patients, and 10 IMRT plans with different beam arrangements for each of nine patients. Plans were compared with target dose conformality, dose to organs at risk, and uncomplicated tumor control probability (UTCP). In every case, the IMRT plans produced a higher UTCP than the 3D-CRT plans, suggesting that for a given prescribed dose, the use of IMRT would result in a greater tumor control probability without radiation-induced complications. Target dose was comparable between 3D-CRT and IMRT, but improved when seven to nine IMRT fields were used. IMRT also reduced the mean dose to the contralateral parotid gland, as well as maximum doses to the brain and spinal cord.[12] This study was only a comparison of dosimetric outcome looking at dose conformality and critical structure avoidance. Others have reported similar observations regarding improved conformality.[13] Thus dose escalation may be feasible with IMRT. If the dose to the target can be increased while maintaining acceptable levels of risk of complications, there should be a resultant improvement in tumor control.[12] More beam angles may improve tumor coverage further, but they may also increase overall treatment time. Automated linear accelerators have removed the need for the therapist to enter the treatment suite between fields, making a longer treatment time with a complex IMRT plan acceptable. However, if fewer beam angles or beam segmentations can deliver acceptable target coverage, it should be considered. The planning optimization process that generates an IMRT plan may not always produce a superior plan to 3D-CRT and is not appropriate in every case.

No prospective data have as yet been published to confirm the clinical benefits of IMRT over 3D-CRT in regards to major and minor salivary gland cancers. However, several recent studies have demonstrated the clinical benefit of IMRT in other head and neck sites such as the nasopharynx,[14–16] oropharynx, and larynx.[17–19]

Future Horizons

Image-guided Adaptive Radiotherapy

Further advances in linear accelerator design have resulted in the development of hybrid CT accelerators that have the capability to acquire real-time 3D images of the patient for analysis. Setup errors due to patient, organ, or target motion, even up to a couple of millimeters, can be detected and adjusted daily prior to treatment by the physician. As computational algorithms become faster, the potential for adaptive IMRT may be realized. This would allow a daily assessment of tumor response. Reduction in the size of bulky tumors occurs at an average rate of 1.8% per day, but the reduction in tumor volume rarely occurs in a symmetrical manner. It has been observed that parotid glands during a course of radiotherapy tend to contract and shift medially.[19] Periodic modifications of the IMRT plan through rapid recalculation of new beam intensity and shape conforming to the changing shape and volume of the tumor and parotid gland may result in a greater therapeutic ratio. Finally, there is a growing desire to incorporate biologic imaging such as PET scans into a four-dimensional model for treatment.

Results of Primary Radiotherapy: Major Salivary Gland Tumors

Results of historical series treating primary or recurrent unresectable disease with external beam alone are presented in **Table 13–1**. Multiple variables predict for local control, including T stage, histology, dose, fractionation schedule, photons versus neutrons, and recurrent versus unresectable disease, tumor differentiation, and, more recently, the use of chemotherapy.

TABLE 13–1 Results of Selected Series Using Radiation for Primary Unresectable/Recurrent Gross Cancers of the Parotid Gland

Author	No. of patients	Median dose (Gy)	Local control (%)	DFS (%)
Catterall & Errington (1987)[31]	65	15.6 (neutron Gy)	72	50
Reddy et al (1988)[22]	15	NA	46	NA
Wang & Goodman (1991)[26]	9	65	100	65
Poulsen et al (1992)[62]	43	40	64	NA
Gabriele et al (1995)[41]	13	66+hyperthermia	62	NA
Armstrong et al (1996)[43]	20	Brachytherapy	60	NA
Douglas et al (2000)[48]	120	19.2 (neutron Gy)	59	73
Huber et al (2001)[49]	75	64 (photons)	20	56
		16 (neutron Gy)	79	52
		8 (neutron Gy) + 32 Gy (photons)	43	53
Airoldi et al (2001)[47]	6	66+chemotherapy	50	NA

DFS, disease free survival; NA, not available

Local control rates for unresectable salivary gland cancers reported with standard fractionated external beam radiotherapy in combination with conventional technology from the 1970s and 1980s were suboptimal, ranging anywhere from 0 to 30%. Treatment results for recurrent tumors are even more dismal with this approach.[20–24] Several series retrospectively include together major and minor salivary gland cancers, as well as various histologies and stages. The heterogeneous nature of the cases, radiation doses, and degree of surgery (partial resection vs biopsy) makes it difficult to draw significant conclusions about survival data reported in these earlier studies. This has led to the investigation of alternative approaches to conventional photon radiotherapy in an attempt to improve on prior experiences.

Altered Fractionation

The rationales for altered fractionated photon radiation using conformal delivery techniques include the need to increase dose intensity and/or dose escalation, decrease overall treatment time, and overcome rapid or accelerated repopulation of tumor cells. However, it has been argued that salivary gland tumors are in fact slow growing and rarely display accelerated repopulation, making accelerated hyperfractionation less compelling.[25] Wang and Goodman[26] reported their results in 1991 using altered fractionation photon irradiation for unresectable parotid and minor salivary tumors. This was the first report in the literature to evaluate this approach for salivary gland cancer. A total of 24 patients with both unresectable major ($N=9$) and minor salivary cancers ($N=15$) were treated with hyperfractionated photon beam radiotherapy with 1.6 Gy per fraction. Doses ranged from 60 to 78 Gy, with a median dose of 68 Gy. Patients with high-grade lesions received treatment to the ipsilateral neck. Of nine parotid cases, the 5-year actuarial local control at the primary site was 100%, and the survival rate was 65%. Most failures were distant, and there were no reported major complications.[26] These results, on the surface, appear impressive. On closer inspection, seven patients (29%) presented with T1–2N0 tumors, and two patients failed in the neck. If the T1–2 patients are eliminated, and the two neck failures are included in locoregional control, then the tumor control rates drop to 71%. The median follow-up with elimination of the early-stage patients changes from 43 to 20 months.[25] No update or expansion of their salivary gland experience has been published to validate these results with longer follow-up. However, this approach may be a reasonable alternative to high linear energy transfer (LET) radiation, to be discussed later. Hyperfractionation was adopted for all advanced head and neck cancers at the Massachusetts General Hospital and became the investigational arm in a recently completed four-arm randomized trial of altered fractionation versus standard fractionation for advanced head and neck cancers, excluding parotid neoplasms. As a result of this trial, either hyperfractionation (1.2 Gy twice daily) throughout the full course of radiotherapy or concomitant boost (1.5 Gy twice daily weeks 5 and 6) has become the standard of care when chemotherapy is not employed.

At Memorial Sloan-Kettering Cancer Center, all unresectable head and neck cancers were treated beginning in the early 1990s with a delayed concomitant boost (DCB) technique prior to the publication of the Radiation Therapy Oncology Group trial in a prospective phase II trial. Twice-daily treatment was given the last 2 weeks rather than through the entire course. The rationale for the DCB was primarily to overcome the potential accelerated repopulation of tumor cells shown to occur after the fourth week of treatment.[27] It also had the advantage of shortening overall treatment from 7 to 6 weeks and intensified the dose. Acute reactions were expected to be greater, but with equivalent late effects similar to conventional fractionation. In a majority of cases, cisplatin chemotherapy was added

concurrently on days 1 and 22 of the radiation course.[28] Grade 3 mucositis usually occurred during the concomitant boost phase, allowing the majority of patients to complete therapy without requiring a treatment break (76%). This trial included 3 of 82 patients with unresectable parotid tumors, making conclusions about this approach difficult. All three patients with salivary gland neoplasms failed locally.

Results with Charged Particle Irradiation

Charged particles have the potential to improve therapeutic gain based on certain physical and biologic characteristics that differ from photon radiation. Charged particles include neutrons, protons, ions of carbon, helium, and silicon. Protons that have a similar biologic effectiveness relative to photons offer more precise dose localization due to steep dose falloff, whereas high linear energy transfer (LET) particles such as fast neutrons and heavy ions like carbon, helium, and silicon offer a greater relative biologic effectiveness (RBE) to photons. LET is a physical property that is a measure of the mean rate of energy deposited along the track of a charged particle by electromagnetic interactions through a cell matrix. Cell damage is the result of the number of ionizing events produced by the particle track in proximity to the deoxyribonucleic acid (DNA). Charged particles produce either a high or low LET depending on the velocity of the particle traversing the cell. The value of the LET increases as charged particles slow down, resulting in more biologic damage because they cause more severe, less reparable damage per unit of track length than low LET irradiation.[29] RBE is a ratio of absorbed doses of two radiations required to produce the same biologic effect. The RBE of a charged particle is dependent on multiple factors, including LET, dose fraction size, tumor hypoxia, and the type of normal tissue adjacent to the tumor. The RBE for protons is thought to be $\sim$1.1 to 1.2 relative to photons compared with an RBE of 3.0 for neutrons and 1.2 to 4.5 for helium, neon, silicon, and carbon.[29]

The oxygen enhancement ratio (OER) is the ratio of dose needed to inactivate hypoxic tumor cells relative to well-oxygenated tumor cells. The degree of tumor hypoxia impacts on tumor repair, and thus the effectiveness of a particular radiation to create DNA damage that is irreparable. The value for protons is 3, which is similar to low LET photons and electrons. The OER is reduced with higher LET radiation-like neutrons, which in turn leads to a higher RBE. Therefore, hypoxic cells normally more resistant to low LET irradiation are more susceptible to cell kill with high LET irradiation (neutrons) because of less dependence on oxygen.

In summary, low LET charged particles derive their advantage from their physical properties, whereas the advantages of high LET radiation include decreased radioresistance of hypoxic tumor cells, decreased repair of radiation cellular damage, and reduced cell cycle dependence.[29]

Results with Fast Neutrons

Neutron radiation has been investigated at centers in the United States and Europe as an alternative to photon radiation in the treatment of unresectable major and minor salivary gland cancers. It became evident in the 1970s and 1980s that for unresectable advanced or recurrent salivary cancers, conventional photon therapy, although offering improvements in locoregional control, failed to improve overall survival. Recurrent patients did particularly poorly.[30] Neutrons, in contrast to photon radiation, deposit energy directly to cellular DNA, as it passes through the cell, and in turn, lead to higher rates of DNA damage. Photons cause cellular damage indirectly, by the creation of free radicals, which in turn cause secondary damage to DNA. The radiobiologic advantages discussed earlier have been put to the test in clinical trials. Catterall and Errington[31] published the initial British Medical Research Council (MRC)–Hammersmith Hospital experience in 1986 using fast neutron therapy for locally advanced or recurrent salivary cancers. Treatment was given to 65 patients, 89% of whom were stage IV. Local control and 5-year survival rates were 72% and 50%, respectively. No patients experienced facial nerve functional loss. In fact, in patients with parotid gland tumors, 77% regained or maintained function. The technology to deliver therapy was by today's standards crude.[31] Shortly after this publication, the collective world experience with neutron radiation for major and minor salivary gland cancers was reviewed by Laramore.[32] In this retrospective analysis of 309 patients treated, a local control rate of 67% was observed versus 26% for patients treated with photons. Bucholtz et al[33] reported a 92% 5-year locoregional tumor control rate in unresectable, previously untreated salivary gland tumors treated with neutrons. This was in comparison to a 5-year local control rate of 51% for recurrent unresectable tumors treated after previous surgery. There was no facial nerve injuries observed in the patients treated with neutrons alone. The authors concluded that the potential morbidity of a debulking surgical procedure before neutron irradiation is not warranted by an improvement in locoregional control over that achievable with neutron therapy alone, and that surgery should be limited to cases with the highest likelihood of achieving negative margins.[33]

Based on improved outcomes from the MRC and other centers, a prospective randomized trial was performed through the Radiation Therapy Oncology Group and the MRC to confirm the superiority of

neutrons. The 10-year local control rate presented in 1993 also favored neutrons over photons (56% vs 17%).[34] Krall et al,[35] in a review of the European experience, published similar findings in 1998, reporting a local control rate of 65% for neutrons and 28% for photons.[35] Prior to this trial, normal tissue toxicity was reported higher with low-energy, fixed beam neutron generators in physics-based laboratories but equivalent to photons when high-energy, hospital-based neutron generators were used.[25,31] Normal tissue toxicities in the RTOG–MRC randomized trial between the two groups were not statistically different.

The largest U.S. experience using fast neutrons for unresectable major salivary gland cancers was published in 1999 by Douglas et al[36] from the University of Washington. Their experience included 120 patients with either unresectable or gross residual disease after attempted surgery treated with curative intent. It also included 19% with recurrent disease, 39% with gross neck disease, and 11% with prior photon beam therapy. The study included 15% with minor salivary tumors and 32% with adenoid cystic histology. The overall 5-year locoregional control rate and cause-specific survival rates were 58% and 39%, respectively.[36] Tumor size was the most important predictor of locoregional control in multivariate analysis. In univariate analysis, surgical debulking appeared to have a superior local control rate (80%) versus 12% if no surgery was attempted. However, this was not evident in multivariate analysis, reflecting the strong influence of tumor size, because tumors ≤ 4 cm were more likely to undergo some type of surgery. Although tumor size has been reported to be prognostic in other series, the potential for selection bias is evident in this retrospective experience and in others.[37] Similarly, primary tumors showed improved locoregional control over recurrent tumors in univariate analysis but not in multivariate analysis. The authors pointed out that this may have been a reflection of tumor bulk. Patients with base of skull involvement and prior radiotherapy also fared poorly. Overall dose and dose constraints to critical structures previously treated limited full curative doses with neutrons that may have accounted for the less favorable outcome in these subsets. Histologic grade was not prognostic for locoregional control, cause-specific survival, or distant metastasis. Histologic subtype, however, was an important prognostic variable. Patients exhibiting adenoid cystic, acinic cell, and basaloid histologies had both superior locoregional control rates and overall survival rates compared with adenocarcinomas. In contrast to other published experiences,[38] lymph node involvement alone was not prognostic of locoregional control or survival. However, patients with regional neck metastases were more likely to develop distant metastases (52% vs 32%).

Results with Carbon Ion Radiation

Schulz-Ertner et al[39] reported the feasibility of combined photon and carbon ion radiation in 16 patients with locally advanced and residual macroscopic adenoid cystic carcinoma (ACC). The median total tumor dose within the gross tumor volume (GTV) was 72 Gy equivalent. Photon radiation therapy (RT) consisted of fractionated stereotactic RT in seven patients; nine patients received stereotactic intensity-modulated RT. Carbon ion boost was delivered at the heavy ion synchrotron (SIS) at the Heavy Ion Research Center (GSI) in Darmstadt, Germany. With a median follow-up time of 12 months, three patients developed locoregional recurrences 9, 11, and 24 months after RT, respectively. Actuarial local control rates were 80.8% and 64.6% at 1 and 3 years, respectively. Overall survival rates were 100% and 83.3% at 1 and 3 years, respectively. Acute side effects greater than Common Toxicity Criteria (CTC) grade 2 were observed in two patients; no patient developed late effects greater than CTC grade 2.[39] Mizoe et al[40] reported 5-year local control rates of 90% for unresectable minor salivary ACC and 100% for parotid tumors treated with carbon ion therapy alone in a dose escalation trial in Chiba, Japan. Patients received either 18 fractions through 6 weeks (70 Gy equivalent) or 16 fractions through 4 weeks (64 Gy equivalent) on a phase I/II dose escalation trial. No late grade 3 or 4 toxicity occurred in either arm. Both doses were equivalent in local control.[40]

The preliminary data from two carbon ion centers have established the safety and efficacy of carbon ion delivery for salivary gland cancers. Overall treatment times are shorter compared with a conventional course of photons, with more favorable dose distributions than neutrons or photons, and the potential for reduced late morbidity. Protons have been used clinically for skull-based tumors, and their role in salivary neoplasms is not established. Certainly their physical dose characteristics make it an attractive alternative to standard 2D and conformal 3D radiation. No meaningful data exist for the use of protons for salivary cancers. However, proton facilities are currently under construction in different regions of the United States for future use in head and neck cancer therapy, as well as other sites of disease.

In summary, the case for high LET radiation therapy is compelling in treating salivary gland tumors, particularly locally advanced, marginally resectable disease and ACC. The differential tissue-sparing effect, cell cycle, and hypoxic insensitivity of high LET, as well as the high RBE combined with more advanced hospital-based systems, make this approach the treatment of choice.

Radiation Combined with Hyperthermia

Local microwave hyperthermia in combination with photon radiation has also been investigated to improve

local control over conventional photon irradiation alone. Gabriele et al[41] treated 13 patients (20 lesions) with either advanced or recurrent parotid tumors (15 primaries, 5 nodal metastases). Heat was applied twice weekly to a temperature of 42°C. Untreated lesions received external beam radiotherapy to 70Gy, and previously treated lesions received 30 Gy. An overall complete response (CR) rate of 80% was observed. The actuarial local control rate at 5 years was 62.3%. No conclusions could be drawn on the impact of tumor size (although the mean maximum diameter for tumors achieving a CR was 3.9 cm compared with 4.25 cm tumors that had a partial response), or on thermal parameters. Acute toxicity was 15% with superficial necrosis. Two of 3 patients healed spontaneously.[41] Only one patient suffered a grade 3 late toxicity of fibrosis. Weishedel et al[42] published similar results with combined hyperthermia and radiation, obtaining a CR rate of 100% in 16 patients with inoperable ACC at a median follow-up time of 33 months. In comparison with historical patients treated with external beam alone, a 39% improvement in local control was observed (100% vs 61%) and a 20% difference in 5-year survival (57% vs 37%).[42] Although crude, the control rates with hyperthermia and photon irradiation appear similar to control rates presented with neutron therapy. Logistically, although the technology of hyperthermia delivery has advanced, not many centers in the United States are still offering hyperthermia as a treatment modality with the exception of a select group of academic settings.

Brachytherapy

Brachytherapy alone or in conjunction with external beam irradiation has been used as a salvage approach in recurrent parotid, submandibular, or sublingual salivary disease after attempted surgical salvage or for unresectable cancers and should be considered if the resources are available, particularly in the setting of prior external beam treatment. Permanent sources such as iodine 125 can be implanted either directly into a tumor or sewn into a Vicryl mesh and placed onto the surface of microscopic or gross residual disease. No dose response data are available, but typically, one aims for a matched peripheral dose of 160 Gy with iodine 125. Likewise, temporary catheters can be implanted in either a planar or multiplanar geometry for the afterloading of iridium 192 sources. General doses range from 45 Gy (microscopic dose) to 60 Gy (gross disease). High dose rate (HDR) fractionated brachytherapy is replacing low dose rate implants because of the reduced exposure to family and hospital personnel. Armstrong et al[43] in 20 cases of recurrent or advanced disease reported the use of brachytherapy with iodine 125 or iridium 192. Prior radiation had been delivered in 15 patients. Likewise, 15 patients were implanted with gross residual disease. Despite this, the local control at 5 years was surprisingly good, approaching 60%. Complications included soft tissue necrosis in two patients treated with conservative management and cerebral abscess from skull base exposure treated with surgery and iodine 125, one of which was fatal.[43]

King and Fletcher[44] published a small experience on 16 patients treated with external beam and brachytherapy as a combined initial approach. The local control rate was similar.

Concomitant Chemoradiotherapy

Only a handful of institutions have recently investigated chemotherapy combined with radiotherapy for unresectable or recurrent gross major and minor salivary gland cancers. Airoldi and colleagues[45] described six patients with T3–4 inoperable parotid cancers treated with conventional radiotherapy and concurrent cisplatin, 100 mg/m^2 on days 1, 22, and 43. Adjuvant cisplatin and etoposide were given for three additional cycles. The median radiation dose was 66 Gy. This regimen achieved a complete response in 3 of 6 patients (50%), partial response in two patients (33%), and stable disease in one patient. The median CR and PR duration was 26 months and 10 months, respectively. Median overall survival was 18 months. No severe late toxicity was observed.[45] Agents shown to have moderate activity for parotid and minor salivary cancer include paclitaxel, carboplatin, and vinorelbine and cisplatin.[45–47]

In summary, although promising response data have been observed, no conclusions can be drawn from the limited data regarding the benefit of concurrent chemoradiotherapy, and it must be considered investigational at this time. However, in certain situations, particularly for unresectable disease in good performance patients, the addition of chemotherapy to radiation therapy is considered acceptable and standard for most advanced head and neck cancers and should be considered if the patient is willing.

Special Management Issues and Outcomes: Unresectable Adenoid Cystic Carcinoma

In many instances, adenoid cystic carcinomas have been included with other unresectable major and minor salivary neoplasms in outcome analyses using conventional radiotherapy. However, several investigators have devoted attention specifically to outcomes related to ACC. As discussed earlier, fast neutron radiation has been investigated as a possible advantage over conventional photons. Douglas et al[48] updated the University of Washington experience from 1985 to 1997. One hundred and fifty-nine patients with unresectable, locally advanced or recurrent, nonmetastatic ACC were treated with fast neutron irradiation. Of the total cohort, 29% arose from the parotid gland. The median total

dose was 19.2 Gy either given three or four times weekly. For major salivary gland ACC, the 5-year locoregional control, cause-specific survival, and overall survival rates were 67%, 82%, and 71%, respectively. Base of skull invasion, positive lymph nodes, limited biopsy versus attempted surgery, and recurrent tumors were associated with a worse outcome in multivariate analysis. The initial size of the tumor was not significant. Patients presenting for treatment without these negative prognostic factors demonstrated a 5-year cause-specific survival rate of 100%. Lymph node status and base of skull invasion were also associated with a higher rate of distant failure. At 5 years, 50% of patients with regional neck metastases developed distant failure versus 26% of node-negative patients. The high rate of distant failure in the node-negative patients (nearly one third) suggests the presence of micrometastatic deposits and the need to explore better combined systemic approaches. Significant or major complications occurred in $\sim$15% of all patients treated, including minor salivary sites.[48]

Huber et al[49] compared photons and/or electrons to fast neutron therapy for patients with advanced ACC of the head and neck. The 5-year local control rate was 75% for neutrons, versus 32% for photons and for mixed beam (neutrons combined with photons). The improved local control, however, did not translate into a survival advantage. A high rate of distant failure (39%) was observed, with positive lymph nodes associated as the most predictive factor. The absence of positive lymph nodes merely delayed the development of distant failure in a subset of patients, similar to the Washington University experience. Neutrons versus photons, surgery and postoperative radiotherapy versus radiotherapy alone, microscopic versus gross residual or inoperable disease, and smaller tumor size were significantly related to local control in multivariate analysis. Severe toxicity was more prevalent with neutrons (19%) than with photons (4%) or mixed beam (10%). The median dose for patients receiving photons in this review was 64 Gy (range 60–70 Gy). The authors state that patients who underwent surgery received the same dose as patients without surgery, doses by today's standards considered suboptimal for gross disease and more appropriate for microscopic residual disease. Although in this study major salivary sites represented only 14 of 75 patients (18%), site of origin (major vs minor salivary tissue) did not predict for local control or survival.[49]

In summary, the data suggest that patients should receive neutron irradiation if possible for unresectable, partially resected, or recurrent unresectable ACC. Local control appears to be superior when compared with conventional photon radiation demonstrating the high RBE of fast neutrons. Cause-specific survival is related to pretreatment tumor bulk or size, histology (ACC vs non-ACC), and the presence of lymph node metastases at presentation. Other factors, such as recurrent disease and base of skull invasion, may again be a reflection of tumor bulk. Due to the high rate of distant failure, primarily a result of lymph node–positive necks, the survival advantage for neutron radiotherapy disappears. The time to distant failure is delayed by a lymph node–negative neck at the time of treatment, as evidenced by the Huber et al[49] data (100 vs 16 months), but still occurs to a large degree. The choice of neutrons versus photons must ultimately be made based on individual patient condition and situations. Realistically, fast neutron facilities are not available throughout the United States, necessitating the use of photons either alone or in combination with chemotherapy. A limited number of facilities in the United States and Europe, however, now offer treatment with second-generation cyclotrons using multileaf collimation, which may reduce treatment morbidity through more conformal delivery of neutrons. What needs to be understood is that with the exception of the RTOG–MRC randomized trial, the majority of data are retrospective. Caution should be exercised when interpreting the unresectable data in regards to prognostic variables affecting locoregional control and cause-specific survival.

The unanswered question is if conformal 3D-CRT or IMRT radiotherapy with photons, with doses $\geq$ 70 Gy, or dose intensification either with altered fractionation or with concurrent chemotherapy would offer similar outcomes to neutrons with an acceptable level of morbidity. Many of the previously mentioned studies delivered suboptimal photon doses that would be unacceptable by today's standards. Because local control is an important end point in a disease that has a long survival, despite the high rate of distant failure, prospective trials are needed to address these questions. The possibility, however, of a future trial does not appear likely.

Recurrent Pleomorphic Adenoma

The standard of care for the management of primary pleomorphic adenomas of the parotid gland is superficial or partial superficial parotidectomy with facial nerve preservation, which results in excellent local control with recurrence rates of $\sim$1%. There are situations where the risk of recurrence is higher, and radiotherapy should be considered. The indications for radiotherapy include multiple recurrent lesions, inadequate margins, facial nerve encasement coupled with nerve preserving surgery, gross unresectable disease, gross recurrent disease, and the rare case of malignant transformation. The issues facing a multidisciplinary team include the natural desire on the part of a surgeon to preserve facial nerve function (due to tumor encasement) even in situations that leave microscopic disease behind, coupled with a concern of the potential for second malignancies induced by radiation. These

tumors typically occur in young adults. The risk of radiation-induced cancers is small but significant and must be considered. Of equal concern, however, is the potential for multiple surgeries for recurrent disease to increase the risk of deforming facial nerve injury. For subgroups of patients with pleomorphic adenomas encasing the facial nerve, or presenting with microscopic or macroscopic recurrent or multifocal disease, the risk of local failure can be as high as 25 to 50% even after repeat surgery. For high-risk patients, the addition of radiation therapy can reduce local failure rates. These tumors have been shown to be radioresponsive to conventional photons/electrons and neutrons. The typical doses range from 50 to 60 Gy, depending on residual microscopic or macroscopic disease. The risk of regional nodal spread is so low as to not warrant elective nodal irradiation except in the rare case of malignant transformation.

Chon et al[50] reviewed the Massachusetts General Hospital experience from 1955 to 1994 of 48 patients treated with surgery and radiation therapy. This study examined the influence of timing of radiotherapy for high-risk patients, comparing a subgroup treated adjuvantly because of high-risk features, with those patients receiving radiotherapy after a first, second, or more recurrence. All patients underwent surgery prior to radiotherapy. The mean follow-up time was 14.5 years. For the 12 high-risk patients treated with immediate adjuvant radiotherapy, the local control rate was 100%. No facial nerve injuries occurred in this group despite doses as high as 70 Gy or with twice-a-day therapy. The local failure rate, however, for first and subsequent recurrences were 7% and 36%, respectively. One patient treated after the third recurrence subsequently developed a squamous cell carcinoma of the buccal mucosa at 15 years. No other malignant transformations occurred. The risk of facial nerve injury rose with more than two surgeries (30%) versus only one (8%). No difference was seen in local control between unifocal and multifocal disease at 10 years.[50] Gleave et al[51] reported a 5% failure rate in patients with recurrent pleomorphic adenoma treated with surgery and postoperative radiation versus 18% for patients treated with surgery alone. Other authors have published similar local control rates of 90% or better, even in the setting of recurrent disease with conventional postoperative photon/electron radiation.[52,53] Buchholz et al[54] reported the results of six patients with recurrent disease treated with neutrons. All patients had an average of three prior surgeries. Two patients were treated for gross unresectable disease. With a median follow-up of 52 months, the local control rate was 100%. A low risk of facial nerve injury was observed.[54]

The risk of radiation-induced carcinogenesis from neutrons is rare and certainly no greater than the risk from conventional photons. The approach to planning, targeting, and delivery of conformal radiotherapy for pleomorphic adenomas is similar to unresectable malignant tumors of the parotid.

Radiation Therapy in the Postoperative Setting: Primary Site

Historical patterns and risk of recurrence have been defined retrospectively by large surgical series. Spiro and associates[55] reviewed the patterns of failure of 288 patients after surgery alone for parotid neoplasms. The Memorial Sloan-Kettering group observed an escalating risk of primary failure with increasing stage. The risk of recurrence by stage was 7% stage I, 21% stage II, and 58% stage III.[55]

Subsequent to that, Harrison and colleagues[56] reviewed the Memorial Sloan-Kettering experience of patients treated with surgery and postoperative conventional radiotherapy for high-risk features. This was not a direct comparison to the earlier Spiro et al[55] report, but it provided a sense of improved local control with the addition of radiation. The indications for radiation therapy in this series included positive margins, advanced local disease, positive nodes, and high-grade disease. The overall 5-year actuarial control rates by T stage were 100% for T1, 83% for T2, 80% for T3, and 43% for T4. Patients with positive nodal disease had a lower locoregional control and survival than node-negative patients (58% vs 83%, and 39% vs 80%, respectively). Eight of eight patients (100%) with ACC were locally controlled after adjuvant elective radiation therapy (ERT) in comparison to three of eight (37.5%) treated with surgery alone, with all failures arising within 4 years of surgery. A trend toward improved local control at 10 years was observed with doses of radiation exceeding 57 Gy (72% vs 53%) in comparison with lower doses.[56] Other authors have reported similar experiences.[57–62] Selected modern series are provided in **Table 13–2** showing results with or without adjuvant radiotherapy.

Referral for radiotherapy is based many times on surgical bias and is typically a patient presenting after surgery with poor prognostic features, as discussed previously. Further complicating any meaningful conclusions of the efficacy of radiotherapy is the heterogeneity of surgical technique (conservative vs radical parotidectomy) and radiation dose and technique. Armstrong et al[63] performed a match-paired analysis of surgical patients to balance out pretreatment variables to determine the efficacy of adjuvant radiation. This analysis represents the closest thing to a prospective evenly matched randomized trial in the literature. In this unique study, 46 patients treated with surgery and postoperative radiation were compared with 46 patients treated with surgery alone. A large group of surgical patients treated at Memorial Sloan-Kettering Cancer

TABLE 13–2 Impact of Adjuvant External Beam Irradiation on Local Control on Major Salivary Neoplasms

		Local control		
Author	No. of patients	Treatment	5-year disease free%	5-year survival%
North et al (1990)[60]	87	S	74	60
		S+RT	96	76
Armstrong et al (1990)[63]*	46	S[23]	66	55
		S+RT[23]	73	68
Poulsen et al (1992)[62]	209	S+RT	76	71
Magnano et al (1999)[58]	126	CS*	62	47
		NCS*	67	
		CS+RT	73	52
		NCS+RT	89	
Kirkbride et al (2001)[57]	159	S+RT	81	76

*Matched pair analysis
CS, conservative surgery; NCS, nonconservative surgery (facial nerve sacrifice); RT, radiation therapy; S, surgery

Center allowed Armstrong to pick out at least 46 patients for well-matched pairs. The analysis showed that surgery alone was adequate for stage I and II salivary cancers. For T3 and T4 tumors and tumors with positive nodal disease, a significant improvement in locoregional control was observed with postoperative radiation. The 5-year locoregional control and determinate survival rates for stage I/II comparing surgery versus surgery and radiation was 91% versus 79%, and 96% versus 82%, respectively. For stage III/IV disease, the 5-year locoregional control and determinate survival rates comparing surgery and surgery plus radiation were 17% versus 51%, and 10% versus 51%, respectively. As one can see, despite the improved local control with a combined approach, the failure rate even with the addition of radiotherapy was suboptimal, particularly for T4 tumors. A trend toward improved survival was also seen for high-grade cancers. Although the indications for radiotherapy seem reasonably clear based on the collective experiences, it is vital that a multidisciplinary approach toward the individual patient be performed with all subspecialties in head and neck cancer management giving input to consider all nuances and recommend a comprehensive strategy.

Postoperative Management of Adenoid Cystic Cancers

The reason ACC is addressed separately is the unique behavior of these tumors, combined with the specific issue of how to adequately address close/positive margins and/or perineural spread as it relates to radiotherapy coverage of the base of the skull and total dose. For stage I tumors with negative margins and no perineural spread, there is no need for adjuvant radiotherapy.[64] For more advanced disease, several authors have shown improved local control with the addition of adjuvant radiation to surgery for ACC, ranging from 72 to 86% with and 11 to 47% without.[65–67] Garden and colleagues[68] addressed the above concerns in a published retrospective analysis of a 30-year experience from the M.D. Anderson Cancer Center. This study was unique in its comprehensive policy of offering a multimodality approach to ACC. Between 1962 and 1991, 198 patients received postoperative radiotherapy after surgery for suspected or known microscopic positive margins. Of the total, 71 patients had major salivary ACC, and 122 presented with minor salivary ACC. Over two thirds (69%) of the entire cohort had perineural spread. The median radiation dose to the tumor bed and follow-up time was 60 Gy and 93 months. respectively. The 10 and 15 actuarial local control rates were 86% and 79%, respectively. Positive margins had a significant impact on local failure compared with close or negative margins. The failure rates were 18%, 9%, and 5%, respectively. Perineural invasion was significant only if a major nerve was involved. Patients with perineural spread of a major named nerve demonstrated crude local failure rates of 18% compared with 9% without. The dose of radiotherapy had a dramatic impact on local control when positive margins were present. Crude control rates were 40% and 88% for doses < 56 Gy and ≥ 56 Gy. The 10-year local control rate declined from 93% with negative margins and no perineural spread, to 83% with either perineural invasion or positive margins, and to 70% when both were present. The site of disease was not a factor in local control. Four patients (2%) failed at the base of the skull, three of four presenting with major nerve involvement. The distant failure rate was 37%, despite local control in 31%. Distant failure rates were no different for negative versus positive margins, but they were higher when stratified by named nerve involvement. The authors recommended a dose of 57 to 60 Gy to the operative bed for negative or close margins and 66 Gy for positive margins. The neck was treated only in cases of positive nodes. Neck failure was rare.

In summary, patients with ACC should receive adjuvant radiotherapy if close or positive margins are suspected or if perineural invasion is evident. Elective coverage of the base of the skull should be included in

a radiation port if a major nerve is involved or if the margins of an involved nerve at the proximal end are positive as it is dissected toward the skull base. Focal perineural invasion is not an indication to electively treat the base of the skull. In some cases, base of the skull inclusion is unavoidable by virtue of the location of the nerve pathway in relation to the primary site, such as the parotid or paranasal sinus regions.[68] Routine involvement of the base of the skull for a sublingual or submandibular site would result in excessive morbidity. Dose is critical and should be tailored based on presentation of margins and nerve involvement. Finally, the high rate of distant failure requires a serious look at adding chemotherapy to the comprehensive management of ACC in a prospective trial.

Elective Treatment of the Neck

Uniform elective treatment of the neck is not indicated after surgical resection of the primary site. The largest study to specifically look at risk variables that predict for microscopic neck metastasis was performed by Armstrong et al[2] in 1992. This analysis was designed to outline indications for elective neck radiation (ENR). The records of 474 patients who underwent surgical resection of a locally confined major salivary gland cancer at Memorial Sloan-Kettering Cancer Center were reviewed. Clinically positive nodes presented in 14%, and clinically occult, pathologically positive nodes occurred in 12% of the 474 patients. In multivariate analysis, tumor size and grade were significant risk factors. Tumors 4 cm or greater had a 20% risk of occult nodal metastases compared with 4% risk for tumors less than 4 cm. High-grade tumors regardless of histologic type had a 49% risk compared with a 7% risk for intermediate-low-risk tumors. What should the radiation oncologist do in the setting of positive occult nodal disease after elective nodal dissection (END)? Armstrong and colleagues[2] also addressed this. The failure rate in patients who underwent END and were found to have occult disease and did not receive radiotherapy was 29%, compared with the 0% failure rate in patients who did receive radiotherapy. Another point brought out by the authors is the high rate of occult neck disease with epidermoid carcinomas, and the concern that the primary site may have been cutaneous in origin. What is not addressed in this or any study is the relative efficacy of ENR versus END in controlling occult disease. It is fair to extrapolate for epidermoid cancers of other head and neck sites that ENR in doses between 45 and 50 Gy will control occult microscopic disease in the neck in greater than 95% of patients. More interestingly, selective ENR can be performed similar to selective END. In this series, a parotid and level II neck dissection would have missed occult disease in 25% of cases. The addition of level III nodes would have reduced this to 10%.

