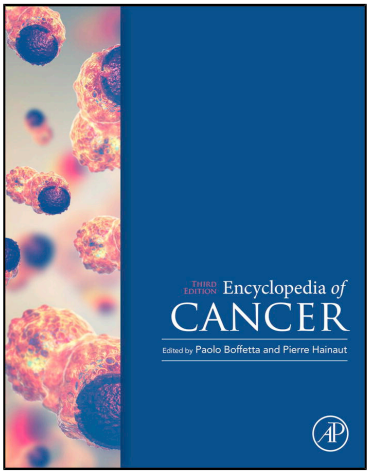

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Laryngeal Cancer: Diagnosis and Treatment

Fernando López Álvarez and Juan Pablo Rodrigo, Asturias Central University Hospital, University of Oviedo, University Institute of Oncology of Asturias (IUOPA), ISPA, CIBERONC, Oviedo, Spain

Glossary

Glottis The glottis extends from an artificial horizontal plane extending bilaterally across the apex of the laryngeal vestibule to approximately 1 cm below the true vocal folds.

Laryngectomy Partial (partial laryngectomy) or complete (total laryngectomy) surgical removal of the larynx, usually as a treatment for cancer of the larynx.

Laryngoscopy A procedure to look at the larynx and pharynx for abnormal areas. A mirror or a rigid or flexible laryngoscope (a thin, tube-like instrument with a light and a lens for viewing) is inserted through the mouth or the nose (fibroscope) to see the larynx. A special tool on the laryngoscope may be used to take samples of tissue.

Supraglottis The supraglottis extends from the tip of the epiglottis to an artificial horizontal plane extending bilaterally across the apex of the laryngeal vestibule, including the epiglottis, the false vocal cords (ventricular bands), the ventricles, the aryepiglottic folds and the arytenoids.

Subglottis The lower part of the larynx between 1 cm below the true vocal folds and the trachea (windpipe).

Tracheostomy The surgical formation of an opening into the trachea through the neck to allow the passage of air. The term "tracheotomy" refers to the incision into the trachea that forms a temporary or permanent opening, which is called a "tracheostomy," however; the terms are sometimes used interchangeably.

Introduction

Cancers of the larynx represents approximately 0.8% of the total cancer risk and is the second most frequent head and neck cancer. The number of new cases of cancer (cancer incidence) is 3.1 per 100,000 men and women per year (based on 2010–14 cases). The American Cancer Society's most recent estimates for laryngeal cancer in the United States for 2017 are that about 13,360 new cases of laryngeal cancer (10,570 in men and 2790 in women) will be diagnosed and about 3660 people (2940 men and 720 women) will die from laryngeal cancer, which is 0.6% of all cancer deaths.

Cancer of larynx is strongly related to cigarette smoking. The role of alcohol in inducing laryngeal cancer remains unclear, although it may be play a role specially in supraglottic cancer.

More than 95% of laryngeal tumors are squamous cell carcinomas (SCC). Other laryngeal malignancies include: verrucous SCC, papillary SCC, nonkeratinizing HPV-positive SCC, spindle cell carcinomas, basaloid SCC, lymphoepithelial carcinomas, acantholytic SCC, adenosquamous carcinomas, salivary tumors and sarcomas, among others.

Glottic, supraglottic, and subglottic cancers represent approximately two-thirds, one-third, and 2% of laryngeal cancers, respectively. Tumors that extend past the ventricle from either a glottic or supraglottic primary are considered transglottic tumors.

Nearly 75% of patients with glottic carcinoma present with hoarseness and often they are diagnosed at an early stage. However, nearly 70% of patients with supraglottic and subglottic laryngeal cancers usually present with advanced disease due to a paucity of symptoms, propensity for local extension, and rich lymphatics resulting in a high incidence of lymph node metastases (mainly supraglottic tumors). Early diagnosis can lead to a reduction in mortality.

Diagnosis

The initial evaluation of patients with suspected laryngeal carcinoma needs to include a detailed medical history to assess clinical risk factors (history of tobacco and alcohol use and environmental exposures) and symptom severity. Moreover, a complete head and neck physical examination should undergo, including examination of all mucosal sites of the upper aerodigestive tract, due to the frequent occurrence of multiple primary tumors in patients with a head and neck tumor. It is advisable an assessment of speech and swallowing function, communication needs, nutrition, health behaviors and availability of social support for what is typically prolonged period of treatment and rehabilitation. Finally, pretreatment dental evaluation is also recommended for patients who will undergo radiation, given the risk of dental infection, damage, and treatment-induced osteoradionecrosis.

Then, if a malignant tumor is suspected, it must be confirmed by obtaining a biopsy of the lesion for histopathological study. Finally, radiologic imaging is performed to obtain precise anatomical details regarding the tumor localization and extension. Fig. 1 represent an algorithm for diagnostic evaluation of a laryngeal cancer.

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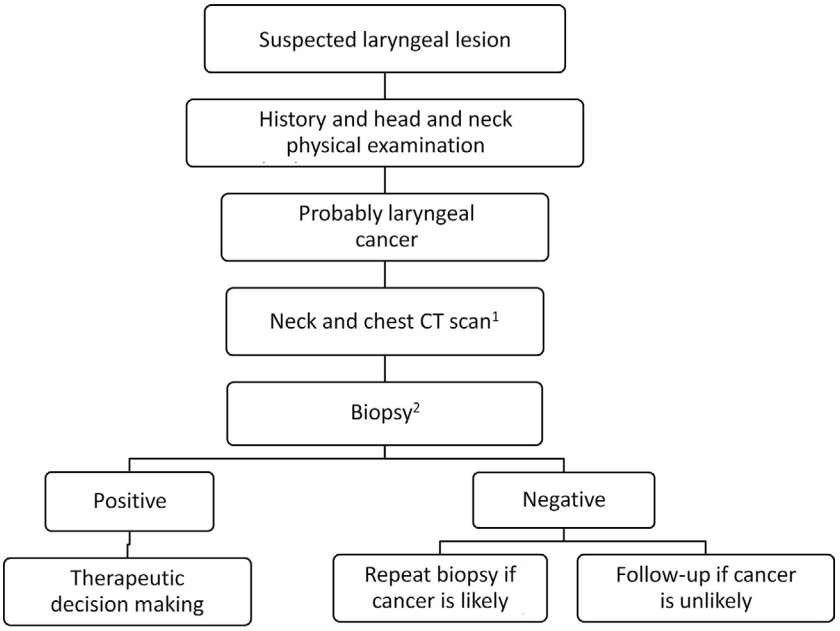

Fig. 1 Algorithm for diagnostic evaluation of a laryngeal lesion. *CT*, computed tomography; *MRI*, magnetic resonance imaging; *PET*, positron emission tomography.

Clinical Evaluation

Patients with primary early-stage tumors arising on the true vocal cords usually present with complaints of dysphonia and hoarseness; sore throat, odynophagia, dysphagia, referred otalgia, pain localized to the thyroid cartilage, hemoptysis, airway obstruction, stridor and neck adenopathy are features of advanced-stage glottic lesions. Early diagnosis is crucial for both improved survival and laryngeal preservation. In general, persistent hoarseness (>15 days) in an adult patient requires endoscopic visualization of the larynx to rule out a tumor.

Supraglottic tumors are usually more advanced than glottic cancer at presentation and patients may experience the following symptoms or signs: discomfort or sensation of a lump in the throat (the most frequent initial symptom), dysphagia, odynophagia, the sensation of something stuck in the throat, occasional respiratory obstruction, hemoptysis, referred pain to the ipsilateral ear (by way of the vagus and auricular nerves) or a mass in the neck; however, hoarseness is not a prominent symptom of supraglottic cancer until the lesion becomes quite extensive.

