Review

Surgical treatment of Pancoast tumours

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Summary

Due to its localisation in the apex of the lung with invasion of the lower part of the brachial plexus, first ribs, vertebrae, subclavian vessels or stellate ganglion, a superior sulcus tumour causes characteristic symptoms, like arm or shoulder pain or Horner’s syndrome. If rib invasion is the only feature, lysis of the rib must be evident on the chest radiograph; otherwise the tumour cannot be defined as a Pancoast tumour. It is important to adequately stage the tumour, because staging significantly influences survival. Survival is better for T3 than T4 tumours and mediastinal lymph node involvement has been found to be a negative prognostic factor. Also Horner’s syndrome and incompleteness of resection worsen survival. The management of superior sulcus tumours has evolved over the past 50 years. Before 1950 it was considered to be inoperable and uniformly fatal. Shaw and Paulson introduced combined modality treatment and for many years, this combination of radiotherapy and surgery was the treatment of choice with a mean 5-year survival of approximately 30%. Postoperative radiotherapy or brachytherapy does not improve survival in patients with complete or incomplete resection. The tumour can be resected through the classic posterior Shaw–Paulson approach or the newer anterior transcervical approach, introduced by Dartevelle. This method facilitates better exposure of the extreme apex of the lung, brachial plexus and subclavian vessels. Regarding the extent of pulmonary resection, en bloc resection of the involved ribs with a lobectomy is recommended. Recent multimodality studies, involving chemoradiotherapy and surgical resection, show promising results regarding completeness of resection, local recurrence and survival, provided that appropriate staging has been carried out. However, careful patient selection and adequate perioperative management with protection of the bronchial stump or anastomosis are important to achieve reasonable rates of morbidity and mortality. As brain metastases remain one of the most common forms of relapse, further studies are needed to examine the role of prophylactic cranial irradiation in patients with complete resection. Also the addition of other chemotherapy agents or biologic agents such as angiogenesis inhibitors or tyrosine kinase inhibitors gives a new perspective in the treatment of Pancoast tumours.

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1. Introduction

Pancoast or superior sulcus tumours produce a characteristic clinical syndrome, which was first described by Edwin Hare in 1838 \cite{1}. In 1924 Henry Pancoast, radiologist, called this tumour, located in the apex of the lung and associated with typical complaints, ‘apical chest tumour’. In 1932 he changed this name to superior sulcus carcinoma \cite{2,3}. His first impression was that the tumour was extrapulmonary in origin, arising from epithelial remnants of the fifth branchial cleft. However, Tobias recognised that its origin was bronchopulmonary tissue and that it was the localisation of the tumour that made it specific and not its origin \cite{4}. Pancoast–Tobias syndrome is a constellation of characteristic symptoms that includes pain down the arm and eventually weakness and numbness along the distribution of the eighth cervical nerve trunk and first and second thoracic nerve trunks, Horner’s syndrome, and radiographic evidence of destruction of the first thoracic rib or vertebral body. It is caused by benign or malignant tumours invading portions of the lower brachial plexus,
The tumour represents less than 5% of all bronchogenic carcinoma and recent reports indicate that its biology is not different from the usual non-small cell lung tumours with its predilection for distant metastases [5–9]. Although Pancoast’s syndrome may be the result of different neoplastic, inflammatory, and infectious diseases, the focus of this review will be on the clinical presentation, diagnosis, and treatment of primary non-small cell bronchogenic carcinoma, which causes the vast majority of cases. This article is a review of the English-language literature mentioned in Pub Med during the past 30 years. Case-reports were excluded.

