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Definition and Management of Superior Sulcus Tumors

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Abstract

There has been a big confusion about the definition of Pancoast Tumor and Superior Sulcus Tumors (SST) which originate from the extreme apex of the lung and cause pains and distinct symptoms/signs at the presentation depending on which critical anatomical structures involved by the tumors. Pancoast Tumor is posteriorly located SST causing Horner's syndrome or more specifically related involvement of sympathetic satellite ganglia etc. We will describe three types of SST by images and options of treatment related location of the tumor as well as molecular or immunologically targeted treatment as a part of multidisciprinally approach.

Keywords: Lung neoplasms; Non-small-cell lung carcinoma; Superior sulcus tumors; Pancoast's syndrome; Differential diagnosis; Diagnostic imaging; Multidisciplinary treatment; Outcome

Definition of Superior Sulcus Tumors

SST is not just the chest wall lesion. Many patients with chest wall lesions were referred to us as having SST. The chest wall lesions need to be treated by different way since they can be resected with adequate margins compared to SST which cannot be resected with adequate margins because of the location and require post operative radiotherapy with chemotherapy before or after resection.

In 1838, Edwin Hare described the first case of Superior Sulcus Tumor who presented with 1) a history of pain, tingling, and numbness in the distribution of the left ulnar nerve, 2) Horner's syndrome, and 3) a palpable mass in the "inferior triangular space" on the left side of his neck. The mass continued to grow until the patient became paraplegic, developed urinary retention, and eventually died of the disease. The postmortem examination revealed a hard tumor extending superiorly toward the origin of the brachial plexus and involving the carotid artery, the cervical sympathetic nerves, the vagal and phrenic nerves, the spine, and intervertebral foramina [1]. In 1932, Pancoast defined the SST as bronchogenic carcinomas that developed in the apex of the lungs and invaded the superior pulmonary sulcus [2-4]. These tumors are situated in the thoracic inlet and invade the lymphatics of the endothoracic fascia and extend to the lower roots of the brachial plexus, inter costal nerves, the stellate ganglion, the sympathetic chain, and adjacent ribs and vertebral bodies. The resulting severe pain and Horner's syndrome (pupillary constriction, ptosis of the upper eyelid, slight elevation of lower lid, sinking in of the eye ball, narrowing of the palpebral fissure, an hidrosis and flushing of the affected side of the face) have been given the name "Pancoast's syndrome" because of his description given above.

Initially, only radiation treatment was attempted since these tumors were thought to be unresectable. The first successful removal of SST was performed in 1950 by Chardack and Mac Callum [5]. In brief, they resected the upper lobe en bloc along with the first and second ribs and roots C7, C8, and T1; they followed this with postoperative radiation therapy to eradicate microscopic foci of the residual tumor. On follow-up, one of their patients treated in this way lived for 5 years and 10 months after treatment, and postmortem examination revealed no evidence of recurrence or metastasis [6].

Shawand colleagues treated SST in 18 patients by preoperative radiation therapy followed by en bloc surgical resection 4 to 6 weeks later. Although not randomized, this study demonstrated a high resectability rate and good palliation, which popularized preoperative radiation therapy for SST. However, this approach masked the exact local extension of the tumor as well as nodal metastases that might otherwise have been successfully treated by resection first and definitive radiation therapy second [7]. Recent improvements in diagnostic tools such as Computed Tomography

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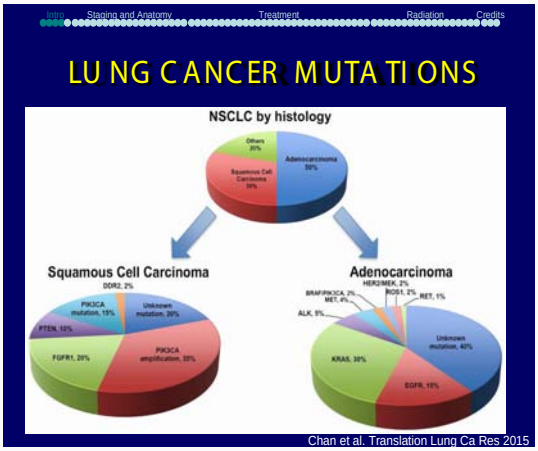

Figure 1: Lung Cancer Mutation [10].

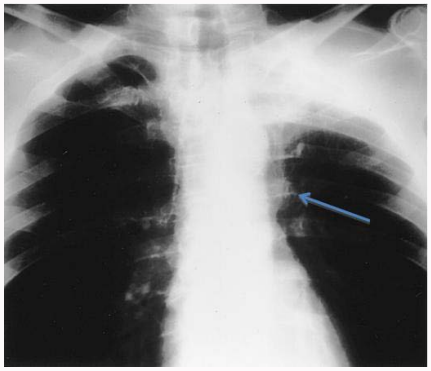

Figure 2: The arrow points a homogeneous shadow extending medially from the apical pleural thickening toward the supra hilar region [8].

[CT], Magnetic Resonance Imaging [MRI], mediastinoscopy and Positron Emission Tomography (PET) have made possible more accurate staging of local extension and nodal disease as well as distant metastatic disease and now allow better treatment selection [8].

Furthermore according to the American College of Chest Physicians (ACCP) clinical guidelines published in 2007, the presence of the Pancoast syndrome is not a prerequisite for a tumor to be designated as a Pancoast tumor [9]. They have recognized that Pancoast syndrome is associated with posteriorly located SST so called Pancoast Tumor. Anteriorly or medially located SST does not have Pancoast Syndrome at early stage.

Diagnosis

Diagnosis of SST requires a physical examination followed by radiographic examination, including CT and MRI, histologic confirmation or cytologic confirmation. More recently the core biopsy would be preferred rather than cytology alone since the molecular or immunologically targeted treatment could be offered depending on EGFR, Kras, ALK, BRAF, PIK3CA, MET, HER2, MEK, RET, FGFR1, PTEN and ROS (Figure 1) as well as positivity of PD-1 or PDL-1 [10,11].

Symptoms

The most important symptom of SST is pain. It is very unusual that SST would be diagnosed early enough without pain, although some of our patients during surveillance were found to have SST without much pain. SST may occur in three locations (which will be shown in later figures), and symptoms and signs are related to the location: anterior, in which they invade major blood vessels such as the subclavian artery; middle, in which they mainly invade the brachial plexus; and posterior, in which they invade satellite ganglia or vertebral bodies. Pain due to SST usually occurs in the shoulder and along the medical (vertebral) body of the scapula. The tumor typically is localized at the apex of the lung and involves parietal pleura. Subsequently, the pain extends down the ulnar distribution of the ipsilateral arm to the elbow (indicates involvement of T1) and, eventually, to the ulnar surface of the forearm and to the fourth and fifth fingers of the involved side of the hand (ulnar nerve involvement). Once the sympathetic chain and the satellite ganglia are involved by the tumor, patients usually develop Horner's syndrome as previously described. The direct extension in to the first or second rib or vertebral bodies usually causes severe pain, and if the spinal canal orc or discompressed, patients might develop paralysis. Patients with SST do not often have hemoptysis, shortness of breath, and/or cough which are usually associated with endobronchial lesions. SST usually originates as a peripheral lung lesion or pleural lesion.