Primary subglottic tumors are usually asymptomatic at an early stage and they do not present until more advanced in size where dyspnea ad stridor are frequent. Dysphonia is relatively common in advanced subglottic tumors due to the involvement of the true vocal cord or direct extension to the recurrent laryngeal nerve. An emergent tracheotomy is not uncommon in these patients.

Late symptoms of laryngeal cancer include weight loss, dysphagia, foul breath and aspiration.

Physical Examination

After the medical history, a thorough clinical examination using a rigid or flexible fiber-optic endoscope is performed (Fig. 2A). It allows an adequate assessment of the surface extent of the primary tumor, the mobility of the vocal cords and performing an initial tumor staging. Accurate evaluation of the primary tumor prior to initiating treatment is vitally important, especially if any voice-sparing surgical procedure is a consideration. It is advisable to document the lesions of the larynx by a photograph or to depict them on a drawing to describe the site of origin of the primary tumor with its local extension to adjacent sites within the same region of the larynx or from one region to another region. Bulky lesions may extend beyond the larynx into the adjacent base of the tongue, pyriform sinus, or retrocricoid region and this should be assessed. The relation to the anterior commissure is very important in glottic tumors and in lesions involving the laryngeal surface of the epiglottis. Determination of the mobility of the vocal cords is critical because there are subtle distinctions between mobile, partially fixed and fixed cords. Fixation of the vocal cord from laryngeal cancer is caused by invasion or destruction of the vocal cord musculature, invasion of the cricoarytenoid muscle or joint or invasion of the recurrent laryngeal nerve. Ulceration of the infrahyoid epiglottis, fullness of the vallecula or palpation of a diffuse, firm fullness above the thyroid notch with widening of the space between on the hyoid and the thyroid cartilages are indirect signs of preepiglottic space invasion. Retrocricoid invasion may be suspect when the laryngeal click disappears on examination or when the thyroid cartilage protrudes interiorly, producing a fullness of the neck. Pain or tenderness to palpation or a small bulge over the thyroid cartilage is suggestive of thyroid invasion.

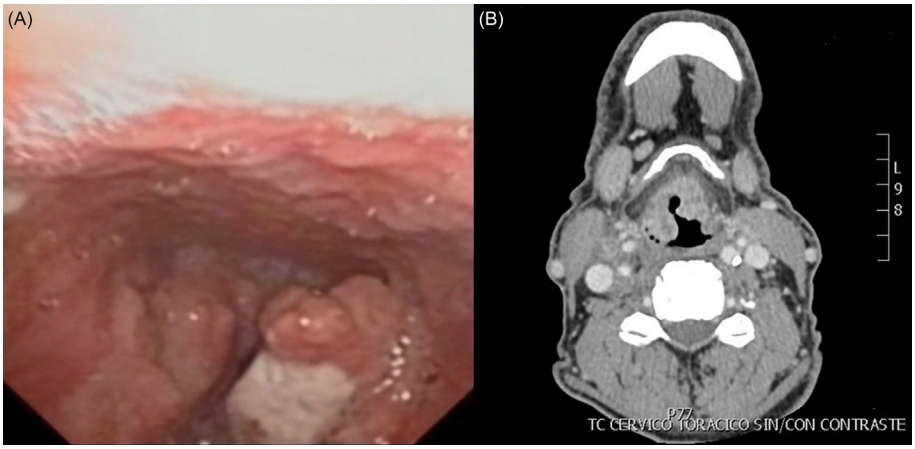

Fig. 2 (A) Endoscopic view of the larynx showing a tumor of the supraglottic. (B) Axial contrast enhanced CT showing an advanced supraglottic carcinoma. Moderately thick lesion arising from laryngeal surface of epiglottis with involvement of preepiglottic space.

Nowadays, apart from the endoscopy with conventional white light, narrow band imaging (NBI) endoscopy should be use in the routine pharyngo-laryngeal examination because it helps to make an early diagnosis of tumors of the larynx. Moreover, it is a useful tool in the postoperative surveillance to detect recurrences. NBI may be used in both flexible fiberoptic or rigid laryngoscopes. NBI is an imaging technique for the depiction of tumor-specific neoangiogenesis. A higher contrast between the mucosal epithelium and blood vessels is achieved in NBI endoscopy using filtered light comparing to white light observations. This allows detection of small suspicious mucosal changes or small tumors, few millimeters in diameter, which are not observable using white light. NBI also allows to define better the extension of tumors, which is crucial for perform targeted biopsy and for determination of resection margins in cancer surgery. NBI is increasingly used for follow-up of patients after treatment for head and neck malignant tumors, when early detection of possible recurrence is crucial.

Other imaging techniques such as auto fluorescence, contact endoscopy and optical coherence tomography (OCT) are increasingly used in ENT practice. However, these techniques have not been reproduced and is consequently not a standardized method.

Sometimes it is necessary to carry out a direct laryngoscopy under general anesthesia. The ventricles, subglottic area, apex of the pyriform sinus and retrocricoid area must be carefully examined when these areas are not well examined by the above techniques and they are at risk of being affected by the tumor. Through the laryngoscope may be introduced rigid telescopes (0, 30,45 or 70 degrees) or microscopic examination can be performed.

A detailed examination of the neck is mandatory whenever a laryngeal tumor is suspected. Regional metastases are the most important negative prognostic factor, decreasing the survival rate by 50%. The subdigastric basin (level II) is the most frequently involved. The submandibular area (level I) is rarely affected and the risk of spinal accessory lymph node (level V) involvement is small. Anterior commissure and anterior subglottic invasion are associated with involvement of the Delphian node. In tumors of the vocal cord, the incidence of clinically positive lymph nodes at diagnosis approaches 0% for T1 lesions and 2% for T2 lesions. This incidence increases from 20% to 65% for T3 and T4 lesions. The supraglottic tumors tend to have a higher rate of lymphatic metastasis and the incidence of clinically positive nodes is up to 60% at the time of diagnosis and 15% are bilateral. Spread to the pyriform sinus, vallecula and the base of tongue increases the risk of lymph node metastases.

The incidence of distant metastases is generally thought to be 10% or less. Although this increases with locoregional extent of disease and is more common with supraglottic (and subglottic) tumors, distant metastases are still found in only a small number of patients diagnosed with laryngeal cancer (15% or less). If spread through the bloodstream does occur, the lungs are the most common site of metastasis, followed by the bones.

Histopathological Diagnosis

Biopsy should be performed at the time of diagnosis, ideally after imaging, but it should not delay the treatment. A correct histologic diagnosis is critical due to the impact on therapeutic approach and prognosis and highlights the need for both a high index of clinical suspicion and adequate representative biopsies. A generous biopsy specimen is taken from the suspicious areas, looking to take tissue samples in depth and avoiding areas of necrosis. The biopsy should be performed through a flexible fiberoptic endoscope or, if this is not possible, by direct laryngoscopy.

Imaging

When malignancy is suspected, computed tomography (CT) scan with contrast enhancement (Fig. 2B) and/or magnetic resonance imaging (MRI) must be performed to define the submucosal extent and deeper margins of the tumor. CT is preferred because it is

Fig. 3 Axial contrast enhanced CT performed in a patient with a tumor invading the anterior commissure and penetrating through the cartilage.

much faster than MRI. Small and superficial mucosal tumors may not be appreciated at CT or MRI and hence, it is mandatory that an endoscopy is done prior to any imaging study. Integration of cross-sectional imaging with endoscopy findings significantly improves the accuracy of T staging. The accuracy of clinical T staging alone for laryngeal cancer to be 57.5%, but as high as 80% when combined with contrast-enhanced CT. CT and/or MRI are valuable to obtain precise anatomical details regarding the tumor localization and extension (preepiglottic and paraglottic space involvement, subglottic extension, cartilage destruction and submucosal and extralaryngeal extension, which may not be obvious on clinical examination) (Fig. 3).