2. Clinical presentation and diagnosis

Superior sulcus tumours may occur in three locations and symptoms 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 the stellate ganglion or vertebral bodies. In case of invasion of the brachial plexus, patients often present with pain that begins in the shoulder and scapular region and then extends down to the ulnar aspect of the arm (T1 dermatome) onto the small and ring fingers (C8 dermatome). This pain can be very intensive and often patients are first submitted to the physiotherapist and neurologist or orthopaedist. With increasing pressure on the nerve roots, muscle atrophy of the ulnar aspect of the hand and loss of the triceps reflex can occur. Because of these aspecific complaints, the time between onset of the symptoms and a correct diagnosis is around 6–10 months [10–12]. In about 20% of the patients tumour invasion of the sympathetic chain and the stellate ganglion causes Horner’s syndrome (ipsilateral ptosis, miosis, and anhydrosis).

Specific pulmonary symptoms like cough, dyspnoea, and haemoptysis are mostly absent in the initial stages of the disease due to the peripheral localisation of the tumour. A pathological diagnosis is often difficult to obtain by fiberoptic bronchoscopy [10,13]. The most sensitive procedure for diagnosis is a percutaneous transthoracic needle biopsy with a diagnostic yield of 95% [10,14,15].

On a chest roentgenogram, the tumour is visible as a small mass or pleural thickening in the apex of the lung with rib and possible vertebral body invasion, although the tumour can be easily missed on a regular chest X-ray. The apical lordotic or slightly oblique views show the apical lesions much better. Computed tomography (CT) and nowadays magnetic resonance imaging (MRI) are the preferred imaging modality for these tumours because they visualise best the relationship of the tumour to adjacent structures like the brachial plexus, subclavian vessels and vertebral bodies [16,17].

Regarding histology, non-small cell lung cancer accounts for 90–95% of the cases. In current reports, adenocarcinoma is the most common histological diagnosis, followed by squamous cell carcinoma and large cell carcinoma [18,19]. Small cell carcinoma is only rarely associated with this syndrome [12,20]. The differential diagnosis of Pancoast’s syndrome includes other primary thoracic neoplasms (mesothelioma, lymphoma, plasmacytoma), infectious processes with organisms such as Actinomyces, Staphylococcus and Echinococcus, neurogenic thoracic outlet syndromes and pulmonary amyloidosis [8]. This wide variety of diseases makes it necessary to make a definitive diagnosis before treatment is started. After the diagnosis of a Pancoast tumour is confirmed, it is important to adequately stage the tumour.

3. Staging and survival

Because of the involvement of the chest wall, these carcinomas are at least staged as T3. Invasion of the vertebral body, or the subclavian vessels upgrades the staging to T4. Staging significantly influences survival. In the study of Rusch and associates actuarial 5-year survival was 46% for stage IIB (T3N0) and 13% for stage IIIB [19]. Both univariate and multivariate analyses showed that T and N status had a significant impact on survival.

In the study of Ginsberg and colleagues, of 22 patients with vertebral body invasion, only 2 survived for 5 years [19]. Other studies support the poor prognosis associated with vertebral body invasion [15,18]. Also tumours with invasion of the subclavian vessel are staged as T4. Dartevelle and co-workers [22], using the anterior transcervical-thoracic approach, have reported a 30% actuarial 5-year survival in 12 patients. In most studies, however, subclavian vessel involvement is a negative prognostic factor [15,18,19].

Lymph node status is a very important prognostic factor [18,23]. In the past, mediastinoscopy was not routinely performed in most studies. Because patients with mediastinal lymph node metastases exhibit poor survival, most surgical groups nowadays recommend staging of the mediastinum by mediastinoscopy or positron emission tomography (PET) scan to document the absence of N2 disease, even if the CT or MRI do not demonstrate enlarged lymph nodes [6–8,24,25]. Some series show that patients with supraclavicular lymph node metastases had a better prognosis than patients with N2 disease. Ginsberg and associates [19] found a 5-year survival of 14% in patients with N3 disease as opposed to 0% in patients with N2 disease. Comparable results were described by Hilaris and co-workers [23], suggesting that tumour involvement of these nodes does not necessarily exclude a curative resection because, in the context of a Pancoast tumour, this form of disease simply represents local contiguous spread [6].
To exclude metastatic disease, a CT of the liver and adrenal glands or PET scan should be performed. As brain metastases are the most frequent form of distant metastases, the question arises if all patients should have a CT or MRI of the head [7,8,26]. Bone scans are mostly performed only if indicated by the patient’s symptoms.