Radiation Target Coverage

For tumors of parotid origin, it would appear reasonable to include the parotid bed up to the base of the skull for deep lobe invasion, along with nodal levels II, III, and IV with exclusion of levels Ia, Ib, Va, and Vb. For submandibular or sublingual origin, levels Ia, Ib, II a, IIb, III, and IV would appear appropriate with exclusion of levels Va and Vb. This would reduce morbidity associated with ENR. For parotid and submandibular sites, there is no need to treat the contralateral neck, even in the setting of gross nodal disease of the ipsilateral side. For sublingual origin, the risk of contralateral spread increases due to the proximity to the midline. This necessitates inclusion of the contralateral level Ia–b, IIa–b, and III nodal regions. Fortunately, the parotid glands can be spared from this approach, as the likelihood of occult disease is low.

Primary Radiotherapy of Minor Salivary Gland Cancers

The indications for choosing primary radiotherapy over surgery are based on site accessibility, extent of local infiltration, resectability, and potential functional/cosmetic loss and medical operability. Because minor salivary glandular tissue arises in multiple sites throughout the oral cavity, oropharynx, nasal and paranasal cavities, larynx, and hypopharynx treatment must be individualized. For example, minor salivary gland cancers are more common on the hard and soft palate than the larynx or hypopharynx. The functional loss of the hard palate and/or soft palate for some patients is devastating, and primary radiotherapy is a reasonable alternative. The risk of neck disease is also low, allowing for more conformal radiation techniques like IMRT to the primary site. Likewise, surgery for the nasopharynx is rarely performed. Minor salivary gland cancers arising in the nasal and paranasal sinuses are usually quite extensive at presentation. Many are unresectable, or would require morbid surgery, depending on the extent of spread to critical surrounding structures.

Radiation doses are similar to doses prescribed for major salivary tumors (66–70 Gy). Elective treatment of the neck is reserved for high-grade lesions and site of origin, rather than histology. Minor salivary gland cancers of the lip, buccal mucosa, palate, and sinonasal tract rarely metastasize regionally and do not require ENR or END.[69] Intermediate-risk sites (oral tongue, floor of the mouth), and high-risk sites (nasopharynx, oropharynx, larynx, and hypopharynx) should be considered for ENR. Doses for ENR are similar to that for major salivary gland cancers.

Results of Primary Radiotherapy: Minor Salivary Gland

Parsons et al[69] published the largest experience with primary radiotherapy in the United States. The outcomes of 95 patients treated at the University of Florida were reviewed, 45 of whom received radiotherapy alone. The predominant site of presentation was the oral cavity, followed by nasal/paranasal sinuses and oropharynx. Overall, local control for patients treated with radiotherapy alone was 21 of 45, ranging from 2.5 to 21 years, including 12 patients with ACC. Local control results according to tumor site showed 64% for oral cavity, 83% for oropharynx, 22% for nasal/paranasal sinuses and nasopharynx (presented together), and 100% for larynx and hypopharynx. Doses of 65 Gy produced a high rate of local control, whereas higher doses (70 Gy) resulted in even higher rates of local control for advanced disease. This was even more evident for adenoid cystic cancers, with local control rates of 2 of 12 for < 70 Gy compared with 10 of 13 for doses $\geq$ 70 Gy. There was no significant difference in local control based on histologic type. Higher failure rates within the nasal/paranasal group were more likely a result of extent of disease rather than site. In multivariate analysis of factors influencing local control, combined surgery and radiation was superior to radiotherapy alone, along with T stage.[69] Despite improved local control rates with combined treatment, the authors noted that the 10-year absolute and cause-specific survival rates with combined treatment were similar to surgery alone results reported by Spiro et al[71] from Memorial Sloan-Kettering Cancer Center. The 10-year cause-specific survival rates at Memorial Sloan-Kettering were 93% stage I, 68% stage II, 58% stage III, and 24% stage IV, respectively, compared with 75%, 58%, and 27% for stage I–II, stage III, and stage IV, respectively, from Parsons et al.[69] Neck failure occurred in only 8% of 39 patients not electively treated. Perineural invasion was not addressed in this study, but Garden et al[68] observed a higher rate of base of skull and distant failure with major named nerve involvement.

Results and Factors Affecting Outcome of Combined Surgery and Radiation Therapy for Minor Salivary Gland Cancer

Postoperative radiotherapy is not indicated for low-grade, early-stage lesions when negative margins are obtained. The indications for radiotherapy in the postoperative setting are similar to major salivary cancers and include positive or close margins, perineural spread, vascular space invasion, T3–4 tumors or tumor with penetration into underlying bone, skeletal muscle, or cartilage, high-grade tumors, multiple nodal involvement, and recurrent disease. Factors affecting local control and survival are not always clear based on conflicting data.[69,70] The local failure rates for 160 patients treated with combined surgery and radiotherapy in the M.D. Anderson Cancer Center experience was 12%.[68] In contrast, a local failure rate of 48% in patients treated with surgery alone was reported from the Memorial Sloan-Kettering Center.[71] Sadeghi and colleagues[72] also showed higher local control rates with the addition of radiotherapy in 47 patients with positive margins after surgery. Local control was 76% in the group of patients receiving radiotherapy versus 47% for those who did not.[72] Parsons et al[69] reported 10-year local control rates with combined treatment of 100% for T1–2 tumors, 100% for T3 tumors, and 33% for T4 tumors. Spiro et al[73] found overall stage to be the most important predictive factor for survival in 378 patients retrospectively staged using the AJCC criteria available at that time. Parsons and associates[69] also observed overall stage to be the most significant factor in survival. The site of origin as an independent prognostic variable in determining outcome is also not clear. Reports of lower local control and survival for nasal cavity and paranasal sinus tumors, for example, are probably a reflection of T stage and not the site of disease.[69] Most investigators report an influence of tumor grade rather than histology on survival.[69–71]

Adenoid cystic carcinomas arising in minor salivary sites, similar to major salivary tumors, have a high propensity for distant spread, approaching 40% in some studies.[69] Despite this, the indolent nature of ACC in many cases results in 5-year survival rates approaching 40%.[67,69] Perineural spread has been observed in nearly 60% of minor salivary gland cancers after surgery.[70] The base of the skull should be irradiated only if a major nerve branch is involved with tumor.[68] Based on regional neck failure patterns, radiotherapy to the involved neck should be considered if multiple lymph nodes harbor disease or if extracapsular penetration is found.[68] It is important to note that a single metastatic lymph node after a selective neck dissection means the neck is still at risk for failure and should be treated with radiotherapy. Although the lymph node drainage patterns by site are generally orderly, midline cancers and tumors arising in sites with rich lymphatic drainage such as nasopharynx, base of the tongue, and larynx should have both necks addressed electively with either surgery or radiotherapy.

Radioprotectors

Chemical radioprotector compounds were initially investigated to provide protection against whole-body radiation exposure in the event of a nuclear catastrophe. The Walter Reed Army Research Institute developed a thiophosphate, WR-2721, as part of a vast development program during the cold war to provide radiation protection to soldiers. WR-2721, also known as

amifostine, has been investigated as a radioprotector in oncology to improve the therapeutic ratio, based on the assumption that a differential uptake of the compound would occur, with higher concentrations in normal tissue compared with tumor cells, leading to greater normal tissue protection.[74] Amifostine requires a dephosphorylation of its phosphate group by alkaline phosphatase to convert into the more active free thiol WR-1065. Normal tissues contain higher concentrations of this enzyme, leading to greater uptake of WR-2721 in normal cells. The active form, WR-1065, acts intracellularly to scavenge and bind oxygen-free radicals and assist in DNA repair after radiation exposure.[75] There also appears to be some degree of chemoprotection with differential sparing of bone marrow and intestinal mucosa with cisplatin, an active agent used in head and neck cancer, as well as alkylating agents.[76,77] Human clinical trials have subsequently been performed in bone marrow cancer, lung cancer, cervical cancer, rectal cancer, and head and neck cancer. Amifostine can be administered either intravenously as a rapid push or subcutaneously 30 to 45 minutes prior to radiation. A phase III randomized trial in head and neck cancer using radiation with or without amifostine administered intravenously was performed with the end point of xerostomia and unstimulated salivary flow. The incidence of grade 2 xerostomia was reduced from 78 to 51%. No tumor protection was observed. Side effects included nausea, vomiting, hypotension, and anorexia.[78] Subsequent investigations are under way to determine the efficacy of amifostine delivered subcutaneously compared with intravenous delivery. It is thought that subcutaneous delivery reduces the degree of nausea and hypotension, making the addition to radiotherapy or chemoradiotherapy more tolerable. Robust oral hydration is essential both before and after administration to reduce nausea and hypotension. Recently published data have dispelled the concern of any tumor protective effect from amifostine.[78,79] The implications for major and minor salivary gland protection are compelling, particularly sparing of the contralateral submandibular gland and parotid from cross-firing and exit beam dose. Amifostine is now being used for head and neck cancer in the United States and elsewhere to reduce xerostomia and acute and late toxicity associated with combined chemoradiotherapy.

Radiation Morbidity

Critical Structures

The proximity of the parotid and other salivary glandular tissue to several critical normal structures in the head and neck makes the task of delivering tumoricidal doses of radiation a challenge. These structures include the mandible, spinal cord, brainstem, temporal lobe, eye, and inner ear. Exceeding the tolerance of these tissues can result in severe late toxicity. Late toxicity would include mandibular necrosis, spinal cord injury resulting in paresis or paralysis, brainstem injury leading to respiratory failure and/or paralysis, temporal lobe necrosis, blindness, and loss of hearing. The dose-limiting tolerance of these tissues has been documented over the years from a compilation of clinical and radiobiologic studies and should be heeded. The threshold doses for various tissue or organs have been defined as the $TD_{5/5}$, or threshold dose expected to causes a 5% complication at 5 years.[8] However, in select cases, a decision must be made to exceed the $TD_{5/5}$ to obtain reasonable target coverage. This should be discussed with the patient and documented in writing. Pre-radiation dental evaluation is essential and advised for all patients. Mandibular complications can be reduced with preventive dental evaluation and extraction of ipsilateral teeth that are distressed. Failure to do so can lead to future infection of the bone. Other dental maneuvers to reduce acute reactions during treatment include the replacement of metallic fillings with composites to reduce radiation scatter to the tongue and the fashioning of a lead-lined dental mold placed intraorally through treatment to reduce scatter.

Less Critical Structures

Less critical but important structures include the salivary glands, temporomandibular joint, middle ear, facial and scalp hair, thyroid gland, oral and nasal mucosa, and lacrimal gland. Late side effects to these structures are not life threatening but can contribute to a reduction in functional quality of life. IMRT, 3D-CRT, or protons can be used to spare ipsilateral or contralateral salivary tissue to reduce the risk of xerostomia. The risk of late xerostomia is related to the mean dose to either the parotid or submandibular gland. As the mean dose rises above 27 Gy, the chance of significant recovery decreases.[7]

Acute toxicity generally occurs 3 to 4 weeks into therapy and is related to multiple factors, including diabetes, Sjögren's syndrome, dose per fraction, accelerated fractionation, concurrent chemotherapy, prior surgery, prior radiotherapy, and the use of amifostine. Acute effects include xerostomia, dental caries, epilation of facial and scalp hair, skin erythema, changes to or loss of taste, oral candidiasis, progressive mucositis of the oral cavity and oropharynx, esophagitis, and acute sialadenitis.

The occurrence and severity of a late toxicity are dependent on factors such as the location and volume of normal tissue treated, total dose and dose per fraction, conformality of the radiation beam arrangements, chemotherapy, lack of proper dental attention prior to

therapy, prior surgery or radiotherapy, recurrent disease, and the use of radioprotectors.

Late side effects include the risk of trismus if a large portion of the temporomandibular joint and/or masseter muscle is exposed to doses greater than 50 Gy, otitis media when the entrance or exit beam is through the middle ear, alopecia due to exit dose, skin and dermal fibrosis that can be exacerbated by prior therapies, chemical, subclinical, or clinical hypothyroidism, and mandibular osteoradionecrosis.

Several studies have shown promise with early intervention of different agents to reduce and reverse acute as well as late toxicity. Antifungal agents, nonsteroidal anti-inflammatory agents, zinc, and pentoxifylline are some of the compounds that have been investigated that appear to reduce some of the acute and late toxicity by limiting mucositis and xerostomia, as well as soft tissue and muscular fibrosis.[80–83] Further clinical development of pharmacological approaches to modification of chronic radiation injuries could lead to significant improvement in the quality of life for radiotherapy head and neck patients

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14

Etiology, Pathogenesis, and Treatment of Radiation-induced Xerostomia

CHRISTOPHER A. SULLIVAN

Xerostomia is a permanent and devastating sequela of head and neck radiation that affects ~40,000 patients annually in the United States.[1] This figure is expected to grow as concomitant chemoradiation therapy and hyperfractionated radiation schemes become the standard of care for most advanced oropharyngeal and laryngeal malignancies due to superior 5-year disease-free survival rates and advantages of organ preservation.[2,3] The resulting salivary hypofunction after radiation and chemoradiation therapy leads to impaired mastication and loss of oral lubrication. This hinders bolus formation and causes dysphagia that limits food choices and leads to nutritional deficiencies. Speech is altered due to the dry, sticky oral mucosal environment that hinders tongue movement and leads to oral motor fatigue. The oral mucosa becomes dry, fissured, and painful. Rampant dental caries and recurrent fungal infections result from alteration of the microfloral environment of the oral cavity and oropharynx. Sleep dysfunction occurs due to the need for patients to moisten their mouths at night by drinking water; this leads to a cycle of polydipsia and polyuria, resulting in frequent arousals and fatigue. Xerostomia associated with head and neck radiation therapy severely degrades the general quality of life and can contribute to depression that is commonly seen in head and neck cancer patients.[4,5]

The early effects of radiation on salivary glands were first characterized by Jean Bergonie in 1911.[6] The existing experimental data on salivary gland radiosensitivity and the theoretical mechanism by which salivary tissue damage occurs during head and neck radiation are well described in animal and primate models. It is generally agreed that radiation causes lipid peroxidation that is catalyzed by heavy metal ions present in the granules of serous cells. This process leads to membrane disruption and release of cellular enzymes, which then cause autolysis and cell death. It is hypothesized that this damage may also include reproductive death of acinar progenitor cells.[1,7,8] The chief histopathologic feature of radiation-induced salivary damage that leads to hypofunction in humans is serous acinar cell loss with relative preservation of ductal structures (**Fig. 14–1A,B**).[9] Recent histopathologic and immunohistochemical studies of chemoradiated salivary glands in humans have shown profound acinar cell loss and ductal progenitor cell preservation, suggesting a higher resistance of these cells to the lethal deoxyribonucleic acid (DNA) damage that is the fate of acinar cells during radiation therapy.[10] Additional theoretical considerations that affect salivary flow after high-dose radiation include destruction of the surrounding capillary vascular structure and fibrosis.[11]

The major salivary glands typically lie within the head and neck radiation fields for most upper aerodigestive tumors, and the amount of glandular damage is felt to be dependent upon radiation dose, fractionation, latency of treatment, the premorbid functional state of the glands, and the ratio of serous to mucinous cells within an individual gland.[1] Irreversible radiation damage begins at 27 Gy.[12] A 50% decrease in salivary flow occurs by 1 week of fractionated therapy, with a transient rise in serum amylase as acinar cell damage occurs. Flow continues to decline throughout the treatment period of 6 to 8 weeks with little or no flow by the end of radiation.[13] Decreased flow is accompanied by increased salivary viscosity, decreased pH, increased concentration

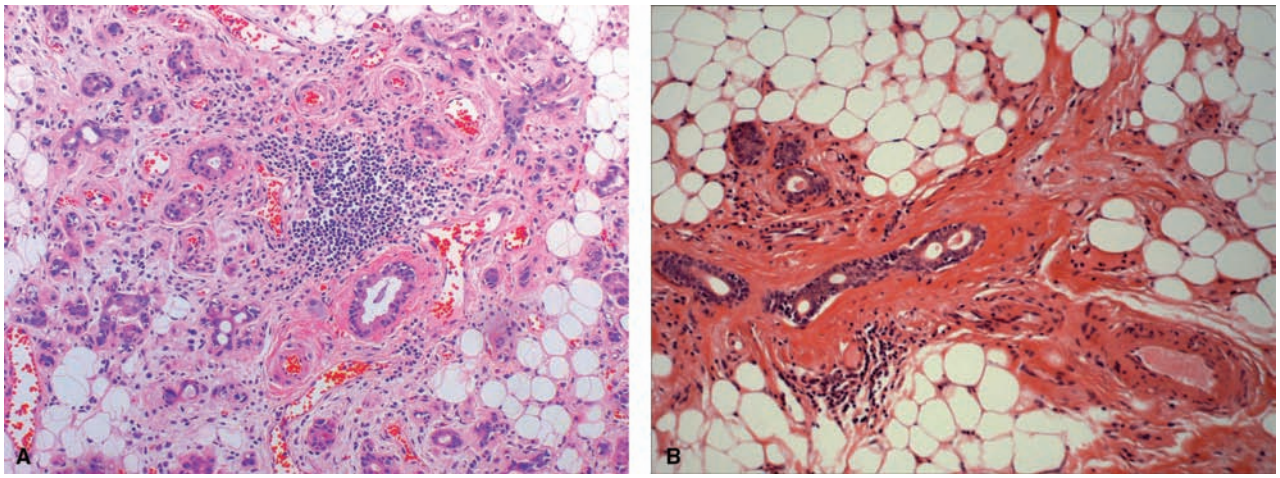

FIGURE 14–1 (A) Human submandibular gland 11 weeks after receiving concomitant chemoradiation therapy (weekly cisplatinum and 5-FU, 52 Gy). Note profound acinar cell loss, persistence of ductal structures, mild periductal fibrosis and metaplasia, associated fat replacement, and lymphocytic infiltration. **(B)** Human submandibular gland 9 years after radiation therapy. Note persistent ductal structures, severe periductal fibrosis, and predominance of fatty degeneration.

of electrolytes, and decreased immunoglobulin A (IgA).[13,14] Radiation for most aerodigestive and salivary malignancies will result in doses between 50 and 72 Gy to the salivary glands, which is well above the 27 Gy threshold and explains the slow recovery over months to years and the permanent salivary morbidity that is experienced by most head and neck cancer patients after radiation therapy.

There is no preventive or curative therapy for xerostomia at this time. Palliative therapies include frequent water drinking, over-the-counter oral sialagogues (sugarless citrus candy, chewing gum), and oral wash preparations such as Biotène and Oral Balance (both Laclede Inc., Rancho Dominguez, CA) and Zendium, which contain glucose oxidase, lactoperoxidase, and lysozyme that help to maintain the microfloral environment and prevent fungal overgrowth. Different types of saliva substitutes are now commercially available, containing different polymers as thickening agents, for example, carboxymethylcellulose (Oralube and Glandosane), polyacrylic acid, and xanthan gum (Xialine).[15] These therapies are generally effective in mild cases of xerostomia but do not work as well in severely afflicted patients because their effects are transient and they require frequent application. The gold standard of pharmacologic therapy for the treatment of xerostomia is pilocarpine hydrochloride. This agent is an orally ingested cholinergic parasympathomimetic with muscarinic action that stimulates salivary cell secretion. It is not known whether this medication adequately replaces salivary amylase, the key oral digestive enzyme present in normal saliva. Due to underlying dysphagia and aspiration, some head and neck cancer patients are unable to swallow this orally based preparation.

In a 12-week randomized, double-blind, placebo-controlled multi-institutional trial, 207 patients who had received more than 40 Gy were treated with 5 or 10 mg pilocarpine hydrochloride three times a day (tid) and showed a statistically significant improvement in mouth dryness and salivary flow over placebo-treated patients. There was no statistical difference in control of symptoms between the 5 and 10 mg treated patients, but sweating and other cholinergic side effects were more common in the 10 mg treated group.[16] In another 12-week, double-blind, randomized, placebo-controlled study, 162 patients were randomized to placebo or pilocarpine. Patients were allowed to control their dosing based on their symptoms; greatest improvements in salivary flow rates and symptoms were achieved with continuous administration of greater than 2.5 mg tid and in patients with no measurable salivary flow at baseline.[17] In both of these placebo-controlled studies, some patients noted improvement in the global assessment of their dry mouth, speaking without liquids, and a reduced need for supplemental oral comfort agents. The most common adverse events related to drug therapy were sweating, nausea, rhinitis, diarrhea, chills, flushing, urinary frequency, dizziness, and asthenia. The most common adverse experience causing withdrawal from treatment was sweating (5 mg tid = 1%; 10 mg tid = 12%). The risk–benefit ratio of pilocarpine has never been established; therefore, despite its existence for more than 30 years, many patients abandon the therapy as a result of its side effects.[18]

The lack of well-tolerated pharmacologic therapies has led to clinical strategies that attempt to prevent radiation damage to salivary gland cells by using various cytoprotectant substances such as amifostine[19] and

modifying the location of the radiation beam to limit salivary gland exposure using a technique called intensity modulated radiation therapy (IMRT).[20]

A surgical method (**Fig. 14–2**) that moves one submandibular gland out of the radiation field into the submental space prior to radiation therapy is a promising new technique that is undergoing phase II trials.[21] The key to this technique is ensuring retrograde blood flow to the transferred gland through the facial vessels. Retrograde flow in the facial artery is assessed by ligating the proximal end just medial to the posterior belly of the digastric muscle and partially cutting the artery distal to the ligature. If there is no flow, the procedure is abandoned. If flow is observed, the facial artery and vein are ligated and cut just proximal to their branches supplying and draining the gland. This leaves the gland pedicled to the distal facial vessels via retrograde flow. The gland is then released from surrounding structures and repositioned in the submental space medial to the anterior belly of the digastric muscle after bisecting the mylohyoid muscle. The gland is anchored to the digastric muscle and periosteum of the mandible with absorbable sutures. The anterior, posterior, and inferior borders of the gland are marked with a 25-gauge wire for future radiation planning. The repositioned submandibular gland and nearby sublingual gland are shielded during radiation therapy. Use of this technique prevented xerostomia in 83% of 38 patients using objective and subjective measures of salivary flow in a long-term follow-up study.[22] This innovative approach, unfortunately, is limited to oropharyngeal tumors and cannot be used safely for oral cancers; recent long-term data on this procedure, though small in numbers, show promise for providing clinical relief in patients with oropharyngeal cancer without increased risk of regional tumor recurrence.[22] Due to the variability of primary tumor site, extension, and lymphatic drainage, no single preventive strategy is universally applicable to head and neck cancer patients; also, the procedure is best performed in large cancer centers where study of large cohorts can be applied. None of the methods described to prevent salivary gland damage, including amifostine, IMRT, and submandibular gland transfer, have shown long-term clinical efficacy in large studies, and their potential role in tumor recurrence remains unquantified at this time.

Acinar cell loss remains the underlying histopathologic correlate to the salivary hypofunction that is

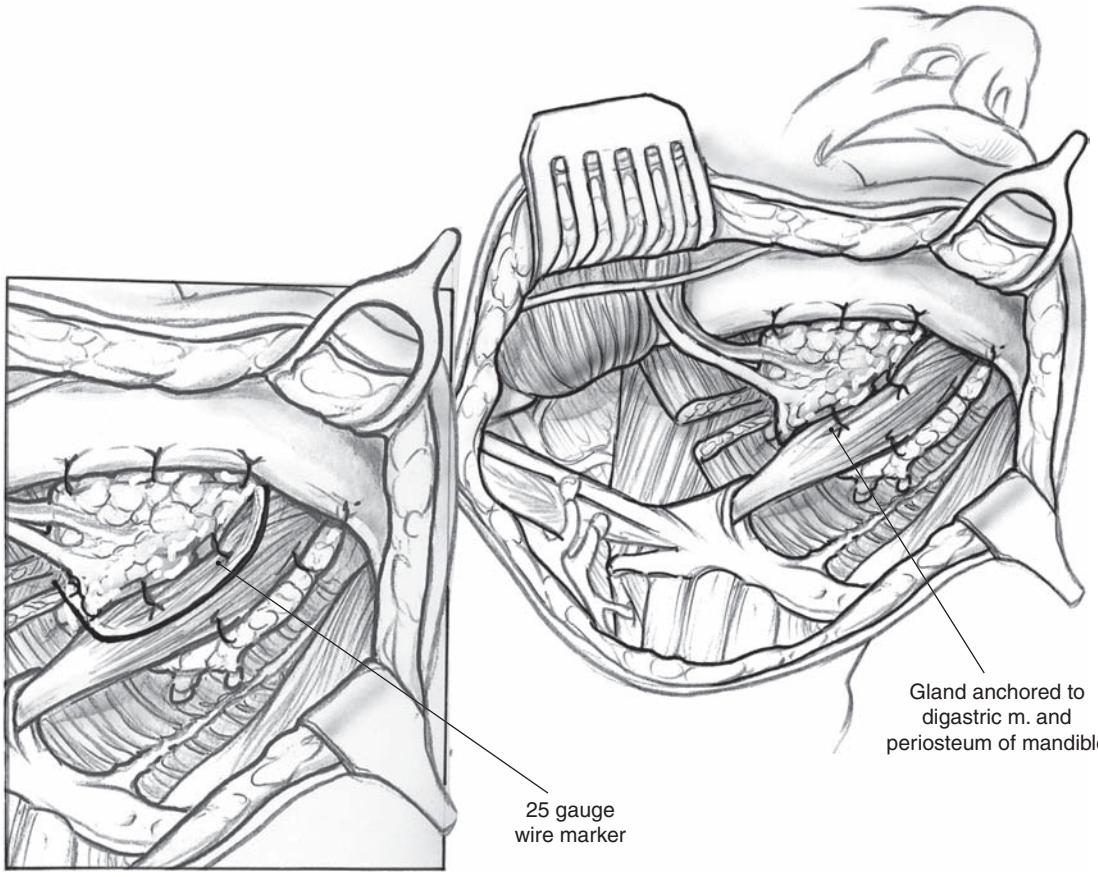

FIGURE 14–2 Submandibular salivary gland transfer.

seen in radiation-induced xerostomia. Pharmacologic strategies have fallen short of providing the ''magic bullet'' for this condition, but they remain the mainstay of treatment. Strategies that will be successful in treating this devastating condition in the future will recognize the critical need to perfect methods for preserving acinar cells and to develop methods for regeneration or replacement of cell loss.

Currently, no regenerative strategy has emerged in humans. It has been shown that the regenerative capacity of salivary tissue resides in the ductal epithelium[10,23] and that damaged acinar cells can be replenished by stem cells in the distal segments of the ductal segments that terminate at the acini.[24] Tissue reengineering strategies in the rat have employed adenoviral-mediated gene transfer of a water channel protein to these ductal cells and demonstrated the transformation of ductal epithelium into acinar cells with a measurable increase in saliva production by the transfected tissue. It is unknown whether irradiated target epithelium would transform into acinar cells in a human model.[25]

De novo tissue engineering of functional salivary gland tissue has recently been described as a potential physiologic solution to the problem of xerostomia.[26] The investigators in this study hypothesized that autologous human engineered salivary cells seeded on polymers could form functional tissues when implanted in vivo. Salivary epithelial cells were isolated from human salivary tissue, expanded in vitro, seeded on biodegradable polyglycolic acid polymer scaffolds, and implanted in athymic mice. These cultured epithelial cells retained their phenotypic and functional characteristics through all stages of subculture (> 7). Scaffolds were retrieved 2, 4, and 8 weeks after implantation, and all tissue constructs had formed a vascular supply and histologically recognizable acinar structures. Functional analysis using immunohistochemistry, Western blot, and reverse transcriptase polymerase chain reaction demonstrated amylase production by the engineered tissue as well as the presence of cytokeratin and aquaporin-5, a critical secretory water channel protein (**Fig. 14–3A–E**). Theoretically, patients undergoing radiation therapy for head and neck cancer could undergo autologous salivary gland tissue collection prior to radiation. Salivary epithelial cells could be isolated from this tissue, expanded in culture, seeded on biodegradable scaffolds, and transplanted back into the patient to serve as a continuous source of saliva.

In summary, radiation-induced xerostomia is a devastating complication of radiation and chemoradiation therapy for head and neck cancer. Current treatment methods are palliative in most cases, and preventive strategies are the best clinical approach at this time because these techniques limit acinar cell loss. Improved understanding of the regenerative capacity of salivary

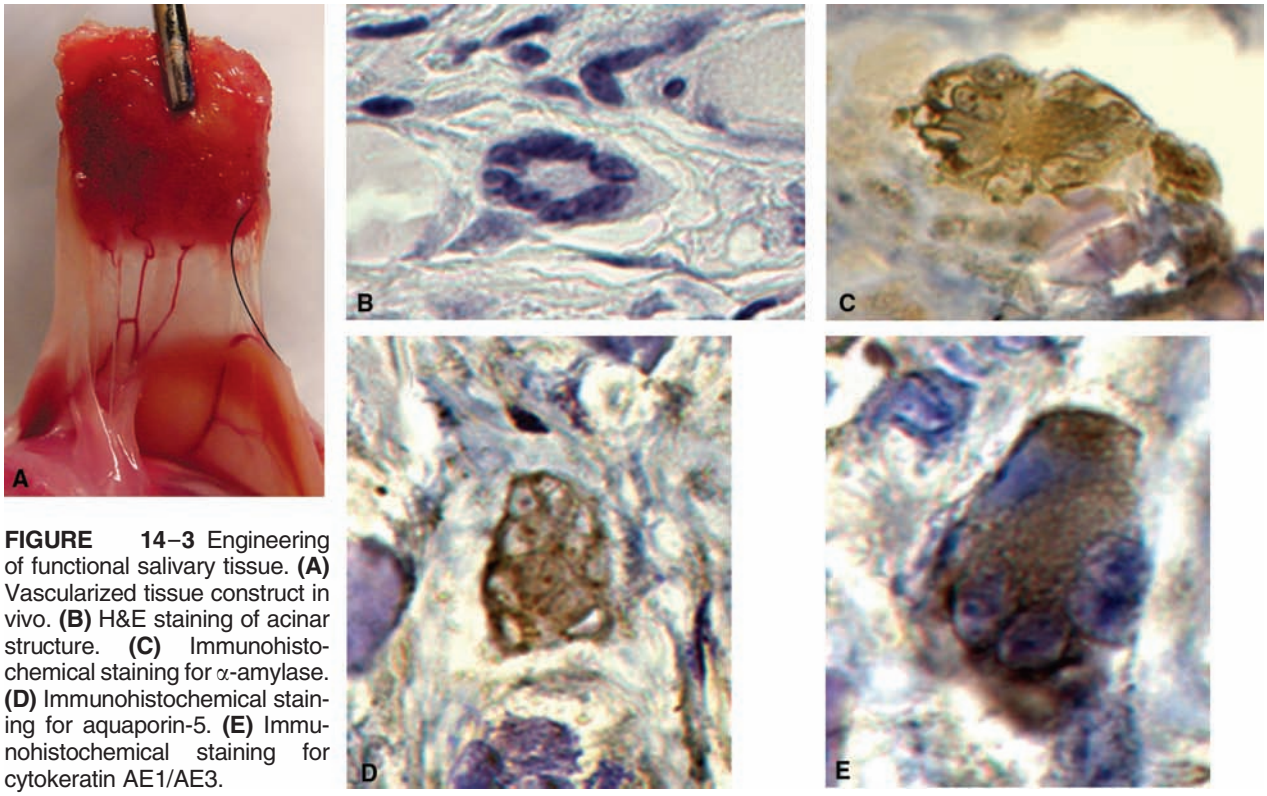

FIGURE 14–3 Engineering of functional salivary tissue. **(A)** Vascularized tissue construct in vivo. **(B)** H&E staining of acinar structure. **(C)** Immunohistochemical staining for α-amylase. **(D)** Immunohistochemical staining for aquaporin-5. **(E)** Immunohistochemical staining for cytokeratin AE1/AE3.

tissue as well as the pathophysiology of radiation damage has led to innovative new research that may in turn lead to the development of new clinical solutions to this problem.

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15

Atlas of Salivary Gland Surgery

SNEHAL G. PATEL

Surgical resection is the most commonly employed treatment modality for tumors of the salivary glands. Safe and effective surgery of the salivary glands is dependent on a detailed knowledge of anatomical relationships in the head and neck and requires precise surgical technique. Surgical anatomy is described in Chapter 1, but pertinent details will be highlighted where appropriate in the following description of surgical technique. The primary goal of surgical therapy obviously is treatment of the disease, but the greatest emphasis must be placed on preservation of function. Examples of potential functional consequences of surgical resection include facial nerve dysfunction after surgery for parotid gland tumors and dysfunction of the lower cranial nerves after surgery for tumors of the parapharyngeal space. These nerve deficits can markedly impact the patient's quality of life, and therefore a great deal of consideration must be given before deliberate sacrifice of a functioning nerve. As a general rule, elective resection of a functioning nerve can be justified only if there is direct infiltration by a malignant tumor, and if the involved nerve is the only anatomical site precluding total resection of the tumor. Rehabilitation of patients after nerve section can be difficult, and this issue is addressed in Chapter 16. The reader is referred to Chapters 9 and 10 for a detailed discussion on the decision-making process in the treatment of salivary gland tumors. The focus of this chapter will be to describe in some detail the most commonly indicated surgical procedures for the management of parotid, submandibular, parapharyngeal, and minor salivary gland tumors. The technical details of ancillary surgical procedures such as neck dissection and its various modifications, sentinel node biopsy for intraparotid nodes, temporal bone resection, and combined craniofacial resection are beyond the scope of this chapter and have been well described elsewhere.[1]

■ Surgery of the Parotid Gland

The decision for surgical excision of a tumor of the parotid gland is mainly undertaken based on the extent of the tumor and the patient's medical fitness for the procedure. Advanced, surgically unresectable malignant tumors are treated with external beam radiation or combined chemoradiation therapy. All other tumors are amenable to resection using one of the procedures listed in **Table 15–1**. The aim of surgical resection is to achieve complete resection of the tumor, and the amount of normal parotid gland removed in the process is largely dependent on the location of the tumor within the gland and its relationship to the branches of the facial nerve. Although the nature of the tumor may influence the extent of resection in some instances, this decision is generally based on the clinical and/or radiologic findings.

The role of diagnostic imaging (Chapter 2) in the evaluation of tumors of the parotid gland has been debated extensively. Preoperative ultrasonography, computed tomography (CT), or magnetic resonance imaging (MRI) rarely alters the management of small tumors of the superficial parotid lobe.[2] Assessment of large parotid tumors, tumors with decreased mobility, tumors

TABLE 15–1 The Nomenclature of Surgical Operations for the Parotid Gland

Superficial parotidectomy
Limited (partial) superficial parotidectomy
Extracapsular dissection
Deep lobe parotidectomy
Accessory parotid resection
Radical parotidectomy
Extended radical parotidectomy

of the deep lobe, patients with preoperative facial nerve dysfunction (rare with benign tumors), and recurrent tumors is enhanced by imaging.

Evaluation of the third dimension of the tumor and its relationship with the plane of the facial nerve is helpful in planning surgery and counseling patients in selected situations. It is also useful in certain situations to determine the relationship of tumor or residual parotid tissue to the plane of the facial nerve. Radiologic demonstration of normal-appearing parotid tissue at the deep margin of a residual or recurrent superficial lobe tumor following previous surgery may provide some assurance that the tissue planes around the nerve are intact. Imaging can also be helpful to evaluate the status of the regional lymph nodes if a malignant tumor is suspected.

Fine-needle aspiration cytology (FNAC) is a simple technique that can provide diagnostic information in selected circumstances (**Fig. 15–1**). Martin and Ellis at Memorial Sloan-Kettering Hospital introduced FNAC in the United States for cancer and allied diseases in 1930,[3] with subsequent interest in salivary gland needle biopsy reported from the Karolinska Institute in Stockholm.[4] It became popular in the United States in the mid 1970s. The first goal of FNAC is to determine the presence or absence of neoplasm, secondly to determine if the neoplasm is benign or malignant, and lastly to define the exact type of tumor present. CT-guided fine-needle aspiration can be helpful for nonpalpable lesions. Seeding of the needle tract with an appropriate-sized needle is extraordinarily unlikely.