CT and/or MRI of the entire neck provide information on nodal disease that may not be clinically evident. A minimum axial diameter more than 10 mm, round or spherical shape, a necrotic node of any size and a node with indistinct spiculated margins (suggesting extra nodal disease spread) are the generally accepted radiological criteria to diagnose malignant nodes at CT and MRI. The sensitivity and specificity of CT to detect nodal disease using these criteria are 90% and 75% respectively.

It is important to note that imaging should be performed before biopsy so that abnormalities that may caused by the biopsy are not confused with tumor.

The general radiological criteria used for tumor involvement include asymmetric soft tissue prominence or thickening, abnormal contrast enhancement, a bulky mass, obliteration of the normal fat planes and spaces, or a combination of these.

A high-resolution CT scan with contrast enhancement (1–2 mm thick sections through the larynx) is generally preferred. Contrast enhancement helps to outline the blood vessels and the tumor. CT delineates the extent of disease and the presence and extent of lymphatic involvement. CT offers high spatial resolution; discriminates among fat, muscle, bone, and other soft tissues; and surpasses MRI in the detection of bony erosion. Nevertheless, MRI is probably better to define subtle extralaryngeal extension and to assess early thyroid cartilage destruction. MRI has a high sensitivity (89%–95%) but lower specificity (74%–84%) as compared to CT for the detection of cartilage invasion. The negative predictive value of MRI to exclude cartilage invasion is also very high, at around 94%–96%. T2-weighted or postcontrast T1-weighted cartilage signal intensity greater than that of the adjacent tumor is considered to indicate inflammation, and signal intensity similar to that of the adjacent tumor was considered to indicate neoplastic invasion. Supraglottic tumors may arise in the epiglottis or in the aryepiglottic folds and false cords. Epiglottic tumors primarily invade into the preepiglottic space. While the tumors arising from the mobile portion of the epiglottis may spread from the preepiglottic space further into the base of tongue and laterally into the paraglottic space, those arising from the petiole often invade the low preepiglottic space and via the anterior commissure, reach the glottis or subglottis. The primary sign of preepiglottic space invasion at imaging is replacement of the normal fat by abnormal enhancing soft tissue. The sensitivity of CT and MRI to detect invasion of the preepiglottic space is 100% and the corresponding specificities are 93% and 84–90%. Tumors arising in the aryepiglottic folds present as exophytic or infiltrative masses. They expand the aryepiglottic fold and spread into the paraglottic space. They may spread further anteriorly into the preepiglottic space or posteriorly to invade the piriform sinus. Tumors originating in the false vocal cords are lateral masses with a strong predilection for submucosal spread into the paraglottic space. More extensive tumor may destroy the thyroid cartilage and spread transglottically into the glottis and subglottis. Tumor spread to the paraglottic space on CT or MRI is seen as replacement of the normal paraglottic fat by the enhancing tumor tissue. Both CT and MRI have a high sensitivity of about 95% to detect paraglottic tumor spread, the specificity, however, ranges between 50 and 75% as peritumoral inflammation may mimic tumor resulting in false positive assessments.

Glottic tumors commonly arise from the anterior half of the vocal cord and spread into the anterior commissure. Anterior commissural disease is seen on CT or MRI as soft tissue thickening of more than 1–2 mm. The accuracy of CT in predicting anterior commissure involvement is about 75%. From the anterior commissure, the tumor may spread further anteriorly into the contralateral cord and the thyroid cartilage or posteriorly into the posterior commissure, the arytenoids, cricoarytenoid joint and the cricoid. While vocal cord mobility is best assessed at endoscopy, disease in the cricoarytenoid joint and interarytenoid region have been described as imaging correlates for vocal cord fixation. The tumor may spread superiorly to access the preepiglottic space and

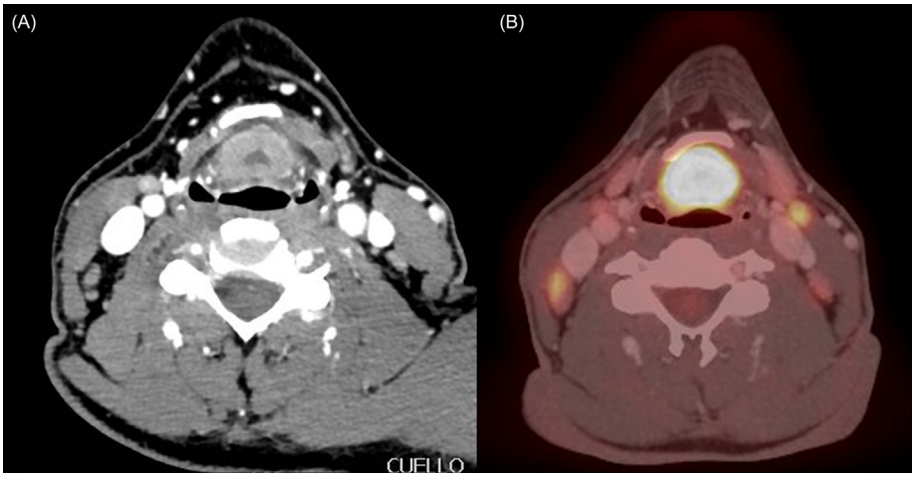

Fig. 4 (A) Axial contrast enhanced CT depicting a supraglottic tumor invading the preepiglottic space. (B) PET-CT showing a hypermetabolic focus of active tumor occupying the preepiglottic space that corresponds to the CT abnormality.

the paraglottic space, or inferiorly to reach the subglottis. Subglottic spread below the anterior commissure is seen as an irregular thickening of the cricothyroid membrane. Tumor may gain access into the extralaryngeal tissues through the cricothyroid membrane.

Subglottic cancer is diagnosed if any tissue thickening is noted between the airway and the cricoids ring. Due to their late presentation, invasion of the cricoids cartilage, trachea and the cervical esophagus with extralaryngeal spread are common findings in these patients at imaging.

Laryngeal tumors encroaching on both, the glottis and supraglottis, with or without subglottic component and when the site of origin is unclear, is termed as transglottic tumor. This tumor spread is frequently through the paraglottic space and is readily identified on CT or MRI. Transglottic carcinoma is frequently accompanied by metastatic lymphadenopathy. Coronal images are particularly helpful in assessing transglottic extension of tumor.

Nowadays, to assess the possibility of diagnosing distant disease and second primary tumors, a chest CT should be routine. Second primary malignancies have been reported in up to 20% of patients with laryngeal cancer.

Moreover, the use of positron emission tomography (PET) scanning with ^{18}F-fluorodeoxyglucose (FDG) and combined CT with PET imaging allow to combine functional and anatomical studies (Fig. 4). FDG imaging has the potential to distinguish between benign and malignant processes, grade tumors, identify metastases, and diagnose tumor recurrence. Although standardized uptake values (SUV) of FDG uptake has been used by some authors to identify tumoral tissue, to date, no universally accepted SUV threshold has been determined to differentiate benign from malignant nodal disease. In head and neck cancer, FDG imaging is useful for detecting clinically occult recurrences and for determining residual disease in the neck following definitive radiotherapy. CT-PET can detect occult disease and use alter the treatment plan in up to 30% of patients. CT-PET has a high negative predictive value but the specificity is not very high. The overall accuracy of in identifying nodal disease is higher than that of CT alone, by almost 20%. However, CT-PET is not useful to exclude the presence of metastases in the clinically N0 neck because PET cannot detect very small tumors (<5–7 mm).