In our series of patients with SST, most patients were treated for osteoarthritis or bursitis of the shoulder with non-steroidal analgesics for an average of 5 to 7 months [12]. Physical examination of these patients revealed increased pain with abduction of the involved side of the arm, muscle weakness, atrophy of the muscle of the hand, loss of the triceps reflex, and Horner's syndrome. Some patients complained of tenderness where the tumor had invaded the ribs or vertebral body. In cases where the tumor extended to the supraclavicular lymph nodes directly or by metastasis, physical examination revealed palpable lymph nodes. In cases where the tumor invaded the spinal canal, physical examination revealed paraplegia or paralysis. If the tumor had metastasized into the Aortopulmonary (AP) window lymph nodes, patients presented with hoarseness due to recurrent laryngeal nerve compression or invasion. Occasionally, patients presented with superior venacaval obstruction when the mediastinal lymph nodes were involved. Other symptoms and signs are weight loss or fatigue.

Imaging Evaluation

SST has to be arising from the above sulcus and more medially located at their early stages. SST has a characteristic appearance on imaging. However, in their early stages, these tumors are often missed by traditional anterior/posterior chest X-rays. Recent advances in Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) have made selection of patients with potentially resectable of SST more accurate [8]. If mediastinoscopy reveals no mediastinal lymph nodes involved, the patient can be treated with surgery followed by radiation therapy with or without chemotherapy. If mediastinoscopy reveals microscopic mediastinal lymph node involvement, the patient can be treated with induction radiation therapy and concurrent chemotherapy followed by surgery. If mediastinoscopy reveals gross mediastinal lymph node involvement (N2), or if CT reveals N3 or T4 lesions, the patient can be treated with concurrent chemotherapy and radiation therapy to relieve symptoms; the outcome of such treatment appears to be better than that of sequential chemotherapy followed by radiation therapy. Whenever possible, to enhance the patient's quality of life, surgery should be considered to improve function and relieve pain

Chest radiographs

The pitfalls of making a diagnosis of SST were pointed out

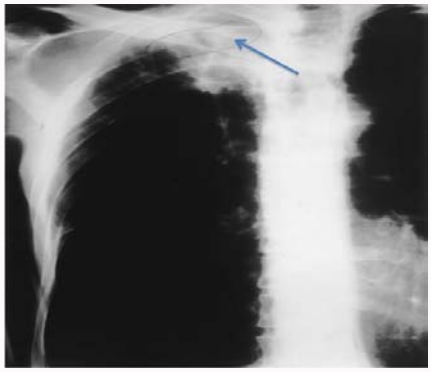

Figure 3: An apical lordotic radiograph showing the apical lesion more definitively as well as the arrow pointing destruction of the posterior second rib [8].

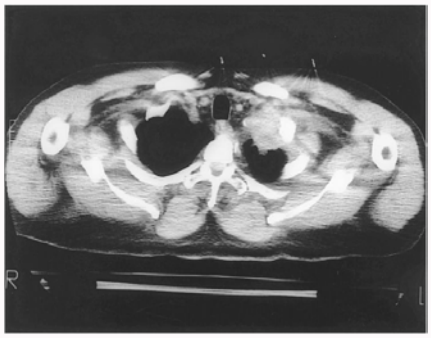

Figure 4: Computed Tomography (CT) scan showing the apical mass invading the left subclavian artery and vein as well as the anterior chest wall [8].

by Simon and his colleagues [13]. The first is that on regular chest radiographs, as of tissue mass without bony distruction can be missed or misinterpreted as pleural thickening. The shadow extending medially from the pleural thickening toward the hilum is a sign of more aggressive of malignant tumor. The apical lordotic or slightly oblique views show the apical lesions much better (Figure 2) [8]. The second pitfall is that an apical lordotic view does not show bony destruction. Additional anteroposterior views of the lower cervical/upper dorsal spine or tomogram may be needed to show bony destruction (Figure 3) [8].

Computed tomography

CT scans are better than conventional radiographs at showing the relationship of SST to the anterior structures (*i.e.,* subclavian artery and vein and trachea) (Figure 4) and posterior structures (*i.e.,* chest wall, ribs and vertebral bodies). The CT scan also provides more information in regard to operability [8]. CT of the thorax is important for staging purposes to show any mediastinal lymph node involvement, pleural effusion, as well as CT of the upper abdomen to reveal any adrenal gland, hepatic or renal metastasis [8].

Magnetic resonance imaging

As compared with CT scans, MRI scans more accurately display the anatomy of SST (63% *vs.* 94%) [8,14]. A sagittal section obtained by MRI can show extension of a SST to the posterior wall of the subclavian artery as well as to mediastinal lymph nodes (Figure 5) an axial scan cannot do this as easily since MRI is not as accurate at demonstrating invasion of tumor into the foramen, spinal cord, and major blood vessels (Figure 6) [8]. In any case, MRI is required to

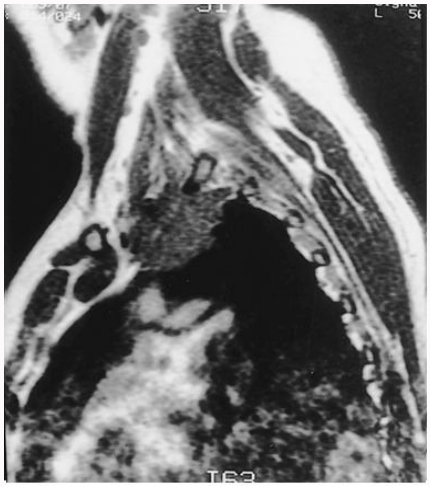

Figure 5: Magnetic Resonance Imaging (MRI) findings. Sagittal scan showing that the tumor extends beyond the apex of the lung but does not involve the brachial plexus; it abuts the posterior wall of the subclavian artery and involves the first rib [8].

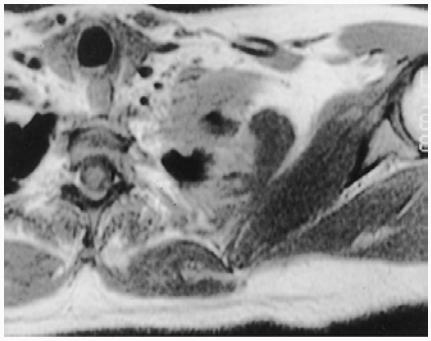

Figure 6: Axial scan showing invasion of the tumor into the foramen, spinal cord, and major blood vessel [8].

demonstrate resectability of the SST. MRI of the brain is important for showing any micrometastasis; patients with SST often present with brain metastases because of the location of the tumor, and more of these patients have adenocarcinoma or large-cell carcinoma of the lung, which are highly metastatic to other sites such as Brain, adrenal glands [8,14,15]. When combined, MRI and CT can reveal extension of the SST into the great vessels at the thoracic inlet (primarily, the subclavian artery and vein); involvement of the trachea or esophagus; invasion of the brachial plexus, chest wall, vertebral bodies, foramen, and spinal cord; mediastinal lymph node involvement by metastasis or direct extension; and extra thoracic metastasis into the brain and upper abdomen. Although the diagnosis of SST by diagnostic imaging is accurate in more than 95% of cases, cytological or histological confirmation of the definitive diagnosis is important as well as lung cancer mutation and PD-1 or PD-L1 status since it will affect treatment approach [14]. For example, one study found that 3% of SST was undifferentiated small-cell lung cancers, which can be treated with chemotherapy and radiation therapy alone with or without Prophylactic Cranial Irradiation (PCI) depending on the response to the chemoradiotherapy to the primary lesion [15].

Positron emission tomography (PET) scan

PET scan is required for staging workup to rule out distant metastasis for lung cancer (Figure 7) [8].