Many surgeons do not perform fine-needle aspiration in the evaluation of a salivary gland mass, arguing effectively that all salivary gland masses require resection to exclude neoplasm and that the extent of surgery can be defined based on clinical judgment. Benign as well as low-grade, low-stage tumors of the superficial lobe of the parotid are adequately treated by a limited resection.

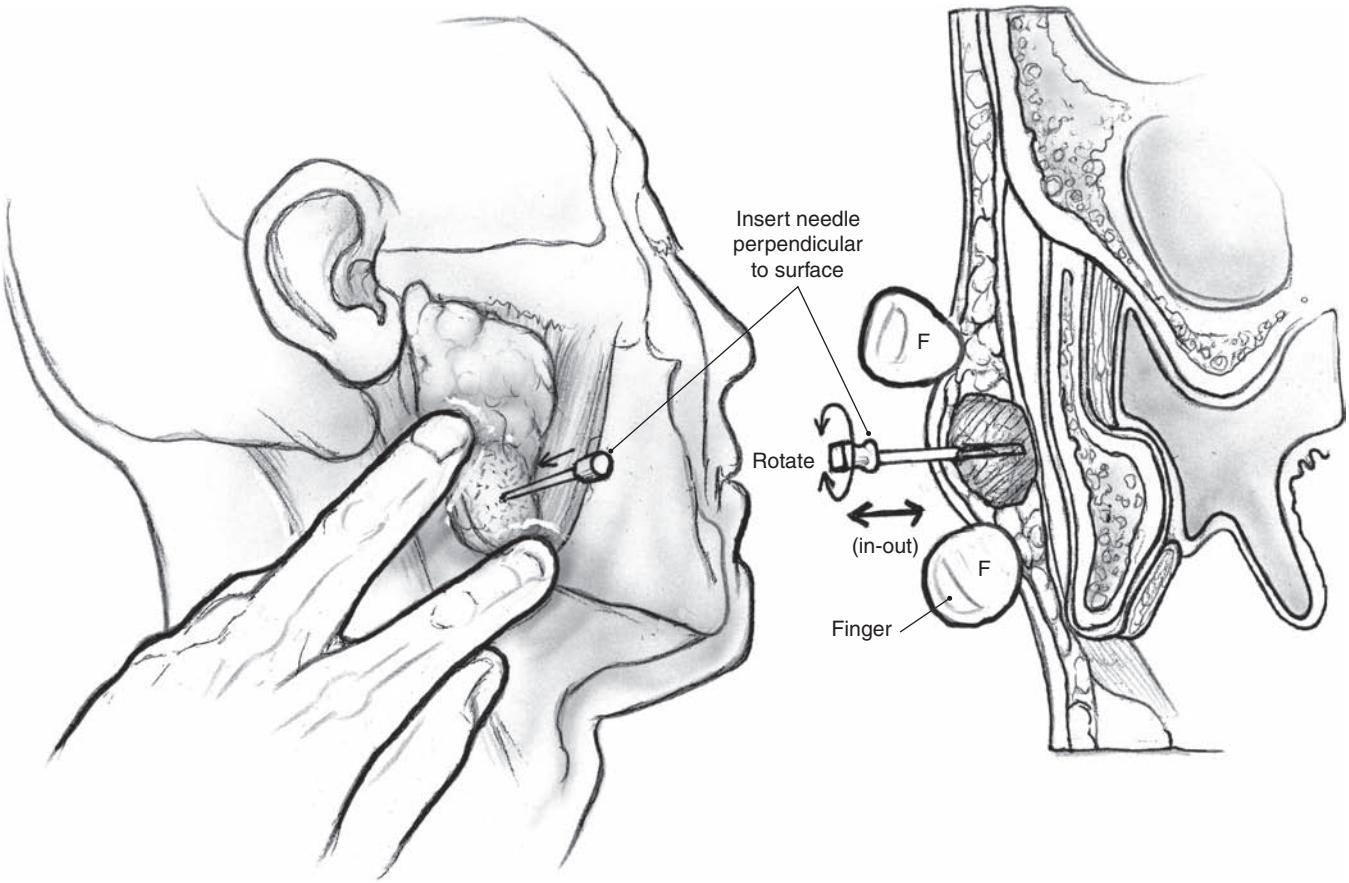

FIGURE 15–1 The technique of fine-needle aspiration cytology (FNAC) for a tumor of the parotid gland.

Higher grade, high-stage tumors need more extensive resection. These attributes of the tumor can almost always be reliably estimated on clinical and/or radiologic examination.

However, fine-needle aspiration can often distinguish between lesions of salivary gland and nonsalivary origin. The sensitivity to the presence of a neoplasm and the specificity to the absence of a neoplasm are as high as 98% with fine-needle aspiration.[5] If of salivary gland origin, aspiration can usually define benign versus malignant and can frequently make a specific diagnosis.[6] Distinguishing between benign and malignant tumors approaches 90% in most series, with overall accuracy as high as 97%.[5] Determining the exact diagnosis of a salivary gland mass can be as high as 70% in the hands of a very experienced salivary gland cytopathologist. Distinction between salivary tumors and lesions of nonsalivary origin, and between benign and malignant neoplasms, is useful in planning therapy.[7] A cytological diagnosis of malignancy is certainly helpful in preoperative counseling, and the surgeon may be able to alert the patient that operative findings dictate sacrifice of the facial nerve. The proliferation of highly trained cytopathologists and advancements in immunohistochemistry have made fine-needle aspiration an important consideration, but the breadth of histological subtypes in salivary gland tumors continues to make specific preoperative cytological diagnosis a formidable goal.

The key to successful FNAC is immediate evaluation of the specimen for adequacy. Immediate interpretation of the cytological specimen by a well-trained cytopathologist can lead to focused studies such as flow cytometry to exclude lymphoma. The experience of the cytopathologist, the person performing the FNAC, and the preparation of the slides are all factors in the accuracy of the procedure. The immediate evaluation of FNAC can be an obstacle for the non-hospital-based clinician, who would require scheduling the procedure at the hospital. For medical-legal reasons, many cytopathologists do not perform fine-needle aspiration, signifying that in some settings the patient's time, the cytopathologist's time, and the clinician's time would have to be scheduled. FNAC for salivary gland lesions must be decided by the surgeon on a case-by-case basis.

The superficial lobe contains the bulk of the volume of the parotid gland, so that most tumors arise from this part of the gland. Superficial parotidectomy or partial superficial parotidectomy is therefore the most common surgical resection required in the treatment of parotid tumors. Superficial parotidectomy is described in detail because the technique of this operation should be used as the basis for any lesser resections that might be possible depending on the location of the tumor within the gland. Partial superficial parotidectomy is safe in selected situations, and proponents of its routine use point to the fact that a substantial proportion of tumors resected by a complete superficial parotidectomy will have exposure of the tumor capsule where the tumor has been dissected off the facial nerve or its branches.[8,9] Local recurrence rates after superficial parotidectomy are dramatically lower with partial or complete superficial parotidectomy compared with those after the tumor has been enucleated without formal dissection of the facial nerve. There is a menu of procedures such as extracapsular dissection (ECD) and partial superficial parotidectomy (PSP) that are available to the surgeon between the extremes of enucleation and superficial parotidectomy (see Chapter 9). Enucleation of a parotid tumor, even if it is obviously benign, results in unacceptably high rates of local recurrence and should not be practiced. There is considerable literature on the relevance of ECD in the management of parotid tumors, but this author does not personally prefer the procedure.

Another area of controversy in surgical technique involves the role of monitoring of the facial nerve. Successful dissection and preservation of the facial nerve and its branches in a previously unviolated surgical field depend largely on the surgeon's technical expertise and familiarity with surgical anatomy. The surgeon can use the nerve monitor (or disposable nerve stimulator) to demonstrate intact function of the dissected nerves at the conclusion of parotidectomy. Facial nerve monitoring for primary cases of mobile parotid tumors of the superficial lobe, less than 4 cm in size, has been reported not to reduce the risks of permanent or transient facial nerve dysfunction.[10] Other retrospective series have shown a lower rate of facial nerve dysfunction with facial nerve monitoring.[11,12] A threshold of intraoperative facial nerve stimulation has not been identified that would predict postoperative facial nerve function.[13] Facial nerve monitoring should be encouraged in a teaching institution, for large, fixed tumors, deep lobe tumors, or recurrent tumors. It has not been proven to reduce facial nerve injury.

Certain intraoperative maneuvers are quite helpful in facilitating the safe conduct of surgery for parotid tumors irrespective of the extent of resection of the gland. An oral endotracheal tube is generally adequate for routine parotidectomy. However, the extra excursion of the jaw that is possible with the use of a nasotracheal tube can be very helpful during surgery for tumors of the deep lobe of the parotid. Precise dissection of the facial nerve requires a bloodless field. In addition to hypotensive anesthesia during nerve dissection, parotid surgery should be carried out with the patient in a reverse Trendelenburg's position. Adequate extension of the neck is imperative if neck dissection is planned or anticipated. The face and the neck are draped with a transparent plastic drape to allow monitoring of

movement of facial muscles. Communication with the anesthesiologist is crucial**.** A short-acting muscle relaxant permitting facial muscle motion on stimulation of the facial nerve is important whether or not intraoperative facial nerve monitoring is used. The perception that the eyelids on the side of the procedure need to be monitored during facial nerve dissection can result in exposure of the cornea with potentially disastrous results. A water-soluble eye ointment should be applied, and the cornea must be protected with a corneal shield, or the eyelids can be loosely taped shut with clear tape.

Superficial Parotidectomy

Superficial parotidectomy can be defined as excision of parotid tissue that lies lateral to the plane of the facial nerve and its branches. Most benign and malignant parotid tumors can be adequately treated with this procedure. Obviously, patients who have clinical evidence of infiltration of the facial nerve are not suitable for this operation.

No specific preoperative preparation is necessary, but patients must be counseled about complications such as temporary and permanent damage to the facial nerve, numbness, gustatory sweating, seroma, hematoma, and cosmetic changes.

The skin incision for superificial parotidectomy shown in **Fig. 15–2** is designed to provide adequate exposure for surgical resection and optimal healing for a good cosmetic outcome. A suitable preauricular skin crease is used in older patients, and the incision then curves around the lobule of the ear to turn anteriorly along an appropriately located upper neck skin crease. If a preauricular skin crease is not easily identifiable, especially in young patients, the upper part of the incision is placed just inside the free anterior border of the tragus of the ear (**Fig. 15–3**). The preauricular skin incision is taken, and the skin is carefully elevated off the tragal cartilage using fine skin hooks and a no. 15 scalpel blade. Alternatively, the use of a fine needle tip electrocautery for the skin incision leads to a postoperative scar comparable to scalpel dissection and simultaneously provides initial hemostasis. Because of the heightened risk to the facial nerve, aggressive use of electrosurgical instrumentation is otherwise eschewed. The anterior skin flap is elevated, keeping the plane of dissection between the subcutaneous fat on the undersurface of the flap and the dense parotid fascia (**Fig. 15–4**).

As dissection proceeds anteriorly and past the angle of the mandible, the uppermost fibers of the platysma muscle are divided in the direction of the skin incision, and the flap is now elevated just deep to the platysma. Dissection of the flap with a fine mosquito hemostat,

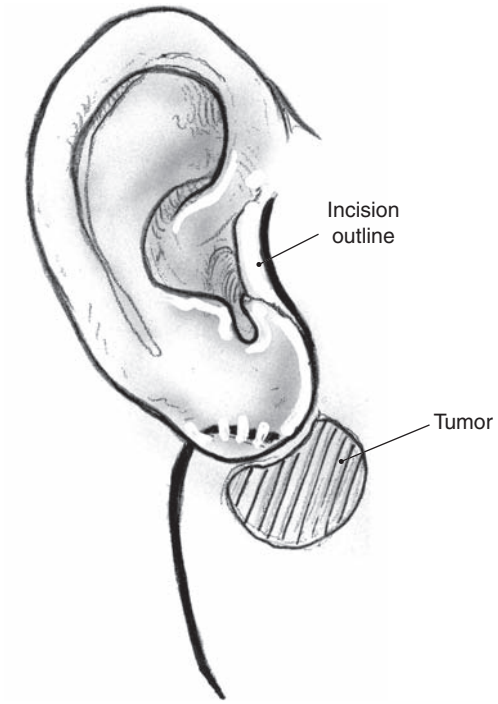

FIGURE 15–2 The incision follows skin creases in the preauricular region and the upper neck.

bipolar cautery, and plastic scissors is an atraumatic, hemostatic technique that is suggested. New and alternative dissection techniques include laser-cutting technologies, ultrasound scalpels,[14] water-jet dissection, and diathermy scissors.[15] The peripheral branches of the facial nerve exit the anterior aspect of the parotid gland and are liable to injury during this phase of the operation. The skin flap is now dissected posteriorly to expose the cartilaginous auditory canal, the mastoid tip, and the upper portion of the sternocleidomastoid muscle. At this stage, elevation of the skin flaps for surgical exposure is complete, and the next phase of the operation is aimed at displaying anatomical landmarks in preparation for identification of the main trunk of the facial nerve. Magnification can be helpful for this portion of the procedure. The fascia covering the muscle is incised parallel to its anterior border to retract the muscle posteriorly and the adjacent parotid tissue anteriorly (**Fig. 15–5**).

The greater auricular nerve runs along the upper portion of the sternocleidomastoid muscle to enter the superficial portion of the parotid gland on its way to the overlying skin. Preservation of the posterior branches of the greater auricular nerve, without compromising the surgical exposure or risk of recurrence, is possible in many cases. This will result in potentially diminished ear lobular and angle of the mandible numbness postoperatively. The greater auricular nerve, however, occasionally needs to be sectioned in order to mobilize the parotid gland off the sternocleidomastoid muscle. Fortunately,

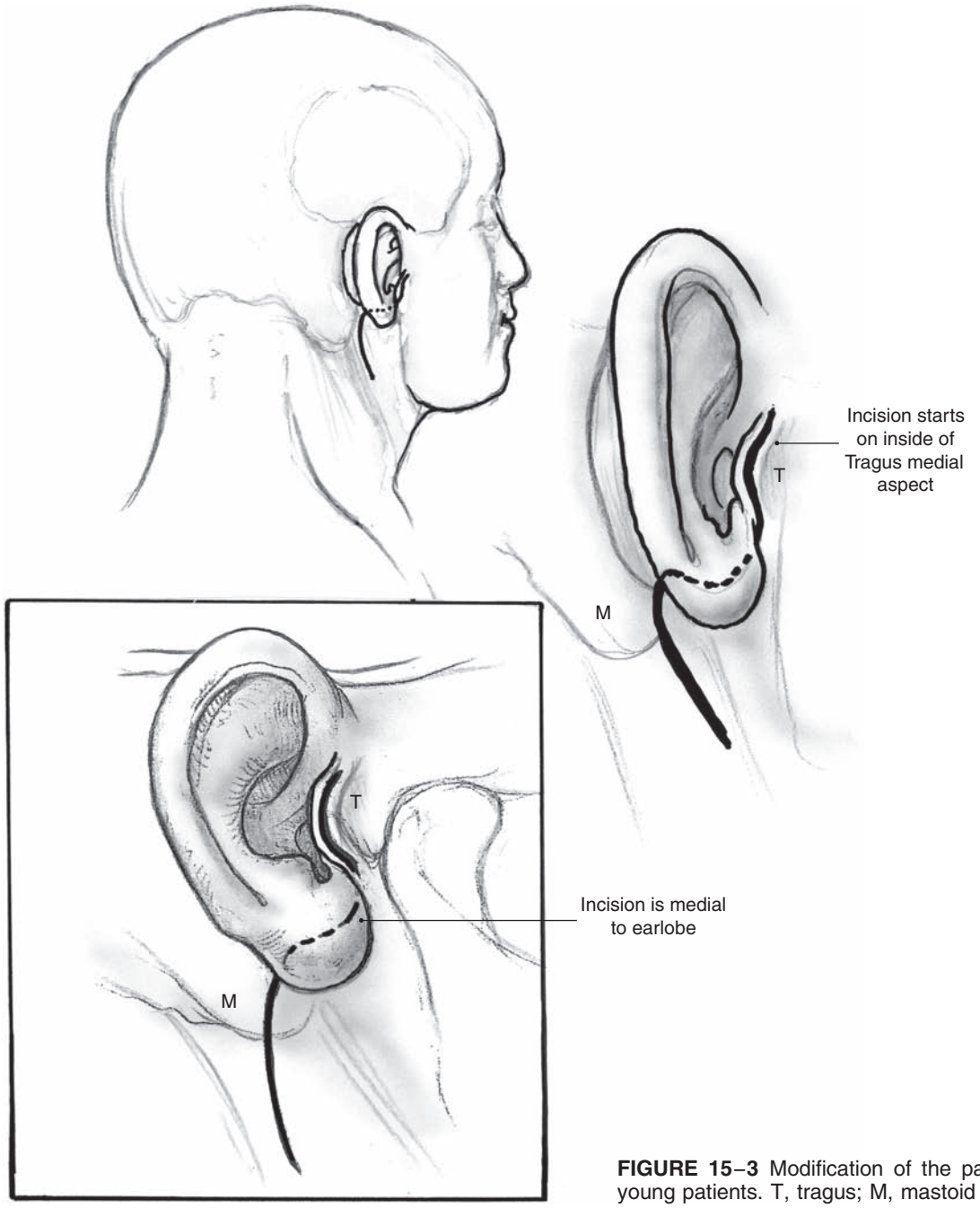

FIGURE 15–3 Modification of the parotidectomy incision in young patients. T, tragus; M, mastoid process.

most patients do not report significant symptoms associated with sacrifice of this nerve.[16] It is good practice to divide the greater auricular nerve close to the lower border of the parotid gland, keeping well clear of any tumor in order to preserve as much length as possible in case the need for cable grafting arises. The posterior belly of the digastric muscle can now be displayed by dissecting off the parotid tissue from the sternocleidomastoid muscle (**Fig. 15–6**). Dissection continues in a cephalad direction in the plane between the auditory canal and the posterior aspect of the parotid gland. This final preparatory step for dissection and identification of the main trunk of the facial nerve must be undertaken with great caution to avoid inadvertent injury to the facial nerve. Careful blunt dissection with a fine hemostat and judicious use of the bipolar cautery allow the surgeon to clearly delineate the posterior belly of the digastric muscle all the way to its insertion into the digastric groove of the mastoid process.

Two deep right-angled retractors are used to gently retract the parotid gland in an anterior direction so that the parotid tissue overlying the main trunk of the facial

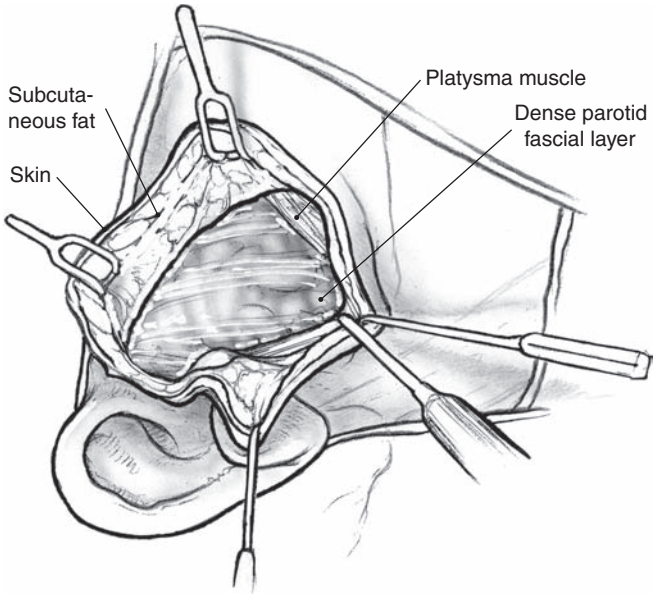

FIGURE 15–4 Elevation of the anterior skin flap.

nerve is put on stretch (**Fig. 15–7**). At this stage it is useful to review the regional anatomical landmarks that aid the safe identification of the main trunk of the facial nerve (see Chapter 1, **Fig. 1–5**). The main trunk of the facial nerve enters the parotid gland high on its posteromedial surface, and its branches travel in an oblique plane to surface at the anterior border of the gland. Certain anatomical structures in the region can be relied upon to guide the dissection of the nerve. The main trunk of the nerve is situated in the notch formed by the superior edge of the posterior belly of the digastric muscle, the anterior border of the mastoid tip, and the

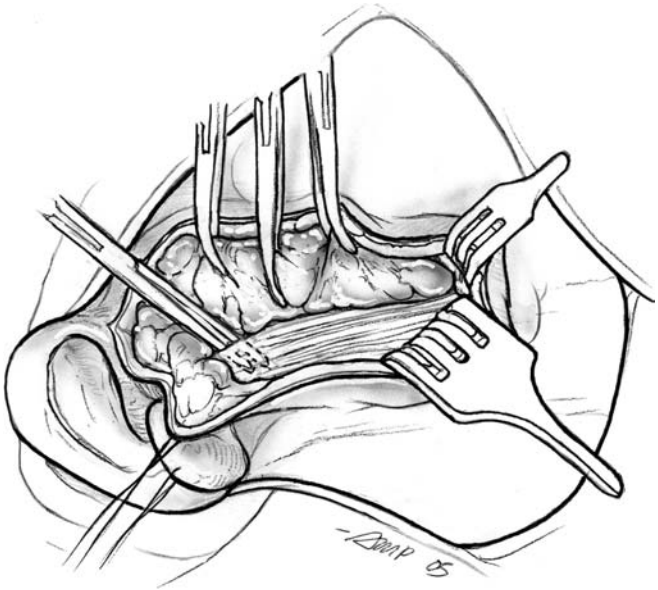

FIGURE 15–5 Dissection of the anterior border of the sternocleidomastoid muscle.

inferior border of the auditory canal. A long, curved hemostat is used to gently spread the tissue in this region along the direction of the nerve (**Fig. 15–8**). This part of the dissection is best carried out in small increments, ensuring absolute hemostasis before the next tissue plane is dissected. As a general rule, a small blood vessel that runs parallel and immediately superficial to the nerve serves to alert the surgeon of its proximity.

An alternative approach to identification of the facial nerve is utilizing the tympanomastoid suture (see Chapter 1, **Fig. 1–6**). This can provide for the experienced surgeon a single landmark approach to the parotid. The tragal pointer has a blunt and variable tip that can change with retraction and lies 1 to 2 cm from the facial nerve.[17,18] It only points to the facial nerve in 20% of cases.[18] The styloid process is deep to the facial nerve and if used to identify the facial nerve risks injury to this nerve. The tympanomastoid suture provides the advantage over other anatomical landmarks in being a fixed landmark with less variability as can be seen with a muscle landmark such as the posterior belly of the digastric. It is a closer anatomical landmark to the facial nerve compared with the posterior belly of the digastric muscle. The tympanomastoid suture is invariably 1 to 3 mm inferior to the pes anserinus of the facial nerve in comparison with 0.5 to 1.5 cm for the posterior belly of the digastric muscle. Some surgeons are uncomfortable with this landmark because it is a palpated and not a visualized landmark like the posterior belly of the digastric muscle.

The retrograde approach to identification of the facial nerve utilizes the retromandibular and/or superficial temporal veins in exposing the marginal mandibularis branch and temporalis branches of the facial nerve, respectively.[19,20] The retrograde approach has largely lost favor because of the variability of the peripheral facial nerve branches including their position at times deep to the venous structures.[21] Most variations of the facial nerve occur distal to the bifurcation of the main trunk of the facial nerve, distal to the pes anserinus. The main trunk is the most consistent portion of the nerve.[22] The retrograde approach continues to be advocated for revision surgery where scar tissue impedes dissection of the facial nerve and for large, bulky tumors that may obstruct visualization of the main facial nerve trunk.

After the main trunk of the facial nerve has been clearly identified, the objective of the next part of the procedure is to dissect its branches and in the process excise the superficial lobe of the parotid gland along with the tumor. This phase of the procedure requires adequate exposure and absolute hemostasis for its safe conduct. It must be reiterated here that the patient should be in a reverse Trendelenburg's position, and

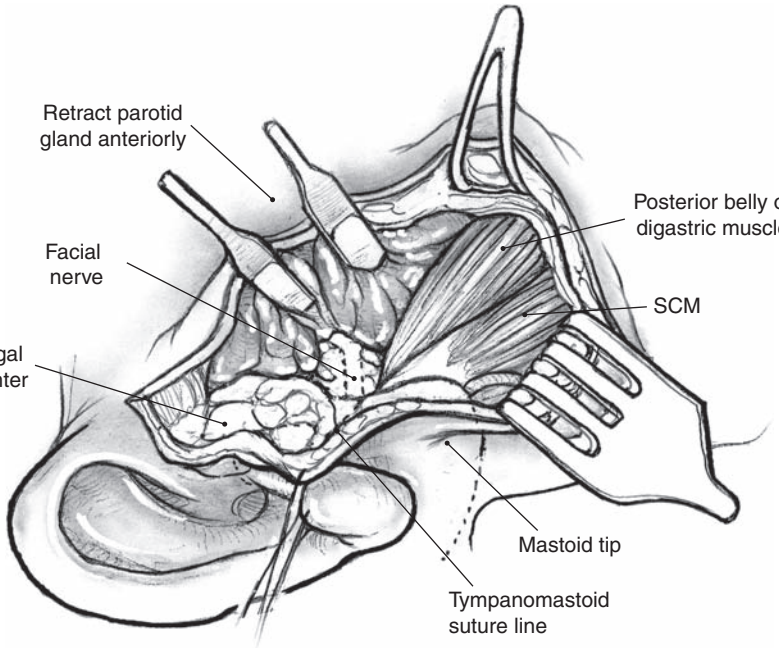

FIGURE 15–6 The posterior belly of the digastric muscle can be displayed by dissecting the posterior border of the parotid gland from the sternocleidomastoid (SCM) muscle.

the anesthesiologist must provide hypotensive anesthesia maintaining the systolic blood pressure around 90 mmHg. The tip of a long, curved hemostat is inserted along the direction of the nerve being dissected, between its superficial surface and the overlying parotid tissue (**Fig. 15–8**). Troublesome bleeding can increase the risk of inadvertent damage to the nerve if the plane of dissection is not maintained directly on the surface of the nerve being dissected. The tip of the hemostat is then lifted up away from the underlying nerve, and the bridge of parotid tissue between the prongs is sharply divided with Reynold's scissors. Bleeding from fine vessels in the divided parotid gland is controlled with bipolar coagulation. Bigger vessels are clamped using fine-tip hemostats and ligated carefully with 4.0 chromic catgut. The main trunk of the nerve is dissected in this manner until its bifurcation becomes visible. Although the main trunk is usually 1 to 3 cm in length, it may be longer if the nerve has been put to stretch by an underlying tumor. The dissection now proceeds in this plane superficial to the nerve so that its divisions and branches are clearly identified. In terms of the sequence of dissection of the divisions of the nerve, dissection of the tumor-bearing half of the superficial lobe is

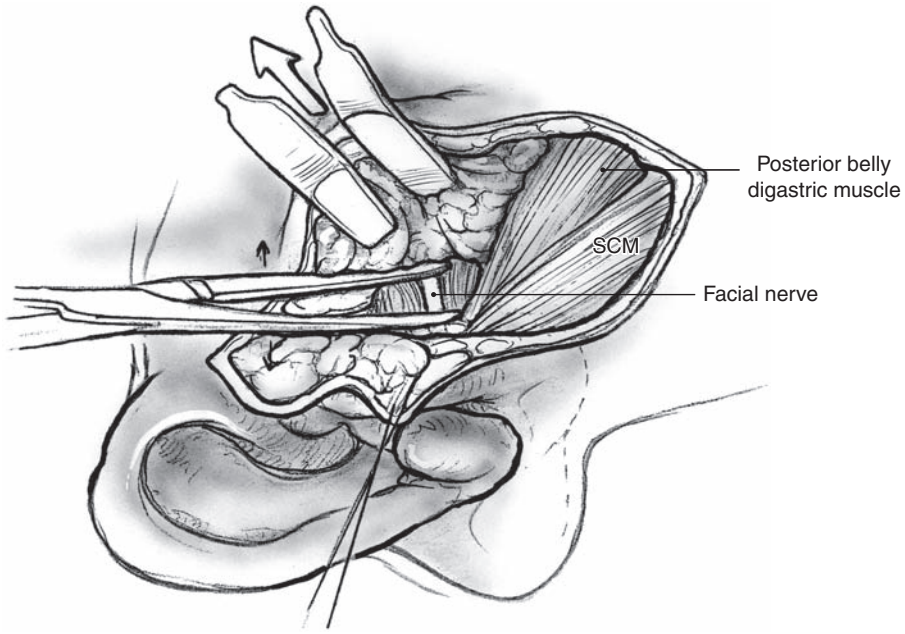

FIGURE 15–7 Gentle retraction with two right-angled retractors provides surgical exposure for dissection of the facial nerve. SCM, sternocleidomastoid muscle.

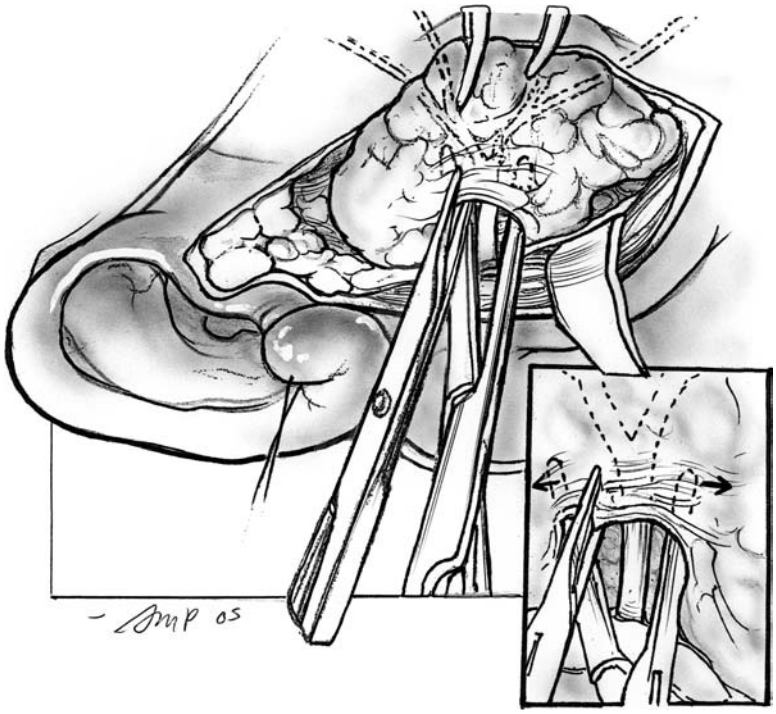

FIGURE 15–8 Dissection of the branches of the facial nerve.

generally completed after the normal gland has been dissected. As the dissection proceeds toward the periphery of the parotid gland, it is important to remember that the nerves run in an oblique deep-to-superficial plane in the posterior-to-anterior direction so that the fine, peripheral branches are at risk of injury. This is especially true for the buccal branches that course parallel to Stensen's duct in the region of the cheek. The duct is carefully dissected free from any adjoining nerves, divided sharply, and its stump is ligated with 3-0 chromic catgut (**Fig. 15–9**).

After delivering the specimen, complete hemostasis must be secured. It is important to reverse hypotension before proceeding to close the surgical wound. Drainage of the surgical bed is achieved by a Penrose drain or closed suction drainage. Closed suction drainage should ensure the tip of the drain is secured away from any branches of the dissected facial nerve. A closed suction drain coupled with absorbable packing over the surgical bed can obviate the need for a compression dressing, providing surveillance for hematoma, and can invariably be removed the following day without risk to the facial nerve. The wound is irrigated with dilute antibiotic solution in saline, and hemostasis is confirmed. The incision is then closed in two layers with interrupted, inverting 3-0 chromic catgut sutures to approximate the subcutaneous tissue, and the skin is closed with interrupted 4-0 nylon sutures or an absorbable subcuticular suture. The suture line is cleaned, and a light film of antibiotic ointment is applied. If a Penrose drain is used, the wound is covered with light dressing held in place with tube gauze. A suction drain does not require a dressing. The patient requires no special postoperative care, and the Penrose drain or suction drain is removed the next day as soon as the discharge tapers out.

Complications of parotidectomy are listed in **Table 15–2**. The most dreaded complication is loss of function of the facial nerve or its branches. Management of this problem is difficult and is discussed in detail in Chapter 16. Temporary functional derangement, including paresis, is not infrequent and is generally unpredictable. However, temporary paresis may be expected when the tumor has been dissected off the nerve. In the absence of overt injury to the nerve, recovery of function generally occurs within 3 months.

Secondary hemorrhage and hematoma formation are often preventible complications. Once the need for surgical exploration of the wound and evacuation of the hematoma is determined, the procedure must be undertaken in the operating room under general anesthetic. It is useful to ensure that the patient's blood pressure is in the normal preoperative range while the wound is being explored. The entire incision must be opened to provide maximal exposure, and it must be emphasized that attempts at limited exploration can result in injury to the facial nerve. After evacuating the hematoma, copious amounts of warm saline are used to irrigate the wound. The greatest caution must be exercised to avoid injuring the facial nerve or its branches during evacuation of the hematoma and attempts at hemostasis. The surgical team must resist the temptation to use the suction cannula in the region

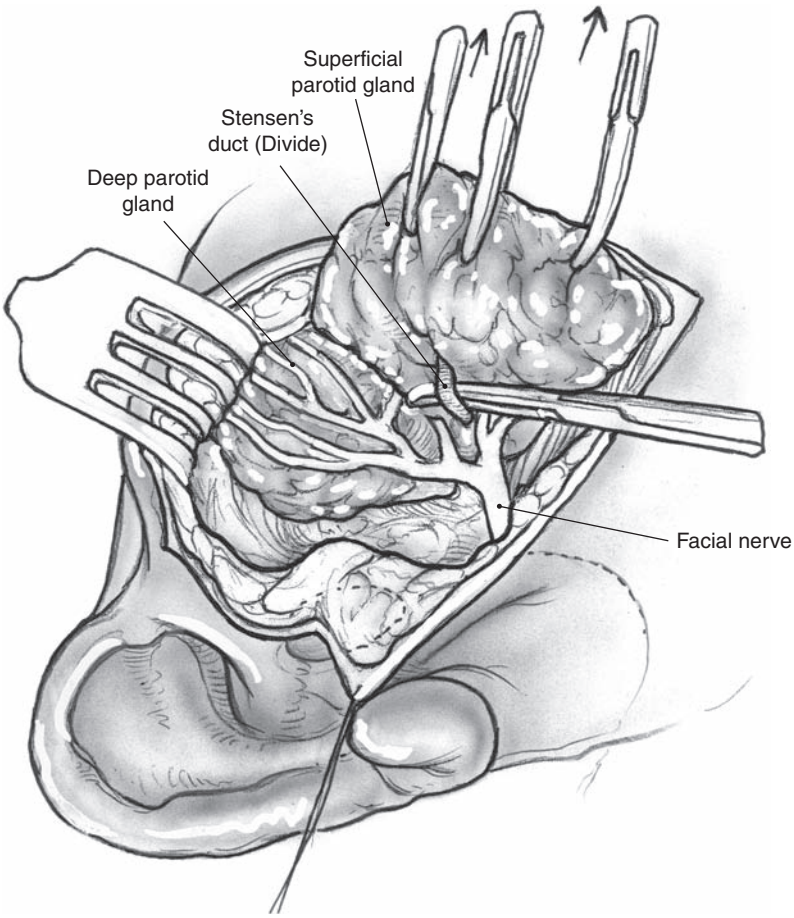

FIGURE 15–9 Dissection and division of Stensen's duct.

of the parotid bed during the exploration. The offending vessel is generally located on the cut surface of the remnant parotid tissue or may be a branch of the retromandibular vein. Before hemostasis is attempted, the relationship of any bleeding vessel to the facial nerve branches must be precisely identified. Fine-tipped micro-hemostats are used, and the bleeding vessel must be carefully ligated. After ensuring hemostasis, the incision is reapproximated in the usual fashion over a Penrose or suction drain.