Staging

Staging is based on TNM criteria developed by the AJCC/UICC (8th edition) (Tables 1–4). This classification incorporates all information available prior to treatment, including the clinical examination, endoscopy, endoscopic biopsy and cross-sectional imaging. The guidelines rely heavily on the use of cross-sectional imaging for the T staging; however, no recommendation is made regarding the preference of one technique over the other. Laryngeal cancer staging is dependent on tumor location and subsite involvement. For supraglottic tumors, the subsites that are important for staging include the suprahyoid and infrahyoid epiglottis, aryepiglottic folds, arytenoids and ventricular bands (false vocal cords). The glottic subsites include the true vocal cords including the anterior and posterior commissure. Other important factors involved in laryngeal cancer staging include the presence of impaired true vocal cord mobility or frank paralysis, base of the tongue involvement, preepiglottic space involvement, paraglottic space involvement and thyroid or cricoid cartilage invasion. It is important to note the fact that a tumor that erodes only the internal cortex of the thyroid cartilage is classified as T3, while if the tumor passes through the cartilage is considered as a T4 tumor.

Those tumors that cause vocal cord fixation, involve base of the tongue preepiglottic or paraglottic spaces, show thyroid or cricoid cartilage invasion, invade tissues beyond the larynx (trachea, soft tissues of the neck, esophagus thyroid gland, strap muscles or extrinsic muscle of the tongue) or are associated with regional lymphatic metastases, are considered as advanced disease. Cancers that invade the prevertebral space, encase the internal carotid artery or extend into the mediastinum are considered incurable with surgery.

Table 1 Primary tumor (T) according to TMN 8th edition

TX	*Primary tumor cannot be assessed*
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Supraglottis	
T1	Tumor limited to one subsite of supraglottis with normal vocal cord mobility
T2	Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis without fixation of the larynx.
T3	Tumor limited to the larynx with vocal cord fixation and/or invades any of the following: postcricoid area, preepiglottic space, paraglottic space, and/or inner cortex of thyroid cartilage
T4a	Moderately advanced local disease. Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx
T4b	Very advanced local disease. Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures
Glottis	
T1	Tumor limited to the vocal cord(s) with normal mobility
T1a	Tumor limited to one vocal cord
T1b	Tumor involves both vocal cords
T2	Tumor extends to supraglottis and/or glottis, and/or with impaired vocal cord mobility
T3	Tumor limited to the larynx with vocal cord fixation and/or invasion of the paraglottics space, and/or inner cortex of the thyroid cartilage
T4a	Moderately advanced local disease. Tumor invades through the outer cortex of the thyroid cartilage and/or invades tissues beyond the larynx
T4b	Very advanced local disease. Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures
Subglottis	
T1	Tumor limited to the subglottis
T2	Tumor extends to vocal cord(s) with normal or impaired mobility
T3	Tumor limited to the larynx with vocal cord fixation
T4a	Moderately advanced local disease. Tumor invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx
T4b	Very advanced local disease. Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

Table 2 Regional lymph nodes (N) according to TMN 8th edition

	Clinical (cN)	*Pathological (pN)*
Nx	Regional lymph nodes cannot be assessed	
N0	No regional lymph nodes metastasis	
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension	
N2a	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension	
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension	
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension	
N3a	Metastasis in a lymph node more than 6 cm in greatest dimension without extranodal extension	Metastasis in a lymph node more than 6 cm in greatest dimension without extranodal extension
N3b	Metastasis in a single or multiple lymph nodes with clinical extranodal extension (skin involvement or soft tissue invasion with deep fixation/tethering to underlying muscle or adjacent structures or clinical signs of nerve involvement)	Metastasis in a lymph node more than 3 cm in greatest dimension with extranodal extension or, multiple ipsilateral, or any contralateral or bilateral node(s) with extranodal extension

Table 3 Distant metastasis (M) according to TMN 8th edition

M0	No distant metastasis
M1	Distant metastasis

Table 4 Stage groups according to TMN 8th edition

Stage 0	Tis N0 M0
Stage I	T1 N0 M0
Stage II	T2 N0 M0
Stage III	T3 N0 M0
	T1–3 N1 M0
Stage IVA	T4a N0–1 M0
	T1-4a N2 M0
Stage IVB	T4b Any N M0
	Any T N3 M0
Stage IVC	Any T Any N M1

Treatment

The primary goal of treatment in head and neck cancer is to achieve optimal oncological outcomes while preserving function and quality of life as much as possible. This is particularly important in the treatment of laryngeal cancer. The larynx has important functions—including breathing, voice making and swallowing, and therefore both the disease and its treatment may significantly affect quality of life. As previously mentioned, 95%–98% of malignant neoplasms of the larynx are squamous cell carcinomas (SCC), so we will only refer to this histological type.

In the treatment of these cancers we have several options available (surgery, radiation therapy, chemotherapy and molecular targeted therapies), which can be used alone or in combination. In general, patients in early stages (I–II) are treated with a single modality therapy, either surgery of radiotherapy. But approximately 40% of laryngeal cancers occur at advanced stages (III–IV) at diagnosis, requiring aggressive treatment that usually involves combining several treatment modalities. Primary treatment decisions may depend on patient desires, tumor extent and location, experience of the treatment team, the adequacy of follow up surveillance, medical comorbidities and long-term voice and swallowing expectations. Since most cases of laryngeal cancer are associated with high consumption of tobacco and alcohol, co-morbidities are common, which not only determine the choice of treatment and compliance, but are an important determinant of overall patient survival.

Treatment of Early Stage (T1–T2) Tumors

Treatment options for T1–T2N0 laryngeal SCC include radiotherapy (RT), transoral laser surgery (TLS), and open partial laryngectomy (see below). Functional results after open partial laryngectomy are usually worse compared to RT and TLS so that this alternative is rarely employed. Given the high probability (>20%) of occult nodal metastasis in supraglottic cancers, even in these initial stages, the neck must be included in the treatment plan of the tumors on this location, and it is usually treated with the same modality therapy (surgery or RT) than the primary tumor.

The decision whether to select RT or TLS (with neck dissection in supraglottic cancers) depends on a number of factors, including the location and extent of the tumor, anatomical circumstances (probability of exposure of the tumor in TLS), the medical condition of the patient, the likelihood of tumor control after treatment, anticipated functional outcome (voice quality), the expertise of the attending physicians and logistical considerations. In this complex decision-making process, we should also include patient preference, after an informed discussion of the pros and cons of each treatment modality.

The likelihood of local control after RT or TLS is equivalent and is approximately 85%–95%. An advantage of RT is that it is applicable to all patients with T1–T2N0 SCCs, whereas TLS could not be used in patients with inadequate exposure of the tumor (due to the location of the tumor or anatomical circumstances). Patients with significant medical comorbidities who are poor candidates for anesthesia may be better treated with RT. On the other hand, in glottic tumors, we must keep in mind that the more of the glottis that is involved with SCC, requiring a wider resection, the poorer the voice quality after TLS. Therefore, RT may be preferred treatment option for patients with more demanding requirements for voice quality. When RT is used, the dose of radiation is from 63 Gy (2.25 Gy/fraction) to 66 Gy (2.0 Gy/fraction) for T1 and 65.25 Gy (2.25 Gy/fraction) to 70 Gy (2.0 Gy/fraction) for T2 disease.

Patients with anterior commissure involvement will provide technical challenges and, even in experienced hands, may have local control rates that are somewhat lower compared with T1–T2 SCCs without anterior commissure invasion. Efficacy of RT is not affected by involvement of the anterior commissure. In addition, voice quality is likely to be worse after TLS in these cases.

One advantage of TLS is that it can be repeated several times in contrast to RT. The ability to repeat TLS may contribute to the fact that the likelihood of laryngeal preservation may be higher when TLS can be offered as initial treatment. Many patients with recurrences after RT will undergo total laryngectomy, although laryngeal preservation may be feasible with salvage open partial laryngectomy or TLS in selected patients after radiation failure.