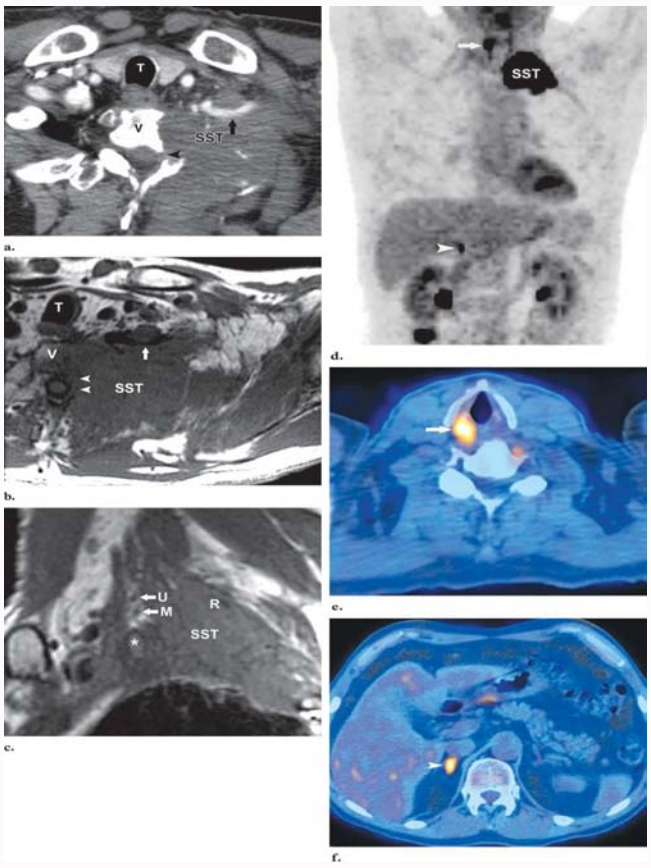

Figure 7: (a) Axial Computed Tomographic (CT) image shows a Soft-Tissue Mass (SST) in the left lung apex, with destruction of the first and second ribs. The tumor abuts the left subclavian artery anteriorly (arrow) and has invaded the T2 Vertebral body (V) medially. There is also extension of the tumor into the T2-3 neurovertebral foramen (arrowhead). T = Trachea. **(b)** Axial MR image at the same level as a clearly shows the mass (SST) invading the T2-3 neurovertebral foramen (arrowheads) and compressing the left subclavian artery (arrow). T = Trachea, V = T2 vertebral body. **(c)** Sagittal MR image at the level of the left superior sulcus shows the mass (SST) invading the fat above the apical pleura and encasing the subclavian artery (*). The Upper (U) and Middle (M) trunks of the brachial plexus are clearly separate from the mass, but the lower trunk has been encased and is no longer visible, which means that the tumor is not resectable. The tumor also has invaded the first Rib (R). **(d)** Coronal maximum intensity projection image from hybrid Positron Emission Tomography (PET)/CT shows intense uptake of fluorine 18 Fluorodeoxyglucose (FDG) in the left Superior Sulcus Tumor (SST) and asymmetric FDG uptake in the right vocal cord (arrow) and in the region of the right adrenal gland (arrowhead). **(e)** Axial fused PET/CT image at the level of the vocal cords shows increased FDG uptake by the arytenoid insertion of the right vocal cord (arrow). Because of paralysis secondary to vagal nerve palsy from the mass in the left superior sulcus, the left vocal cord is not FDG avid. **(f)** Axial fused PET/CT image at the level of the adrenal glands shows an FDG-avid right adrenal nodule (arrowhead) that was found at subsequent biopsy to be an adrenal metastasis [8].

Figure 7 shows that superior sulcustumorina 56-year-oldman with sensory loss in the region of the left ulnar nerve distribution and with hoarseness. This patient has stage IV SST with right adrenal gland metastasis and a very large primary in the left apex of his lung causing paralyzed vocal cord on the left and compensating right vocal cord picking up FDG uptake [8].

Intensity of FDG uptake is correlated with the outcome of non-small cell lung cancer [16].

Also PET is a very important after chemoradiotherapy or radiotherapy for follow-up study to distinguish residual tumor from

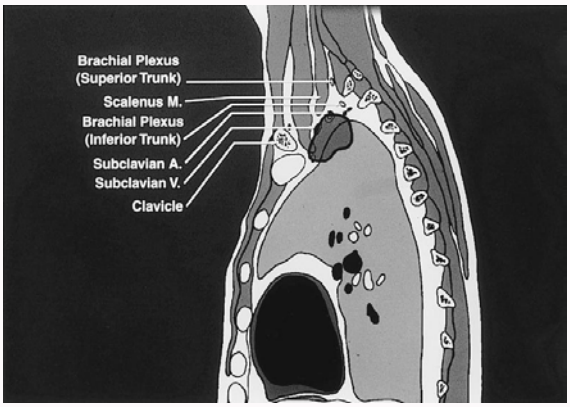

Figure 8: A more anteriorly located superior sulcus tumor invading the subclavian artery [8].

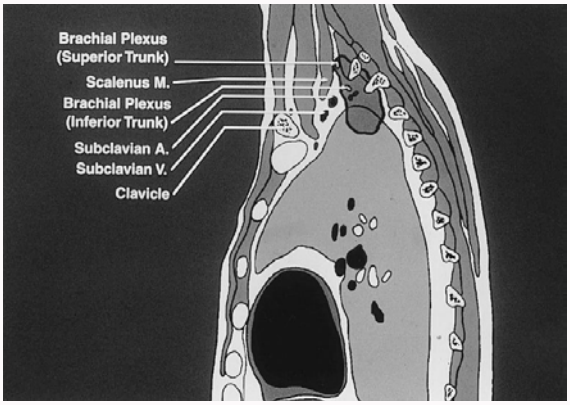

Figure 9: Medial location of the superior sulcus tumor involving the brachial plexus extending more superiorly where surgery might be contraindicated.

fibrotic change. Without FDG uptake which means metabolically negative PET usually confirms that inactive cancer and not active residual or recurrent cancer where patients received radiotherapy.

Bronchoscopy and CT guided fine needle aspiration and core biopsy

According to Hepper and colleagues, accurate diagnosis of SST by bronchoscopy occurs in only 16% of cases [17]. In comparison, Attar and colleagues found that fiber optic bronchoscopy was cytologically diagnostic in 13 of 43 patients (30%), and Miller and colleagues found sputum cytology and bronchoscopy diagnostic in 31% of their patients [18,19]. Because of the location of SST, needle biopsy and, more recently, CT guided Fine-Needle Aspiration (FNA) are practical approaches to a positive diagnosis. For instance, Mc Goon described a transcervical technique that took a supraclavicular approach lateral to the sternal head of the sternocleidomastoid muscle, which passed through the scalene fat pad [20]. Siderys and Pittman reported the direct insertion of a Vim-Silverman needle through the second and third intercostal space into the posterior chest of a patient in prone position [21]. Walls and colleagues reported 26 of 27 patients with SST by CT-guided posterior FNA [22]. However, though very accurate diagnostically, CT-guided biopsies are relatively costly as compared with fluoroscopically and ultrasonically guided biopsies [23].