Sialoceles can occur after parotid surgery and can also be seen after penetrating parotid injury. A sialocele is a discrete collection of saliva, either within a duct (and thus here represents a retention cyst) or after trauma or other disruption of the gland (and here is not present in an epithelial-lined space but is rimmed by an inflammatory reaction, a pseudocyst). Treatment is almost always effective with serial aspiration or even observation alone. Resolution occurs in 4 to 6 weeks. Antibiotics covering *Staphylococcus aureus* can be used in the initial time period. An external salivary fistula can occasionally develop, which also usually resolves spontaneously. The very rare resistant case has been treated with oral anticholinergics, tympanic neurectomy, and more recently botulinum toxin.[23]

Numbness after parotidectomy generally recedes after 6 months. Even with preservation of the posterior branch of the greater auricular nerve, patients can still have lobular and angle of mandible skin numbness and must be thus advised.

Reconstruction of the postparotidectomy defect can be performed using AlloDerm (Life Cell, The Woodlands, TX).[24] An inferiorly based platysma muscle–cervical fascia–sternocleidomastoid muscle flap[25] or sternocleidomastoid muscle transposition flap after parotidectomy can also be used to improve the cosmetic result.[26] In the latter procedure the muscle must be freed from its mastoid and skull base attachments with inferior dissection until rotation of the flap is possible to reach the zygomatic arch superiorly and

TABLE 15–2 The Complications of Superficial Protidectomy

Acute	Paresis or paralysis of facial nerve or its branches
	Bleeding or hematoma
	Seroma
	Salivary fistula
Late	Sensory deficits
	Cosmetic deformity
	Frey's syndrome

masseter muscle anteriorly, where it is sutured.[27] This technique, like other interposition flaps, will not prevent Frey's syndrome. Its use must be balanced with the significant risk of masking recurrent disease, additional operative time, trauma to the greater auricular nerve, and the observation that many patients will not complain of the defect even after total parotidectomy.[27]

Frey's syndrome is another late complication of parotid surgery. Lucie Frey, whose patient was a Polish soldier treated for a typhoid abscess of the parotid gland, published her classic report of gustatory sweating in 1923.[28] Frey's syndrome (gustatory sweating) results from abnormal neural connections between parasympathetic cholinergic nerve fibers of the parotid gland, with severed sympathetic cholinergic receptors innervating sweat glands and vessels of the face, and manifests as gustatory sweating, facial flushing, a sensation of warmth over the preauricular and temporal area, and piloerection. Most cases develop from parotid surgery, although neck dissection, thoracocervical sympathectomies, and submandibular gland resection can also cause Frey's syndrome.[29] Frey's syndrome is objectively assessed by Minor's starch-iodine test, where a solution of iodine, castor oil, and absolute alcohol is applied to a patient's cheek and then dusted with starch powder. Almost all patients subjected to Minor's starch-iodine test will exhibit signs of Frey's syndrome, but only 15 to 25% report subjective symptoms to their physician.[30,31] Infrared thermography is a noninvasive test that provides a qualitative visual analysis of the cutaneous capillary response in Frey's syndrome.[32]

The incidence of Frey's syndrome is reportedly dependent on the amount of normal parotid parenchyma dissected: total parotidectomy (47%), superficial parotidectomy (17%), and partial superficial parotidectomy (10%).[9] Many treatments have been proposed for Frey's syndrome. Thickness of the flap has not correlated with patient symptoms. Application of topical 20% aluminum chloride solution has met with little success and poor compliance, as has atropine or application of scopolamine hydrobromide ointment before meals. Fat and fascia lata interpositions have failed to reduce gustatory sweating.[33] The sternocleidomastoid muscle flap has been promoted to reduce the incidence of Frey's syndrome in one report, but refuted in another.[34,35] Limited success has been achieved with tympanic plexus neurectomy.[31] Botulinum toxin is being used increasingly, blocking the release of acetylcholine at the neuromuscular junction and peripheral cholinergic nerve terminals, and preventing neurotransmission.[36]

Partial Superficial (Limited) Parotidectomy

Selected tumors in certain locations within the parotid gland are easily amenable to partial superficial parotidectomy (see Chapter 9, **Fig. 9–7**). The surgeon must be able to visualize the relationship of the tumor to the underlying branches of the facial nerve clearly. These relevant branches do need to be identified and preserved during the operation. The surgical operative steps of this limited procedure are therefore identical in principle to superficial parotidectomy, but the dissection is limited to only part of the gland. As in complete superficial parotidectomy, the facial nerve is dissected distally from just beyond the pes anserinus to the proximal offshoots of the nerve branches with a fine plastic hemostat, bipolar cautery, and plastic scissors. If the tumor is located in the tail of the parotid gland, as frequently occurs, the marginal mandibular branch of the facial nerve and the inferior branches of the buccal branches are dissected distally. No further dissection of the frontozygomatic branches is executed beyond the previously mentioned proximal exposure. For tumors located more superiorly, more distal dissection of the marginal mandibular branch is avoided. Two centimeters of normal parotid gland is obtained around the tumor, except where it abuts the facial nerve or superficial fascia. Expected rates of transient facial nerve dysfunction and subjective Frey's syndrome are 20% and 10%, respectively, with partial superficial parotidectomy.[30] Irrespective of the amount of normal parotid tissue resected, the proximity of the deep surface of the tumor to the underlying branches of the facial nerve usually determines the extent of the surgical ''margins.'' It is important that this concept is used in properly selected patients. In patients with a mixed tumor less than 4 cm in size, mobile, and located in the superficial lobe, the rate of recurrence is no higher with partial superficial parotidectomy, compared with complete superficial parotidectomy.[9]

Surgery for Tumors of the Deep Lobe of the Parotid Gland

The ''deep'' lobe of the parotid gland is defined as the parotid tissue that lies medial to the plane of the facial nerve. In terms of volume, this constitutes less than 20% of the salivary tissue, and therefore tumors of this part of the gland are rare. The vast majority of deep lobe tumors are benign, and depending on their location within the gland, they may present in either the retromandibular area or as a parapharyngeal mass. Preoperative histological diagnosis is usually not necessary because radiologic imaging is extremely reliable in differential diagnosis. Image-guided FNAC can be performed, but access can be complicated. Open biopsy is not recommended and, especially if done transorally, may tremendously complicate subsequent definitive excision.

Dissection of deep lobe tumor is accomplished after removal of parotid parenchyma lateral to the facial nerve. The tumor is dissected from branches of the facial nerve

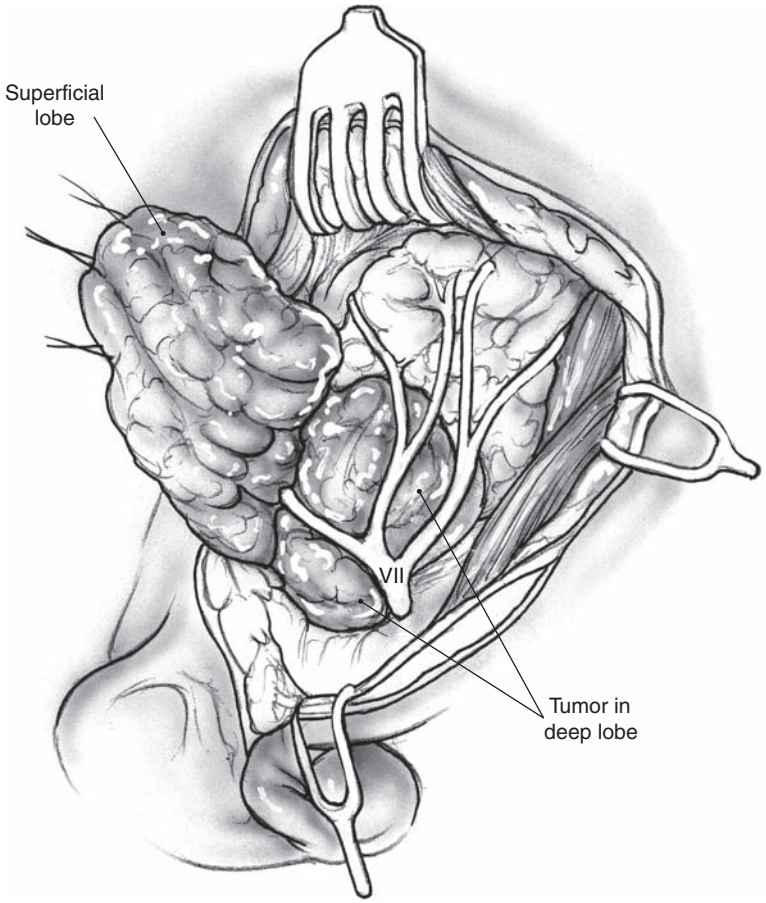

FIGURE 15–10 As the superficial parotidectomy nears completion, the deep lobe tumor is seen deep to the facial nerve and its branches.

with a fine hemostat, bipolar coagulation, and plastic scissors. For the deep lobe tumor, greater areas of exposed capsule can be expected than from dissection of a tumor from the superficial lobe. Careful handling of the deep lobe parotid parenchyma and the capsule of the tumor will reduce the risk of rupture. A higher rate of transient facial nerve dysfunction can be expected.[9]

Transcervical-Transparotid Approach for Tumors of the Deep Lobe of the Parotid Gland

Deep lobe tumors located in the retromandibular region and most parapharyngeal space tumors are essentially amenable to surgical resection by a transcervical-transparotid approach. The preoperative considerations are the same as described for superficial parotidectomy above, but there are certain important technical variations that may help increase surgical exposure of the deep lobe tumor. Nasotracheal, as compared to the usual oral endotracheal, tube provides an extra few centimeters of excursion of the lower jaw that can be crucial in accessing the tumor. Complete muscle relaxation obviously helps, and this may be requested once superficial parotidectomy and dissection of the facial nerve are complete. Other surgical maneuvers for improving access to the parapharyngeal space will be described below.

The operation commences with a superficial parotidectomy and dissection of the facial nerve. Although a formal superficial parotidectomy may not always seem necessary, it certainly is advisable for adequate exposure of most deep lobe tumors. After completion of the superficial parotidectomy, the tumor of the deep lobe of the parotid gland should be visible stretching the facial nerve and its branches over it (**Fig. 15–10**). The nerve and its branches are carefully dissected off the underlying tumor using a nerve hook and sharp, fine scissors to minimize trauma. The tumor can now be mobilized all along its periphery using gentle digital dissection combined with careful sharp division of fibrous bands, while the nerve and its branches are gently retracted cephalad (**Fig. 15–11**). Blunt dissection must be gentle to avoid rupture, and the specimen should be inspected carefully to ensure complete removal of all lobules of the tumor. The surgical bed requires no special reconstruction. After meticulous hemostasis, the incision is closed in layers over a Penrose or suction drain.

Tumors of the deep lobe that grow into the parapharyngeal space can often present as a submucosal lateral pharyngeal mass that is easily visible through the open mouth (see Chapter 9, **Fig. 9–8**) It must be emphasized that such a tumor should under no circumstances be approached per orally for either diagnostic

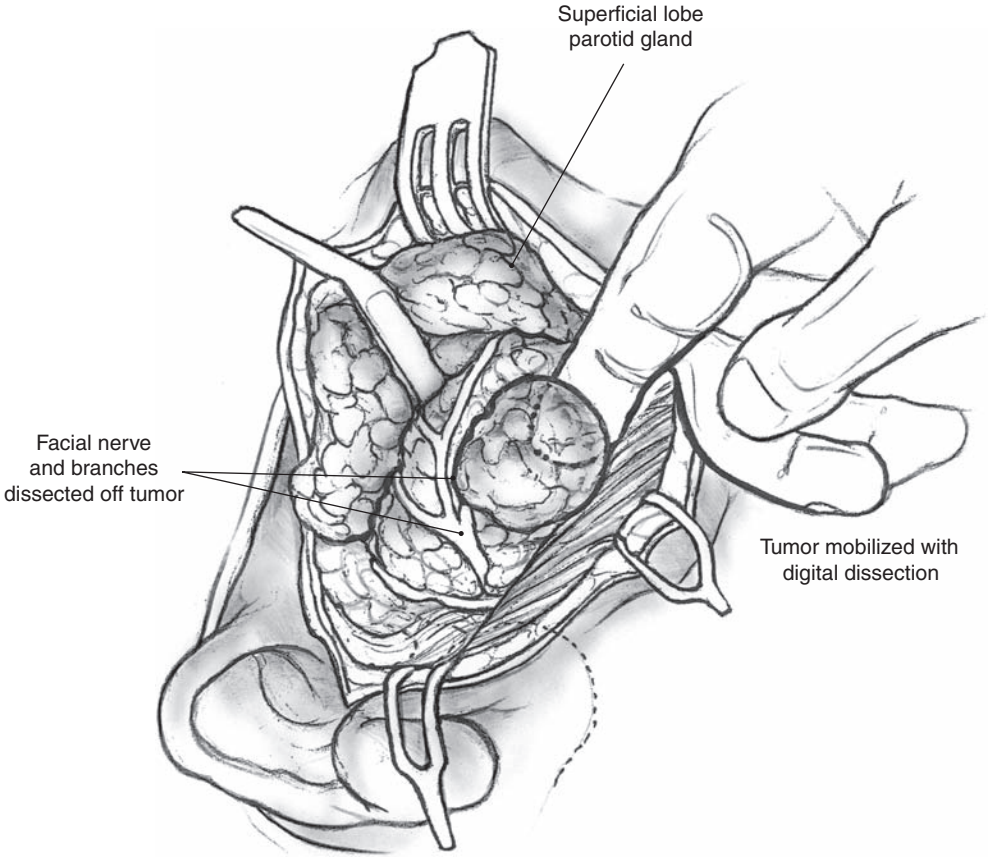

FIGURE 15–11 Dissection of a deep lobe parotid tumor. The facial nerve and its branches are carefully dissected off the tumor, then retracted with nerve hooks, and the tumor is mobilized using gentle digital dissection.

biopsy or for surgical resection. Radiologic imaging using CT and/or MRI scans is mandatory, not only because it can reliably exclude other parapharyngeal space tumors, but also because it allows the surgeon a clear perception of the three-dimensional extent of the tumor (see Chapter 2, **Figs. 2–13, 2–14, 2–15**). The combined transcervical-transparotid approach described above is most often adequate for these tumors as well. In addition to the anesthetic considerations described above, certain intraoperative maneuvers can be very useful in enhancing access to the parapharyngeal space. A bone hook can be used to pull the angle of the mandible in an upward direction to improve access between it and the tumor. Although dislocation of the mandible at the temporomandibular joint and forward displacement may help, this maneuver is not easy and is generally not recommended. Division of the posterior belly of the digastric muscle, the stylohyoid complex, and/or the stylomandibular ligament can widen access, but it may affect function postoperatively. Retraction of the sternocleidomastoid muscle and excision of fibrofatty and lymphatic tissue at level II should be standard procedure, but if greater anteroinferior access is required, the submandibular gland can be excised without major sequelae. Digital dissection of the tumor, especially on its superoposterior aspect, cannot be carried out under direct vision. It is therefore crucial that the surgeon be familiar with regional anatomy, including visualization of the internal jugular vein, carotid artery, and cranial nerves (CN) IX, X, XI, and XII (see Chapter 1, **Figs. 1–8, 1–9**), and dissect very carefully in the parapharyngeal loose areolar tissue to avoid fracturing the tumor. Any areas of resistance that are felt as fibrous bands must be patiently delineated by measured digital dissection and divided sharply. The specimen must be carefully inspected for complete excision, and closure of the incision is accomplished in the usual fashion over a Penrose or suction drain.

Mandibulotomy Approach for Tumors of the Deep Lobe of the Parotid Gland

The vast majority of tumors of the deep lobe of the parotid gland, even those that are of considerable dimension, are resectable by the transcervical-superficial parotidectomy approach described above. This approach, however, is inadequate and may indeed be hazardous under certain circumstances. The mandibulotomy approach is indicated in situations that require more comprehensive exposure of the parapharyngeal space (**Table 15–3**).

The mandibulotomy, or mandibular swing, approach has been well described in the literature,[37] as have the pros and cons of the various types of mandibular osteotomy.[1]

TABLE 15–3 Indications for the Mandibulotomy Approach to Tumors of the Deep Lobe of the Parotid Gland

Malignant tumor
Locally recurrent tumor
Previously violated surgical field, especially for attempted peroral resection of a malignant tumor
Tumors that cannot be safely removed with the transcervical/transparotid approach

The paramedian mandibulotomy is the preferred route of access to the parapharyngeal space for a number of reasons (**Table 15–4**). The osteotomy is designed to pass through an area of bone between the diverging roots of adjacent teeth in order to avoid the need for dental extraction and also so that the bone cut does not expose the adjacent dental roots. In most patients, the site that fulfills this condition is located between the lateral incisor and canine teeth. For obvious reasons, the site of the osteotomy must be planned preoperatively on a radiograph. Radiographic imaging is also mandatory to avoid placing the osteotomy through pathologic bone, an event that can result in nonunion of the osteotomy with all its attendant complications. Similarly, dental sepsis should be controlled before the operation, or an alternative osteotomy site must be selected. The vertical limb is placed to bisect the space between the lateral incisor and the canine teeth on the side of the tumor, and extends about a centimeter to a level just beyond the tips of the dental roots. This is important to avoid exposure or amputation of the dental roots, both of which will result in nonvital insensate teeth. The osteotomy is then angled down toward the symphysis to create a notch. This notch provides better stability to the healing mandibular segments against shearing forces compared with a straight, vertical osteotomy.

After a nasotracheal anesthetic tube has been placed, the patient is placed in a reverse Trendelenburg's position, and skin incision for a lower cheek flap approach is outlined (**Fig. 15–12**). The incision begins in the midline on the lower lip and extends vertically down the midline of the chin and the upper neck up to the level of the hyoid bone, where it turns laterally into an appropriate skin crease. The horizontal limb of the incision continues over the sternocleidomastoid muscle, where it turns upward to continue into the preauricular region as a standard parotidectomy incision.

TABLE 15–4 The Pros and Cons of the Paramedian Mandibulotomy Approach

Pros
Provides wide exposure to the parapharyngeal space
Does not require division of inferior alveolar (preserves sensation to the teeth) or mental nerve (preserves sensation to the chin and lower lip)
Requires division of only the mylohyoid muscle with minimal disruption of the swallowing mechanism and the stabilizing muscular forces of the muscles of mastication
Does not need extraction of any teeth
Postoperative care is easier because the suture line is located anteriorly in the mouth.
The osteotomy and hardware used to fix it do not interfere with any portals of radiation therapy that may be necessary for adjuvant treatment of the tumor.
Cons
Technically more demanding
Delayed union or nonunion can cause significant pain and morbidity.

The first stage of the operation consists of a superficial parotidectomy, with identification and preservation of the facial nerve and its branches as described above. Appropriate dissection of the cervical nodes is then completed if indicated.

The next phase involves exposure of the mandible for a paramedian mandibulotomy through a lower cheek flap. The lower lip is incised sharply and cleanly in the midline, and the full thickness of the lip and the chin are then divided down to a point about 0.5 cm away from the reflection of the mucosa in the gingivobuccal sulcus. The mucosal incision is turned to the side away from the tumor for approximately 2 cm, so that a limited lower cheek flap may be elevated on

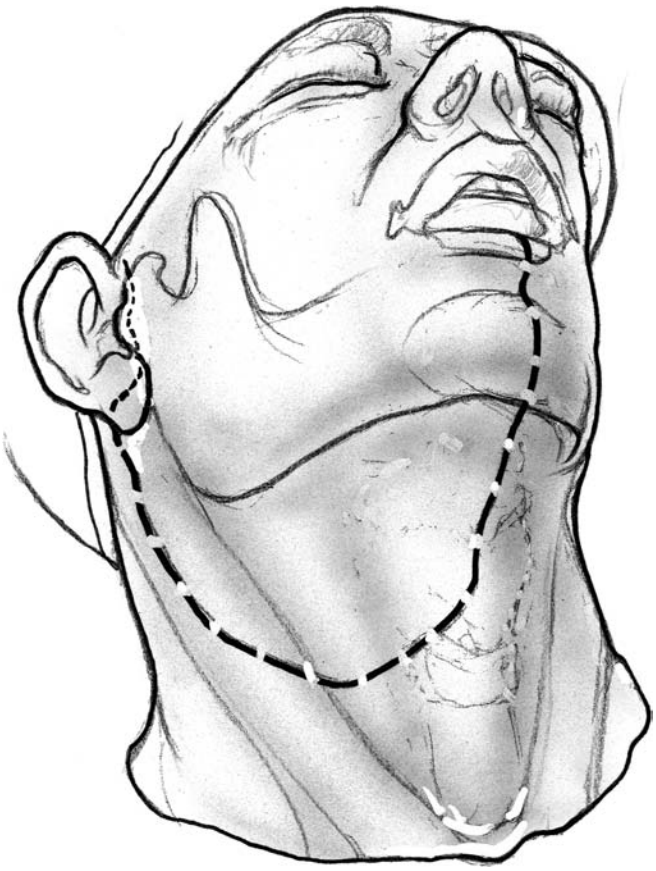

FIGURE 15–12 Outline of the incision for lower cheek flap approach.

that side. The soft tissue over the mandible is then elevated in a plane just superficial to the periosteum, taking care to stop well short of the mental foramen where the mental nerve exits. The proposed osteotomy site, medial to the mental foramen**,** is marked out, and the periosteum of the mandible is incised along it. Two titanium mini-plates are contoured to straddle the osteotomy, one on the anterior surface of the mandible and the other along its inferior border. Drill holes are made to prelocalize these mini-plates that are then stored away for later use (**Figs. 15–13, 15–14**). An important consideration in positioning the mini-plates and placing drill holes is to avoid injuring the dental roots. The osteotomy is now completed using a fine blade on a high-speed power saw. The vertical limb is taken first, starting from the upper border of the lower gum in the space between the lateral incisor and the canine teeth. The angled limb of the osteotomy is started from the lower border of the mandible, and as the blade of the saw approaches the vertical limb, great care must be taken to avoid overriding it. A gentle tap with a fine osteotome completes the osteotomy. Bleeding from the cut ends of the mandible is controlled using bone wax.

The mandibular segments are distracted with loop retractors, and the mucosa of the floor of the mouth on the side of the tumor is incised. The hypoglossal nerve is observed and preserved. The mucosal incision starts anteriorly at the site of the osteotomy and is continued into the floor of the mouth, so that a cuff of mucosa about 1 cm wide is left attached to the lower gum (**Fig. 15–15**). An adequate cuff of attached mucosa allows safe closure of the floor of the mouth at the conclusion of the procedure. The incision in the floor of the mouth is continued posteriorly up to the anterior tonsillar pillar, progressively retracting the divided mandible laterally. Any further extension of the incision will require division of the lingual nerve as it crosses over to enter the tongue. The mucosal incision can also be modified posteriorly to include a portion of the lateral pharyngeal wall that may be adherent to underlying tumor, either by direct infiltration or more commonly as a result of adhesion from a previous attempt at peroral biopsy or excision (**Fig. 15–15**). As dissection proceeds, the tongue is pulled anteriorly and away from the tumor, and division of the mylohyoid muscle allows wide retraction of the mandibular segments to provide adequate exposure to the parapharyngeal space (**Fig. 15–16**).

The facial nerve and its branches are carefully elevated off the underlying deep lobe tumor and retracted cephalad. As described before, gentle digital dissection is used to mobilize the tumor laterally, while its medial and superior aspects can be safely dissected via the exposure afforded by the mandibulotomy. Circumferential mobilization of the tumor is thus completed to ensure adequate monobloc excision, and the tumor is delivered. If a significant amount of lateral pharyngeal wall mucosa needed resection, reconstruction using either a pectoralis major myocutaneous flap or a microvascular free flap becomes necessary. This amplifies the magnitude of the procedure several-fold,

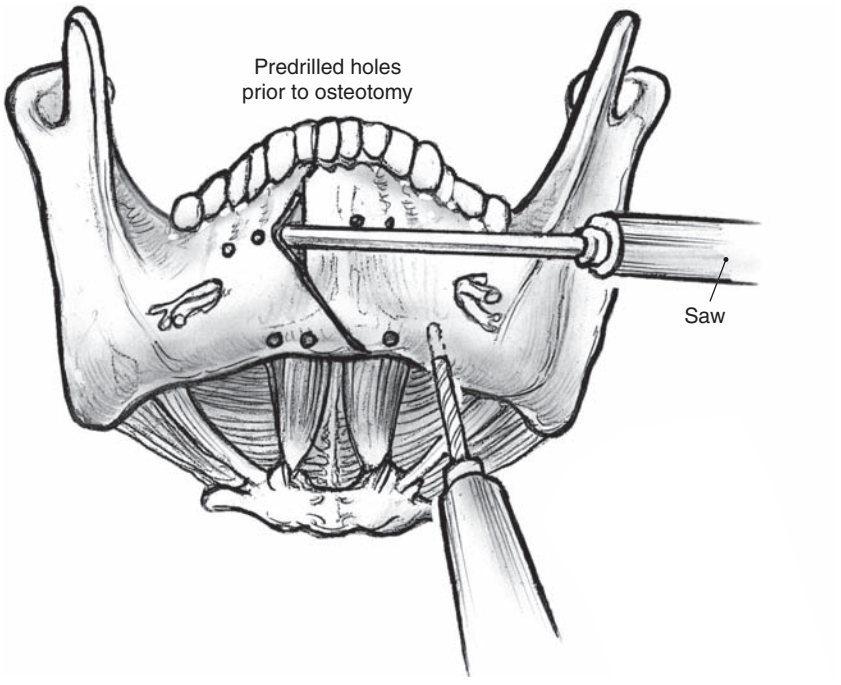

FIGURE 15–13 The site of mandibulotomy is marked on the mandible, and holes are drilled prior to mandibulotomy.

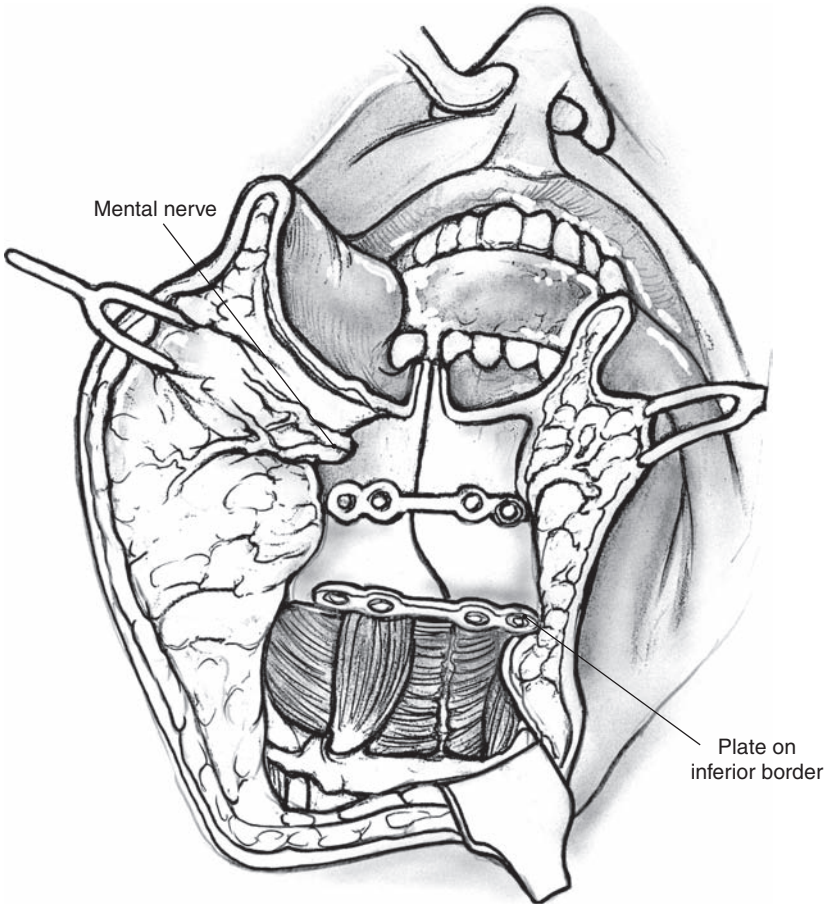

FIGURE 15–14 Mini-plates are prelocalized prior to the osteotomy. Diagram shows accurate approximation of the mandibulotomy using contoured mini-plates and screws.

and hence the need to reemphasize that any peroral attempt at biopsy or excision of these tumors is absolutely contraindicated.

After ensuring hemostasis, a nasogastric feeding tube is inserted and secured in place. The incision in the mucosa of the floor of the mouth is repaired with interrupted chromic catgut sutures starting posteriorly and proceeding in an anterior direction. The contoured mini-plates and screws of appropriate length are now used to secure the mandibular segments in accurate approximation at the site of the osteotomy (**Fig. 15–14**). Closure of the lower lip incision and cheek flap can now begin. A 5-0 nylon suture is taken to accurately align the vermilion border of the lower lip. This suture is held long and used to guide subsequent closure of the mucosa of the lower lip and the gingivolabial sulcus. The skeletal muscle and the mucosa of the lip are approximated in two separate layers with interrupted 3-0 chromic catgut sutures starting at the vermilion and working toward the lower gum. Before closure of the rest of the incision, the divided stumps of the mylohyoid muscle are sutured with chromic catgut sutures. Two closed-suction drainage tubes are inserted into the neck, and the remainder of the incision is closed in two layers. It is important to ensure that the suction drains are placed away from the facial nerve and its branches.

Postoperatively, the patient is fed through the nasogastric tube for about a week. If a trial of puréed food is successful, the patient's intake can be gradually advanced to a soft diet over the ensuing days. The nasogastric tube is removed when the patient's oral intake is able to meet the daily nutritional requirement. Meticulous oral hygiene is essential to good healing and avoiding sepsis at the osteotomy. As healing progresses, the patient can gradually return to a normal diet, and the mandibulotomy should eventually result in no dietary restrictions. The lip and neck incisions also heal with minimal cosmetic deformity.

Resection of an Accessory Parotid Tumor

Accessory parotid tissue is most commonly located anterior to the parotid gland, along the course of Stensen's duct. Accessory parotid glands have been described to be either round or triangular in shape and almost always contain anastomoses of the zygomatic and buccal branches of the facial nerve within their substance. Although this tissue is susceptible to most salivary pathology, tumors of the accessory parotid

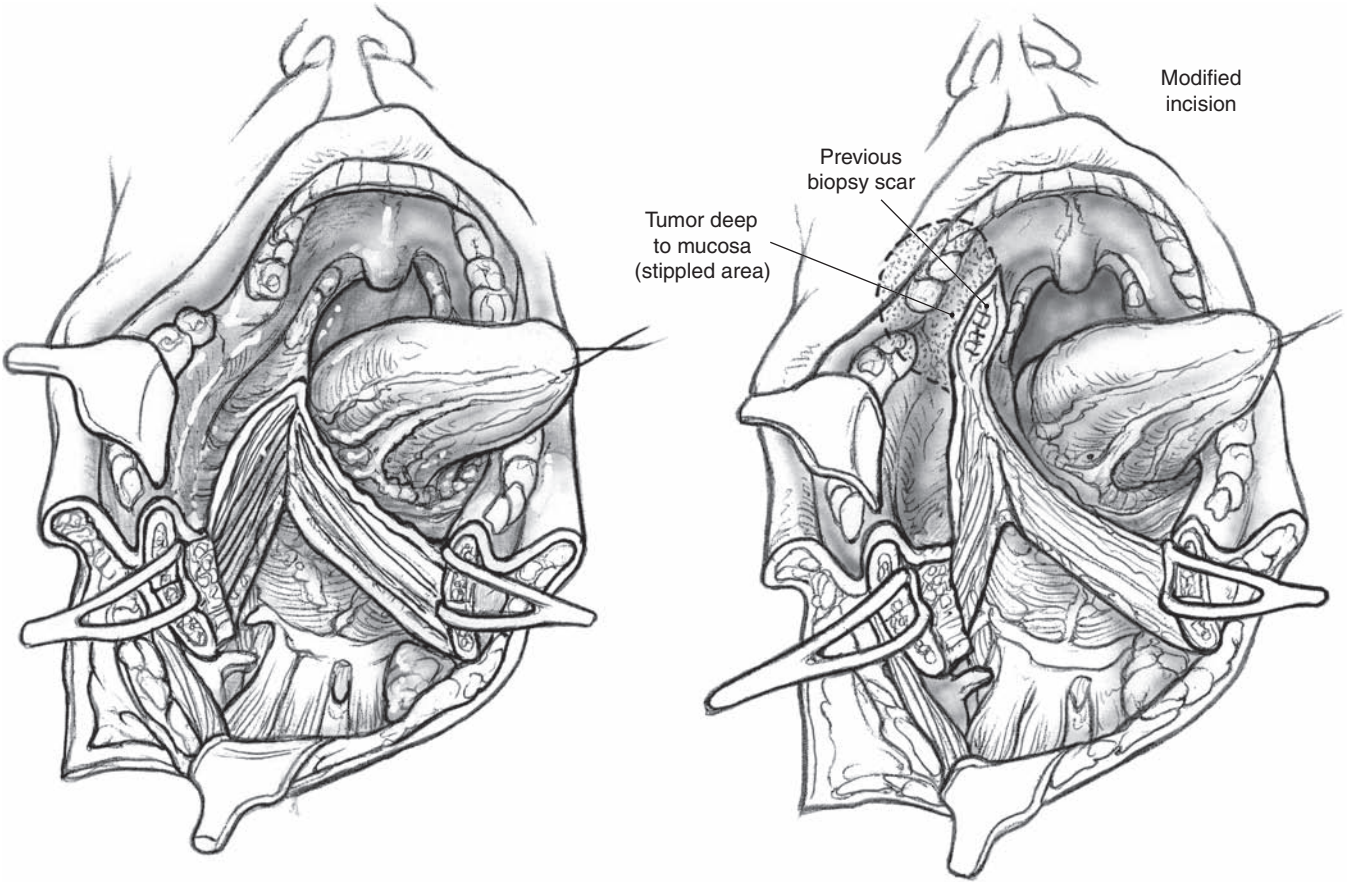

FIGURE 15–15 The mucosa of the floor of the mouth is incised to preserve a 1 cm wide cuff of mucosa attached to the lower gum. The mucosal incision can be modified to include a portion of the lateral pharyngeal wall mucosa that may be adherent to underlying tumor.

glands are more frequently malignant than those of the parotid glands themselves.

The patient with a tumor of the accessory parotid gland generally presents with a firm, well-defined mass in the cheek. Clinical examination of the mass should provide the surgeon a good idea about its anatomical extent, but imaging can be very helpful in delineating its relationships to the parotid gland and the masseter muscle. Although a formal superficial parotidectomy with dissection of all the branches of the facial nerve is a good policy, more limited dissections are appropriate for smaller tumors, provided the surgeon recognizes the importance of meticulous dissection of the branches of the nerve in proximity of the tumor.

Surgical resection of an accessory parotid tumor requires a greater degree of surgical exposure of the cheek compared with a superficial parotidectomy. Any attempts at limiting the skin incision, or worse, placing it directly over the tumor can only increase the risk of nerve injury and should be discouraged. Because the tumor is located anteriorly in the cheek, surgical exposure requires a longer cheek flap. The standard parotidectomy incision is modified as shown in **Fig. 15–17**. The transverse extension toward the temple should be taken with great caution after the temporal and zygomatic branches of the facial nerve have been identified. The anterior skin flap is elevated to obtain adequate exposure of the tumor. Safe conduct of the operation depends on identification of the peripheral branches of the facial nerve. An experienced surgeon should be able to dissect the nerve branches as they exit the parotid gland without any difficulty, but it is always safe to perform a superficial parotidectomy so that the relevant branches can be identified as they come off the main divisions of the nerve. Superficial parotidectomy is also indicated if the tumor abuts the substance of the parotid gland and is malignant or if the Stensen's duct has to be resected with the tumor. The branches of the facial nerve and Stensen's duct are situated in close proximity to the accessory parotid tumor. Identification and dissection of Stensen's duct may be easier if its mucosal opening has been cannulated and a probe has been left in place at the start of the procedure. The branches of the facial nerve are carefully dissected, and the tumor is excised. The incision is closed in layers as described above after superficial parotidectomy.