4. Treatment and results

The management of superior sulcus tumour has evolved over the last decades and consisted of surgery alone, radiotherapy alone, pre- and postoperative radiotherapy, or most recently, preoperative chemoradiation [6,7,27–29].

Before 1950 it was considered to be inoperable and uniformly fatal. Heburt and Watson [30] reported survival without treatment between 3 and 24 months. In 1953 Chardack and MacCallum [31] reported the first 5-year survival in a patient who initially underwent resection followed by 65 Gy of radiation. Subsequently, Shaw [32] presented a series of 18 patients who were treated by preoperative radiotherapy followed by en bloc resection with up to 51 months survival. And for many years, this combination of radiotherapy and surgery was the treatment of choice.

4.1. Radiotherapy alone

Radiotherapy was initiated by Haas and associates [33] in patients with otherwise hopeless thoracic neoplasms. This treatment resulted in good pain relief and improvement of survival. In 1950, Binkley [34] reported the first cure using interstitial brachytherapy.

The doses of radiotherapy used usually ranges between 50 and 70 Gy. In most studies, long-term survival rates are low [35]. This is particularly due to the fact that these studies often include patients with advanced disease and poor performance status. In selected patients, 5-year survival is about 20%, but these results cannot be compared with those of surgical series because of differences in patient selection [20,35–37].

4.2. Combined modality: radiotherapy and surgery

The combination of preoperative radiotherapy with doses between 30 and 35 Gy followed by surgical resection was first reported by Shaw and his colleagues in 1961 [32]. Paulson and associates [38] used this approach, updated it on several occasions and found that preoperative radiation including the primary tumour, mediastinum and supraclavicular region facilitated surgical resection and that combined treatment was potentially curative. In their series overall 5-year survival was 31% and for patients with no nodal involvement 44%. In most studies, 5-year survival ranges between 10 and 56% (Table 1). Patients with a complete resection had improved 5-year survival rates of 40% [12,19,39,40]. Results of preoperative radiotherapy followed by surgery in 225 patients in the Memorial Sloan-Kettering Cancer Center published by Rusch and colleagues showed that a complete resection was achieved in only 64% of T3N0 and 39% of T4N0 tumours. Five-year survival was 46% for stage IIB, 0% for stage IIIA and 13% for stage IIIB. Locoregional disease was the most common form of relapse (40%) [21].

Usually, the dose of preoperative radiotherapy ranged between 30 and 35 Gy. Because of a well known dose–response curve in patients with non-small cell lung cancer which suggests that standard treatment is in the range of 50–60 Gy, Attar and Miller gave preoperative doses of radiotherapy of 40–60 Gy [35,41]. However, both groups noticed an increase of postoperative morbidity and mortality and so lowered the dose to 30 Gy. Fuller and Chambers [39] also used as much as 60 Gy preoperatively, but their study showed no survival advantage. No large phase II or III trials have been reported testing the standard approach of induction radiotherapy in patients with superior sulcus tumours.

The potential benefits of preoperative radiotherapy include a decrease in the size of the tumour, with improved respectability, and a reduction in the number of viable cells, which theoretically prevents dissemination of the tumour during surgery [32,38]. Surgery is usually performed 2–4 weeks after the last radiation.

Shahian and colleagues reported on 18 patients who were treated with preoperative radiotherapy. Fourteen of these patients also received postoperative radiotherapy because of N2 disease, positive resection margins, or both. Overall 5-year survival was 56%. They believed that this ‘sandwich’ radiation would improve survival [42]. Ginsberg [19] also reported four long-term survivors in a group treated with sandwich radiotherapy, but too few patients have received this treatment to assess its outcome and radiobiologically it is not recommended.