Another advantage of TLS is the shorter length of treatment. In cases where the neck is not dissected, TLS can be done on an outpatient basis whereas RT is delivered once daily on weekdays over 5–7 weeks. In relation to this, an important point to be taken

into consideration is that TLS is the most cost-effective treatment of early laryngeal SCC, radiation therapy being 2–4-fold more expensive. The presence and extent of a cost differential will vary with the medical system.

Regardless of the modality chosen, physicians should track their own patient's functional and survival data rather than rely on the best reported results from the most experienced institutions. Analysis of outcomes should include tumor control, survival, functional outcomes (quality of voice) and larynx preservation rates.

Treatment of Advanced Stage (T3–T4) Tumors

For years, total laryngectomy (with postoperative radiotherapy in high-risk cases) was the only treatment option for patients with intermediate to advanced laryngeal cancer (T3–T4). In addition, either ipsilateral or bilateral neck dissections should be performed in these cases, based on tumor location and extent of nodal metastasis (if present).

Over the past two decades, great progress has been made in the management of this disease, with multimodality approaches aimed at laryngeal preservation reshaping the treatment landscape. In response to the common use of total laryngectomy, the nonsurgical approaches have often been referred to as "organ preservation" strategies. In many institutions, it appears that there are organ preservation strategies and then there is surgery. In contrast, we think there are both nonsurgical organ preservation strategies and surgical organ preservation strategies (Fig. 5). The key is that in both approaches the goal is to spare the functions of the larynx. A new paradigm has emerged in which both the surgical and nonsurgical approaches have equal value in functional laryngeal preservation. However, in T4 tumors laryngeal preservation rates are much lower and often present complications which compromise laryngeal function. In addition, patients with T4 tumors treated with up-front surgery had superior overall survival than those treated with CRT, and therefore in these cases total laryngectomy continues to be recommended.

Surgical options for functional laryngeal preservation

In addition to the time-honored approaches of vertical partial laryngectomy and horizontal or supraglottic laryngectomy, the options for conservation laryngeal surgery have significantly improved over the past two decades. Transoral minimally invasive surgery and supracricoid partial laryngectomy (SCPL) have emerged as important function-preserving approaches for patients with laryngeal cancer.

After either partial laryngectomy or open resection, absence of adverse features, including extra nodal spread, positive margins, perineural invasion, or lymphovascular invasion, allows for observation of the patient with no need for adjuvant therapy. When these high-risk features are present, adjuvant RT is recommended.

Vertical partial laryngectomy (VPL)

VPL (or vertical hemylaryngectomy) encompasses a spectrum of procedures ranging from laryngofissure with cordectomy to extended hemi-laryngectomy. Common to all these procedures is vertical transection of thyroid cartilage and glottic resection extending into the paraglottic space (Fig. 6). In VPL, vertical incisions are made through the thyroid cartilage near the anterior commissure and just anterior to the posterior edge of the thyroid cartilage. The resulting resection includes the true vocal cord and immediate sub glottis, ventricle, false vocal cord, and arytenoepiglottic fold, and usually crosses just in front of the vocal process of the arytenoid posteriorly. This area can extend around the anterior commissure to involve the anterior one-third of the opposite vocal cord if required. When the anterior commissure is removed, the procedure is termed a frontolateral hemylaryngectomy.

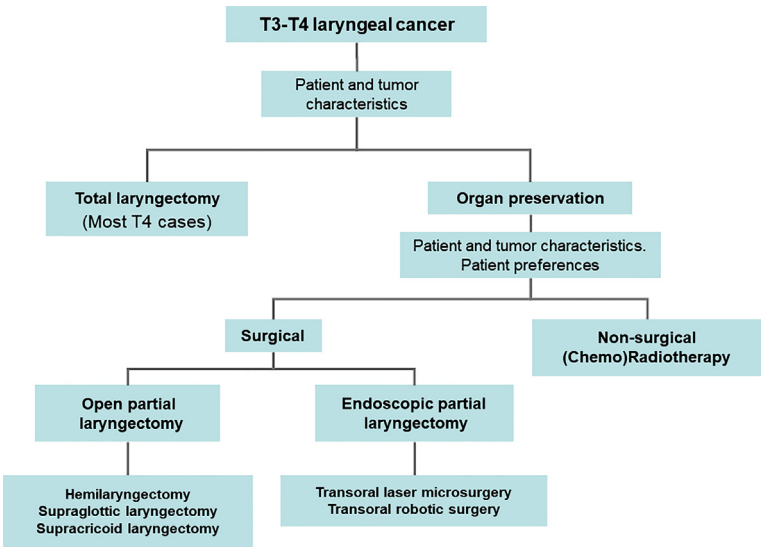

Fig. 5 Algorithm for treatment of advanced laryngeal cancer.

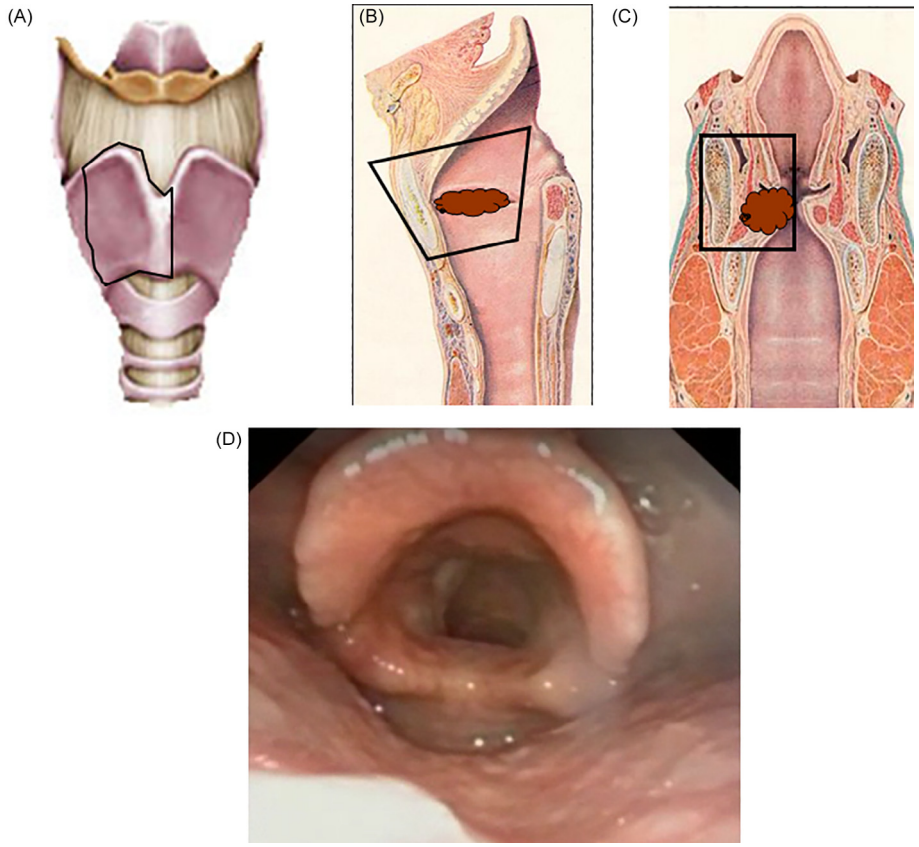

Fig. 6 Vertical partial laryngectomy. (A) Incisions in laryngeal framework. (B) and (C) Sagittal and coronal views showing the resected portions of the larynx. (D) Endoscopic picture of the larynx after a right hemilaryngectomy.