More recently, a core biopsy of the pathological specimen is required to obtain mutation status and PD-1 and PD-L1 positivity for induction treatment or adjuvant treatment. Also when more standard chemoradiotherapy followed by surgery will fail, molecular

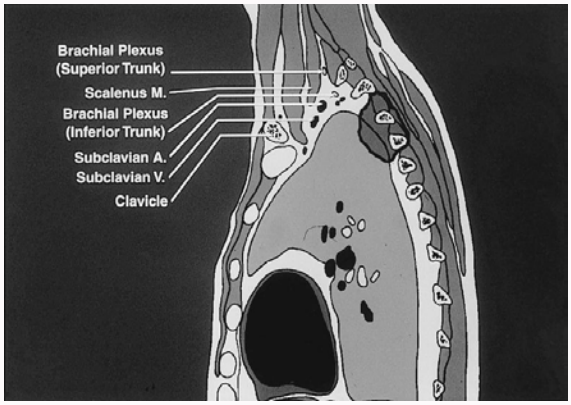

Figure 10: Superior sulcus tumor located posteriorly (typical Pancoast's tumor) [8].

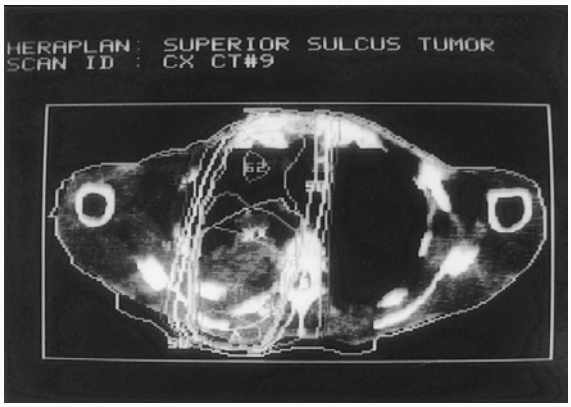

Figure 11: If the tumor is located posteriorly, a posterior boost can be arranged without giving high dose to the spinal cord or more anterior structure [13].

targeted treatment immunotherapy will be applied based on the markers. Molecular targeted treatment based on the mutation would be important for stage IV patients with SST [10,11].

Staging

Staging is a key to deciding on treatment of SST. Paulson emphasized the importance of mediastinoscopy since his patients did very poorly if the mediastinal or hilar lymph nodes were involved: only 3 out 17 patients with hilar or mediastinal nodal involvement survived 1 year and none survived 2 years [23]. In contrast, 44% of the patients with no nodal involvement survived 4 years or longer. After preoperative radiation therapy and subsequent surgery, Paulson also advocated scalene node biopsy if the scalene nodes are palpable prior to initiation of treatment. Attar and colleagues affirmed that adequate preoperative assessment is extremely important because patients who had positive mediastinal lymph nodes died shortly after surgery [18]. As these reports illustrate, it is important to document the exact location of the SST as well as extent of the disease since location will influence the resectability of the tumor and the radiation therapy dose arrangement.

If resection is contraindicated, tumors can be treated with concurrent chemotherapy and radiation therapy. Depending on the location of the tumor, radiation therapy can be given anteriorly or posteriorly. The contraindications for surgery include extensive invasion of the brachial plexus, subclavian artery, and vertebral

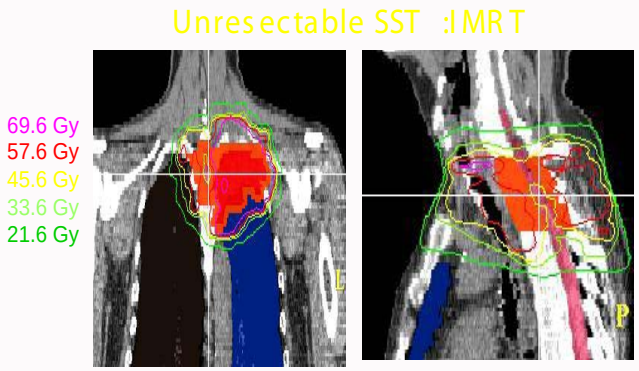

Figure 12: Unresectable SST treated by 1.2 Gy bid with total does 69.6 Gy to GTV with concurrent chemotherapy [8].

bodies; mediastinal involvement (particularly perinodal); venous obstruction, and distant metastases [15]. SST located more anteriorly tend to invade the subclavian artery (Figure 8); SST located medially tend to involve the brachial plexus and extend more superiorly, thus contraindicating surgery or indicating sacrifice of the brachial plexus if necessary (Figure 9) [8]. SST located more posteriorly (*i.e.,* typical Pancoast's tumors), may produce Horner's syndrome due to the involvement of the satellite ganglia or vertebral bodies with or without extension of the tumor into the foramen (Figure 10) [8]. If the SST is more anteriorly located, an anterior boost of radiation can be given without compromising tumor control or damaging more normal tissue. If the tumor is located more posteriorly, a posterior boost can be arranged without subjecting the spinal cord or more anterior structures to high doses of radiation (Figure 11) [8].

Treatment and Results

Pre-operative radiation therapy and surgical resection

The combination of preoperative radiation therapy and subsequent surgical resection to treat SST was first reported by Shawand his colleagues in 1961 [7]. Paulson used this approach and updated it on several occasions [24-26]. In brief, the SST, chest wall, and superior mediastinum were given, bilaterally, 300 cGy of radiation per day in 10 fractions over 12 days up to a total tumor dose of 3000 cGy. Three weeks after completion of radiation therapy, patients underwent en bloc resection of the tumor along with the involved chest wall including the entire first rib and posterior portion of the second and third ribs. In addition, the resection sometimes included part of the first three transverse processes of the thoracic vertebrae and nerve roots, the eighth cervical nerve root, the lower trunk of the brachial plexus, part of the stellate ganglion, and the dorsal sympathetic chain. The involved lung was resected either by lobectomy or segmental resection. The entire procedure was accompanied by dissection of the regional hilar and mediastinal lymph nodes. More recently, patients in our institution have had mediastinoscopy prior to this radical dissection; if they are found to have any positive contralateral mediastinal lymph nodes or mid-low mediastinal lymph nodes, they usually receive chemotherapy and radiation therapy rather than radical surgery.

In a series reported by Paulson, 131 patients were started on pre-operative radiation therapy to be followed by en bloc surgical resection [25]. Of these, 78 patients (60%) completed preoperative radiation therapy followed by radical dissection. The mortality rate around surgery was 2.6%, and the overall survival was 31% at 5 years,

26% at 10 years, and 22% at 15 years. Three of 17 patients who had involvement of either the hilar or mediastinal lymph nodes survived 1 year, and none who had positive lymph nodes survived beyond 2 years. Among the 61 patients who had no nodal involvement at the time of surgery, the 5-year survival was 44%, 10-year survival was 33%, and 15-year survival was 30%. Miller and his colleagues administered preoperative radiation therapy at doses of 2000 to 4000 cGy over time-spans of 4 days to 4 weeks [19]. Attar and his colleagues administered it at doses of 5500 to 6000 cGy preoperatively over 1 month [18]. However, both groups noted a high rate of morbidity and mortality and so set the dose at 3000 cGy. Beyer and Weisenburger administered preoperative dose of at least 5500 cGy, which induced a better response and appeared to increase survival [27]. They treated 28 patients with SST: in 15 patients treated with pre-operative radiation therapy followed by surgery, the 5-year survival was 45%; in 13 patients treated with radiation therapy alone, the 5-year survival was much worse; the overall 5-year survival was 22% [27]. Devine and associates used two different dose levels: 3000 to 3500 cGy over 2 weeks in 25 patients, and a higher dose of 4500 to 5000 cGy over 5 to 5½ weeks in 15 patients [28]. They noted no difference in the resectability or survival between the two dose levels. Miller and colleagues reported on 26 patients who had pre-operative radiation therapy followed by en bloc resection and noted a 5-year survival of 32% [19]. Stanford and colleagues reported on a similarly treated group and noted a 5-year survival rate of 49.7% [29].