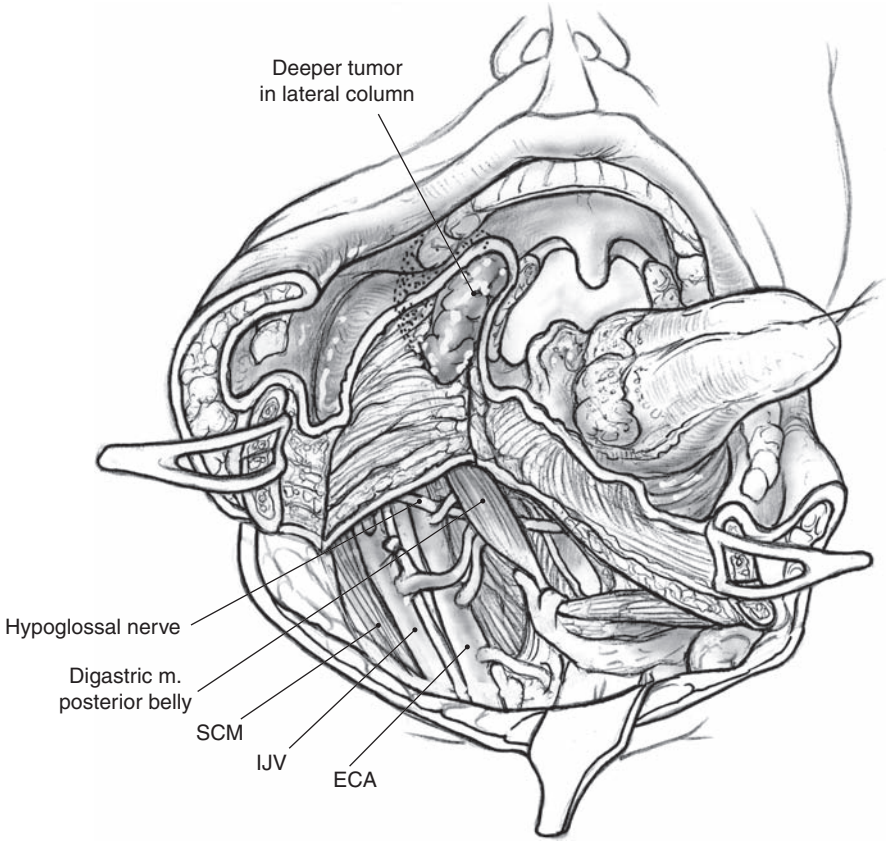

FIGURE 15–16 Division of the mylohyoid muscle allows wide retraction of the mandibular segments and provides adequate exposure of the parapharyngeal space. ECA, external carotid artery; IJV, interal jugular vein; SCM, sternocleidomastoid muscle.

Management of Recurrent Tumor of the Parotid Gland

Although local recurrence is relatively rare following parotidectomy for mixed tumor of the parotid gland, surgical management of this situation can be problematic. The major concern in undertaking surgery for these patients is obviously the increased risk of injury to the facial nerve. If the tumor recurs after enucleation, surgical resection is relatively straightforward because the tissue planes around the branches of the facial nerve remain intact. However, the likelihood of nerve injury is appreciably higher in the patient who develops multifocal recurrence in the surgical bed following superficial parotidectomy and complete dissection of the facial nerve. Multifocal recurrence often requires treatment of the preauricular skin (**Fig. 15–18A,B**). The skin defect can usually be reconstructed using a local flap, but more extensive reconstruction such as a microvascular free flap may become necessary for larger defects. The operation begins as usual by entering and often excising the preauricular and upper neck incisions. The facial nerve and its branches are immediately deep to the skin owing to previous superficial parotidectomy, and patient, meticulous dissection is imperative to nerve preservation. The use of a nerve integrity monitor is recommended in this situation, and magnification of the surgical field can also be helpful. If there is significant fibrosis around the anatomical location of the main trunk of the facial nerve, a retrograde approach can be selected. The anterior aspect of the skin incision is excised, and an anterior skin flap is developed to identify the peripheral branches of the facial nerve if a retrograde dissection is selected. With this technique peripheral branches are dissected toward the main trunk of the nerve, resecting the overlying skin and recurrent tumor nodules in the process. The posteriorly based cervical flap is elevated in a plane deep to the platysma muscle and sutured in place over a Penrose drain or suction drain (**Fig. 15–19**). (Refer to Chapter 9 for a discussion of recurrent mixed tumor.)

Radical Parotidectomy with Resection of the Facial Nerve

Deliberate sacrifice of the facial nerve or its branches is clearly indicated if the patient's tumor has resulted in clinically evident nerve deficit. Under all other circumstances, the decision to section the nerve is made intraoperatively and is based on a number of interrelated factors. Attempts to salvage a nerve by splitting a tumor that encases it, even if it is benign, are ill advised as local recurrence is guaranteed. However, there is no

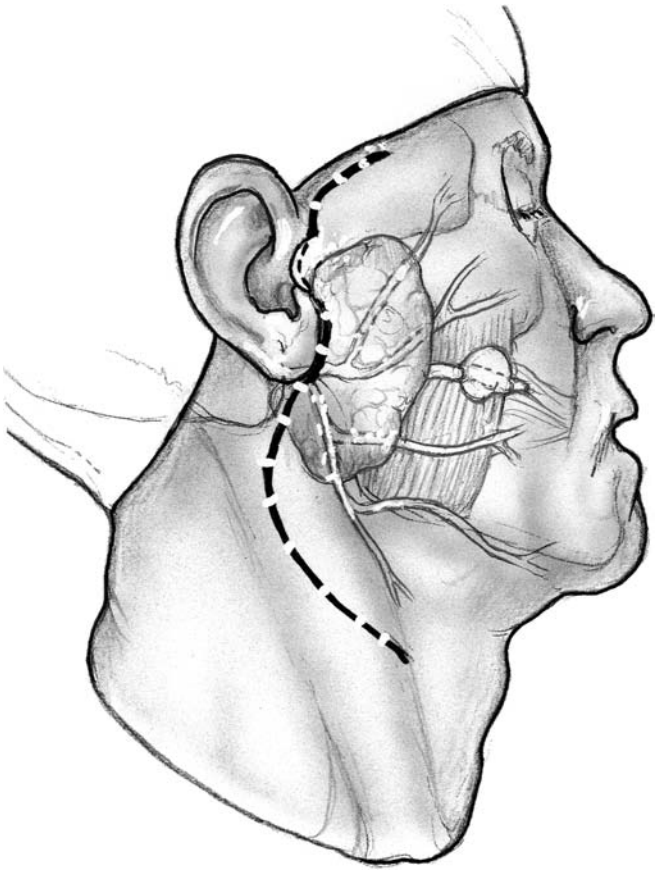

FIGURE 15–17 Modification of the superficial parotidectomy incision for resection of an accessory parotid tumor.

justification for sacrificing a functioning nerve to provide a ''margin'' for resection of a tumor that abuts but does not actually involve the nerve. In cases of locoregionally extensive tumor, the morbidity of facial nerve resection cannot be justified if the surgeon is unable to completely clear tumor from other adjacent structures.

Fig. 15–20 depicts a patient with a locally recurrent tumor following superficial parotidectomy. Radiologic imaging is helpful in this situation to assess the three-dimensional extent of the tumor. As the decision to sacrifice the involved branches of the facial nerve is made intraoperatively, it is important that the patient agree with this plan of action, and the surgical consent should cover this possibility. The surgical team should have the appropriate operating room setup for nerve reconstruction. The indications and technique of nerve grafting are described in detail in Chapter 16.

Surgical access may be through the scar of a previous parotidectomy, which should be excised. It may be difficult to identify and preserve any meaningful length of great auricular nerve in this setting, but this should always be the aim, especially in patients who have not had previous parotidectomy. After the anterior skin flap has been elevated, the main trunk of the facial nerve must be identified even if facial nerve sacrifice has been planned preoperatively. Obviously, the ease with which this is possible and the length of main trunk that can be preserved depend on its relation to recurrent tumor, and every effort is made to maximize the length of normal nerve without compromising tumor excision. The branches of the nerve that are uninvolved and not in immediate proximity to the tumor can be preserved intact depending on the location of the tumor. In the patient depicted in **Fig. 15–21**, the configuration of the recurrent tumor allows preservation of the upper division along with its temporal and zygomatic branches. The lower division, however, is sectioned proximal to the tumor, and the margin of its stump is examined intraoperatively for tumor involvement. It should be noted that a histologically ''negative'' nerve margin is by no means indicative of the absence of perineural spread that is well known to skip areas of normal nerve, especially in adenoid cystic carcinoma. As resection of the tumor proceeds, the peripheral branches of the lower division are identified and divided at a safe distance anterior to the tumor. Margins of excision from these branches are examined to rule out the presence of tumor, and their stumps are very carefully tagged with fine silk sutures so that they can be easily identified during the nerve graft procedure. The deep margin of the resection extends to include fibers of the masseter muscle and the periosteum at the angle of the mandible (**Fig. 15–21**). After nerve grafting is complete, the incision is closed in the usual fashion over a Penrose or suction drain. The postoperative care and results of facial nerve section and reconstruction are considered in detail in Chapter 16.

Radical Parotidectomy with Sleeve Resection of the External Auditory Canal

The external auditory canal lies in close proximity to the parotid gland and is at risk of invasion by aggressive tumors. This situation, however, is more likely in patients who have recurred following previous surgery and radiation therapy. If the tumor has perforated into the auditory canal but does not extend to involve the external ear or the bony external auditory canal, a sleeve resection of the cartilaginous external auditory canal can be performed. Obviously, the operation should not be contemplated without detailed radiographic assessment of the region and determining the local extent of the tumor in relation to the external auditory canal. The tumor is almost always locally extensive and involves multiple structures including the facial nerve by virtue of the regional anatomy. Adequate surgical resection of such a tumor requires radical parotidectomy with resection of skin, external auditory canal, ascending

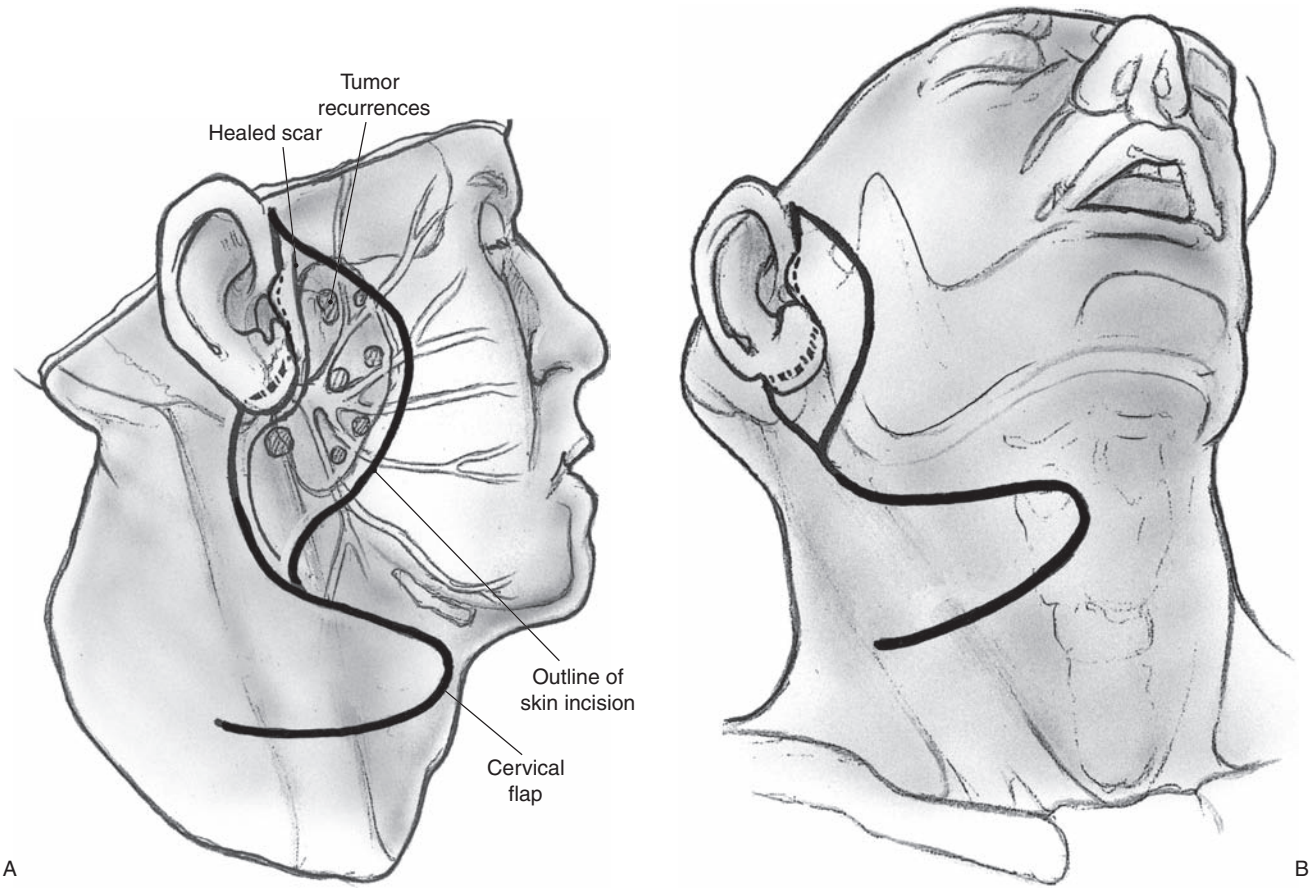

FIGURE 15–18 (A,B) Multifocal tumor recurrence in the preauricular region following superficial parotidectomy. An area of skin will have to be excised and reconstructed using a posterior cervical flap.

ramus of mandible, and a comprehensive neck dissection. As discussed above, deliberate sacrifice of a functioning nerve can create a therapeutic dilemma, and informed participation of the patient is crucial to successful outcome. A functioning facial nerve is rare in this situation, and complete surgical resection is unlikely without its sacrifice.

The skin incisions are designed to encompass the involved preauricular skin along with the scar of any previous surgery. The preauricular skin will need to be sacrificed not only because of tumor involvement but also because of decreased viability following previous surgery and radiation therapy. An S-shaped vertical incision is dropped down the neck to provide access for neck dissection. The preauricular skin crease incision begins in the temple as shown and curves around the lobule of the ear to continue posteriorly, so that this superiorly based flap can be elevated with an intact vascular supply to the pinna (**Fig. 15–22**). A comprehensive neck dissection is completed in an inferior to superior direction, so that the contents of the neck remain attached to the mastoid process.

Resection of the primary tumor now begins with division of the body of the mandible, so that an uninvolved plane of tissue can be dissected deep to the tumor. The ascending ramus of the mandible is divided without breaching the mucosa of the oral cavity. The divided ramus is held in a bone forceps and rotated laterally, so that the pterygoid muscles on its medial aspect can be divided. The pterygoids must be sectioned carefully after careful palpation to obtain an adequate margin of normal muscle. Dissection continues superiorly to divide the zygomatic arch and the temporalis muscle at the level of the arch. This completes the anterior dissection, and the pre- and postauricular skin incisions are now taken to elevate a superiorly based flap containing the pinna. With the external ear lifted up along with the flap, the cartilaginous external auditory canal comes into view. The cartilage of the canal is divided sharply with a knife close to the external ear and proximal to the tumor, maintaining a good margin from it. This releases the pinna, and the superior flap can now be elevated to expose the mastoid and temporal regions. A radical mastoidectomy is completed, and the cartilaginous canal is divided distal to the perforating tumor at its junction, with the bony external auditory canal leaving a cuff of normal external auditory canal skin attached to the canal. The internal jugular vein is

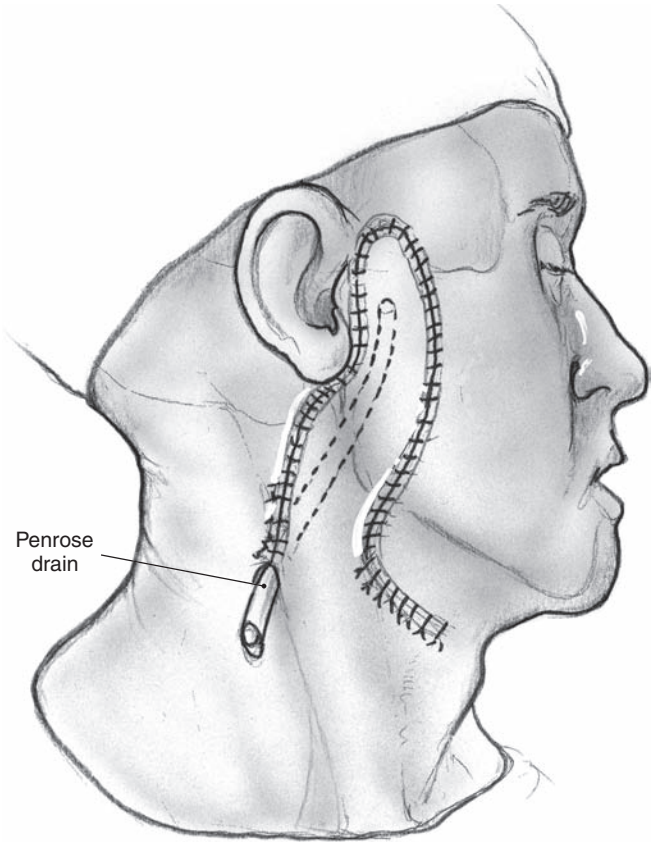

FIGURE 15–19 The cervical rotation flap is used to reconstruct the surgical defect.

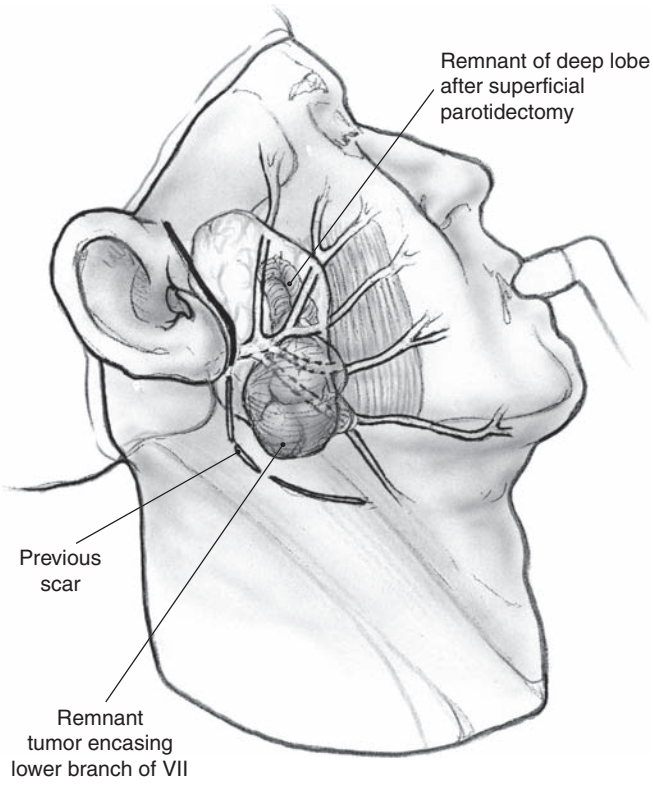

FIGURE 15–20 A recurrent tumor of the parotid gland that encases the branches of the lower division of the facial nerve.

dissected, ligated, and divided at the level of the jugular foramen. At this point, the specimen can be delivered by incising the capsule of the temporomandibular joint and disarticulating the mandibular head. After hemostasis is secured, the remnant cartilaginous external auditory canal is sutured to the skin around the remaining bony external auditory canal. Thus a sleeve resection of the external auditory canal is achieved without compromising the pinna or the middle ear. The repaired external auditory canal is packed with Xeroform gauze. The preauricular surgical defect will need reconstruction with either a pectoralis major myocutaneous flap or a free rectus abdominis flap. The neck incision is closed primarily in layers over closed suction drains.

Temporal Bone Resection and Management of Skull Base Invasion

Locally extensive tumors of the parotid gland can extend to involve one or more of the numerous anatomical structures of importance in the vicinity. Surgical treatment of these tumors may require resection of part or whole of the temporal bone. Involvement of the skull base of the middle cranial fossa complicates the surgical management even further. It must be emphasized that successful outcome after temporal bone resection or combined craniofacial resection depends on close multidisciplinary cooperation apart from meticulous surgical technique. The reader is referred to a specialist atlas for more detailed description of these procedures.[1,38]

■ Surgery of the Submandibular Salivary Gland

Chronic obstructive and inflammatory pathology frequently affect the submandibular gland. Conservative measures usually produce symptomatic relief, and successful extraction of offending stones may cure the problem before it becomes chronic. A fair proportion of patients, however, will experience multiple inflammatory episodes and require excision of the chronically inflamed gland. The other common indication for surgery includes neoplastic disease, which is more frequently malignant in the submandibular gland compared with the parotid gland. Preoperative differential diagnosis is not easy in the absence of overt signs of malignant behavior. As discussed above, the role of FNAC remains unclear because an aspirate negative for malignant cells cannot rule out malignancy with

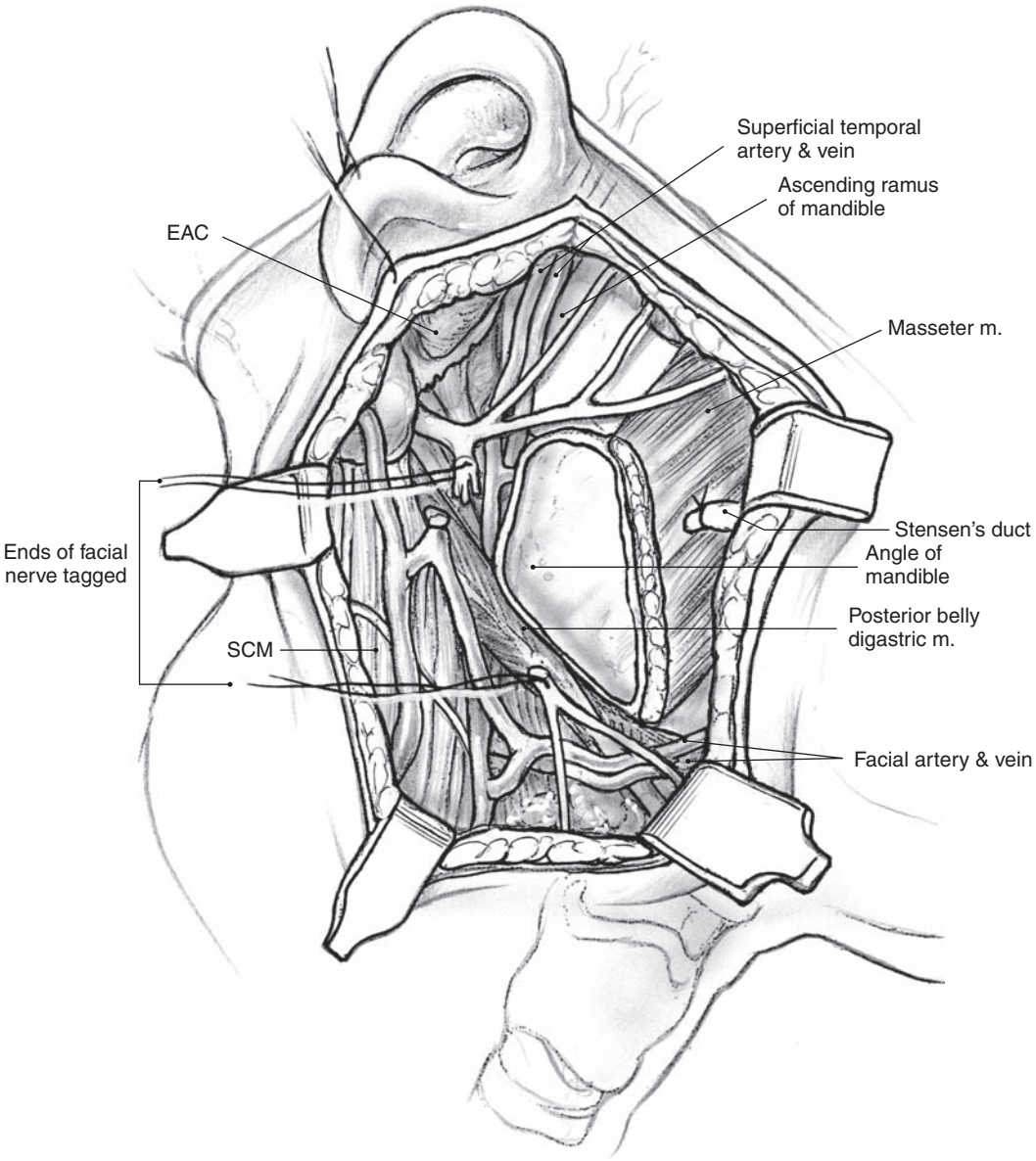

FIGURE 15–21 The surgical field after resection of the tumor shows the divided ends of the peripheral branches of the lower division of the facial nerve. EAC, external auditory canal; SCM, sternocleidomastoid muscle.

certainty. Similarly, cross-sectional imaging generally does not add much to the clinical examination in the routine situation. In actual practice, the diagnosis commonly remains unresolved until after surgical excision and histopathologic examination of the specimen. Both of these investigations, however, can be extremely useful to prepare the patient and the treating physician for a major surgical resection if the tumor is clinically suspicious for malignancy.

Safe and successful surgery of the submandibular gland, like that of the parotid, requires a detailed understanding of regional anatomy (see Chapter 1, **Figs. 1–10, 1–12**). The intimate relationship of the gland and Wharton's duct to sensory and motor nerves places the patient at risk for considerable functional deficits if these structures are injured during the operation.

Excision of the Submandibular Gland for a Benign Tumor

The typical patient with a submandibular tumor presents with a diffuse, palpable mass in the submandibular triangle. The skin incision for submandibular gland excision is designed to provide access to the gland with minimal risk to the marginal mandibular branch of the facial nerve (**Fig. 15–23**). The incision is usually placed along an upper neck skin crease located at least two fingerbreadths from the angle and inferior border of

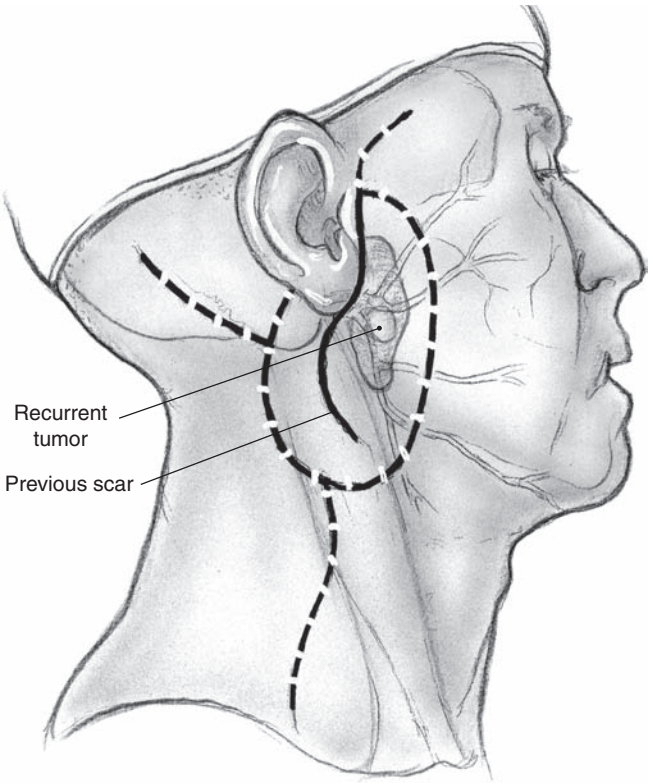

FIGURE 15–22 The skin incision is designed to preserve the vascular supply of the external ear.

the mandible. The marginal mandibular nerve exits the lower half of the parotid gland and quite frequently loops over the surface of the submandibular gland before turning upward. The surface marking of the nerve usually changes once the patient is on the operating table with the neck extended. It is important that the incision be marked with the patient's head in flexion so that the appropriate skin crease is chosen. Another useful maneuver is to palpate the pulsations of the facial artery at the inferior border of the mandible. This marks the anterior border of the masseter muscle and the skin incision must be at least two fingerbreadths inferior to this point.

The operation is best performed under general anesthesia with an oral endotracheal tube in place. With the patient in the supine position and the neck extended to the opposite side, the skin is incised up to the platysma muscle. Upper and lower skin flaps are elevated in the subplatysmal plane, but the upper flap is not dissected fully until the marginal mandibular nerve has been identified. The upper skin flap is elevated superficial to the platysma muscle for a short distance. The muscle is then incised at the projected location of the marginal nerve, approximately two fingerbreadths anterior and two fingerbreadths below the angle of the mandible. The incision is carefully taken through the platysma muscle down to the underlying fascia over the submandibular gland. A curved hemostat is now used to dissect the platysma off the submandibular fascia, and the muscle is divided carefully over the hemostat to protect the marginal nerve that is usually located on the fascia. Once the nerve has been identified, the remainder of the platysma is divided, and the upper skin flap is elevated to the level of the inferior border of the mandible (**Fig. 15–24**). The marginal nerve is usually tethered down by the cervical branch of the facial nerve and the posterior facial vein, and complete elevation of the upper flap requires their division. The next step of the operation is to obtain anterior access to the submandibular gland. The anterior belly of the digastric muscle is dissected to allow caudad retraction of the gland (**Fig. 15–25**). A number of small blood vessels are encountered during this dissection, and these should be ligated and divided to avoid unnecessary blood loss. Further dissection exposes the mylohyoid muscle, and its nerve and blood supply are divided. Dissection continues along the superior border of the gland, between it and the inferior edge of the mandible, to ligate and divide the facial vessels as they exit at the posterior border of the gland. Great care must be taken to avoid injury to the marginal mandibular or other branches of the facial nerve during this dissection. Division of the facial vessels releases the gland and permits caudal retraction to provide exposure of the floor of the submandibular triangle. The free border of the mylohyoid muscle is retracted anteriorly to further open up this space; this brings into view the lingual nerve and its parasympathetic contribution to the submandibular gland. The nerves of the floor of the submandibular triangle are covered by a well-defined layer of fascia and are safe from injury if the surgeon restricts all dissection superficial to this fascia. Caudad traction on the submandibular gland helps delineate the secretomotor ganglion and fibers connecting the lingual nerve to the gland (**Fig. 15–26**). These fibers are divided carefully, placing the hemostats close to the gland to avoid picking up a knuckle of the lingual nerve in the process. The Wharton's duct is now identified anteriorly deep to the mylohyoid muscle as it arises from the portion of the gland deep to the muscle. The extent of dissection of Wharton's duct depends on the indication for submandibular gland excision. If the gland is being resected for chronic sialadenitis, the duct is dissected as far anteriorly as possible to include its entire length with the specimen. The terminal portion of Wharton's duct hooks over the lingual nerve close to the floor of the mouth, and the nerve is at risk for injury during this maneuver. Extensive dissection of the duct is not necessary if the gland is being resected for neoplastic disease, and the duct is divided at a suitable point closer to the gland and ligated with 3-0 chromic catgut. The hypoglossal nerve is situated deep to Wharton's

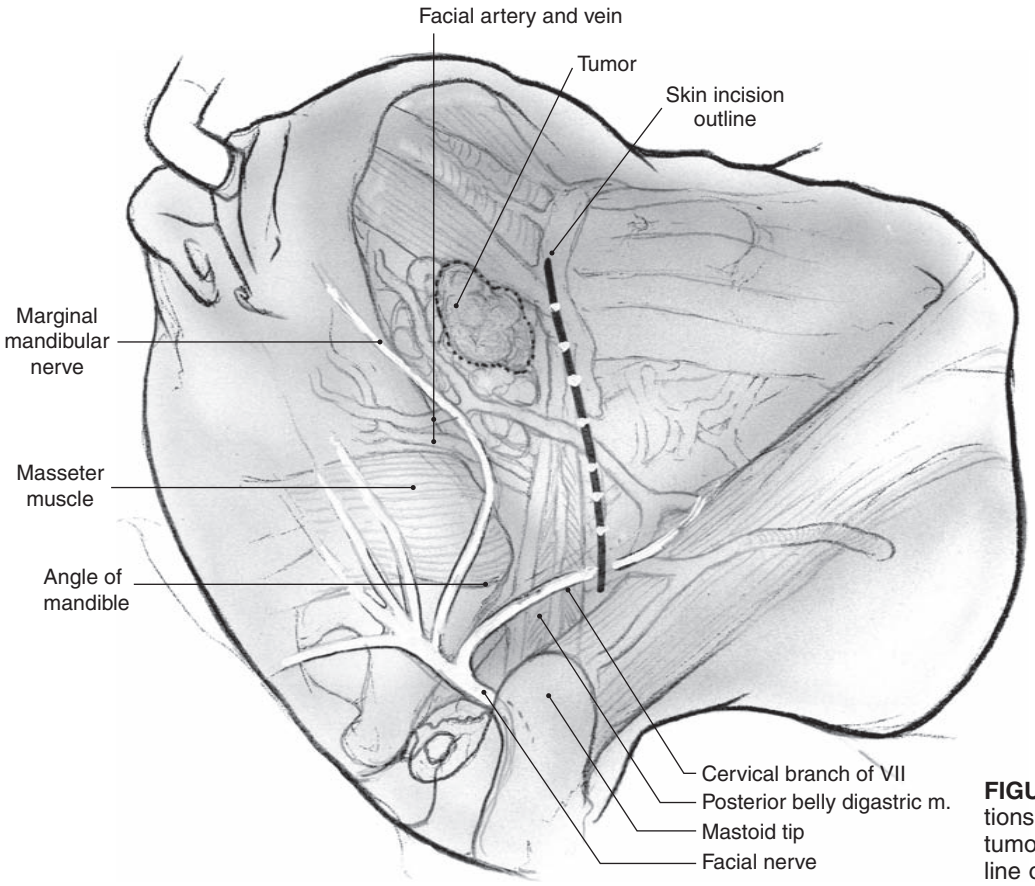

FIGURE 15–23 The typical relationship of a submandibular gland tumor with the mandible and outline of the skin incision.

duct at this level. Dissection should be restricted to the plane superficial to the fascia covering the nerve, as troublesome bleeding from the venae comitantes can occur, and attempts at hemostasis can result in injury to the hypoglossal nerve. Finally, the facial artery is ligated and divided at the superior edge of the posterior belly of the digastric muscle to deliver the specimen (**Fig. 15–27**). Hemostasis is secured, and the incision is closed in layers over a Penrose drain.

No special postoperative measures are necessary. The patient is allowed to swallow clear liquids and a puréed diet for the first 24 hours and should be able to progress to regular diet over the following day. Wound drainage usually tapers off quickly, so that the Penrose drain or suction drain can typically be removed in 1 to 2 days. (A suction drain with absorbable packing over the surgical bed can obviate the need for a dressing and can be removed the following day.)

Radical Excision of the Submandibular Gland for a Malignant Tumor

Surgical excision of the submandibular gland for a suspected malignant tumor with no overt signs of infiltration of adjacent structures is essentially similar to that for benign tumors. In fact, in actual practice the diagnosis of malignancy may not be available to the surgeon until after the gland has been excised and examined by the pathologist. However, if a malignant tumor is suspected, the operation should be modified to include adjacent lymph nodes in the suprahyoid triangle. Small tumors that have not extended beyond the gland can be safely encompassed in such a limited dissection as well. Tumors that have spread beyond the gland to involve adjacent structures need appropriate radical excision depending on the extent of infiltration. A radical resection may include adjacent muscles, nerves including the lingual, hypoglossal, or marginal mandibular, or even a rim or segment of the mandible. A comprehensive neck dissection is indicated for clinically palpable nodes; elective neck dissection is reserved for high-stage tumors.