It is a well-established procedure for T1 and T2 glottic cancers. Some authors believe that patients with fixation of the true vocal cord (T3) caused by direct invasion of the cancer into the thyroarytenoid muscle are still candidates for a vertical hemylaryngectomy. However, in patients with vocal cord fixation caused by cricoarytenoid joint invasion a hemilaryngectomy should not be considered. Other contraindications are involvement of the posterior commissure or the thyroid cartilage, and extension superiorly to the aryepiglottic fold.

With this technique overall local control and laryngeal preservation rates, between 82 and 95% have been reported for T1–T2 cases, and 5-year survival rates were greater of 90%. The local control and 5-year survival rates were lower for T3 cases, with reported local control rates between 73% and 85%. These results reflect the continuing value of the VPL in selected cases. However, currently, with the advancement of laser surgery, the role of the VPL is questionable. For most patients with lesions amenable to VPL, laser surgery provides equal local control rates, with superior voice and swallowing function and less complications. And because the relatively high recurrence rates in T3 cases, VPL was replaced by supracricoid laryngectomy for these cases in many centers.

Supraglottic laryngectomy

Supraglottic laryngectomy involves resection of the epiglottis, the false vocal cords, the aryepiglottic folds, the hyoid bone (in most cases), the upper aspect of the thyroid cartilage, and the contents of the preepiglottic space (Fig. 7). The resection can be extended to include one arytenoid, the tongue base or pyriform sinus.

The result is that the patient has a nearly normal voice but a significant challenge in developing normal swallowing caused by the loss of the protective mechanisms of the epiglottis and false cords. Rehabilitation, which involves temporary tracheostomy in all patients and a temporary feeding tube (usually nasogastric), is achieved in most patients within 1 month of surgery with removal of the feeding tube and tracheostomy. The rehabilitative process is complicated by either preoperative or postoperative radiation therapy as well as extension of the surgical resection to include the tongue base, arytenoid cartilage, or pyriform sinus.

Supraglottic laryngectomy is indicated in all T1–T2 supraglottic cancers, but also in patients with T3 and T4 supraglottic tumors that involve preepiglotic space or one arytenoid, or that extend into the pyriform sinus or the tongue base. Massive tumors with cartilage erosion, subglottic extension, or involvement of the lateral wall of the pyriform sinus remain subject to total laryngectomy. In addition, the patient must have adequate pulmonary function to be a candidate for a supraglottic laryngectomy.

Local control was better for those with tumor confined to the endolarynx (>90%), but was over 80% for all sites, and laryngeal preservation rates described are also over 80% cases. Overall five-year survival rates are comparable to that obtained with total

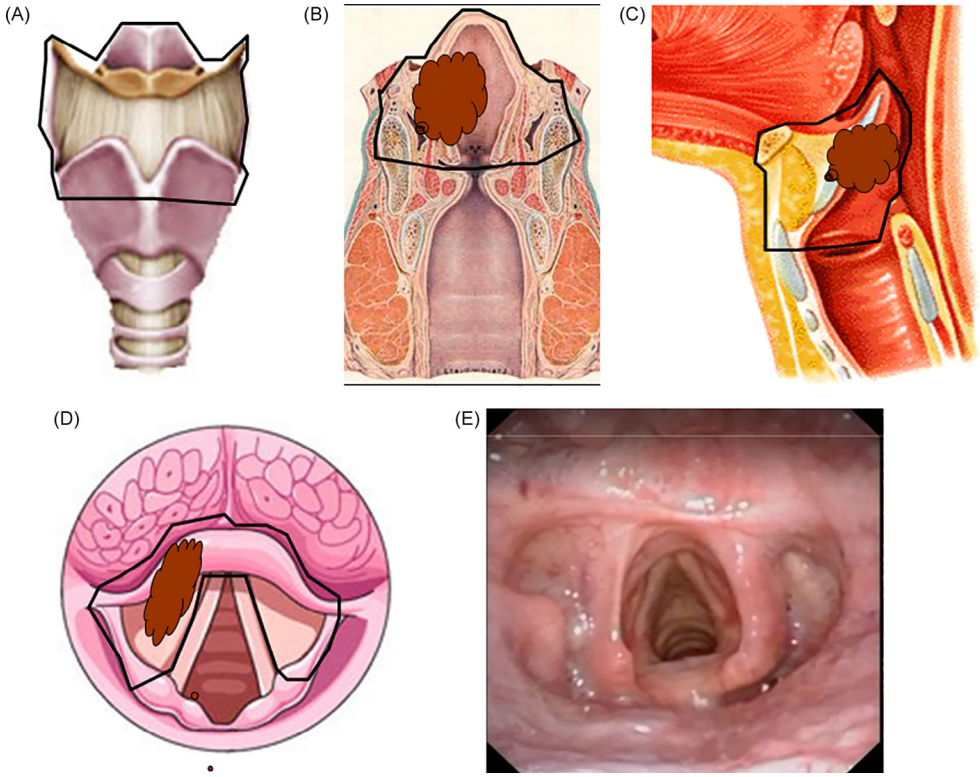

Fig. 7 Supraglottic laryngectomy. (A) Incisions in laryngeal framework. (B–D) Coronal, sagittal, and axial views showing the resected portions of the larynx. (E) Endoscopic picture of the larynx after a supraglottic laryngectomy.

laryngectomy, and range from 67% to 90%. These rates are over 85% for stage I–II tumors, between 75% and 80% for stage III, and between 55% and 70% for stage IV patients. However, in these tumors survival rates depends more from the presence and extension of nodal metastases than the size of the primary tumor.

The laryngeal preservation rates with this technique are very good, with overall reported rates over 85% of patients. However, these rates were lower (60%–80%) in T3–T4 tumors. In addition, functional results were good to fair, with more than 90% of patients achieving decannulation and oral diet.

Nowadays, conventional supraglottic laryngectomy is being replaced by laser supraglottic laryngectomy because the oncological results of transoral laser surgery for early and moderately advanced laryngeal cancer appear to be comparable to those of classic supraglottic laryngectomy, and the endoscopic approach offers functional advantages.

Supracricoid laryngectomy (SCPL)

The SCPL is an alternative to (chemo) radiation therapy, supraglottic laryngectomy, and near total and total laryngectomy in selected cases of supraglottic and transglottic carcinoma. This procedure is a true functional preservation technique and should be considered as a conservative laryngeal technique as it preserves physiological rehabilitation of speech, swallowing, and respiration without a permanent tracheostomy.

SCPL involves resection of the following structures: the true vocal cords, the false vocal cords, the aryepiglottic folds, the epiglottis (to a variable degree), the subglottic to the superior aspect of the cricoid cartilage, the thyroid cartilage, and the contents of the pre- and paraglottic spaces. The resection can include one arytenoid but must preserve the hyoid bone (Fig. 8). Two different reconstructions are possible depending on the extent of disease involving the epiglottis. In cases in which only the inferior portion of the epiglottis is involved, the suprahyoid epiglottis can be preserved and used in the reconstruction (cricohyoidoepiglottopexy, CHEP). In cases in which it is not oncologically feasible to preserve the epiglottis, the reconstruction will involve the impaction of the base of tongue/hyoid complex to the cricoid cartilage (cricohyoidopexy, CHP).

Supracricoid laryngectomy with cricohyoidoepiglottopexy (SCPL-CHEP) is indicated in glottic tumors: T2 (especially with anterior commissure involvement), T3 and selected T4 (limited thyroid cartilage invasion). Is contraindicated in cases with fixation of the cricoarytenoid joint, invasion of the posterior commissure, cricoid invasion, extralaryngeal spread of tumor or poor pulmonary function.

Supracricoid laryngectomy with cricohyoidopexy (SCPL-CHP) is also indicated in T2–T4 laryngeal tumors: supraglottic tumors extended onto the vocal cord or anterior commissure and in transglottic tumors. Limitations are the same than with SCPL-CHEP, and also invasion of the hyoid bone.