Martini reported on 145 patients treated at the Memorial Sloan Kettering Hospital in New York City over a 36-year period [30]. Sixty-eight of 148 patients had surgery alone, and 48 patients had pre-operative radiation followed by resection. Only 9% of the 68 patients who had surgery alone had completely resected tumors as compared to 23 patients who received pre-operative radiation followed by complete resection. Martini also claimed that without CT or MRI, it was difficult to evaluate the resectability during that time period [30]. Devine and his colleagues reported on a series of patients who completed pre- operative radiation therapy followed by surgery and noted a 2-year survival of 29% and a 5-year survival of 14% [28].

In a study by Komaki et al., [31], patients with Stage IIB tumors had a 5-year survival of 47%. However, patients who had surgical resection followed by radiation therapy had a 5-year survival of 56%, and patients who received both preoperative and postoperative radiation therapy with chemotherapy had a 5-year survival of 87% (although here were only eight patients among this group). Surgery was very important prognostic factor in Stage IIB patients. In comparison, patients with Stage IIIA and Stage IIIB tumors had 5-year survivals of 14% and 16%, respectively. Surgical resection was not an important prognostic factor in these patients since all had adequate CT and MRI studies of the chest as well as a metastatic workup and mediastinoscopy before initiation of treatment.

Pre-operative and Postoperative Radiation Therapy

Shahian and his colleagues reported on 18 patients who were treated with pre-operative radiation therapy followed by resection (14 of these patients also underwent supplemental postoperative radiation therapy to treat positive lymph nodes or positive margins at the resection site, or both) [32]. The overall 5-year survival for the entire series was 56%. Shahian and colleagues believed that postoperative radiation therapy, in addition to pre-operative radiation therapy for patients with unfavorable findings such as positive lymph nodes or positive margins, would improve the survival [32]. Hilaris and Martini found that, if a tumor was not resectable at the time of surgery after pre-operative radiation therapy, then a combination of radon seed implants and external radiation therapy (40 Gy in 4 weeks) would provide better local control and a survival rate comparable to that for external radiation therapy alone. The median survivals were 12 months *vs.* 6 months, respectively [33]. At M. D. Anderson Cancer Center, 143 patients with SST had single-modality or combined treatment [31]. Those patients with T3N0M0 tumors who had pre-operative and postoperative radiation therapy (with or without chemotherapy) did extremely well and had a 5-year survival of 87% (however, there were only eight patients in this group).

Surgical resection alone

Patients with SST are not usually treated with surgery alone since SST arises at the extreme apex of the lung which would make adequate surgical margin impossible by surgery alone. At M. D. Anderson, only 5 of 143 patients with SST, (3%) had surgery alone [31]. In studies by Martini and Hilaris, 9% of the total 68 patients had resectable tumors as compared with 23% of the total 48 patients who had preoperative radiation therapy [30]. However, some patients with well-localized disease and fairly small tumors can be treated with radical surgery that includes adequate margins. Nevertheless, this treatment approach is not the usual protocol for treating SST, although radical surgery may be considered in patients who have been followed after treatment for a primary neoplasm in the head and neck or at any other site by routine chest X-ray or CT of the chest. Attar and colleagues reported a 3-year survival rate of 60% in five such patients, very similar to results reported by Komaki and colleagues [18,31].

Surgical Resection Followed by Postoperative Radiation Therapy with or without Chemotherapy

Postoperative radiation therapy does not improve survival in patients with carcinoma of the lung that had complete surgical resection without gross or microscopic residual tumor or regional lymph node involvement including hilar or mediastinal lymph nodes. This applies to SST as well, even though their resection may leave positive margins.

Martini reported on170 patients with SST who were treated at the Memorial Sloan-Kettering Hospital from 1938 to 1978 [30]. Of these patients, 127 underwent surgery; although the staging work-up was not complete and inoperable patients were treated more palliatively, the 5-year survival rate was 17% for these patients *vs.* 3.4% for the inoperable patients. Among the 127 patients who underwent surgery, 20 patients had curative surgery after pre-operative radiation therapy; their 5-year survival rate was 29%. The remaining 107 patients who underwent surgery received postoperative brachytherapy their 5-year survival was14%.

A report from M. D. Anderson Cancer Center on 85 patients with SST noted that combined surgery and radiation therapy was more effective at controlling the tumors and improving survival than either modality by itself [34]. In that study, 43 patients were categorized as having Stage IIIA disease and 42 patients as having Stage IIIB disease (according to the old AJCC classification used in1992) [35]. Surgery was a significant factor in improving local control and survival among the Stage IIIA patients. Those patients who had Stage IIIB unresectable Non-Small-Cell Lung Cancers (NSCLC) arising from the superior sulcus was treated by chemotherapy and radiation therapy. The

2-year survival was 46.5% for patients with Stage IIIA disease *vs.* 21% for patients with stage IIIB disease. When surgery was included in the treatment, 52% of patients (13 of 25) lived longer than 2 years as compared with 22% (13 of 60) when the lesion was unresectable [34].

In a more recent series from M. D. Anderson Cancer Center, 81 patients had unresectable lesions: 45 were treated with radiation therapy alone, 32 with radiation and chemotherapy, and 4 with chemotherapy alone [31]. Sixty- two patients had resectable lesions: 5 patients had surgery alone and 57 had pre-operative radiation therapy followed by surgery, or surgery followed by postoperative radiation therapy, or both pre-operative and postoperative radiation therapy with or without chemotherapy. In analyzing their series, patients with Stage IIIA according to the old AJCC system were divided into 2 groups according to the new AJCC system: Stage IIB (Tx N0 M0) (n=36) and Stage IIIA (positive lymph nodes) (n=31) [36]. The 5-year survival differed significantly between Stage IIB and Stage IIIA patients: 47% *vs.* 14%, (P-value<0.01). (It is interesting to note that the 5-year survival for patients with Stage IIIA and IIIB disease, according to the new classification system, was almost identical: 14% *vs.*16%). The 5-year survival for those patients, who had surgery with or without adjuvant and neoadjuvant treatment, was 37%, as compared with 11% for those patients who did not have any surgery. This difference was statistically significant [31]. Darteville and his colleagues reported on a group of patients who did not receive pre-operative radiation therapy:14% had surgery alone and 86% had surgery followed by postoperative radiation therapy [37]. The 2-year survival was 50% and the 5-year survival was 31%. The median follow-up was 2.5 years. The surgical approach in this series was aggressive. Some patients underwent a large L-shaped anterior cervical incision for removal of theme-dial half of the clavicle, dissection or resection of the subclavian vein, division of the anterior scaleneus muscle, and resection of the cervical portion of the phrenic nerve if it had been invaded by the tumor. The subclavian and vertebral arteries were exposed, the brachial plexus was dissected up to the spinal foramen, the invaded ribs were resected, and the chest wall and primary SST were removed en bloc, either directly or by extension of the surgical incision in to the deltoid pectoral group (Figure 9). This approach has been used occasionally at M. D. Anderson Cancer Center.