■ Surgery of the Sublingual Glands

Tumors of the sublingual glands are extremely rare, but the frequency of malignancy is high. Due to their location and mode of presentation in the floor of the mouth, it is often difficult to distinguish a sublingual gland tumor from a minor salivary gland tumor of the floor of the mouth. On a practical basis, this hardly

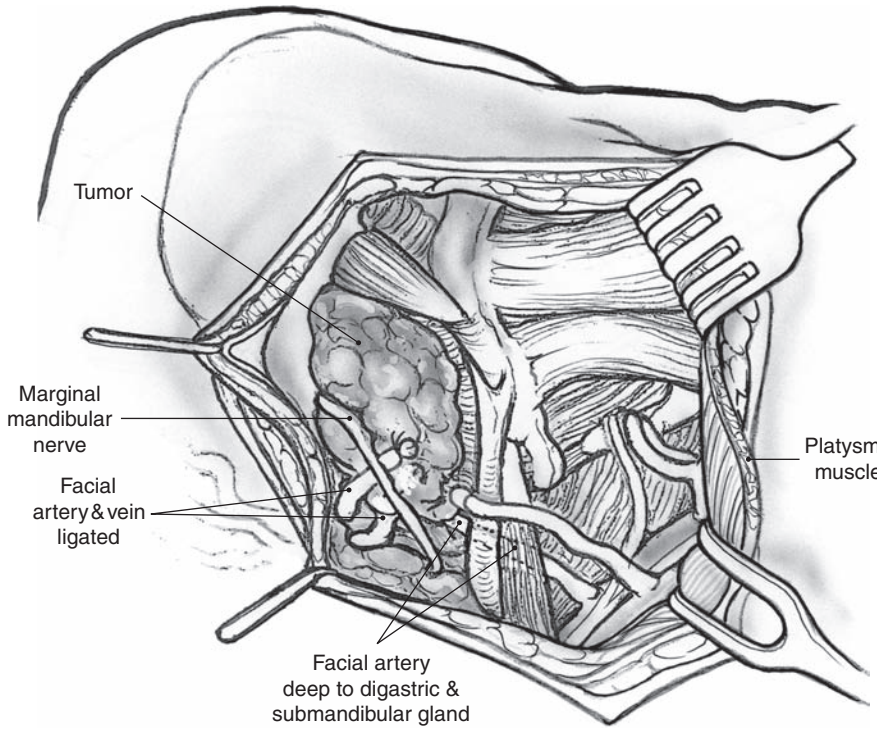

FIGURE 15–24 The platysma is incised, and the marginal mandibular nerve is identified.

makes a difference because the surgical approach to both entities is the same.

Clinical examination, especially bimanual palpation of the floor of the mouth, is a reliable method of assessing local extent of tumor in experienced hands, but radiologic imaging is always helpful. Imaging also enhances clinical examination in evaluation of the relationship of larger tumors to the inner cortex of the mandible and the neck for regional metastases. Biopsy of these submucosal tumors can be difficult if attempted with the usual cup forceps, which may only sample the overlying normal mucosa. A fine dermatologic punch is extremely useful and provides a good tissue core for histologic diagnosis in the office.

Benign tumors or malignant tumors smaller than 2 cm can be readily treated with a peroral local excision.

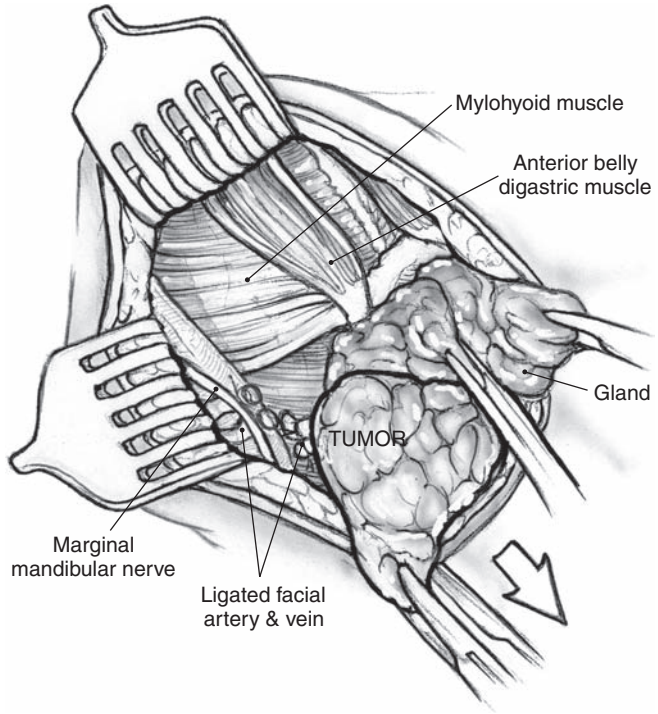

FIGURE 15–25 Dissection of the anterior belly of the digastric muscle in the submental triangle.

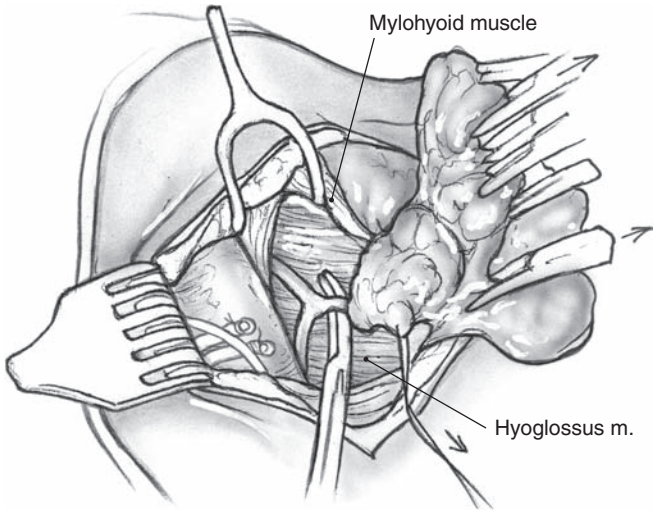

FIGURE 15–26 Division of the secretomotor fibers to the submandibular gland.

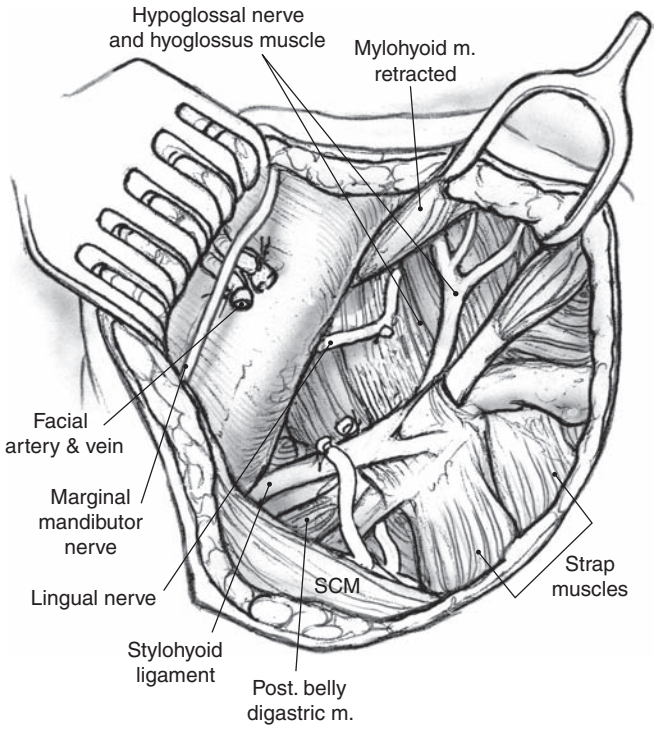

FIGURE 15–27 Anatomical relations after removal of the submandibular gland. SCM, sternocleidomastoid muscle.

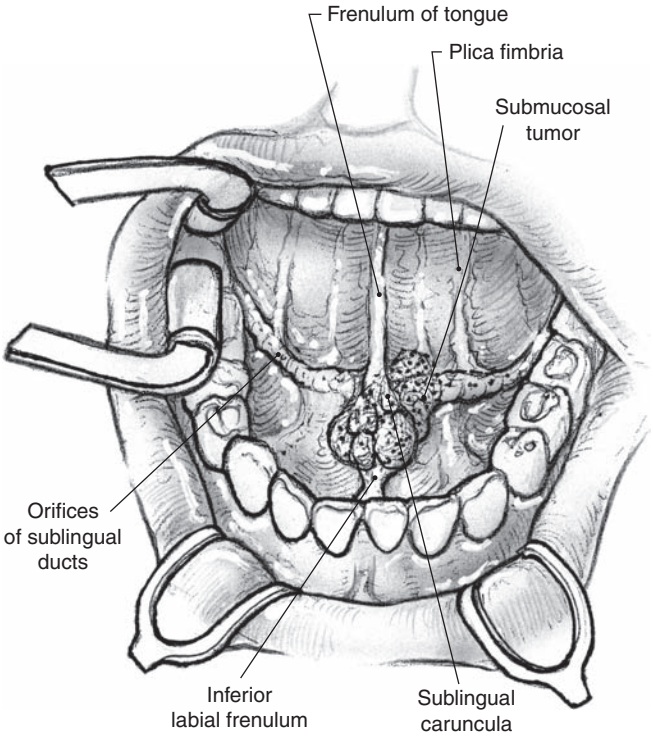

FIGURE 15–28 Surgical exposure through the open mouth is adequate for excision of a small sublingual gland tumor.

Larger malignant tumors require more radical excision. Accurate preoperative delineation of the extent of the tumor is crucial because any underestimation of involvement of the floor of the mouth musculature or adjacent mandible can lead to a drastic change in the surgical plan. The patient depicted in **Fig. 15–28** has a tumor of the sublingual gland that is suitable for peroral local excision. The operation is best carried out under general anesthetic with a nasal endotracheal tube. The jaws are held open with a self-retaining retractor, and an Adair clamp placed on the dorsum of the tip of the tongue helps expose the anterior floor of the mouth. The extent of mucosal resection around the tumor is marked with an electrocautery (**Fig. 15–29**). Mucosal margins of approximately 1.0 to 1.5 cm around the clinical extent of the tumor should be sufficient. Although the chances of local recurrence are higher with close or positive margins, unnecessary excision of the musculature of the tongue or floor of the mouth can impact the function of the patient. Satisfactory surgical excision with good margins around the tumor in all dimensions, especially the deep soft tissue, therefore depends on the surgeon's clinical judgment. Because the major sublingual glands lie in close proximity to each other, both glands almost always need to be excised even for unilateral pathology. The sublingual tumor is thus resected with a cuff of the underlying musculature of the ventral tongue for an adequate deep margin coupled with the opposite gland (**Fig. 15–30**).

The sublingual glands drain directly into the overlying mucosa of the floor of the mouth but are intimately related to Wharton's ducts and their mucosal puncta. The Wharton's ducts are identified and can be preserved for transposition if the resection is being

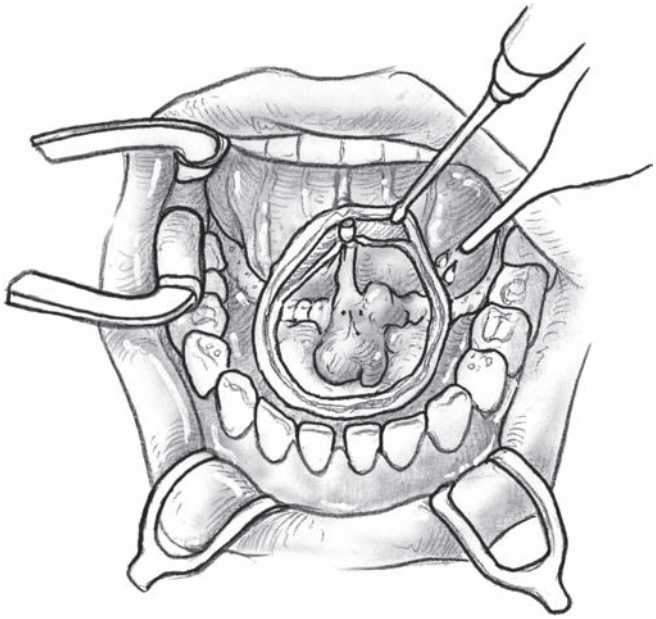

FIGURE 15–29 The extent of mucosal resection around the tumor is marked with an electrocautery.

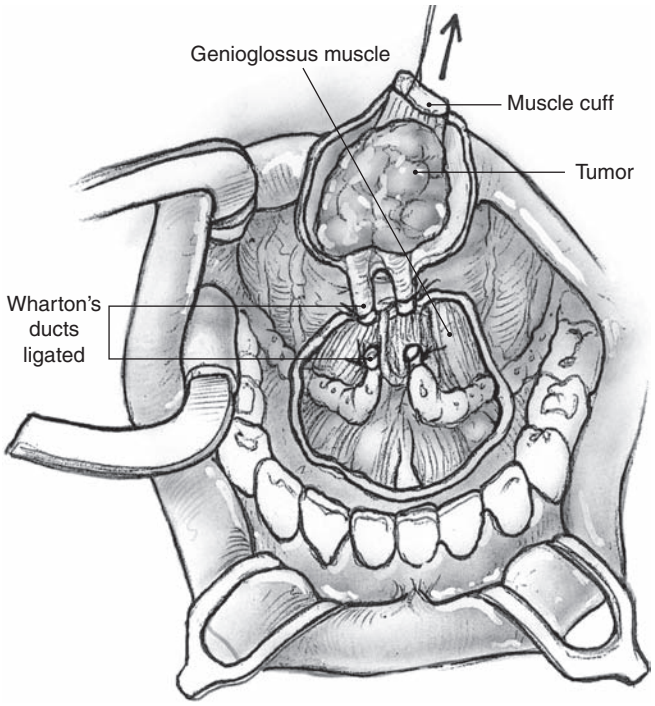

FIGURE 15–30 The sublingual gland tumor is resected with a cuff of underlying muscle for an adequate deep margin of resection.

performed for a benign tumor. It may be possible to transpose the opposite Wharton's duct following excision of even a malignant sublingual gland tumor, and every attempt should be made to preserve this function. The ducts are dissected for an appropriate length and transected at an oblique angle with a sharp knife well clear of the tumor. The mucosa of the lateral floor of the mouth at the posterior edge of the surgical defect is buttonholed, and the transected duct is brought out to the surface and sutured in place with fine, absorbable sutures (**Fig. 15–31**). It is generally advisable to resect the submandibular salivary gland if sufficient length of its duct is not available for it to be transposed or if the tumor is in close proximity to it. The surgical defect is reconstructed using a full-thickness skin graft harvested from the supraclavicular region. The graft is tacked into position using chromic catgut sutures and is secured in place with a Xeroform gauze bolster (**Fig. 15–32**).

Postoperatively, the patient is fed through a nasogastric feeding tube for approximately 1 week. Oral hygiene is maintained with frequent oral irrigation and rinsing. The Xeroform bolster is removed at the end of the week, and any skin tags around the surgical defect are trimmed. The nasogastric tube is removed, and the patient is started on clear liquids and gradually progressed to puréed food. The operation results in no functional deficit, as the mobility of the tongue with limited resections essentially returns to normal.

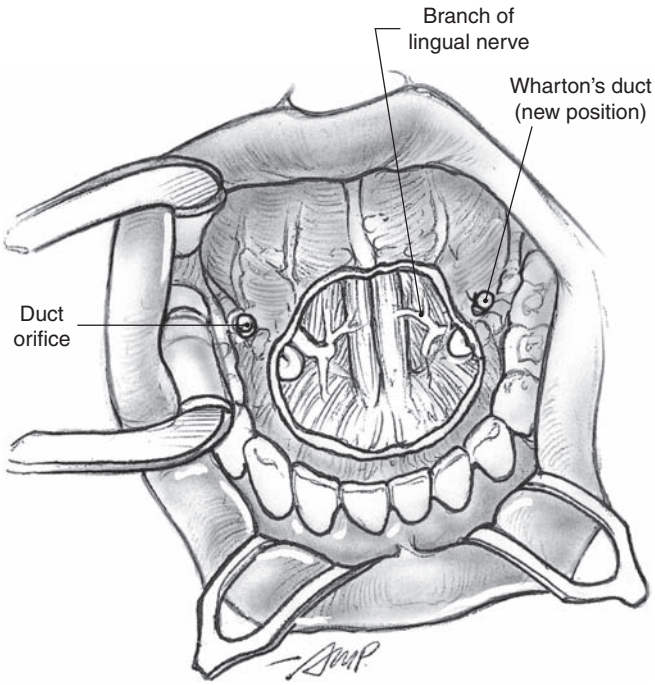

FIGURE 15–31 The stumps of the Wharton's ducts are transposed posterior to the surgical defect.

Larger tumors with more extensive involvement of the floor of the mouth require radical surgical excision. The tumor is resected en bloc with the structures of the adjacent floor of the mouth. Depending on the extent of the tumor, resection of the lingual nerve,

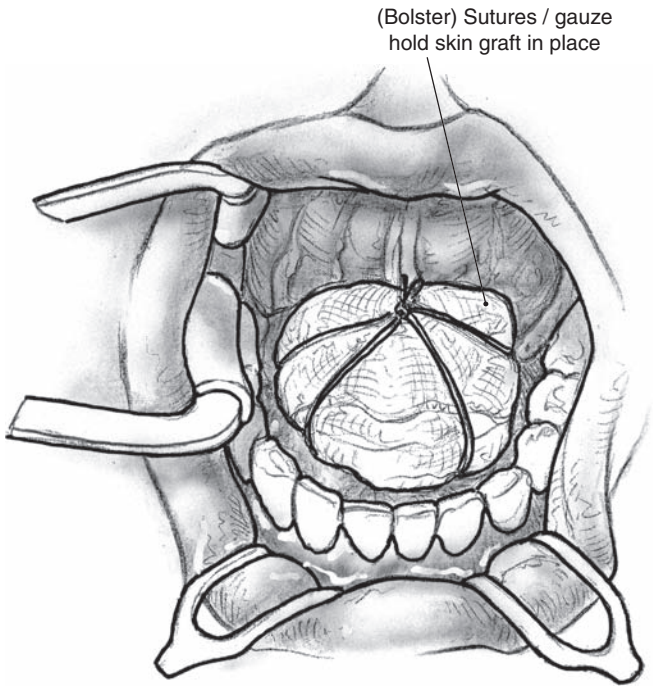

FIGURE 15–32 A Xeroform gauze bolster and black silk tie-over sutures are used to secure the skin graft.

submandibular gland, and even the mandible or the hypoglossal nerve may become necessary. Marginal mandibulectomy is appropriate for a tumor abutting the inner cortex, but actual involvement of the bone is best treated with a segmental resection. Reconstruction of these defects is complicated and may require microvascular free flaps, including the free radial forearm or fibula flaps.

■ Surgery for Tumors of the Minor Salivary Glands

The mucosa of the upper aerodigestive tract contains minor salivary glands in varying concentrations. Although tumors of the minor salivary glands are rare, the majority of them are malignant. They are usually submucosal and are covered by a normal-appearing smooth mucosa. Biopsy of these lesions using conventional cup forceps may not sample the submucosal tumor, and as described above, the fine dermatologic punch is capable of producing very reliable tissue cores. Accurate assessment of the local extent of these lesions is crucial to planning the surgical excision and almost always requires radiologic imaging. For minor salivary gland neoplasms involving the nasal cavity or paranasal sinuses, imaging will help not only to differentiate tumor from inflammatory process but also to determine the extent of the neoplasm. Imaging, as well as endoscopy, is necessary for pharyngo-laryngo-tracheal neoplasms.

Imaging studies will also allow differentiation of a parapharyngeal space tumor extending from the parotid and a parapharyngeal tumor of minor salivary gland origin. Parapharyngeal tumor excision via a transcervical approach has been described earlier for parapharyngeal tumors originating from a parotid tumor. Deep lobe parotid tumors with parapharyngeal extension generally require superficial parotidectomy prior to removal of the tumor. Parapharyngeal minor salivary gland tumors may require only dissection of the inferior division of the facial nerve.

Depending on the site of origin of the tumor and its extent, surgical operations for treating minor salivary gland tumors in other locations can range from a simple peroral excision of a hard palate tumor to more complex procedures, such as radical maxillectomy and tracheal sleeve resection. A discussion of all of these procedures is beyond the scope of this chapter, and detailed descriptions are available elsewhere.[1]

■ Conclusion

Surgery for tumors of the salivary glands encompasses a wide range of techniques and procedures. Successful outcome and optimal postoperative rehabilitation depend on a detailed knowledge of regional anatomy, meticulous technique, and multidisciplinary cooperation.

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16

Facial Paralysis Rehabilitation

ARA A. CHALIAN AND SARAH H. KAGAN

Patients with facial paralysis suffer significant functional, aesthetic, and psychosocial sequelae. Even single branch weakness or paralysis may leave patients with significant functional disability and aesthetic deformity. Spontaneous recovery from facial paralysis is rare except in some inflammatory conditions. Consequently, treatment of underlying conditions must be augmented with nerve repair and reconstruction of associated deficits to achieve optimal rehabilitation. This chapter reviews repair and reconstructive options for rehabilitation of patients with facial paralysis resulting from congenital, traumatic, inflammatory, idiopathic, and neoplastic conditions. The diagnosis of these congenital, inflammatory, idiopathic, and neoplastic processes, assessment of trauma, and the role of decompression and pharmacological management are, however, not the focus of this discussion and are not reviewed here. This discussion begins with an overview of physician–patient communication. The signs and symptoms of facial paralysis are then reviewed, followed by an outline of physical examination and diagnostic evaluation of facial paralysis. Planning surgically based rehabilitation follows, with discussion of surgical options, technique, and associated nonsurgical rehabilitative care and detailed analysis of primary options.

Physician–Patient Communication

Communication is the single most important aspect of successful surgically based rehabilitation for facial paralysis. Communication between the physician and the patient forms the foundation for therapeutic intervention most likely to result in optimal outcomes. Surgical repair and reconstruction have inherent risk to facial nerve function. Nuances of restoration and degrees of dysfunction are difficult for many patients to appreciate and accept. The range of recovery and potential for synkinesis and mass motion are not easily instilled even with detailed patient and family teaching. Both patient satisfaction and risk management issues are apparent in the context of repair for existing deficits, risk of less than full functional return, and possible complications. Thus building rapport with the patient and family and leading frank discussions that include realistic descriptions of the plan, the risks, and the expected course are essential. Finally, professional, empathic bedside manner and patient rapport are invaluable in the postoperative phase of rehabilitation.

Facial Paralysis

Signs and Symptoms

Facial paralysis is a condition made complex by the anatomical and functional intricacy of the facial nerve. A range of partial to total facial nerve injuries can manifest in a single branch or the entire nerve as facial paresis or paralysis. The branches of the facial nerve, as described in Chapter 1, comprise arborizations of the upper (temporofacial) and lower (cervicofacial) divisions. These include the temporal, zygomatic, buccal, marginal mandibular and cervical branches. **Table 16–1** outlines signs and symptoms by facial nerve branch.

TABLE 16–1 Branch Facial Nerve Deficits with Associated Signs and Symptoms

Branch deficit	Sign and symptom
Upper frontal	Brow ptosis
Upper zygomatic	Lagophthalmus
	Ectropion
	Corneal and conjunctival exposure
Zygomatic/buccal	Malar flattening
	Loss of nasolabial fold
	Nasal obstruction alar displacement
	Nasal twisting
	Lip commissure ptosis
Lower buccal/marginal	Oral commissure incompetence
	Lower lip ptosis
	Dysarthria
	Drooling

Prominent physical signs found in facial paralysis affect the brow and eyelid complex, the midface, and the oral complex. Brow and eyelid signs include brow ptosis, lagophthalmus, ectropion, and corneal and conjunctival exposure. The midface may show paresis or paralysis, nasal deviation, alar base drift, and nasal valve collapse. Oral complex signs include oral commissure ptosis, lip laxity, and oral incompetence. The effect of adjacent anesthesia and hypesthesia are often underestimated, especially in facial paresis as opposed to paralysis. Findings of twitches, tics, subtle asymmetries, and numbness may not be primary complaints for patients but are nonetheless important to elicit in a thorough assessment.

Patients complain of a variety of disabling symptoms associated with these signs. Potential loss of vision or visual acuity is common with corneal and conjunctival exposure. Nasal obstructive symptoms and malposition of the nasal base accompanies midface paralysis. Ptosis begets dysarthria and oral incompetence from oral commissure drift inferiorly and oral tone loss due to denervation of the orbicularis oris. Malposition of the lower lip, stemming from marginal mandibular branch weakness or combined inferior and buccal facial weakness, is also common. Aesthetic asymmetry is also disturbing to patients who see brow ptosis, nasolabial fold flattening, asymmetric faces, and exaggerated asymmetry with smile or other emotionally expressive states.

■ Facial Aesthetics

Facial aesthetics mandates a more qualitative approach to assessment. The smile is a central element of facial aesthetics in facial paralysis. Rubin[1] posits that smile pattern can be studied and classified as one of three types. The ''Mona Lisa'' smile is the most common at 67%; it is a product of the dominant action of the zygomaticus major. The corners of the mouth move laterally and superiorly, and the upper lip moves minimally.[1] The canine smile (31%) is a vertical elevation of the upper lip and then lateral lift of the corners of the mouth.[1] The toothy or full denture smile is rare at 2%.[1] It is created by simultaneous contracture of the depressors and elevators of the lips and commissure of the mouth.

The combined effects of dysfunction and aesthetic asymmetry generate significant psychological impact and social stigma. Often these conditions are the sequelae of the treatment of a potentially life-threatening carcinoma. Physical and mental functional status, along with the complex issues of age, identity, body image, and familial and social role, influences patient and family response and coping strategies during rehabilitation. Optimistic patients seem to transcend the symptoms of paralysis and participate more effectively in the rehabilitation plan. Factors such as grossly dysfunctional interpersonal or family dynamics, suspected substance use, and a significant psychiatric history are likely to influence coping and participation in rehabilitation and may augur behavioral complications during recovery or worsening perception of symptoms. Presence of these or similar factors in the history or assessment warrant appropriate psychosocial or psychiatric consultation. These consultations may be extremely helpful as the reconstructive plan is designed and implemented.

■ Patient Assessment

Patient assessment in facial paralysis is necessarily detailed and must include both systemic and focal considerations.[2] Patients typically present with a personal impression of acute onset facial paralysis. The history or exam may reveal that this acuity may or may not be the case; often, facial paralysis was subtly present and ultimately became visible to the patient and family. The medical history, as a highly important aspect of assessment, generally illuminates the underlying etiology and may offer significant prognostic implications. For example, ~80% of patients with Bell's palsy will recover complete function in the subsequent 6 months.[2] A history of varicella infection can be associated with later development of herpes zoster oticus resulting in facial paralysis. The rare schwannoma and neurofibroma can also manifest with facial paralysis as the presenting symptom. More ominously, a history of a malignant neoplasm with high distant metastatic potential, such as breast, lung, and renal cancers, may result in facial nerve involvement and subsequent paralysis. Similarly, history of local temporal or cheek skin cancers or parotid tumors with high potential for locoregional recurrence and perineural invasion in the absence of

a significant mass may create facial nerve pathology and consequent paralysis.

In the presence of known facial nerve invasion by primary neoplasms or metastases, tumor status, adjacent nerve and muscle status, and radiotherapy history and future treatment plans including radiotherapy should be assessed for their influence on the rehabilitation plan and effect on the surgical bed. The impact of radiation has been argued in both pre- and postoperative contexts. Conley[3] felt that the impact of radiation was minimal, and this was confirmed by McGuirt and McCabe[4] experimentally. Fisch[5] studied 42 grafted patients and reported that the function of nerve grafts could be diminished by 75–25% in patients undergoing post-operative radiotherapy.[5] The theoretical impact is on neovascularization of the surgical bed, though the nerve grafts per se are felt to be radio-resistant. We successfully utilize grafts for patients who will undergo radiotherapy.

A careful general history, including constitutional factors, is complemented by a detailed otorhinolaryngologic assessment along with the patient's story of the paralysis and associated symptoms. Major points to elicit in history taking are outlined in **Table 16–2**.

■ Physical Examination

Physical examination begins with a complete head and neck and cranial nerve examination. Cranial nerve examination should emphasize the facial, trigeminal, hypoglossal, and glossopharyngeal nerves. Further, special attention should be focused on temporalis and masseter function and tone, as these muscles may be used in the reconstruction. Otologic evaluation must also be included, as should oral cavity and mandibular assessment. The facial exam includes assessment of resting position and tone, symmetry, and partial or total weakness. Previous scars and incisions should be fully evaluated, and photographs or line drawings of scars and related findings may be helpful in diagnosis and follow-up.

Specific facial features to assess include brow position, eyelid position, and ectropion. The position of the lacrimal puncta should be carefully evaluated. An ophthalmology consultation may be indicated if any concerns about corneal protection or integrity arise or if further assessment of these structures is required. The appearance and position of the malar fat pad, suborbicularis oculi fat pad (SOOF), and nasolabial fold are important to note. Position of the nasal ala and caudal septum is often altered with inferior and medial drift of the ala and twisting of the nose to the nonparalyzed side. Lip tone, commissure position, lip length, and ability to purse the lips are generally altered. The associated gross functions of oral competence, speech, and mastication should be assessed concurrently. These functions are generally assessed qualitatively rather than quantitatively.

Clinical facial nerve function should be graded by standardized scales and refined by descriptors to further assist in the assessment of the deficit. The

TABLE 16–2 Major Points in History for Facial Paralysis

	General	Otorhinolaryngology	Paralysis
Overall	Self-rated health		Onset
	Functional status		Time
	Nutritional status		Perception
	Immune status		Symptoms
	Health/lifestyle habits		Pain
	Vocation/recreation		Dysesthesia
	Life expectancy		Paresthesia
			Other
Trauma	Potential donor sites	Facial trauma	Antecedent
		Head injury	
Medical	Inflammatory condition	Otologic conditions	Oncologic
	Upper respiratory infection	Otitis media	Pathology
	Herpes simplex infection	Otitis externa	Perineural invasion
	Herpes zoster exacerbation	Otomastoiditis	
	Lyme disease	Mastoiditis	
	Comorbidity	Cholesteatoma	
	Diabetes mellitus	Malignancy	
	Other chronic illness	Skin	
	Malignancy	Parotid	
	Metastatic status	Other head and neck	
Surgical	Oncologic	Oncologic	Parotid
	Other	Otologic	Skull base
Radiation	Potential donor site	Facial	Future need
		Oncologic	Oncologic etiology
		Dermatologic	

House-Brackmann scale is the current standard grading system for facial nerve function.[6] The Facial Nerve Disorders Committee of the American Academy of Otolaryngology–Head and Neck Surgery adopted the scale in 1985 as a reproducible, easily used clinical tool.[6] The House-Brackmann scale affords a general quantification of facial nerve function. Nonetheless, initial trauma or rehabilitative procedures may result in each branch or facial region having a different grade of function. Thus each branch or region should also be considered individually. Most easily, the face may be divided into the horizontal thirds, as in aesthetic surgery, and graded in separate exams.

■ Diagnostic Testing

The evaluation of facial paralysis should include imaging and other diagnostic studies as appropriate to the patient's history and current condition. Cross-sectional imaging, including magnetic resonance imaging (MRI) and computed tomography (CT) of the neck and often the temporal bone, is often undertaken as an initial step.[7] If the facial nerve is dysfunctional but CT is negative, MRI may help localize the site of facial nerve abnormality.[7] It will show abnormal enhancement at the site of the nerve pathology. Abnormal enhancement on MRI has been the only positive finding in some patients who have facial paralysis secondary to perineural invasion of previously resected skin neoplasms.[8–10] Positron emission tomography (PET) may also be performed if primary imaging does not reveal a gross lesion invading the facial nerve. Additionally, PET affords the diagnostic asset of the ability to rule out distant metastasis.

Functional testing is equally essential to complete evaluation. Often assessment of the visual anatomical and functional sequelae (including corneal anatomical and functional protective mechanisms and lacrimation) is necessary. Schirmer testing or visual and corneal assessments are important to protect the health and vision of the eye, especially for patients with xerophthalmia and/or corneal anesthesia from multiple neuropathy. Auditory and neurovestibular assessments may be indicated for internal auditory canal lesions. If a history of skin cancer is identified, workup may include biopsy of scar or other lesions in the field. Patients with newly diagnosed or concurrently evaluated parotid or other neoplasia require imaging pursuant to the mass itself, as well as excellent examination of the facial nerve. At baseline, neurological function of the parotid compartment and ear and skull base region function may be normal, impaired, or paralyzed for the preoperative patient undergoing facial resection.

Neuromuscular diagnostic testing evaluates nerve function and injury. Electromyography quantifies the potential of the facial nerve to reenervate the muscle. Electroneuronography comparatively qualifies the function of the neuromuscular unit. Hence, neuromuscular testing is critical to a successful rehabilitation plan.

Electromyography (EMG) helps define the ability of the muscle to be reinnervated.[11] EMG aids in identification of denervation atrophy or subclinical innervation, particularly if facial paralysis is long-standing (e.g., a duration of a year or longer). The normally innervated muscle will have functional motor axons; which will stimulate the motor end units of the muscles and generate normal voluntary action potentials. Facial muscles undergoing reinnervation will be identifiable as they generate polyphasic potentials. These may precede visible facial motion or tone. The normal muscle that is denervated will give the EMG pattern called denervation or fibrillation potentials. The denervated muscle will be electrically silent, reflecting denervation atrophy or in congenital cases potential absence of the muscle. The EMG technician or neurologist should indicate which muscles need to be assessed if not all regions of the face are involved.

Electroneuronography (ENoG) (also known as electroneurography or neuromyography) is helpful in quantifying the type of injury that the facial nerve has sustained, particularly in acute nontraumatic or surgical facial paralysis when the integrity of the nerve is not in question. EnoG assesses the integrity of the nerve–muscle unit through comparison with the unaffected side.[12] As a comparative technique, ENoG is useful in judging the need for decompression for inflammatory or traumatic conditions and monitoring nerve recovery. In surgical cases, neuropraxia with an intact nerve is most often treated expectantly with supportive management of sequelae. Electrical testing with ENoG will assist in postoperative counseling. The plan for rehabilitation after resection of intracranial lesions involving resection of the facial nerve will be addressed based on how much of the facial nerve root remains.

■ Surgical Rehabilitation

Rehabilitation Plan

Developing a plan for rehabilitation requires careful consideration of the individual needs of the patient, including comorbid disease and other relevant medical concerns, extent of paralysis and rehabilitation potential, and patient and family capacities and expectations, along with the technical capabilities of the surgeon. Discrete physical factors encompassing but not limited to the surgical bed and the length and other characteristics of planned procedures must also be considered. Immediate needs are balanced against potential and

capacity to create achievable short- and long-term rehabilitative goals in partnership with a well-informed patient and family. The postoperative plan and resultant expectations for patient and family participation should be clearly laid out in that partnership. Incorporation of physical therapy and other rehabilitative modalities including biofeedback are best programmed into the initial rehabilitative plan as optional or actual interventions.

The ideal repair and reconstruction plan results in normal facial appearance at rest and symmetric spontaneous emotional function, and symmetric voluntary function with no significant surgical scarring or delay in return of function. Ideal medical management limits side effects and results in full function without deficit. Unfortunately, if the facial paralysis results from removal or transection of the nerve, this is usually a goal that is not attainable. The goals and expectations should then be realistically reviewed by the patient and surgical team, to define the plan and achieve the best results possible. If the nerve is paralyzed from an inflammatory etiology, the clinical decision will be whether to decompress the facial nerve, or the middle ear and mastoid in cases of otomastoiditis. In cases of Lyme disease and viral neuronitis, for example, the treatment plan will involve consultation with an infectious disease specialist and the selection of an appropriate antibiotic or antiviral, most often with concomitant pulsed corticosteroids.

Ideal surgical management—the focus of this chapter—involves minimal or imperceptible donor site morbidity for nerve or muscle grafts with optimal return of function after reinnervation and engraftment occur. At its core, the plan for surgical repair and rehabilitation is based simply on the functional status and anatomical integrity of the facial nerve or its branches and muscle end organs. Nerve growth is the rate-limiting factor in reinnervation, and the quality of reinnervation affects overall rehabilitation. Muscle motor end-plate status is tied to reinnervation and thus is equally important when given that innervation, at the rate of 1.0 to 1.5 mm growth per day, could take 6 to 9 months for most grafts. Full restoration of static and dynamic facial aesthetics is, in a sense, the ''holy grail'' of facial nerve paralysis rehabilitation. Functional return is never complete with the current armamentarium of surgical and allied procedures; in measures of both subtle and, often, gross performance status.