Table 1
Preoperative radiotherapy followed by surgical resection for patients with superior sulcus tumours

<table>
<thead>
<tr>
<th>First author (year)</th>
<th>No. of patients</th>
<th>Complete resection (%)</th>
<th>5-year survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attar (1979) [35]</td>
<td>19</td>
<td>NS</td>
<td>23 (3-year)</td>
</tr>
<tr>
<td>Paulson (1985) [38]</td>
<td>78</td>
<td>NS</td>
<td>31</td>
</tr>
<tr>
<td>Devine (1986) [37]</td>
<td>40</td>
<td>NS</td>
<td>10</td>
</tr>
<tr>
<td>Shahian (1987) [42]</td>
<td>18</td>
<td>50</td>
<td>56</td>
</tr>
<tr>
<td>Hilaris (1989) [23]</td>
<td>82</td>
<td>NS</td>
<td>29</td>
</tr>
<tr>
<td>Sartori (1992) [18]</td>
<td>42</td>
<td>NS</td>
<td>25</td>
</tr>
<tr>
<td>Ginsberg (1994) [19]</td>
<td>124</td>
<td>56</td>
<td>26</td>
</tr>
<tr>
<td>Maggi (1994) [12]</td>
<td>60</td>
<td>60</td>
<td>17.4</td>
</tr>
<tr>
<td>Attar (1998) [27]</td>
<td>28</td>
<td>NS</td>
<td>27</td>
</tr>
<tr>
<td>Dartevelle (1999) [47]</td>
<td>70</td>
<td>NS</td>
<td>35</td>
</tr>
</tbody>
</table>

NS, not stated.
4.3. Surgical technique

Surgical resection remains the treatment of choice for superior sulcus tumours. The goal is to resect the upper lobe with the invaded ribs and transverse processes and all invaded structures such as the lower trunk of the brachial plexus, stellate ganglion and upper dorsal sympathetic chain. The problem is that the apex is a small, rigid, bone encased area which is difficult to access and that surrounding structures are either difficult to resect macroscopically free of tumour (vertebrae) or that resection can leave important deficits (brachial plexus, subclavian vessels). In patients with involvement of the brachial plexus or the spine, a combined thoracic, orthopaedic and neurosurgical approach can improve resectability and local control [43].

Different surgical approaches have been described. As a general rule, superior sulcus tumours not invading the thoracic inlet are completely resectable through the classic posterior Shaw–Paulson approach [32]. This consists of a posterolateral thoracotomy with a high posterior parascapular incision carried to the base of the neck. This method allows good access to the posterior part, but poorer access to the more anterior structures like the subclavian vessels. Chest wall reconstruction is rarely needed because the defect is covered by the scapula. A newer alternative approach is the anterior transcervical approach, popularized by Dartevelle and colleagues [22]. This method facilitates better exposure of the extreme apex of the lung and cervically based structures (brachial plexus and subclavian vessels). The incision parallels the lower sternocleidomastoid muscle and courses over the manubrium and then turned medially below the clavicle. Resection, division or retraction of the clavicle opens the thoracic inlet. This approach shows lower morbidity than the posterior approach because the posterior chest wall muscles and the shoulder are undisturbed. However, these osteomuscular resections can cause postoperative alterations in the shoulder mobility and cervical posture. To avoid these deformities Grunenwald and colleagues [44] developed a transmanubrial technique, through a manubrial L-shaped transaction and first costal cartilage resection, which allows retraction of an osteomuscular flap including but sparing the clavicle and its muscular insertions. Recently, both Dartevelle and Grunenwald developed a technique which is a combination of a transcervical or transmanubrial and posterior midline approach. This technique makes it possible to resect posteriorly located superior sulcus tumours extending into the intervertebral foramen without intraspinal extension [43,45,46].

Regarding the extent of pulmonary resection, a lobectomy is recommended [19,25]. Ginsberg and associates [19] reported a survival benefit (lobectomy 60% versus limited resection 33%) and a reduction in local recurrence in patients who underwent a lobectomy.