Recent phase II trial at MDACC (PI: R Komaki) revealed that 32 patients with resectable or marginally resectable superior sulcus tumors at The University of Texas MD Anderson Cancer Center from 1994 to 2010 were enrolled in a prospective trial. Surgery involved segmentectomy or lobectomy with en bloc resection of the involved chest wall and complete nodal staging; Radiation Therapy (RT) began 14 to 42 days later to a dose of 60 Gy in 50 fractions (1.2 Gy per fraction) if surgical margins were negative or 64.8 Gy in 541.2 Gy fractions if margins were positive. Two cycles of etoposide (50 mg/m^2) and cisplatin (50 mg/m^2) were given during RT, and another 3 cycles were given after RT. Eleven patients underwent Prophylactic Cranial Irradiation (PCI) [38].

The results showed that this protocol completion rate was 78%. Gross total resection was accomplished in all 32 patients; 28% underwent R1 resection. Operative mortality was 0%. The most common surgical complication was postoperative pneumonia (25%). At a median follow-up time of 53.4 months (range, 2-154 months), the 2-year, 5-year, and 10-year rates of locoregional control were 84%, 76%, and 76%; distant metastasis-free survival, 52%, 48%, and 48%; disease-free survival, 49%, 45%, and 45%; and overall survival, 72%, 50%, and 45%, respectively. The brain was the most common site of distant failure (n=5), but no patient who received PCI experienced brain metastasis. We have concluded that surgery followed by postoperative chemoradiation is safe and effective for the treatment of marginally resectable superior sulcus tumors [38].

In contrary to the published guidelines, in this recent prospective phase-II study mentioned above, the authors support that primary surgery followed by chemo-radiotherapy has at least equal good results with that reported by the SWOG 9416 and JCO 9806 trials in patients with resectable or marginally resectable Pancoast tumors [38,39]. Indeed, the results of the above mentioned study could be partially affected by the appropriate selection of patients for primary surgery and by the large experience of their institution with surgical resection of Pancoast tumors and therefore it is questionable if these results could be easily reproduced in other centers.

Patients who have positive margins or microscopic N2 disease need postoperative radiation therapy. According to the recent randomized study, postoperative concurrent chemotherapy for N2 disease did not improve survival [40].

Patients who have not had pre-operative radiation therapy, but whose tumor margins are grossly positive need definitive dose of radiation therapy (66 Gy without chemotherapy or 60 Gy to 63 Gy with concurrent chemotherapy). Since most patients with SST present with adenocarcinoma or large cell carcinoma, prophylactic cranial irradiation needs to be considered early in the course of treatment.

Recently, VATS has been used to minimize the surgical trauma during resection of Pancoast tumors through a trans-manubrial approach by avoiding the need to proceed with a second incision (thoracotomy) to accomplish lobectomy and mediastinal lymph node dissection [41]. Videoscopic assistance facilitates the performance of a formal lobectomy through the initial manubriotomy incision which serves as the utility thoracotomy [42]. Videoscopic assistance can also be useful during the initial steps of the procedure to determine the appropriate level of chest wall resection avoiding that way the resection of extra (non-involved) ribs [43].

Inoperable or unresectable superior sulcus tumors

Patients with SST who are considered to be medically inoperable or surgically resectable should be considered candidates for curative or palliative radiation therapy with concurrent chemotherapy if patients could tolerate. Morris and his colleague reported on 26 cases in which SST were treated with high- dose radiation therapy (7000 cGy/7 weeks or higher) [44].

Ahmad and colleagues reported on 48 patients treated by radiation therapy alone using either cobalt-60 or cesium-137 teletherapy up to a total sum or dose of 5000 to 6000 cGy over 5 to 6 weeks [45]. The actuarial 3-year survival rate was 28% and the 5-year survival rate was 21%. There were no severe complications among the patients treated with radiation therapy alone except for some fibrotic changes that were recognized in the radiographs-changes that did not cause any symptoms in the patients. Van Houtte and colleagues reported on 31 patients with SST treated with external high-energy radiation therapy up to a total tumor dose of 2000 to 7000 cGy [46]. The overall 5-year survival rate was 18%. The doses below 5000 cGy and bone invasion were associated with a higher local recurrence rate.

Komaki and colleagues reported on 36 patients with SST who were treated with external radiation therapy between 1963 and 1977 at the

Medical College of Wisconsin [9]. Local control correlated positively with field size and median survival. All patients who survived beyond 2 years exhibited local control of the tumor. No patient survived beyond 2 years if treatment failed locally. Between 1978 and 1983, an additional 32 patients with inoperable SST were studied. Relief of pain was achieved in 91% of all patients who presented with pain. Three-fourths of the patients with Horner's syndrome responded to the radiation therapy. The disease-free survival rates were 65% at 12 months, 38% at 24 months, 25% at 36 months, and 15% at 48 months. Again, no patient survived beyond 2 years if treatment failed locally. The patterns of failure showed that the brain was the most common site of distant metastasis after the completion of radiation (23 of 68 patients, 34%) [47].

From the M.D. Anderson Cancer Center, Komaki and colleagues reported on 85 patients with SST [34]. The 60 patients who had medically or surgically inoperable SST and were treated by radiation therapy alone or radiation therapy with chemotherapy had a 2-year survival of 22%. In contrast, the 25 patients who had resectable tumors had a 2-year survival of 52%. In a more recent series, they reported on 77 patients who had unresectable or medically inoperable lesions: 45 patients received radiation therapy alone, and 32 patients received a combination of radiation therapy and chemotherapy. Those patients who received radiation therapy alone had an overall 5-year survival of 9% and a 5-year local control rate of 51%. In contrast, patients who received combined radiation therapy (≥ 66 Gy given on a hyper fractionated regimen) and chemotherapy (oral VP-16 and cisplatin) had a 5-year survival of 36% and a 5-year local control rate of 63% (Figure 12) [31,48]. Patients who received sequential chemotherapy or concurrent chemotherapy (with <66 Gy of radiation) had a 5-year survival of only 7% as compared with the higher dose radiation therapy group. Twelve patients who received ≥ 66 Gy of radiation with either sequential or concurrent chemotherapy had a 5-year survival of 33%. The results suggest that patients who had medically or surgically inoperable SST and who received concurrent chemotherapy and radiation therapy at a dose of >66 Gy achieved the best 5-year survival [31,48]. If the SST was inoperable or unresectable but the patient had a good performance status, definitive dose with smaller fraction size with concurrent chemotherapy would be the best way to give curative dose to the tumor without causing brachial plexopathy due to the radation damage to the nerve [48].