■ Surgical Repair

The nature of paralysis (i.e., complete vs partial and paralysis vs paresis) and neuromuscular status, as well as the etiology, influences prognosis for functional return and options for rehabilitation. Factors affecting the surgical bed, such as a history or plan for radiation therapy, previous surgeries in the field, and related anatomical and tissue changes like fibrosis further narrow the rehabilitative surgical options. Repair and overall rehabilitation are dictated by status of the nerve, whether intact, transected, resected, or congenitally absent; muscle status, as having reinnervation (polyphasic), denervation (fibrillation potentials), or denervation atrophy as measured by EMG; and prognosis with expectation of likely, ambiguous, or absent functional return. The partially or completely intact nerve may be treated with a combination of drug therapy, surgical decompression, and monitoring. The completely transected or resected nerve with functional neuromuscular potential, however, warrants primary anastomosis or nerve grafting for repair.

Surgical repair of the facial nerve is accomplished through end-to-end anastomosis or nerve or neuromuscular grafts. Anastomosis is indicated in acute traumatic or surgical transaction as the anatomy of nerve ends allows. Nerve grafts are employed when the nerve cannot be approximated and the neuromuscular unit has sufficient functional innervation potential as judged by EMG and ENoG. Further, surgical support for the intact motor end plate may be accomplished with temporary or ''babysitter'' nerve grafts from adjacent cranial motor nerves. Neuromuscular flaps and grafts are necessitated by absent innervation potential.

Patients with persistent facial weakness after reinnervation with either nerve grafts or neuromuscular flaps present an interesting challenge. If they do not show denervation potentials on EMG, then a new interposition, cross-face nerve, or transposition hypoglossal nerve graft can be performed. These patients are not benefited by neurotization procedures such as nerve–muscle pedicles or nerve to muscle–innervated muscle grafts into the muscle. This type of procedure will not work unless the nerve supply to the muscle is transected. Moreover, the issue of graft take in preexisting facial paralysis has been debated; nonetheless, we undertake graft procedures as the opportunity cost is low. Grafting may be delayed, or both graft and static procedures may be utilized in the context of this clinically equivocal debate.

Anastomosis or primary repair; nerve grafts including interposition graft, cross-face nerve graft, trigeminal to facial nerve graft, and hypoglossal to facial nerve graft; dynamic sling procedures; static or adynamic sling procedures; and adjunctive aesthetic procedures are outlined in the following section. Summary for each type of procedure is offered, along with discussion of indication, procedure, and technique for selected operations. Nerve graft donor sites are also delineated.

Anastomosis or Primary Repair of Nerves

Indication

Transection of the facial nerve or its branches is best treated with primary repair (**Fig. 16–1**). Sharp lacerating transection is most easily repaired at the time of presentation or within 48 and, at the latest, 72 hours so the distal nerve can be identified with nerve stimulators. If a surgical delay is warranted for other reasons, such as physiological instability, then nerve repair becomes more difficult after 24 to 72 hours. Importantly, nerve stimulation with neuromuscular response is lost after this period. Further, local inflammatory changes make the distal nerve end difficult to identify. The nerve may still be identified anatomically, confirmed with frozen section histologic assessment, and then repaired. In all cases, the surgical bed should be well vascularized.

Procedure and Technique

The nerve ends are isolated and cleared of connective tissue from the nerve sheath for the first millimeter or two from the edge of the transection. In delayed repair for deficits with no loss of nerve length, primary repair is preferred, with freshening of the nerve and epineurium, followed by primary neurorrhaphy. The nerve may be mobilized if resection is required. However, mobilization can further alter blood supply, and one must weigh the extent of mobilization with the potential harm versus benefit. The effects of tension and the benefit of eliminating tension in peripheral nerve repair suggest that an interposition nerve graft is a better option than mobilization.[13–16] Though the facial nerve is thought to have topographic orientation, the orientation cannot be identified even with magnification and is thus clinically insignificant in repair.[17–21] The epineurium is anastamosed in an end-to-end or end-to-side fashion with monofilament microsutures.[22] In delayed cases the edges of the nerve ends should be freshened. The nerve fascicles (endoneurium) may extend beyond the retracted epineurium but will usually be overcome through anastomosis.

Fine monofilament sutures (e.g., 8.0, 9.0, or 10.0) are placed through the epineurium. The fewest number of sutures are used to minimize inflammation, although the actual number varies based on size of the nerve. For example, distal anastomosis to facial branches 6 to 8 cm from the stylomastoid foramen usually requires one or two sutures. The facial nerve trunk at the level of the pre- or post-stylomastoid foramen may need 3 to 5 sutures. Needle size is at the discretion of the operator. Loop or microscope magnification is required, as are jeweler's microforceps and a micro-needle driver, preferably of the nonlocking type. Adhesive, bioabsorbable and Silastic couplers and tube guides have also been used.[23]

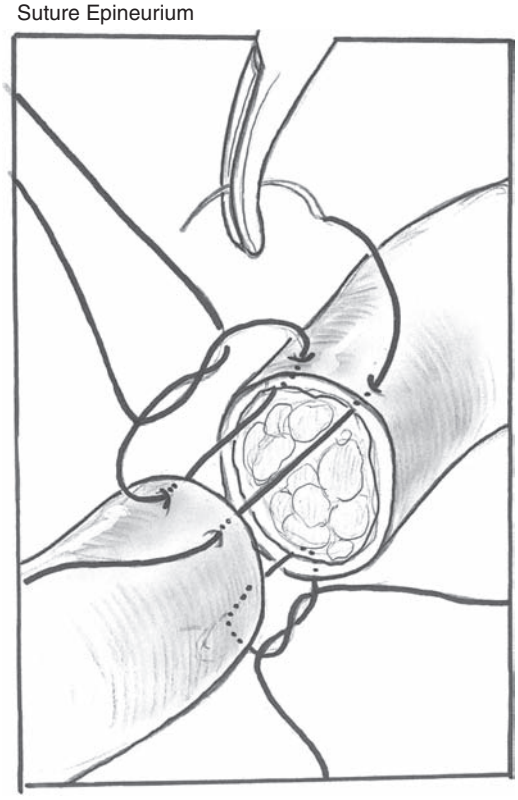

FIGURE 16–1 End-to-end anastomosis of epineurium in primary nerve repair.

Nerve Grafts (Interposition Nerve Grafts)

Indication

Segmental defects of the main trunk of the facial nerve, pes, or individual branches are best treated with interposition nerve graft. This technique allows for multisegment rehabilitation to end-plate intact muscle. The direction of the nerve graft is debated as being of variable clinical importance. If multiple branches are needed, then orientation is based on anatomy of the graft. In simple segment branch grafts, some authors have postulated that reversing graft direction facilitates neural regeneration.[22]

Procedure and Technique

A nerve graft placed in the mastoid to graft to the vertical segment of the facial nerve can be secured with one, two, or often no sutures depending on the ''fit'' in the canal.

Segmental Defects in the Field of Soft Tissue Injury

For facial nerve injuries in the area of significant tissue necrosis such as blast injury, avulsion, or crush injury, the primary goal is to identify the distal and proximal ends of the nerves. These should be tagged with monofilament sutures. Most often these cases will require nerve grafting when the bed is suitable. If the soft tissue envelope is absent, then the area will

require flap reconstruction of the skin and envelope. This may be a local fasciocutaneous flap or a remote tissue transfer such as a pedicled or microvascular flap. For patients with acute loss of facial nerve continuity due to laceration, tumor resection, or other process causing anatomical disruption of facial nerve continuity, the primary reconstructive goal is reestablishment of facial nerve continuity with primary or interposition graft repair.

For patients with preexisting paralysis and the presence of neoplasm, muscle status may be the most important element of repair. Electromyography must be used to assess the status of the muscle in cases of segmental nerve defect presenting for delayed repair or patients with prolonged duration of tumor and paralysis. The muscle loses motor action plates if it has been denervated for more than 12 to 18 months. The nerve graft cannot cause activation of denervated muscle, and hence the use of muscle replacement with muscle-free flap or use of adjacent muscles driven by other motor cranial nerves (i.e., trigeminal) must be considered.

Nerve Graft Donor Sites

Sural Nerve

The sural nerve allows for the longest, largest caliber nerve graft (**Fig. 16–2**). This graft offers a distant harvest/donor site option that allows for two-team harvest and ablation. It is contraindicated in patients with neuropathy from chemotherapy, diabetes, or trauma, with venous stasis disease, and with arterial insufficiency, as the normal patient will experience some anesthesia over the lateral inferior foot as a result of harvest.

Clinical Pearls

1. The nerve is adjacent to the small saphenous vein/sural artery vein.
2. The nerve can be harvested through a linear vertical incision or multiple stair-step (~1 cm) incisions with intervening subcutaneous dissection along the course of the nerve.
3. A vein stripper may be used to harvest the nerve.
4. The nerve graft obtained can be up to 25 to 40 cm in length, contingent upon the height of the patient.

Cervical Sensory Nerves

Cervical sensory nerves make an ideal graft with sufficient length and branching to meet the needs of a complex multisegment facial nerve defect. The great auricular nerve, given its terminal two or three branches, can serve as the major graft branch (**Fig. 16–3**). The great auricular nerve can be traced to Erb's point at the posterior border of the sternocleidomastoid. From Erb's point, the adjacent sensory nerves, such as the transverse cervical nerve and posteriorly directed sensory branches, can be followed peripherally and inferiorly into levels IV and V. This technique yields grafts up to 14 cm long with four or five branches as the nerves fuse at Erb's point to a single branch and are followed deep to the root of the neck posteriorly to the sternocleidomastoid muscle. This graft should be harvested prior to starting a neck dissection if it is clinically indicated and not prohibited oncologically.

Medial Antebrachial Cutaneous Nerve

The medial antebrachial cutaneous nerve from the volar forearm offers a graft option with low donor site morbidity. The volar forearm is subsequently anesthetic, but most patients do not perceive this as a significant deficit. The graft is of appropriate size and length (at least 10–15 cm), and arborizations allow for three to five branches if needed. Further, this nerve graft can be harvested with and separated from a radial forearm flap in the case of microvascular reconstruction of the ablative defect. The bulk of the graft can also be kept embedded in the flap and the distal ends isolated for anastomosis, providing a vascularized nerve graft. The length of the graft is substantial if followed to distal arborizations.

Clinical Pearl

1. The sural nerve site is preferable if a radial forearm flap is not being harvested simultaneously.

Cross-Face Nerve Grafts

Cross-face nerve grafts provide the most precise rehabilitative option for patients who have complex multisegmental facial nerve defects where resection ablates the proximal facial nerve. Contralateral facial nerve branches are used to drive affected facial muscles. One of the branches from the unaffected side is employed in this technique, thereby weakening somewhat the function of that contralateral face as a result of the graft. However, this weakness affords secondary benefit in helping to restore overall facial symmetry. The cross-face nerve graft can ''drive'' innervate muscle on the injured facial nerve side. The muscle must have intact motor end plates. This technique provides the optimal option for these difficult cases, as very specific nerve branches from the contralateral facial nerve are used as the motor nerve for driving the contralateral matching muscle unit. This procedure should provide the most near symmetry in cases of successful engraftment. The nerve grafts are most often harvested from the sural nerve site, which allows for appropriately lengthy nerve grafts.

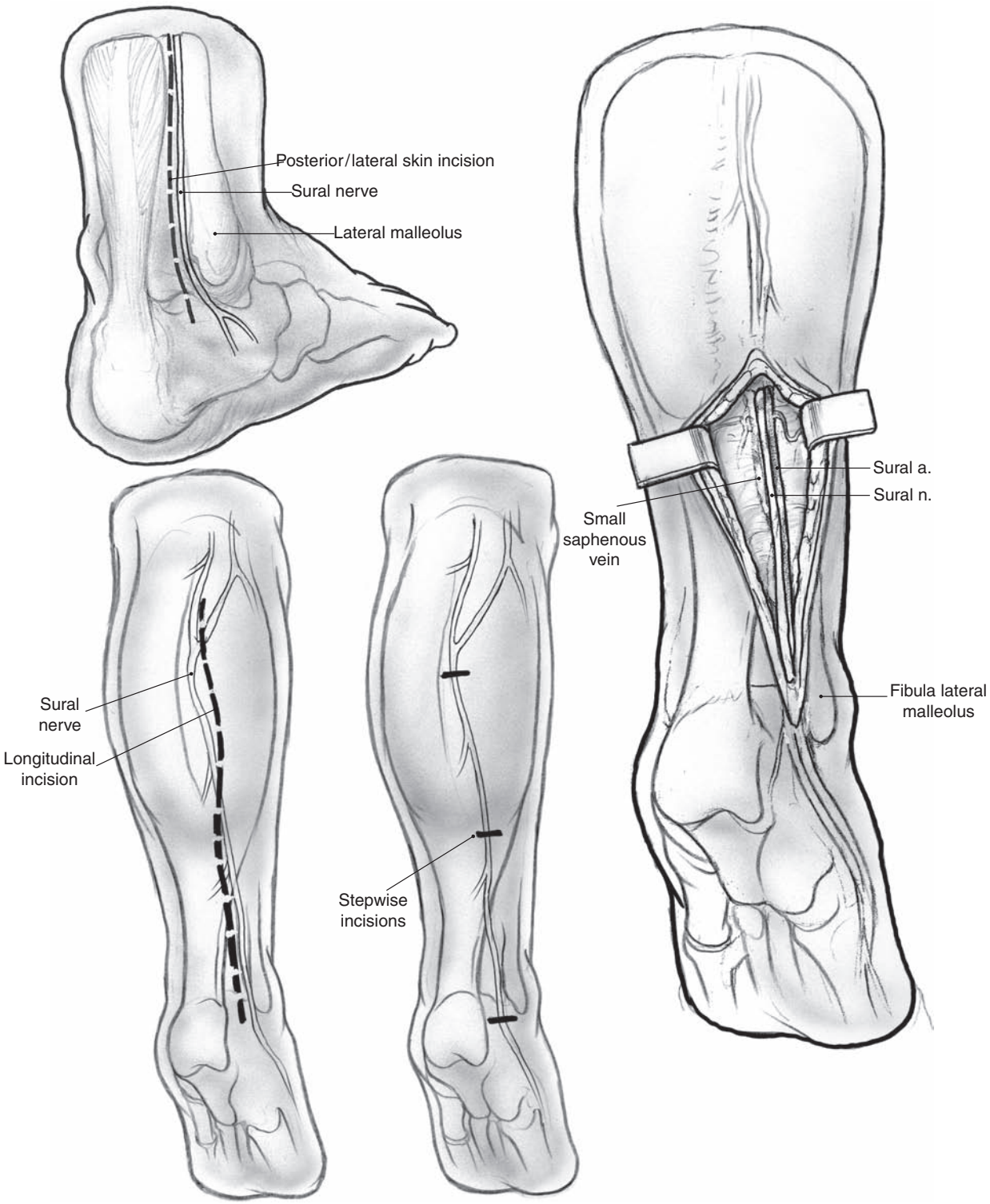

FIGURE 16–2 The sural nerve provides the longest, largest caliber graft. Stepwise or longitudinal incisions are utilized for harvest.

Cross-Face Nerve Graft to Intact Muscle

Multisegment rehabilitation to end-plate intact muscle with cross-face nerve grafts is required for patients who have no remnant proximal facial nerve. For example, this technique is useful for patients with internal auditory canal lesions with no proximal nerve available for interposition grafting procedures.

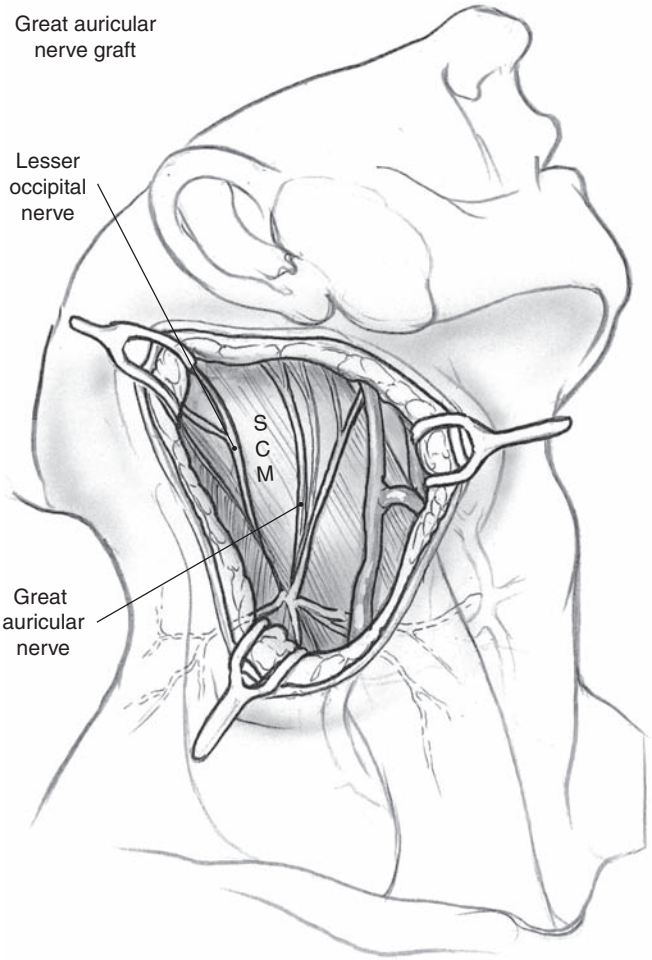

FIGURE 16–3 The great auricular nerve, when traced to Erb's point, allows for harvest of a multibranched graft. SCM, sternocleidomastoid muscle.

Cross-Face Nerve Grafts to Neuromuscular Free Flaps

Multisegment rehabilitation to muscle without intact motor end plates is necessary in cases where there has either been muscle dennervation or muscle tissue loss from surgical resection, trauma, or another condition. The procedure provides muscle that can be driven by the facial nerve from the contralateral face. These candidates may be equally well served by the dynamic solution of ipsilateral temporalis or masseter flaps driven by the trigeminal nerve. This is, however, not an appropriate procedure for patients with high-risk tumors and high likelihood of mortality in the near term.

Transposition Hypoglossal Nerve Graft

Indication

Skull base surgery patients with known transection of facial nerve at the internal auditory canal (IAC) or brainstem, with no suitable proximal remnant for grafting, are primary candidates for a hypglossal nerve graft (**Fig. 16–4**). This procedure is also an option for patients who have an intact injured nerve with paralysis and denervation. However, the donor deficit from hijacking the trigeminal or hypoglossal nerves can be significant and hence deserves judicious consideration. The option of hypoglossal or trigeminal facial anastomosis may serve as definitive rehabilitation or as a ''babysitter'' with concurrent cross-face nerve grafts to the affected branches.[24]

Procedure

The procedure for hypoglossal to facial nerve transfer has evolved to avoid the need for a secondary interposition graft. Instead of segmental resection, ~40% of the ipsilateral, hypoglossal nerve is separated from the fascicle. The portion of the nerve is then mobilized and anastmosed to the facial nerve stump. Reinnervation ensues over the next 3 to 4 months.

Technique

Most commonly, this anastomosis uses a short interposition graft to the cut end of the hypoglossal nerve. Alternatively, a less morbid approach is to partially transect one third to just less than half or ~40% of the hypoglossal nerve cross section. This portion is then anastomosed to the interposition nerve graft.[25,26] An alternative, which has the least morbidity, is the end-to-side anastomosis of an interpostion graft through epineural windows.[22,27,28] If the facial nerve is absent, the ansa hypoglossi innervated strap muscle can be used to neurotize the facial mimetic muscles (**Fig. 16–5**).

Transposition Mandibular Branch of Trigeminal Nerve Graft

Indication

Indications for transposition hypoglossal nerve graft apply to use of the mandibular branch of the trigeminal nerve.

Procedure

The nerve can be mobilized to anastomose to a common facial trunk or upper/lower division as definitive or ''babysitter'' prior to cross-face nerve grafts.

Technique

The muscle or a portion can be mobilized on the neurovascular pedicle to dynamically animate the oral commissure and lips. The mobilized strip of muscle will be sutured to the oral commissure–upper/lower lip at the vermilion-cutaneous junction.

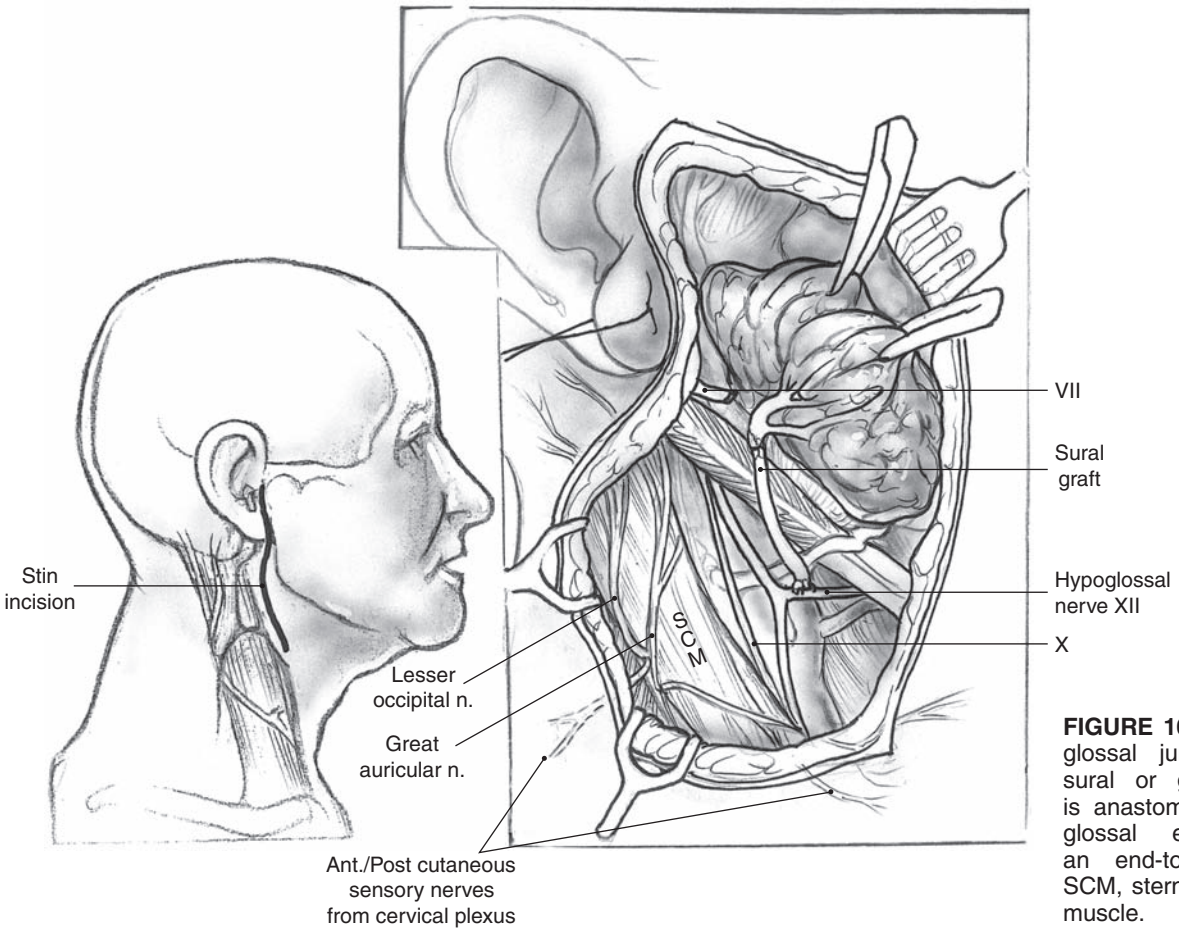

FIGURE 16–4 In a hypoglossal jump graft, the sural or great auricular is anastomosed to hypoglossal epineurium in an end-to-side fashion. SCM, sternocleidomastoid muscle.

Dynamic Slings

Dynamic support of involved facial musculature is achieved through a variety of means. The masseter muscle and trigeminal nerve may be transferred to address the midface and oral complex. The temporalis muscle can be employed to restore the lip and oral complex.

Masseter Muscle Transposition

Indication

Masseter muscle transposition offers definitive dynamic support to the affected midface, lips, and oral commissure (**Fig. 16–6**). Further, its use can afford temporary support to patients with oral incompetence and nerve grafts or paresis who are expected to regain function or to supplement function in patients with incomplete recovery. The masseter flap can also be used in combination with an interposition graft to the upper face. The vector of pull of the temporalis muscle flap overall reconstructs a better smile because the temporalis muscle is thinner, longer, and has a greater contraction excursion. In addition, the masseter flap will create a bulge in the corner of the mouth and a concavity over the mandible. The masseter flap can be rotated, however, following special situations such as after radical cancer surgery to the parotid. The lateral lip and oral commissure will undergo myoneurotization after fresh denervation of the respective facial muscles.

Technique

The neural innervation to the masseter muscle arises deep to the zygomatic arch and deep to the masseter muscle running from posterosuperior to anteroinferior and must be preserved. The periosteum of the mandible must be elevated along with the masseter muscle, as sutures will not hold to muscle alone. The entire muscle is used.

Temporalis Muscle to Lip Complex Transfer

Indication

This procedure dynamically restores position and tone to the lateral lip and oral commissure, and function to the midface lip and lateral nose with good outcomes (**Fig. 16–7**). It provides temporary support for patients with oral incompetence and nerve grafts or paresis who are expected to regain function and supplements

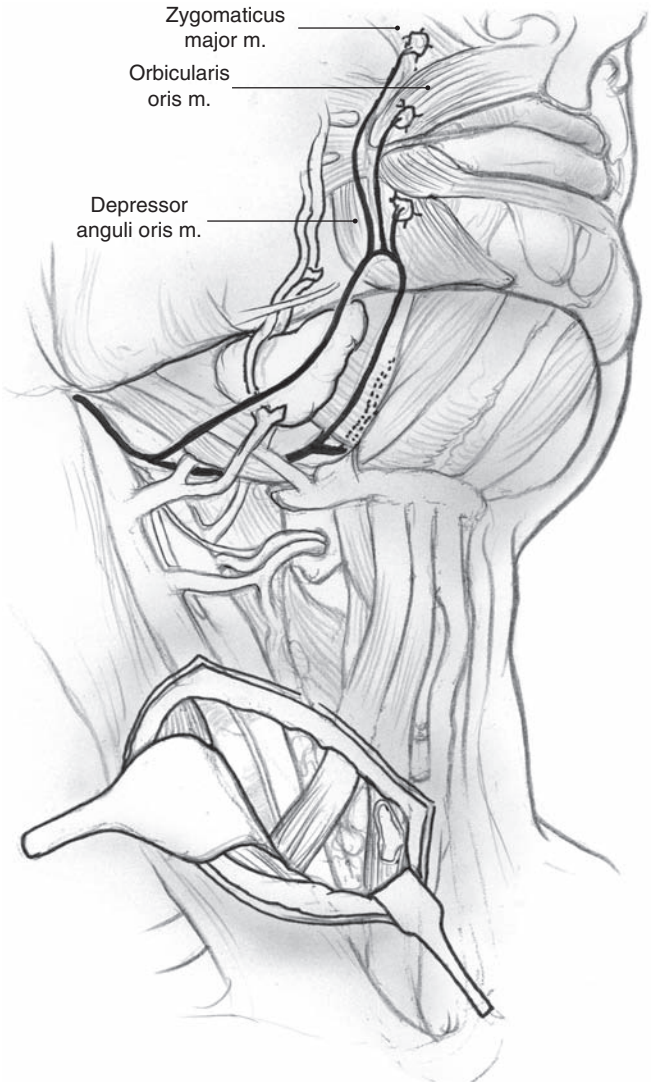

FIGURE 16–5 Ansa hypoglossi innervated strap muscle can be employed for neurotization if the facial nerve is absent.

function in patients with incomplete recovery. The superficial temporoparietal fascia can be used to minimize scaphoid defect from mobilizing a portion of the temporalis muscle. Bulk and bulge are generally minimized through atrophy over time after careful appraisal of the initial volume of tissue transferred. The expected amount of excursion of the lip that can be achieved in this transfer is ~1.5 to 2.0 cm.

Technique

The neurovascular supply to the temporalis muscle is from the deep surface of the muscle. Previous radical parotidectomy or mandibulectomy may have damaged the blood supply and should be considered in planning the use of this procedure. The middle one third of the muscle is used, after the overlying and posterior temporoparietal fasciae are mobilized and reflected out of the way. To help further refine the choice of the temporalis muscle segment, the vector of pull can be diagrammed at the oral commissure and extended out to the temporalis.

Procedure

1. The temporalis muscle flap is designed to be ~1.5 to 2.0 cm at the base (zygoma). It can be made wider at the distal portion.
2. Dissect the flap off the temporoparietal bone to the zygomatic arch; the arch will serve as the fulcrum. The neurovascular pedicle is on the deep surface. Just above the level of the zygomatic arch one should be careful not to divide the fibers prior to assessing the pedicle.
3. The distal dissection into the cheek inferiorly to the lip should be in a subcutaneous plane not only to avoid intact nerve or nerve grafts, for patients who may be able to recover nerve function, but also because this is the plane of insertion of the facial mimetic muscles.
4. The distal end of the muscle is then split into two or three segments. Most often two are ideal. They are then sutured to the surface of the orbicularis oris at the mucocutaneous junction of the vermilion.
5. The repair is performed with permanent suture with buried knots. Braided or monofilament permanent suture, usually 3.0 or 4.0 size, is suitable.
6. Muscle strips should be drawn taut, with an intraoperative lip position that of a casual smile, essentially overcorrected from baseline symmetric commissure position.
7. The length of the muscle strips should not be augmented with temporoparietal fascia or other material, as it may fibrose and prevent direct transmission of muscle force to the orbicularis oris and commissure. If necessary, the lip or midface subunit should be mobilized to reach the graft by superficial and/or subperiosteal dissection.
8. The temporoparietal fascia is then mobilized into the defect.
9. If autologous fat or dermal allografts are used, longer-term antibiotic coverage may be beneficial, though I personally do not augment with allograft.
10. The grafts should be sutured into position.
11. A short-term drain, cool compresses, and analgesics are helpful in wound healing and pain management.
12. After a period of early postoperative healing, physical therapy for muscular training through

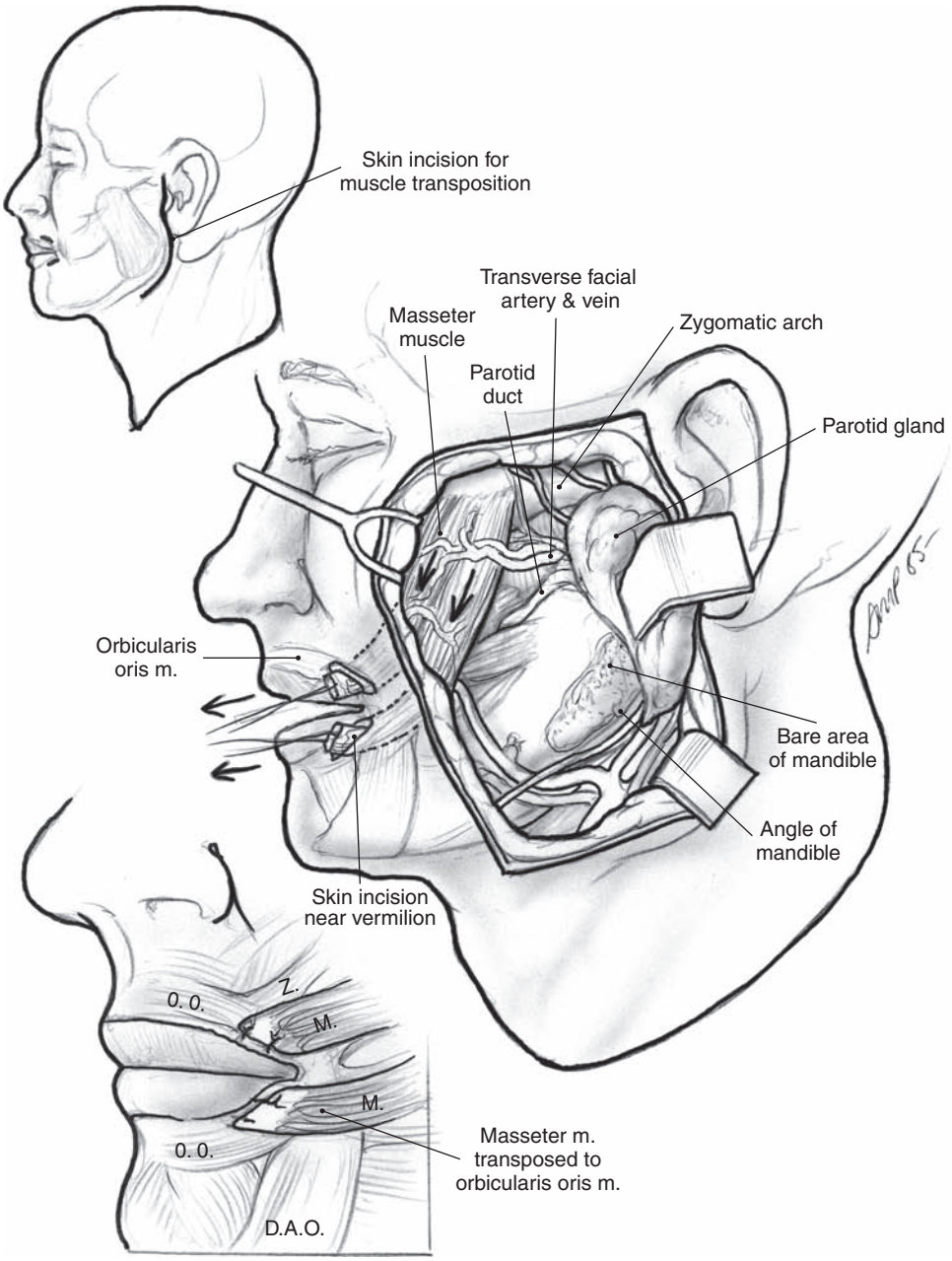

FIGURE 16–6 The masseter muscle is mobilized, divided into two branches, and sutured to the surface of the orbicularis oris to achieve definitive dynamic support. Overcorrection is recommended.

mimed mastication and other exercises can be instituted for training and restoration of symmetry.

Neuromuscular Grafts

Indication

Reconstruction of defects with intact nerve but absent muscle (e.g., cases of midface or lip tumors with resection of the facial mimetic muscle as the end functional unit) are addressed through application of neuromuscular grafts. Serratus, gracilis, and pectoralis minor muscles are all suitable donor sites.