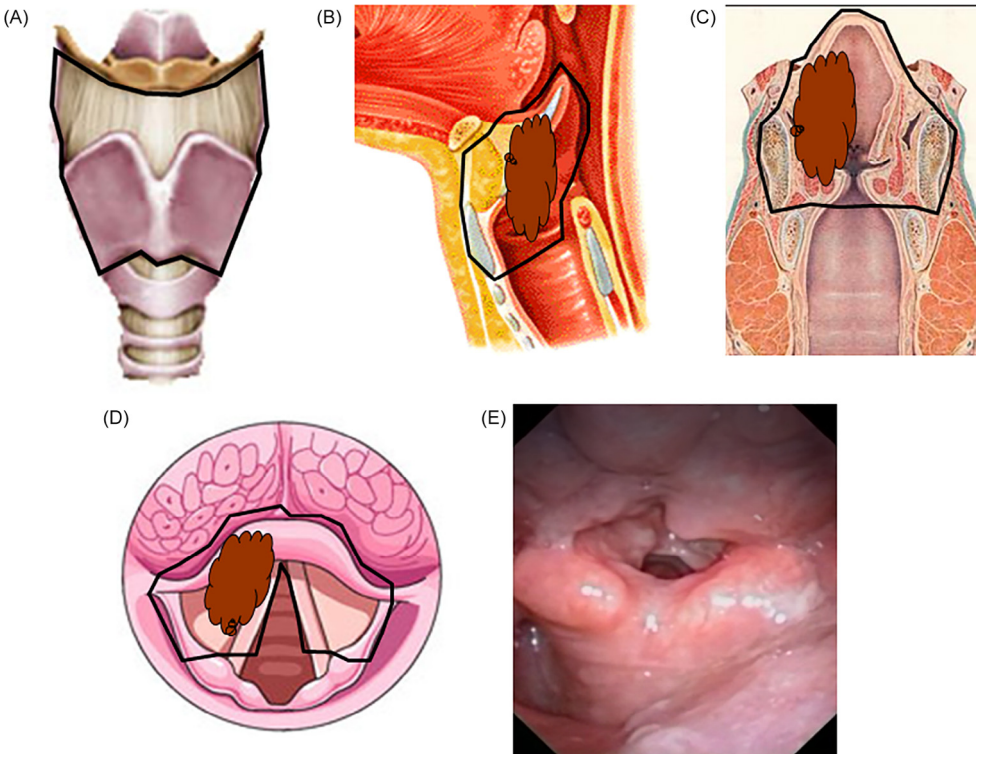

Fig. 8 Supracricoid laryngectomy (with crico-hyoidopexy). (A) Incisions in laryngeal framework. (B–D) Sagittal, coronal, and axial views showing the resected portions of the larynx. (E) Endoscopic picture of the larynx after a supracricoid laryngectomy.

Local control and organ-preservation rates with SCPL as primary therapy in patients with T2 and selected T3 lesions exceed 90% and are comparable with—if not better than—rates seen with chemotherapy and radiation and with total laryngectomy.

With respect to functional outcomes, although speech and swallowing are restored following SCPL, voice quality is substantially different postoperatively, although subjective voice analysis rank voice as globally "acceptable" by the patient and the physician. Restoration of normal swallowing may take several weeks and requires intensive rehabilitation; nonetheless, more than 80%–90% of patients can be expected to have swallowing function restored within the first year.

Transoral laser surgery

Transoral laser surgery (TLS) is minimally invasive and is performed under suspension-direct laryngoscopy, with an operating microscope, microsurgical instruments, and the surgical CO_2 laser. In conjunction with SCPL, this has been one of the two areas of greatest development in conservation laryngeal surgery in recent years.

The approach challenges a basic surgical tenet, as the tumor is transected and removed piecemeal through a laryngoscope. However, transection reveals the depth of tumor penetration and allows for clear visualization of tumor margins during the procedure.

In contrast to open laryngeal surgery, the cartilaginous laryngeal framework and the infrahyoid muscles are preserved during endoscopic resections, which is believed to improve postoperative function. Additionally, the concept of adequate margins is viewed differently for endoscopic resections: the goal is preservation of as much adjacent normal tissue as possible while ensuring a clear margin.

With respect to patient selection, exposure through the laryngoscope dictates which tumors can be managed by TLS. It is a well-established procedure for T1–T2 glottic or supraglottic carcinomas, as previously indicated. Additionally, some authors indicated this technique in selected T3 glottic tumors (fixation of the true vocal cord caused by direct invasion of the cancer into the thyro-arytenoid muscle), T3 supraglottic tumors (with limited preepiglotic space invasion) and also in some T4 cases (limited base of tongue invasion).

Several reports have shown good oncologic results in intermediate and advanced laryngeal cancer. The 5-year local control with laser alone and laryngeal preservation rates are approximately 95% and 98% for T1 tumors, 85% and 95% for T2 tumors, and 70% and 75% for T3 tumors. These results compare well to those of standard supraglottic laryngectomy. Regardless of the surgical technique employed, negative margins are essential in limiting local recurrence. Tumor involvement of the surgical margin after TLS has been associated with higher rates of local recurrence and distant metastasis, lower specific survival rate, and the necessity of salvage surgery.

Functional outcomes following TLS for laryngeal cancers are excellent. By maintaining one valve of the larynx, the airway is protected and voice and swallowing can be resumed with appropriate rehabilitation. Aspiration occurred in most patients soon after surgery, but recovered within 1–6 months, with recovery being faster in partial resections. Functional results depend on the extent of the resection. The return of voice quality also depends on the depth and extent of resection.

The functional results of TLS are generally superior to those of the conventional open approach, in terms of the time required to restore swallowing, tracheotomy rate, incidence of pharyngocutaneous fistulae, and shorter hospital stay. These functional advantages can be attributed to the more conservative nature of the endoscopic procedure, because normal tissues are not disrupted during the procedure. With open procedures, the thyroid cartilage, soft tissues and infrahyoid and suprahyoid muscles are divided, and the hyoid bone is frequently resected. There is invariably airway compromise and a need for a temporary tracheotomy. With endoscopic resection, tracheotomy is almost never indicated. Avoidance of tracheotomy and preservation of the strap muscles may facilitate faster return and ensure improved long-term swallowing function.

Transoral robotic surgery

The concept of robot-assisted surgery is gaining popularity for multiple different specialties, and more recently in minimally invasive head and neck surgery. The overriding advantages from the proponents of robot-assisted surgery are the excellent 3-dimensional visualization and 2- or 3-handed surgery through minimally invasive approaches that are afforded by the instrument. The wider angle of vision and angled lenses increases the range of the endoscopic visual surgical field compared with the "line of sight" visual field gained by microscopes. The 2-dimensional visualization provided by single channel optical systems in current endoscopes lacks the depth perception of 3-D vision provided by the binocular optical systems used in standard microsurgery. The 5-mm robotic endoscope commonly used has a dual-channel optical system coupled with a dual charge-coupled device, which allows for 3-D visualization of the surgical field at the surgeon's console. Another advantage of the technology used in the da Vinci robotic instrumentation is its ability to provide movement at the instrument tip with 7° of freedom and 90° of articulation and motion scaling. This allows the surgeon, who sits at the console with an adjustable arm, support to perform precise tremor-free movement in a deep and confined space, with working angles usually not achievable with nonrobotic instruments.

Weinstein and O'Malley have previously reported on the development and refinement of a novel procedure called transoral robotic surgery (TORS) in preclinical experimental models. These foundational studies established the technical feasibility of TORS to gain access to the oral cavity, oropharynx, hypopharynx, supraglottis, and glottis, and they also introduced basic concepts of patient safety and methods for controlling active bleeding.