Proton Beam Therapy (PBT), through its characteristic Bragg peak, has the potential to decrease the toxicity of radiotherapy, and, subsequently improve the therapeutic ratio. Herein, we provide a primer on the physics of proton beam therapy for locally-advanced Non-Small Cell Lung Cancer (NSCLC), as well as in special situations such as re-irradiation and post-operative radiation therapy. PBT will spare normal tissue damage surrounding the tumor. Especially low does 5 Gy scattering to the heart when we treat mediastinal nodal disease for the lung cancer [49]. SST is located at the apex of the lung and usually fixed in the inlet of the supraclavicular fossa. It would be best treated by Intensity Modulated Proton Treatment (IMPT) if scanning proton is available. Also IMPT requires collaboration of the physicists. At UT MDACC, retrospective study has been published. IMPT was used for oropharyngeal carcinoma patients has the ability to reduce the dose to organs at risk compared to Intensity-Modulated Radiotherapy (IMRT) while maintaining adequate tumor coverage. Their aim was to compare the clinical outcomes of these two treatment modalities. They performed a 1:2 matching of IMPT to IMRT patients. Our study cohort consisted of IMPT patients from a prospective quality of life study and consecutive IMRT patients treated at a single institution during the period 2010 to 2014. Patients were matched on unilateral/bilateral treatment, disease site, HPV status, T and N stages, smoking status and receipt of concomitant chemotherapy. Survival analyzes were performed using a Cox model and binary toxicity endpoints using a logistic regression analysis. They included 50 IMPT and 100 IMRT patients were included. The median follow-up time was 32 months. There were no imbalances in patient/tumor characteristics with the exception of age (mean age of 56.8 years for IMRT patients and 61.1 years for IMPT patients, p-value=0.010). Statistically significant differences were not observed in overall survival (Hazard Ratio (HR)=0.55; 95% confidence interval (CI): 0.12–2.50, p-value=0.44) or in progression free survival (HR=1.02; 95% CI: 0.41–2.54; p-value=0.96). The age-adjusted Odds Ratio (OR) for the presence of a Gastrostomy (G)-tube during treatment and at 3 months post-treatment are respectively (OR=0.53; 95%CI: 0.24-1.15; p-value=0.11) and (OR=0.43; 95% CI: 0.16-1.17; p-value=0.10). When considering the pre-planned composite endpoint of grade 3 weight loss or G-tube presence, the odds ratios at 3 months and 1 year were respectively (OR=0.44; 95% CI: 0.19-1.0; p-value=0.05) and (OR=0.23; 95% CI: 0.07-0.73; p-value=0.01). They concluded that IMPT was associated with reduced rates of feeding tube dependency and severe weight loss without jeopardizing outcome [50]. At present time, a prospective multicenter randomized trial is ongoing.

These patients who received concurrent chemoradiotherapy would get benefit to receive adjuvant immunotherapy which improved overall survival [51]. In the future, we need to find more early stage of SST by screening or surveillance CT scans which has shown improvement of 6 years survival. In these early cases, patients may not have pain and hopefully they can be treated more limited operation or combined surgery followed by molecular targeted or immunotherapy with or without post operative radiotherapy or proton treatment depending on mediastinal staging and margins [52,53].

Summary

Metastatic work-up for SST includes careful history taking and examination to find symptoms and signs due to involvement of anatomical structure by the tumor. MRI of the brain (CT of the brain if MRI cannot be done), PET scan, CT of the chest upper abdomen and MRI of the upper thorax and lower neck, and mediastinoscopy or Endo-Bronchianchial Ultrasound guided mediastinal nodal evaluation (EBUS) to evaluate distant metastasis as well as the direct extension of the disease into blood vessels, mediastinal nodes, brachial plexus, vertebral bodies, ribs, sympathetic satellite ganglia and the spinal canal.

It is critical to obtain adequate specimen to determine tumor mutation status and positivity of PD-1 or PDL-1 for SST as we started to do other site of NSCLC which will influence adjuvant treatment.

Resectable SST that has not distantly metastasized or involved regional lymph nodes (as determined by an adequate staging system, including mediastinoscopy) can be treated with combined surgery and radiation therapy with or without chemotherapy. At present, there is no significant difference between the results of pre-operative and post-operative radiation therapy for resectable SST, although SWOG trial recommends preoperative chemoradiotherapy.

Since SST is not common in the Lung Cancer, it is difficult to do prospective randomized studies, although it can be done by

international trials if definition of SST is stricter and collaboration would be established by surgeons, medical oncologists and radiation oncologists.

The management of SST has been improving, along with the use of MRI, CT and PET imaging studies to stage and delineate the primary tumor and lymph node involvement and the application of spiral CT to planning optimization. Since SST at the apex of the lung are less mobile than tumors at the base of the lung, the SST now can be treated more effectively using sophisticated3-dimentional conformal (3DCRT), IMRT or IMPT.

In fact, the improvement in local control means that treatment failures now occur less often at the primary tumor site and more often at sites of distant metastasis. In the future, newer tools such as Position-Emission Tomography (PET) scanning might even be used to detect lymph node and other distant metastases in patients with SST and thus further improve treatment including high technology treatment by intensity modulated proton beam treatment with more molecular targeted agents and post operative immunotherapy as adjuvant treatment.

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References

1. Hare ES. Tumor involving certain nerves. Lond Med Gaz. 1838;1:16-8.
2. Pancoast HK. Importance of careful roentgen ray investigation of apical chest tumors. JAMA. 1924;83(18):1407-11.
3. Pancoast HK. Superior Pulmonary Sulcus Tumor: Tumor characterized by pain, Horner's Syndrome, destruction of bone and atrophy of hand muscles Chairman's address. JAMA. 1932;99(17):1391-6.
4. Tobias JW. [Sindromeapic-costo-vertebral dolorosa por tumor, apexiano. Su valor diagnostico en el cancer primitivopulmonar]. Rev Med Lat Am. 1932;19:1522-56.
5. Chardack WM, Mac Callum JD. Pancoast syndrome due to bronchogenic carcinoma: successful surgical removal and postoperative irradiation. J Thorac Surg. 1953;25(4):402-12.
6. Chardack WM, Mac Callum JD. Pancoast tumor: five-year survival without recurrence or metastases following radical resection and postoperative irradiation. J Thorac Surg. 1956;31(5):535-42.
7. Shaw RR, Paulson DL, Kee JL. Treatment of Superior Sulcus Tumor by Irradiation Followed by Resection. Ann Surg. 1961;154(1):29-40.
8. Bruzzi JF, Komaki R, Walsh GL, Truong MT, Gladish GW, Munden RF, et al. Imaging of non-small cell lung cancer of the superior sulcus: part 1: anatomy, clinical manifestations, and management. Radiographics. 2008;28(2):551-60.
9. Shen KR, Meyers BF, Larner JM, Jones DR. American College of Chest Physicians. Special treatment issues in lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). Chest. 2007;132(3):290S-305S.
10. Chang, et al. Translation Cancer Research. 2015.
11. Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2016;375(19):1823-33.
12. Komaki R, Roh J, Cox JD, Lopes da Conceicao A. Superior sulcus tumors: results of irradiation of 36 patients. Cancer. 1981;48(7):1563-8.
13. Grover FL, Komaki R. Superior sulcus tumors. In: Roth JA, Ruckdeschel JC, Weisenburger TH, editors. Thoracic oncology. 2nd ed. Philadelphia: Saunders; 1995;225-38.
14. Heelan RT, Demas BE, Caravelli JF, Martini N, Bains MS, McCormack PM, et al. Superior sulcus tumors: CT and MR imaging. Radiology. 1989;170(3):637-41.
15. Johnson DH, Hainsworth JD, Greco FA. Pancoast's syndrome and small cell lung cancer. Chest. 1982;82(5):602-6.
16. Sasaki R, Komaki R, Macapinlac H, Erasmus J, Allen P, Forster K, et al. [18F] fluorodeoxyglucose uptake by positron emission tomography predicts outcome of non-small-cell lung cancer. J Clin Oncol. 2005;23(6):1136-43.
17. Hepper NG, Herskovic T, Witten DM, Mulder DW, Woolner LB. Thoracic inlet tumors. Ann Intern Med. 1966;64(5):979-89.
18. Attar S, Miller JE, Satterfield J, Ho CK, Slawson RG, Hankins J, et al. Pancoast's tumor: irradiation or surgery? Ann Thorac Surg. 1979;28(6):578-86.
19. Miller JI, Mansour KA, Hatcher CR Jr. Carcinoma of the superior pulmonary sulcus. Ann Thorac Surg. 1979;28(1):44-7.
20. McGoon Dc. Transcervical Technic For Removal Of Specimen From Superior Sulcus Tumor For Pathologic Study. Ann Surg. 1964;159:407-10.
21. Siderys H, Pittman JN. Percutaneous needle biopsy of the lung in cases of superior sulcus tumor. J Thorac Cardiovasc Surg. 1967;53(5):716-20.
22. Walls WJ, Thornbury JR, Naylor B. Pulmonary needle aspiration biopsy in the diagnosis of Pancoast tumors. Radiology. 1974;111(1):99-102.
23. Wallace S, Carrasco CH, Charmasangavej C, Zornoza J, Chuang VP. Contributions of interventional radiology to diagnosis and management of the cancer patient. In: Bragg DG, Rubin P, Youker JE, editors. Oncologic imaging. New York: Pergamon Press. 1984;587-93.
24. Paulson DLIII. Superior sulcus carcinomas. In: Sabiston D, Spencer F, editors. "Gibbons surgery of the chest." Philadelphia: Saunders;1983;1:121-33.
25. Paulson DL. Technical considerations in Stage III disease: the "superior sulcus" lesion. In: Delarue NC, Eschapasse H, editors. "Inter- national trends in general thoracic surgery." Philadelphia: Saunders; 1985;1:121-33.
26. Paulson DL. Carcinomas in the superior pulmonary sulcus. J Thorac Cardiovasc Surg. 1975;70(6):1095-104.
27. Beyer DC, Weisenburger T. Superior sulcus tumors. Am J Clin Oncol. 1985;8:24-5.
28. Devine JW, Mendenhall WM, Million RR, Carmichael MJ. Carcinoma of the superior pulmonary sulcus treated with surgery and/or radiation therapy. Cancer. 1986;57(5):941-3.
29. Stanford W, Barnes RP, Tucker AR. Influence of staging in superior sulcus (Pancoast) tumors of the lung. Ann Thorac Surg. 1980;29(5):406-9.
30. Martini N, McCormack P. Therapy of stage III (nonmetastatic disease). Semin Oncol. 1983;10(1):95-110.
31. Komaki R, Roth JA, Walsh GL. Multidisciplinary approach for 143 patients with superior sulcus tumors treated at The University of Texas MD Anderson Cancer Center. Int J Radiat Oncol Biol Phys. 2000;48(2):347-54.
32. Shahian DM, Neptune WB, Ellis FH Jr. Pancoast tumors: improved survival with preoperative and postoperative radiotherapy. Ann Thorac Surg. 1987;43(1):32-8.