Technique

Basic technique includes transplantation of muscle and nerve with engraftment to native facial nerve branch stump. Options encompass the serratus for multiple strips or the gracilis for single strip of muscle. Serratus can be harvested with low donor site morbidity with a pedicle based on a branch of the thoracodorsal artery and vein. The long thoracic nerve is parallel to the pedicle. The proximal first through approximately fourth strips of the serratus must be preserved to prevent winging of the scapula. The gracilis vascular supply is a branch of the profunda femoris artery and vein and occasionally from the medial circumflex femoris vessels. The motor nerve supply is the anterior

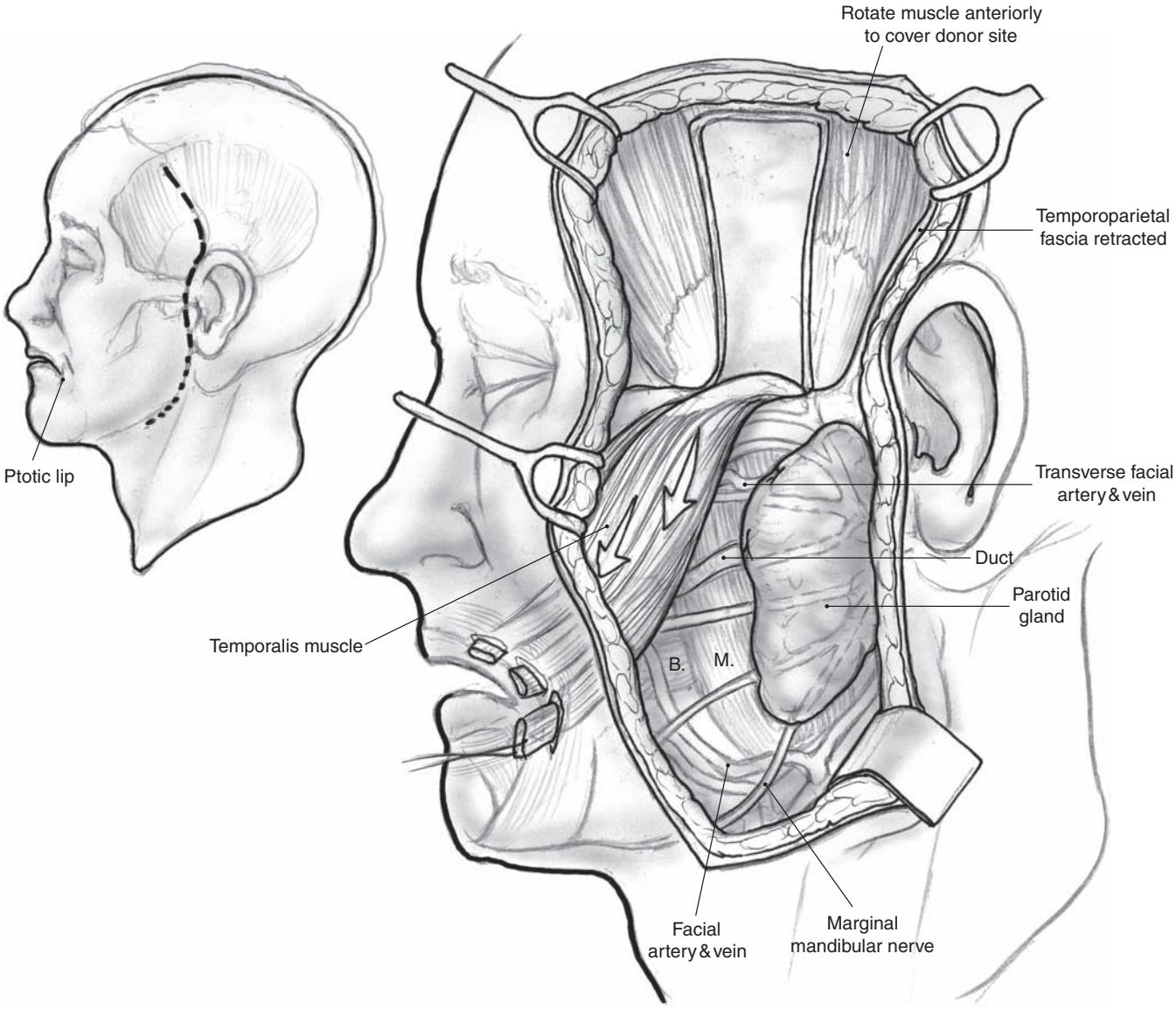

FIGURE 16–7 The middle third of the temporalis muscle is mobilized, divided into three branches, and sutured to the surface of the orbicularis oris to achieve definitive dynamic support. Overcorrection is recommended.

branch of the obturator nerve. The pectoralis minor was pioneered by Terzis and colleagues to rehabilitate facial mimetic and periorbital muscles.[29,30] Its harvest results in minimal donor site morbidity. The vascular supply is variable, stemming from the lateral thoracic artery (predominant presentation), direct branch of the axillary artery, or pectoral branch of the thoracoacromial artery. Venous drainage is similarly variable and includes venae comitantes and a direct vein. Innervation is predominantly provided by a major branch of the median pectoral nerve. This graft has a short pedicle. All of these muscles are revascularized, based on their pedicles, to the superficial temporal, facial, or adjacent arterial and venous vessels. Use of these reconstructive options in rehabilitation of facial paralysis requires skill in microvascular techniques.

■ Complex Challenge: Functionally Incomplete Innervation

The challenge of incomplete facial nerve or graft function is clinically difficult to address. Electrophysiologically, the involved facial muscle has an intact nerve motor unit but is incompletely innervated or is an injured muscle. Hence, function will be compromised. Possible solutions include contralateral partial chemical denervation with botulinum toxin (Botox) or contralateral nerve transection or division of the partially functional nerve graft with reanastomosis. The option of augmenting midface position with a dynamic temporalis muscle sling or facial static suspensions or lip/lid shortening procedures is a useful adjunct. The solution that is not an option is a nerve muscle pedicle from

the nonfacial nerve muscle donors. This neurotization procedure cannot be performed if muscle is even partially innervated.

Adjunctive Aesthetic Procedures

Most broadly, rehabilitation of functional and aesthetic signs and symptoms associated with affected branches of the facial nerve are addressed through an array of reconstructive surgical options. **Table 16–3** outlines facial nerve branch deficits, associated signs and symptoms, and options for surgical nerve, functional, and aesthetic repair and reconstruction within the rehabilitation plan. Repair of Stensen's duct is often necessary, given its anatomical proximity to the facial nerve, to complete reconstruction in cases of trauma.

Targeted aesthetic procedures offer reconstructive refinements to address specific needs of individual patients. Brow ptosis is addressed through brow lifts, either endoscopic or direct midforehead (**Fig. 16–8**). Techniques from aesthetic surgery should be adopted, within the surgeon's skill base, and targeted to meet the patient's needs. In the case of nasal valve collapse, alar battens offer an effective reconstructive option. Lagophthalmos can be addressed with gold weight placement and canthoplasty levator release. Ectropion repair may be achieved with canthoplasty and wedge resection or classic tarsorrhaphy to fuse the eyelid closed for temporary or permanent protection of the cornea/eye. Canthoplasty is important to augment the treatment of the paralyzed eye. Temporal and zygomatic grafts often are difficult to perform for advanced skin cancers invading into the parotid in this area. If this is the case, the lateral canthoplasty will correct the ectropion. Patients and physicians should be aware that the effects of gravity and aging will usually lead to further laxity and may require intermittent revisions of this procedure. In aesthetic treatment of ocular signs of facial paralysis, eye care, including emollient ointment and artificial tears, is necessary to ensure eye health.

Gold Weights

Indication

Lagophthalmos, inadequate eyelid closure, with resultant risk for exposure keratitis

Procedure

Placement of a gold, or alternatively titanium, weight into the eyelid allows passive closure of the eyelid to correct the Bell's phenomenon. The effect of concurrent canthoplasty or brow lift should be considered if this procedure is undertaken. The weight should then be test fitted with the new brow and lid position. The eyelid canthal spring is not addressed here, as it requires significant surgical experience to minimize incidence of complications such as device extrusion.

Technique

1. The gold, or titanium, weight should be test fitted on the eyelid prior to starting the procedure.
   a. With the patient sitting up, the weight should be held to the lid with a small portion of Steri-Strip or cutaneous adhesive, such as benzoin or mastisol. The weight may amplify or cause ptosis, triggering

TABLE 16–3 Branch Facial Nerve Deficits, Associated Signs and Symptoms, and Rehabilitative Options

Branch deficit	Sign/symptom	Procedures
Upper frontal	Brow ptosis	Brow lifts Endoscopic Direct midforehead
Upper zygomatic	Lagophthalmus Ectropion Corneal and conjunctival exposure	Gold weight Levator procedures Canthoplasty Lateral Medial Tarsorrhaphy Tarsal strip
Zygomatic/buccal	Malar flattening Loss of nasolabial fold Nasal obstruction alar displacement Nasal twisting Lip commissure ptosis	Fascial suspension Midface and SOOF lifts Microvascular neuromuscular grafts Nasal valve spreader "batten" grafts
Lower buccal/marginal	Oral commissure incompetence Lower lip ptosis Dysarthria Drooling	Fascial slings Lip excisions

SOOF, suborbicular oculi fat

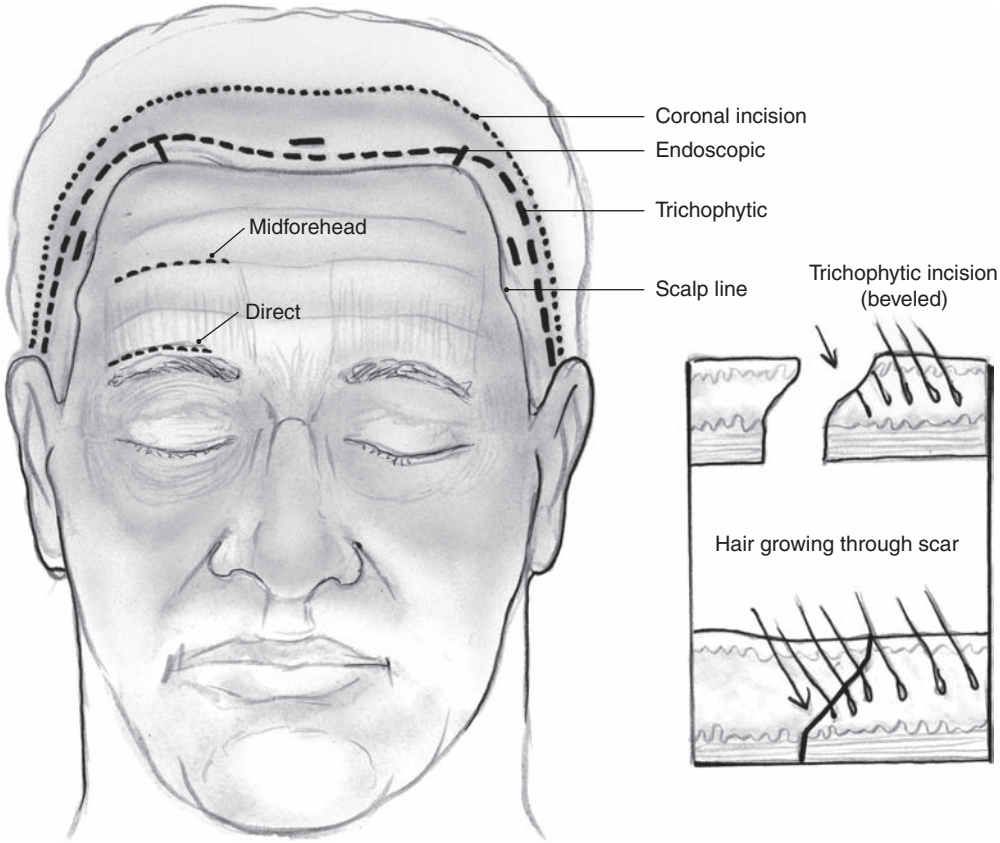

FIGURE 16–8 The multiple approaches and incisions for brow and forehead lifts are delineated in schematization.

assessment of the lid–limbus relationship. The patient's perception of field of view should also be elicited.

   i. The most commonly used weights are those of 0.8 to 1.0 g.
   ii. The patient can be assessed prior to surgery in the office; many companies offer trial weights for office use.

2. Local anesthesia with or without sedation provides adequate anesthesia for placement.
3. The incision is placed in the supratarsal crease, ~1.5 cm or adequate length to allow satisfactory dissection and exposure of the tarsus.
4. Dissection extends, in the submuscular plane, to the tarsal plate.
5. The gold or titanium weight is placed in the dissected pocket.
6. The weight is secured to the tarsus with permanent monofilament, ~5.0, preferably clear suture.
7. The orbicularis is coapted with a fine Vicryl 5.0 suture.
8. Cutaneous closure is achieved with absorbable or monofilament.
9. Cool compresses can be provided for the first 24 hours postoperatively to minimize swelling and pain.

Static slings offer the option of fine-tuned static repositioning of the face. The slings are positioned to elevate the oral commissure, re-create a nasolabial fold, and lateralize and lift the nasal alar base. Fascia lata, Alloderm (Life Cell Corporation, Branchburg, NJ), suture material, Gortex (W.L. Gore and Associates, Flagstaff, AZ), and barbed sutures or sutures with studded alloplastic pledgets have been used. The material for the sling most often used is the autologous fascia lata. The fascia lata can be harvested from the lateral thigh under local anesthetic if the procedure is being done under local anesthetic with sedation. The fascia lata can be retrieved with a fascia lata stripper, which is often available in most operating rooms. If not, two or more small incisions on the lateral thigh can be used to harvest the fascia. The fascia is classically suspended to the zygomatic arch or temporalis fascia. Alternatively, it can be attached to the infraorbital rim periosteum or the bone itself for a more secure position. Permanent sutures may be used.

Face lift and suspension techniques may be borrowed from aesthetic surgery as part of the rehabilitation planning for facial nerve paralysis. For example, the subperiosteal face lift can be used to augment midface rehabilitation through suspension techniques to address the nasolabial fold and oral commissure with simultaneous midface subperiosteal lifting.

Lip resections target signs and symptoms of facial paralysis stemming from anesthetic, adynamic tissue in the oral complex. Resection of the lower lip can help restore position and decrease the amount of anesthetic and adynamic tissue in the lower face. Fascial strips or allografts can also be used to create a cerclage that will tighten and can also be used to suspend the lower lip. This procedure can combat lip ptosis and oral incompetence with drooling. The typical lip wedge resection techniques with multilayer muscular mucosal and cutaneous repair are performed to shorten the adynamic portion of the lip. This resection should be performed as laterally as possible to avoid injuring any partially innervated muscle from the contralateral orbicularis innervation. The cerclage with autograft fascial strip or allograft (i.e., Alloderm or donor fascia or pericardium) is placed in a plane between the orbicularis oris and skin. This technique is not one that is often required, unless there is bilateral injury. It can be traumatic to the neurologically intact side and therefore is of limited benefit.

Stensen's Duct Repair

Indication

Traumatic injury to the duct generally necessitates simple or complex repair.

Procedure

Repair of the duct is achieved with stenting and repair of adjacent injury to the gland.

Technique

1. The distal segment edge of Stensen's duct can be identified by retrograde cannulation through the ampulla intraorally. Loop magnification and lacrimal duct probes can be utilized. An imaginary line drawn through the tragus and the mid-upper lip defines the duct trajectory in the buccal subunit and thereby aids in its identification.[31]
2. If suitable stents are not available, angiocatheters, large-caliber suture, or other small-caliber silicone tubes are a reasonable and appropriate substitute to aid in identification of the duct.
3. The proximal portion of the duct can be more difficult to identify, and use of magnification will be helpful. Milking the gland can often lead to expression of saliva from the cut end of the proximal duct, making identification possible.
4. In the case of a double transection, the intervening segment may be anatomically identifiable. Apposition of the adjacent parotid tissue by traction of the parotid fascia will aid in anatomical identification. If an intervening segment of the gland is absent, a small-caliber vein graft can be used as a stent.
5. Anastomosis of the duct is achieved most precisely with magnification. Use of monofilament microsutures, ranging in size from 7.0 to 9.0, is the most common technique.
6. Suitable stents include silicone catheters, small-gauge angiocatheters, and lacrimal stents. The stent is brought out of the ampulla and secured to the adjacent buccal mucosa with a suture. The stent can be left in situ for 10 to 14 days and is most important in cases of significant trauma to the duct.[31]
7. Tension on the repair is minimized by coapting adjacent parotid tissue. This strategy is also important in adjacent neurorrhaphy of the buccal branches, which are most often injured concurrently.
8. Antibiotic coverage should cover the gram-positive flora and other indicated flora based on the type of injury and the extent of oral contamination.
9. Postoperative management should include and encourage hydration, possible massage, and pain management.
10. For the patients who have inadequate structural duct remnants to repair, there are two options. One is to marsupialize the remnant of the duct that is attached to the body of the gland to the buccal mucosa, if possible; the other is to tie off the duct and allow the gland to undergo fibrosis and atrophy.

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17

Medicolegal Perspectives in Salivary Gland Diseases

SHERRY C. McREYNOLDS AND AXEL KOCH

This chapter will address and compare how medical malpractice is proved in the United States and Germany, the prevalence and characteristics of malpractice claims involving salivary gland surgery, and what you can do to decrease your chances of being sued and to increase your chances of a successful outcome if a lawsuit is filed.

General Considerations

In the United States, health insurance is a patchwork of private and government programs. There are an estimated 50 million uninsured Americans. The United States presently has the highest per capita expenditures on health care in the world. Germany has a universal health insurance program managed by the government.

Malpractice premiums paid by the otolaryngologist–head and neck surgeon in the United States vary by region. The rates paid in Philadelphia, Pennsylvania, in 2004, for example, are approximately $70,000.00 per year for $1 million of insurance for a single event. The otolaryngologist–head and neck surgeon in Germany pays approximately US$2000 per year for US$3 million coverage for personal injuries and US$300,000 coverage for special and financial damages.

In the United States, a malpractice attorney often handles cases only for the plaintiff (patient) or the defendant (physician). In Germany, a malpractice attorney is often active for patients as well as doctors. Legal professional fees for a plaintiff's settlement in the United States and Germany are different. In a $100,000 settlement in the United States, the plaintiff's attorney would receive a previously agreed upon percentage (could be more or less than one third) of the total amount plus reimbursement for expenses. Some states have statutes setting a ceiling on the percentage that the plaintiff's attorney may take in certain circumstances. In Germany, a settlement of US$10,000 would go to the patient minus expenses. The patient would pay one third of expenses, and the physician would pay two thirds. If the costs for the patient's and physician's attorney were each US$2000 and court costs were US$1000 (total expenses US$5000), the patient would subtract one third of US$5000 from the total of US$10,000.

How Medical Malpractice Is Proved

Unlike Germany, where the malpractice law is the same throughout the country, there is no national medical malpractice statute in the United States. Each of the 50 states has its own medical malpractice laws. However, all states (and Germany) use a fault-based system of liability, which means something more than a bad result is necessary for the plaintiff to prevail in a lawsuit. That something more is usually negligence.

To win a medical negligence suit, the plaintiff must prove four major elements: (1) that the physician had a duty or obligation to practice within the standard of care, usually shown by the presence of a professional relationship; (2) that the physician failed to meet the applicable standard of care; (3) that the patient suffered damages or injury; and (4) that the physician's failure to meet the applicable standard of care caused the patient's injury or damages.

Similarly, in Germany, the plaintiff must prove that the doctor committed malpractice, that he or she suffered damage, and that there is a causal relation between the act of malpractice and the damage.

The plaintiff has the burden of proving his or her case by a preponderance of the evidence, which means the plaintiff must prove only that the defendant physician more likely than not breached the standard of care in a manner causing injury to the plaintiff. In Germany, the plaintiff has the burden of objectively proving that medical treatment was incorrect or that insufficient information was provided to the patient before the procedure.

The standard of care requires that the physician use the degree of skill and care that the reasonably prudent physician would use in the same or similar situation. In the United States, the testimonies of the expert witnesses are critical aspects of the malpractice case. In most circumstances, an expert witness is required to testify as to both the applicable standard of care and the defendant's specific failures to meet that standard. The attorneys for the parties retain and arrange payment for the expert witnesses who will testify specifically on behalf of either the plaintiff or the defendant. In some cases, a defendant may serve as his or her own expert witness. A jury or a judge hearing evidence without a jury must sort out the conflicting testimony of the expert witnesses in a single trial and reach a conclusion as to the liability of the defendant. The parties have decided whether the trier of fact will be a judge alone or a jury.

This sharply contrasts with the German system, in which the judge decides when expert assistance is needed and then selects the expert and defines his or her role. Although a party may provide an expert, if the opposing party contends he or she is wrong, the judge will appoint an expert. The parties may make the case so difficult that the judge cannot solve the problems with his or her own knowledge and will appoint an expert. In most German malpractice cases, there is only one expert, rather than the battle of experts so characteristic of the U.S. case. Unlike the United States, in which there is a single trial in which the lawyers present evidence previously gathered in a long period of discovery, the German trial may consist of a series of hearings. The trier of fact is always the judge. There is no jury.

Expert witnesses review medical records and other documents in the particular case and render an opinion based on their education, knowledge, and experience. Textbooks, journal articles, manufacturer's instructions and recommendations, standards and guidelines set by professional organizations, and written institutional policies and procedures may also play a role.

The qualifications of an expert witness in the United States may be challenged by the opposing party. The judge then decides whether the expert is qualified to testify. If the expert testifies, the weight given to that expert's testimony will be up to the trier of fact.

Most states have some exceptions to the requirement for expert witness testimony. The defendant's own testimony admitting a breach of the standard of care or the defendant's violation of a criminal or civil statute may eliminate the need for expert witness testimony. If it is determined that the finder of fact can call upon his or her own knowledge, experience, and wisdom to determine and apply the appropriate standard of care without an expert, in some states, expert testimony may not be required under the ''common knowledge'' doctrine. When the circumstances in the case provide no credible explanation for the events in the absence of someone being negligent, the doctrine of res ipsa loquitur (the thing speaks for itself) may also apply in some states and eliminate the need for expert witnesses. Although some state statutes specifically describe permitted exceptions to the requirement of an expert witness, others do not. In Germany, there is no requirement that there be expert testimony.

In claims of a lack of informed consent, whether expert testimony is required depends on the state. In states that use a physician-based standard, expert testimony is required to determine whether the defendant has met the standard of care in obtaining the plaintiff's consent. Expert testimony is not required in states that use a reasonable patient standard. In those states, the question of whether the doctor has disclosed risks a reasonable patient would find material is left up to the trier of fact.[1] The German system uses both of these standards.

Obtaining the patient's informed consent for surgery is an essential process. The physician who will perform the surgery cannot delegate his or her legal obligation to advise the patient of the nature and purpose of the recommended procedure, the possible risks of the procedure, and the alternatives to the procedure. Recently, in some states, informed consent has also encompassed a requirement that the physicians disclose differential success rates, their ''batting averages.'' Recordings of subjective estimates and impressions of the doctor do not have to be made in Germany.

In the German system, the doctor in attendance has a duty to inform the patient about the extent and range of the intended treatment, the associated risks, and the possible alternatives and/or new methods or techniques if recognized and certified for treatment in Germany. A lack of information or false information has legal consequences only if a typical treatment risk occurs and the doctor failed to mention this possibility in advance.

The question of whether the allegedly negligent act caused the plaintiff's injury also generally requires

expert testimony in the United States. Many states require ''but for'' causation, which means that if the injury to the plaintiff would not have occurred ''but for'' the defendant's wrongful act, then the defendant's act can be judged to be the cause of the plaintiff's injury. In other states, the trier of fact can conclude that the defendant caused the plaintiff's injury if the defendant's act was a ''substantial factor'' in bringing about the plaintiff's injury. In Germany, the judge normally does not require an expert witness on causation.

If malpractice is found, the trier of fact also determines the amount of damages to be awarded. In the United States, most damages are compensatory, which means the plaintiff may be compensated for past and future medical expenses, past and future loss of earning potential and income, and pain and suffering. When gross negligence is found, punitive damages may also be awarded. Unlike compensatory damages, they may not be covered by the physician's malpractice insurance. Although a German judge may award compensatory damages, which include pain and suffering, there are no punitive damages.

A small number of U.S. malpractice cases actually go to trial. Alternatives to trial include settlement and arbitration, which is a more informal presentation of evidence to one or more court-appointed or party-selected, neutral arbitrators, who make a decision, which may or may not be binding and final depending on the state and the circumstances. Of the cases that go to trial, few result in a written judicial opinion.

This differs from the German system, in which the judge first tries to reach a compromise between the parties. The majority of the cases are completed out of court. If that fails, a series of hearings may follow, with the judge deciding each case in a written judgment containing full findings of fact and the application of the law.

■ Prevalence and Characteristics of Malpractice Claims Involving Salivary Gland Diseases

More than 20 professional liability insurers in the United States report information about their closed malpractice claims to the Physicians Insurers Association of America (PIAA), the largest repository of medical malpractice claims' data in the world. The statistics below are from PIAA's comprehensive analysis of malpractice data.

PIAA showed a total of 79 malpractice claims relating to salivary gland surgery during the period from January 1, 1985, through June 30, 2003. The largest number of claims (27) related to benign neoplasms of the salivary gland. Nineteen of these claims were for improper performance of a treatment or procedure. The remaining claims were for ''no medical misadventure,'' which means that no medical mishap or real medical incident occurred, but suit was brought anyway; performance of a nonindicated or contraindicated procedure; delay in referral; and one for intubation problems. Most claims involved minor or significant permanent injury. Although none of these cases went to trial, 14 of the 27 claims (52%) resulted in indemnity payments to the plaintiff, with the average payment ranging from $4000 to $300,000.[2] Another large category of claims (21 claims) related to malignant neoplasms of the salivary gland. The most frequent allegation of malpractice in this category was diagnosis error (14 claims), but there were other claims of no medical misadventure, improper performance, and one for surgical foreign body retained. Most of these cases resulted in death, but some reported lesser injuries. One death case was tried or arbitrated and resulted in a judgment for the defendant doctor. Indemnity payments were made in only two claims, with payments of $45,000 and $100,000.[2]

Another large category for malpractice claims (21 claims) is classified as ''other excision of salivary gland lesion.'' Improper performance of the procedure (nine claims) and diagnosis error (five claims) were the most frequent allegations of malpractice, but there were also claims of procedure not performed, delay in performance, and procedure performed when not indicated or when contraindicated. Most of the claimed injuries were either major temporary injuries or minor permanent injuries. Two cases were tried or arbitrated: One involved an insignificant injury and resulted in a judgment for the doctor; the other claimed a minor permanent injury and resulted in a $45,000 award. A total of 15 of the 21 claims (71%) resulted in payments, which ranged from $3000 to $800,000.[2]

Four claims related to incision of the salivary gland. The most frequent allegation was improper performance. One case resulted in a judgment for the defense. One claim paid $509,604. Two claims were dismissed without payment. There was also no payment in a claim related to ''salivary gland or duct disease resulting in incision of the salivary gland.''[2]

Five claims related to ''salivary gland or duct disease resulting in other excision of the salivary gland lesion.'' One resulted in an award of $45,000 to a plaintiff with a minor permanent injury. Payment was also made in two other cases, with the average indemnity ranging from $3000 to $75,000.[2]

In Germany, diagnosis errors and treatment errors are frequent claims. However, the amount of money awarded by the judge is usually significantly lower than the U.S. awards, with most awards ranging between US$1000 and US$100,000.

Injury to the facial nerve is probably the most frequent injury claimed in salivary gland surgery malpractice cases. An examination of 53 malpractice cases in which facial nerve injury occurred between 1985 and 2000 revealed that 9 arose from benign neoplasms of the parotid, 1 from malignant neoplasm of the parotid, and 15 from non-neoplastic disease of the parotid or other benign conditions of the head and neck.[3]

Successfully defending a case in which the facial nerve is severed or damaged during surgery is particularly challenging and often does not have the desired result, as exemplified by the following cases.

In a 2000 case, an oral surgeon's defense that he was not trained or experienced in parotid gland surgery was unsuccessful. He had performed surgery to remove a mass that he thought was attached to the temporomandibular joint. It turned out that it originated in the parotid gland and adhered to the temporomandibular joint. When the mass and parotid gland tissue were removed at surgery, branches of the facial nerve were dissected, causing permanent damage.

The plaintiffs alleged that the oral surgeon breached the standard of care by incising directly into the soft tissue and circling the mass without identifying the facial nerve. The defendant admitted he did not see the parotid gland or the facial nerves during surgery.

Awarding a total of $650,000, the judge, who heard the case without a jury, stated that ''any physician in any specialty had a duty to identify the facial nerves and insure that they were not cut.''[4]

A plaintiff's facial nerve was severed, causing permanent partial facial paralysis during surgery to remove a parotid tumor. At the 1992 trial, it was undisputed that it was negligent to sever the facial nerve during surgery in which the tumor was located in the superficial layer of the parotid gland. Plaintiff's expert witness further testified that it was negligent to fail to observe that the nerve had been severed before closing the facial tissue. The defendant testified that he and his assistants had failed to notice that the nerve had been severed seven eighths of the way through, but observed that the nerve appeared thin and that there was no response when the trunk of the nerve was electrically stimulated. The jury award of $950,000 was upheld on appeal.[5]

In a 1991 case, an otolaryngologist performed a partial parotidectomy because of concern that two rapidly developing and tender lumps behind the ear might be malignant. At surgery, the doctor had difficulty identifying the inferior branch of the facial nerve. The superior branch of the facial nerve was not identified or isolated. The defendant removed both ''lumps'' and surrounding portions of the parotid gland. Before closing, he stimulated the exposed nerve, and only the lower half of the plaintiff's face moved. Upon awakening, the plaintiff showed signs of facial paralysis.

Plaintiff's expert witness testified that defendant should have used four preoperative diagnostic procedures—computed tomography (CT) scan, magnetic resonance imaging (MRI), sialogram, and fine-needle biopsy—and that these would have shown the lumps were inflammatory, not malignant, and surgery would not have been required. In addition, plaintiff's expert testified that defendant had failed to meet the standard of care because he had identified only the lower division of the facial nerve, rather than its main trunk and both upper and lower divisions. The jury's total verdict of $608,330 was affirmed on appeal.[6]

A plastic surgeon was sued when the plaintiff's facial nerve was severed during surgery to remove a lump in plaintiff's cheek. Plaintiff's expert witness contended that the defendant failed to locate the nerve during surgery and failed to refer the patient to a specialist when he determined the lump was deeper than expected. The defendant admitted that he had cut the nerve but denied that his actions had breached the standard of care. A jury awarded $283,000 in 2000.[7]

In a 1978 California case, plaintiff was referred to a head and neck surgeon for an inflamed nasal cyst. The surgeon discovered a second lump below her ear and diagnosed a parotid gland tumor. Because of concern about possible malignancy, he recommended removal. The plaintiff was reluctant to have surgery because she had had the lump for at least 10 years, and it had never bothered her. The doctor discussed the nature and risks of the surgery and urged that she have surgery within 6 months. After obtaining a second opinion that confirmed the first opinion, she consented to surgery.

A parotidectomy was performed by the head and neck surgeon. During surgery, the facial nerve was unintentionally severed before it was identified. The surgeon removed the cyst and sutured the nerve back together. The patient, who suffered permanent facial paralysis, left the defendant's care and sought treatment elsewhere.

At trial, plaintiff's experts testified that the unintentional severing of the facial nerve before identifying it was a breach of the standard of care. The defendant's experts testified that an accidental cutting of the facial nerve was within the standard of care. The defendant testified that any surgeon who performs enough parotidectomies is bound to cut a nerve by mistake, and this time ''my number came up.''

The jury found for the defendant. However, the appeals court reversed the judgment on the ground that the jury had incorrectly been instructed on contributory negligence based on the defense attorney's closing argument that the plaintiff had chosen to leave the defendant's care after the injury and sought incompetent medical assistance. He argued that she could have avoided her present condition if she had continued to treat with the defendant surgeon.[8]

Not all cases involve facial nerve injury. In a 1977 case, the issue was whether the defendant surgeon had negligently severed a major blood vessel during surgery to biopsy a lesion on the right side of the mandible. Laboratory analysis later confirmed that the tissue removed was part of a salivary gland inclusion cyst.

While closing, the assistant surgeon noticed blood oozing from the operative site. He applied pressure and continued suturing. A few minutes later, the oozing had still not stopped. The surgeon inspected the oozing and found substantial swelling beneath the tongue. Swelling increased, and a nasal tracheal tube was inserted. During insertion, the patient inhaled the contents of his stomach into his lungs and bronchi. In spite of flushing to remove as much vomitus as possible, his condition continued to deteriorate. A tracheostomy was required, followed by placement on a respirator for 6 days. During that time, he developed a heart arrhythmia and a bronchial mucous plug requiring surgical removal. The plaintiff recovered and returned to work a couple of months later.

Plaintiff's expert testified that the defendant breached the standard of care by perforating the medial cortical plate of the mandible and lacerating either the lingual artery or the sublingual branch of the lingual artery. The defense expert witness testified that it was unlikely that the sublingual artery was damaged and attributed the bleeding to the abundant venous blood supply characteristic of salivary glands. Additionally, he testified that the cyst in the plaintiff's jaw was an anatomical abnormality and may have contained an abnormal blood supply.

Trying the case without a jury, the court found that the bleeding and swelling in plaintiff's mouth was caused by damage to one or more of the blood vessels supplying the cyst, and that there was no evidence that the defendant's drilling of the bone and curettage of the glandular tissue deviated from the standard of care. Finding in favor of the defendant, the court dismissed the complaint.[9]

In 1998, a defendant otolaryngologist was performing a parotidectomy to remove a tumor. The Penrose drain, which was placed, broke off during removal. The remaining piece of drain was discovered several years later during resection surgery for a suspected recurrent tumor.

Plaintiff's expert testified that the defendant breached the standard of care by failing to inspect the end of the drain and noting that approximately a 1-inch piece had broken off. The defense expert witness testified that the standard of care did not require inspection of the drain unless breakage was suspected. Even if it had been inspected, he believed it would have been difficult to see. The defendant further contended that plaintiff's pain was caused by a neuroma, not the drain. After an hour's deliberation, the jury returned a verdict in favor of the defendant.[10]

Plaintiffs often allege a lack of informed consent in cases involving the salivary gland and facial nerve injury. A 1993 California case demonstrates the importance of documenting the discussion of risks in obtaining informed consent. A 43-year-old female, who had suffered from recurrent infections of her parotid gland, underwent a partial parotidectomy. A year later, she had a complete parotidectomy, in which her left facial nerve was severed, causing permanent facial paralysis.

Plaintiff testified that she had not received information about alternative treatments. However, the defendant, an otolaryngologist, testified that plaintiff had been given treatment options but decided to proceed with the surgery. The court found that the record supported a finding that she had not only been informed of available treatment options, but also several alternative treatments had been attempted before surgery was performed.

The plaintiff also testified that she had not been warned of the risk of facial nerve paralysis. The doctor testified otherwise and had noted in the medical record: ''Procedure and potential complications explained, i.e., facial nerve paralysis.''

The court found that the plaintiff's testimony was not credible and that she had failed to prove that the doctor had breached his duty of care. The judge, hearing the case without a jury, found in favor of the defendant doctor.[11]

How to Prevent a Malpractice Suit, or Increase the Chances of Winning If Sued

In both Germany and the United States, effective patient communication, including informed consent, and documentation are two things the surgeon must do to help prevent malpractice suits or to increase the chances of winning in the event of being sued.

One of the major causes of medical malpractice lawsuits is a communication breakdown between the physician and the patient. A 1997 study used audiotapes to document different conversational behaviors between physicians who had never been sued and those with a history of malpractice claims.[12] The study found no association between the content of the doctor–patient conversation and malpractice claims, but found a strong link between lawsuits and how the content was presented. Orienting the patient about what to expect and being sure that information and instructions given were understood made a difference. The study also showed that physicians who had not been sued spent slightly longer with patients (8.3 minutes vs 15 minutes). The author concluded, ''By practicing a few simple

communication techniques, many physicians could significantly reduce their risk for malpractice claims.''[12]

To help prevent a communication breakdown: listen carefully to the patient; exhibit empathy and respect for the patient; address the patient's fears and concerns; provide an opportunity for the patient to ask questions, then answer the questions honestly; inform the patient about treatment options, alternatives, and possible risks; and involve the patient in all medical care decisions, including treatment for a complication.

Documentation of what was discussed in obtaining informed consent is critical in the United States. Without that documentation, what was said often becomes merely the patient's word against the doctor's. Good documentation, which corroborates the doctor's testimony, could well be the difference between a verdict for the plaintiff or the defendant doctor.

In Germany, documentation is equally vital. Before the procedure or treatment, the patient is provided with a detailed information sheet, which he or she signs. If the required information is not given to the patient, the patient's consent may be inoperative. Doctors must always document their diagnostic and therapeutic measures, as well as the patient's signed information sheet. Any deviation from standard treatments, and especially the reason for doing so, must be clearly written.

Documentation is an essential factor in winning any malpractice suit. Illegible, inaccurate, incomplete, and, worst of all, altered records may result in a loss in an otherwise defensible case. Records should never be altered in the face of a lawsuit. Although some malpractice cases may be difficult to defend, an attempted cover-up is almost impossible to defend.

The use of electrophysiologic intraoperative facial nerve monitoring has not been proven to reduce the risk of temporary or permanent facial nerve dysfunction (see Chapter 15 for an expanded discussion). It therefore is not the standard of care for parotid surgery, particularly for parotid surgery involving a mobile, small, superficial lobe neoplasm. Nonetheless, there is a 21% reported reduction in malpractice litigation in parotidectomy cases, where there was inadvertent injury to the facial nerve, when nerve monitoring was incorporated in the procedure.[13]

Unfortunately, in today's legal climate, not all malpractice cases may be prevented even when the surgical care is exemplary. When litigation cannot be prevented, the surgeon's good rapport with the patient, effective communication, and complete and accurate documentation will increase the chances of successfully defending the lawsuit.

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