Although the present literature reports early findings, without long-term oncologic outcomes, the results are consistently encouraging. Indeed, some institutions have shown that transoral robotic surgery programs can be successfully established yielding excellent clinical results.

Nonsurgical organ preservation protocols

In the 1990s, organ preservation treatment protocols combining chemotherapy and radiotherapy were introduced as an alternative to total laryngectomy with the objective to preserve a functional larynx without compromising oncological outcome.

The effectiveness of concomitant chemoradiation (CRT) as an effective organ preservation strategy was initially established by The Department of Veterans Affairs (VA) Laryngeal Cancer Study Group in 1991. Their conclusions were subsequently confirmed by the GETTEC and RTOG 91–11 trials and two individual data meta-analyses.

According to the different treatment guidelines (European Society of Medical Oncology -ESMO-, National Comprehensive Cancer Network -NCCN-, American Society of Clinical Oncology -ASCO-) the current standard of treatment for patients with T3 laryngeal carcinoma who desire a nonsurgical organ preservation treatment is concomitant radiotherapy with cisplatin, with salvage surgery in cases of persistent disease, or induction chemotherapy followed by definitive radiation/chemoradiation or surgery depending on clinical response. The dose considered standard for cisplatin by most researchers is 100 mg/m^2 administered on days 1,22, and 43 of radiotherapy, and radiation therapy is administered with a conventional fractionation (2 Gy/day to give 70 Gy in 7 weeks). With these treatments, the larynx is preserved in approximately 2/3 of patients.

Although initially not addressed by the VA protocol, it was recognized later that instead of organ preservation, functional preservation is a more relevant outcome. This functional preservation is defined as an "in situ" larynx without need for permanent tracheostomy and permanent gastrostomy at 2 years after finishing the treatment. Despite the various randomized trials that have all confirmed that the CRT approach achieves survival rates similar to treatment with total laryngectomy, none have shown improvement in survival rates with an organ preservation approach. Furthermore, some investigators have been concerned about the long term toxic effects of CRT treatment on laryngeal function and the decreases in overall survival rates with nonsurgical treatment reported more recently from large tumor registries and long-term follow-up of original trials. This raises a critical question of whether the results of a complex multidisciplinary treatment approach developed in controlled clinical trials by skilled investigators can be effectively generalized to standard practice.

Patients specifically included in the pivotal trials were predominantly patients with T3 tumors located at supraglottis, half of them without vocal cord fixation and a small proportion of patients with T4 tumors with minimal invasion to the cartilage, which do not represent the entire spectrum of "advanced larynx cancer." When the results of CRTs were extrapolated and applied in clinical practice and low volume nonteaching centers, selection criteria may not have been applied as strictly as suggested, and many patients who would not have been candidates to receive CRT (most T4 cancers) were included in this type of treatment. There

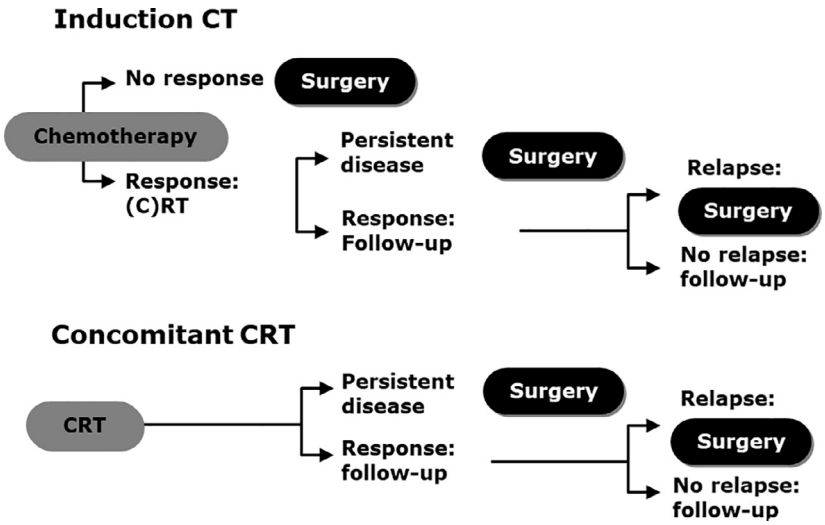

Fig. 9 Role of the salvage surgery in the context of nonsurgical treatment protocols of laryngeal cancer.

are few data about the rate of cartilage invasion or vocal cord fixation in these large cohort studies, but it could be expected to be higher than those reported in pivotal trials.

Therefore, despite state of the art treatment facilities, survival may be decreased due to an incomplete treatment dose, lack of supportive care and treatment of adverse effects of these treatments, loss of follow up, etc. Moreover, if salvage laryngectomy, which is part of an organ preserving strategy (Fig. 9) to obtain comparable survival rates between nonsurgical and surgical treatments, is not offered to patients in case of recurrence, survival is hampered in this patient category. It is highly probable that salvage surgery is not offered due to the lack of organized strategies to assess primary response to CRT, to the delay in the detection of early recurrences, to the lack of surgical experience in resection and reconstruction and for the lack of support from health systems to manage postoperative complications and rehabilitation.

For advanced laryngeal cancers, as laryngectomy is seen as a "mutilating" treatment and organ preservation is an important achievement in treatment, organ preservation protocols will be used more frequently and laryngectomy will be avoided as primary treatment or even when salvage is necessary. In the VA trial, salvage laryngectomy was more frequently done in patients with glottic tumors, vocal cord fixation, and gross invasion of the cartilage and T4 tumors, which indicates early evidence of worse therapeutic response to CRT in these patients. However, CRT was still offered to all patients under the assumption that it will offer better quality of life in comparison with laryngectomy.

There is enough evidence to say that treatment of T4 advanced larynx cancer should consider total laryngectomy since survival outcomes appear better than with CRT in most reports. For patients with T3 tumors, definitive CRT strategies are acceptable on the condition that all resources for the administration of the treatment, follow-up and surgical salvage are available. The entire factors mentioned gives some light to the contradictory results but also offer information for physicians who treat patients with advanced larynx cancer, in order to consider not only the results derived from CRT, but to consider geographical, cultural and socioeconomic conditions before offering the treatment.

The introduction of new systemic therapies should be analyzed carefully before applying them in patients with advanced larynx cancer in order to avoid indiscriminate administration to patients that are not going to get clinical advantages from its use. Customization of treatment is also critically important if overall survival rates are to be improved upon. Future developments of more precise functional imaging capabilities to monitor the response to nonsurgical therapies and possible persistence/recurrence of cancers could allow earlier intervention leading to changes of therapy or salvage surgery which would be expected to enhance survival results. The development of useful biomarkers reflecting disease characteristics such as chemo- or radiosensitivity could be useful in more precise decision making, thereby reducing redundancy of treatments and toxicities.

In summary, decision making for treatment of patients with advanced laryngeal cancer has never been more complex. Primary treatment decisions may depend on patient desires, tumor extent, experience of the treatment team, the adequacy of follow up surveillance, medical comorbidities and long-term voice and swallowing expectations.

Prognosis

Some authors have explored prognostic factors that affect survival in larynx cancer and identified that age, sex, functional status, comorbidities, tumor stage and subsite, type of therapy and treatment of recurrences are closely related with this outcome.

Five-year disease-specific survival is excellent (>95%) in early stage (I–II) patients, and can be considered good (70%–80%) in intermediate stage (III) patients. In advanced disease stages (stage IV) 5-year survival rates drop to 50%–60%. The main cause of death is local-regional recurrence, with distant metastasis being infrequent (less than 10%).

See also: Larynx Cancer: Pathology and Genetics.

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