The reported surgical morbidity ranges from 7 to 38% with surgical mortality generally around 5–10% [10,18,23]. Surgical complications include spinal fluid leakage, Horner’s syndrome and nerve deficits, hematothorax, chylothorax and prolonged ventilatory support. The postoperative course is usually characterized by atelectasis because of the concomitant extended chest wall resection and phrenic nerve resection.

Invasion of the subclavian vessel is a relative contraindication, but successful surgical resection has been described [15,22]. Absolute surgical contraindications are the presence of extrathoracic metastases, mediastinal lymph node involvement, invasion of the brachial plexus above T1 as supported by sensitive or motor deficits in the nerve distribution of the median and radial nerves or vertebral body invasion with invasion of the spinal canal [47].

4.4. Induction chemoradiotherapy and surgery

Because of the reported improved results of combined treatment with chemotherapy and irradiation in patients with stage IIIA and IIIB non-small cell lung cancer, it seemed logical to apply such therapy to patients with Pancoast tumours (Table 2). The combination of radiotherapy and radiation-sensitizing chemotherapy increases the chance of performing a complete resection. At the current time concurrent treatment is favoured above sequential treatment, but concurrent chemoradiotherapy can be more toxic than sequential and requires close monitoring of the patient.

Table 2
Preoperative chemoradiotherapy followed by surgical resection for patients with superior sulcus tumours

<table>
<thead>
<tr>
<th>First author</th>
<th>No. of patients</th>
<th>Complete resection (%)</th>
<th>4-year survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martinez-Monge (1994) [48]</td>
<td>18</td>
<td>76</td>
<td>56</td>
</tr>
<tr>
<td>Rusch (2001) [28]</td>
<td>111</td>
<td>92</td>
<td>55, patients with CR 70 (2-year)</td>
</tr>
<tr>
<td>Wright (2002) [49]</td>
<td>15</td>
<td>93</td>
<td>84</td>
</tr>
</tbody>
</table>

CR, complete resection.
Martinez-Monge and associates reported on a series of 18 patients with Pancoast tumours treated with cisplatin-based chemotherapy followed by simultaneous preoperative chemoradiation and irradiation, after which the patient underwent resection with insertion of brachytherapy catheters. Resectability rate was 76.4% and a complete pathologic response was seen in 70.5%. Local failure rate was only 9% and 4-year actuarial survival was 56%. However, mortality was 16.7% [48]. Same results were described by the Southwest Oncology Group which conducted a prospective phase II North America Intergroup study looking at preoperative chemoradiotherapy [28]. This study included 111 patients with T3-4 superior sulcus tumours without mediastinal lymph node metastases. 102 patients completed the induction treatment of two cycles of cisplatin-based chemotherapy concurrent with 45 Gy of radiation. Of 95 patients eligible for surgery, 83 underwent a resection, which was complete in 76 (92%). Fifty-four patients (65%) had either a pathologic complete response or minimal microscopic disease. The 2-year survival was 55% for all eligible patients and 70% for patients with a complete resection. Overall treatment mortality was only 4.5%. Assessment of response to induction treatment was difficult. Only 40% of the patients with radiologically stable disease and 27% of the patients with a radiologic partial response had significant gross residual tumour at thoracotomy. This shows that radiologic response to induction treatment has to be viewed with caution and usually underestimates the results of treatment. The intent of the study was to treat all patients with two additional cycles of the same chemotherapy regardless of whether a resection was performed, but in the postoperative group, this was only feasible in a small group of patients.

Better results of combined chemoradiotherapy followed by surgery compared to induction radiation are also described by Wright and colleagues [49]. However, surgery has to be considered a high-risk procedure after induction chemotherapy or chemoradiotherapy. Careful patient selection and adequate perioperative management with protection of the bronchial stump or anastomosis are important to achieve reasonable rates of morbidity and mortality [50,51].