33. Hilaris BS, Martini N, Luomanen RK, Batata M, Beattie EJ Jr. The value of preoperative radiation therapy in apical cancer of the lung. Surg Clin North Am. 1974;54(4):831-40.

34. Komaki R, Mountain CF, Holbert JM, Garden AS, Shallenberger R, Cox JD, et al. Superior sulcus tumors: treatment selection and results for 85 patients without metastasis (M0) at presentation. Int J Radiat Oncol Biol Phys. 1990;19(1):31-6.

35. Beahrs OH, Henson De, Hutter RV, Kennedy BJ. Manual for staging of cancer. American Joint Committee on Cancer. 4th ed. Philadelphia: JB Lippincott. 1992;117-22.

36. Komaki R, Perkins P, Allen P, Vaporciyan A, Cox J. Multidisciplinary approach for the management of superior sulcus tumors. Proc Am Soc Clin Oncol. 1998;17:491a.

37. Dartevelle PG, Chapelier AR, Macchiarini P, Lenot B, Cerrina J, Ladurie FL, et al. Anterior transcervical-thoracic approach for radical resection of lung tumors invading the thoracic inlet. J Thorac Cardiovasc Surg. 1993;105(6):1025-34.

38. Gomez DR, Cox JD, Roth JA, Allen PK, Wei X, Mehran RJ, et al. A prospective phase 2 study of surgery followed by chemotherapy and radiation for superior sulcus tumors. Cancer. 2012;118(2):444-51.

39. Rusch VW, Giroux DJ, Kraut MJ, Crowley J, Hazuka M, Winton T, et al. Induction chemoradiation and surgical resection for superior sulcus non-small-cell lung carcinomas: long-term results of Southwest Oncology Group Trial 9416 (Intergroup Trial 0160). J Clin Oncol. 2007;25(3):313-8.

40. Keller SM, Adak S, Wagner HJ, Herskovic A, Komaki R, Brooks BJ, et al. Randomized prospective comparison of adjuvant mediastinal radiation (RT) with or without concurrent chemotherapy with cisplatin and etoposide (PE) for patients with completely resected 51-3N1-2M0 non-small cell lung cancer (NSCLC): US. Int J Radiat Oncol Biol Phys. 1999;3(45):145-6.

41. Truin W, Siebenga J, Belgers E, Bollen EC. The role of video-assisted thoracic surgery in the surgical treatment of superior sulcus tumors. Interact Cardiovasc Thorac Surg. 2010;11(4):512-4.

42. Linden PA. Video-assisted anterior approach to Pancoast tumors. J Thorac Cardiovasc Surg. 2010;140(3):e38-9.

43. Nakajima T, Watanabe A, Nakazawa J, Higami T. Transmanubrial approach with video-assisted thoracoscopic surgery for left superior sulcus tumour with dense adhesion after replacement of descending thoracic aorta. Interact Cardiovasc Thorac Surg. 2012;14(6):906-8.

44. Morris RW, Abadir R. Pancoast tumor: the value of high dose radiation therapy. Radiology. 1979;132(3):717-9.

45. Ahmad K, Fayos JV, Kirsh MM. Apical lung carcinoma. Cancer. 1984;54(5):913-7.

46. Van Houtte P, MacLennan I, Poulter C, Rubin P. External radiation in the management of superior sulcus tumor. Cancer. 1984;54(2):223-7.

47. Komaki R, Putnam JB Jr, Walsh G, Lee JS, Cox JD. The management of superior sulcus tumors. Semin Surg Oncol. 2000;18(2):152-64.

48. Lee JS, Komaki R, Fossella FV, Glisson BS, Hong WK, Cox JD. A pilot trial of hyperfractionated thoracic radiation therapy with concurrent cisplatin and oral etoposide for locally advanced inoperable non-small-cell lung cancer: a 5-year follow-up report. Int J Radiat Oncol Biol Phys. 1998;42(3):479-86.

49. Chang JY, Komaki R, Lu C, Wen HY, Allen PK, Tsao A, et al. Phase 2 study of high-dose proton therapy with concurrent chemotherapy for unresectable stage III nonsmall cell lung cancer. Cancer. 2011;117(20):4707-13.

50. Blanchard P, Garden AS, Gunn GB, Rosenthal DI, Morrison WH, Hernandez M, et al. Intensity modulated proton beam therapy (IMPT) versus Intensity modulated photon therapy (IMRT) for oropharynx cancer patients – a case matched analysis. Radiother Oncol. 2016;120(1):48-55.

51. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. N Engl J Med. 2017;377(20):1919-29.

52. National Lung Screening Trial Research Team, Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011;365(5):395-409.

53. Komaki R, Derus SB, Perez-Tamayo C, Byhardt RW, Hartz A, Cox JD. Brain metastasis in patients with superior sulcus tumors. Cancer. 1987;59(9):1649-53.