At the moment, a prospective phase II intergroup trial (S0220) is being conducted by the Southwest Oncology Group. In this study, patients will receive induction chemoradiotherapy with cisplatin/etoposide and then go on to receive consolidation taxane cytotoxic chemotherapy in the postoperative setting which appeared to be effective even in tumours previously treated with or resistant to cisplatin [52].

5. Recurrence and prognostic factors

Control of locoregional disease remains the major challenge in treating Pancoast tumours. Despite the relative improvement in survival of patients with superior sulcus tumours treated with combined preoperative radiotherapy and operation, there is still a high incidence of local recurrence between 25 and 70%. In the study of Ginsberg of 69 patients with complete resection, two-third of the cases had local recurrence [19]. Most frequent sites are the spine, chest wall and lung [21]. However, treatment with combined preoperative chemoradiation seems to lower this incidence of local recurrence [28,49]. In the study of Rusch and associates, local recurrence was only 23%. This concurrent treatment appears to change the most common side of relapse from local to distant. Brain metastases are one of the most common forms of relapse, accounting for 40–80% of distant recurrences, especially in patients with poorly differentiated large cell carcinoma and adenocarcinoma [9,19,23]. This raises the question whether patients with a complete resection should be treated with prophylactic cranial irradiation (PCI) [23,28,36]. In general, few studies have routinely used PCI in patients with non-small cell bronchogenic carcinoma. Eberhardt and colleagues [53] did not perform a randomized investigation of PCI in their study, but the overall brain relapse was remarkably reduced in the group that received PCI even though no impact on survival was noted. In the study of Stuschke and associates [54], regarding PCI in locally advanced non-small cell lung cancer after multimodality treatment, this treatment reduced the rate of overall brain metastases from 54 to 13% (P < 0.0001). Bone metastases appear to be to second most common side of distant disease [23,41].

Factors associated with poor prognosis are extension of the tumour into the basis of the neck, mediastinal lymph node involvement, invasion of vertebral bodies or great vessels, presence of Horner’s syndrome, and incomplete-ness of resection. The value of histology per se as a prognostic factor is controversial [8–10,19,21].

6. Conclusion

After Shaw introduced combined modality treatment for patients with a superior sulcus tumour, this combination of preoperative radiotherapy followed by surgery was the treatment of choice with a mean 5-year survival of approximately 30%. In several studies, it appeared that N2 disease and incomplete resections had an adverse impact on survival and that postoperative radiotherapy or brachytherapy did not improve survival in patients with complete or incomplete resections.

During the 1990s, studies have focused on prognostic factors and adequate staging, on determining the role of brachytherapy and on exploring new surgical techniques that facilitated complete resection. Despite these reports, complete resection rate and 5-year survival were low and locoregional recurrence remained the predominate form of relapse.
These results emphasized the need for improved therapy for superior sulcus tumours. A multimodality approach, involving chemoradiotherapy and surgical resection shows promising results, provided that appropriate staging has been carried out. In the study of Rusch and colleagues cisplatin based chemotherapy with concurrent radiation followed by surgery is feasible and resectability and overall survival were improved. However, careful patient selection and adequate perioperative monitoring are very important, regarding the higher morbidity and mortality rates in some studies after induction chemotherapy.

As brain metastases are one of the most common forms of relapse, the question rises whether patients with a complete resection should be treated with PCI. Given the proven efficacy of this treatment to prevent metastases to the brain in small cell lung cancer, the introduction of PCI into the treatment of non-small cell lung cancer in the curative setting seems promising.

Another approach to diminish the incidence of distant metastases can be the addition of another chemotherapy agent, like docetaxel, or biologic agents such as angiogenesis inhibitors or tyrosine kinase inhibitors.

Therefore, further studies are needed to minimize morbidity and mortality and to examine the best combination of induction chemotherapy and biological agents and the role of prophylactic cranial irradiation.

References