High Relapse-Free Survival After Preoperative and Intraoperative Radiotherapy and Resection for Sulcus Superior Tumors*

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Study objectives: Relapse-free survival in patients with sulcus superior tumors.

Design: Prospective registration study.

Setting: Department of surgical oncology of a university hospital.

Patients: Twenty-one patients treated with preoperative radiotherapy (46 Gy), lobectomy and chest-wall resection, and intraoperative radiotherapy (10 Gy).

Results: After a median follow-up of 18 months, 18 patients (85%) were free from locoregional relapse, while 8 patients were still alive.

Conclusions: The results show that this protocol can achieve excellent local tumor control and can even be used for palliative treatment. (CHEST 2003; 124:1841–1846)

Key words: brachytherapy; chest wall resection; external beam radiotherapy; lung cancer; sulcus superior tumor

Abbreviations: FIT = flexible intraoperative template; SST = sulcus superior tumor

A sulcus superior tumor (SST) was first published as a case report by Hare in 1838. In 1924, Henry Pancoast described an unusual growth in the apical region of the lung, and 8 years later he reported a syndrome caused by this particular growth in seven patients; since that time it has been referred to as a Pancoast tumor. Because other malignant tumors, such as soft-tissue sarcomas, can cause the same symptoms, these tumors are currently called SSTs. SSTs are rare, comprising <5% of all lung cancers. An SST caused by primary lung cancer occurs in the apex of the lung and frequently invades the upper two of three ribs, the vertebral body, the lower part of the brachial plexus (C8, Th1, and Th2), the stellate ganglion, and the subclavian vessels.

For the mentioned reasons, the natural course of an SST typically has a very high morbidity caused by pain in the C8, Th1, and Th2 dermatomes (invasion of the brachial plexus), impaired arm and shoulder function (motor nerve damage), hoarseness (paralysis of the recurrent nerve), Horner syndrome (invasion of the sympathetic branches), pulmonary symptoms, and weight loss. Almost all patients will die within 12 months after diagnosis. Because SSTs are in close proximity to vital structures such as the brachial nerve plexus, brachial vein/artery, and the vertebral bodies, it was for long thought that the SST was not amenable to surgery.

Palliative treatment by radiotherapy alone was first described by Haas et al., a relatively long survival has been reported with this technique. Shaw and colleagues described the combination of surgery and radiotherapy in 18 patients, 12 of whom were still alive at (the relatively short) follow-up. Since the work of Paulson, surgery combined with radiotherapy has become the standard treatment for SST: patients without lymph node metastases had a 5-year survival rate of 31%.

Factors associated with a poor prognosis are N2 and N3 disease, T4 disease (invasion of great vessels or vertebral body), incomplete resections, and Horner syndrome. Clinical factors associated with
improved survival include good performance status, a weight loss of < 5%, and achievement of local tumor control and pain relief after treatment.12

The optimal combined management of SST remains controversial. Various combinations of surgery and radiotherapy have been reported. Preoperative radiotherapy followed by surgical resection with or without intraoperative or postoperative radiotherapy resulted in a mean 5-year overall survival rate of 25%, surgery followed by intraoperative or postoperative radiotherapy had a mean 5-year survival rate of 17%, and radiotherapy as a single modality a mean 5-year survival rate of 15%.3,12 Although preoperative radiotherapy followed by surgery appears superior to radiotherapy alone, this has not been confirmed by randomized clinical trials. Even the use of intraoperative radiotherapy as a goal for optimal delivery of the radiation dose is under debate; however, due to differences in staging, inclusion criteria, and uneven distribution of prognostic factors, a meaningful comparison between series is not possible.12 With the combined treatment it is believed that the prognosis of SST is comparable to that of other lung cancers invading the chest wall (stage IIB).13

Distant metastases (especially brain metastasis) are the most common cause of relapse (40 to 80%), particularly in patients with large-cell carcinoma and adenocarcinoma. After distant relapse, almost all patients die within 1 year.1,2,12

Data on local tumor control after combined treatment are scarce and conflicting. Even if prognosis is poor, local tumor control is of importance from a palliative point of view. The aim of the present study is to investigate the effect of intraoperative brachytherapy in combination with preoperative external beam radiotherapy and resection on local relapse-free survival.

PATIENTS AND METHODS

Between June 1996 and March 2001, 26 consecutive patients with the clinical diagnosis of SST were entered in a strict protocol for staging and treatment (Table 1). Of these, 23 patients were considered resectable with curative intent based on clinical and radiologic staging and negative mediastinoscopic findings. Radiologic staging consisted of a spiral CT-scanning protocol of the thorax and the thoracic inlet (slice distance 5 mm) and use of an IV contrast agent. The adrenal glands were also scanned to exclude adrenal metastases. Cervical mediastinoscopy was performed using a protocol in which at least the lymph nodes according to Naruke et al14 (No. 2, No. 4, and No. 7) were sampled. The follow-up period lasted until January 2002 (ranging from 5 to 58 months).

Preoperative Radiotherapy

The preoperative external beam radiotherapy consisted of 46 Gy in 23 fractions: 2 Gy per fraction, 5 fractions per week. The treatment was CT planned, and usually two anterior-posterior/posterior-anterior fields were used. The target volume included the primary tumor, with at least 2-cm margin, the ipsilateral supraclavicular fossa, the whole vertebral bodies at the level of the primary tumor and the ipsilateral mediastinal lymph nodes (locations 1 to 4). The cranial field border was usually placed above C6 and the caudal border at the level of the tracheal carina. In case of N1 nodes, the hilar region was also included. After radiotherapy, a new CT scan of the chest was made including the adrenals. If no progression was found, surgery was performed 4 to 6 weeks after the radiotherapy (Fig 1).

Surgery

All patients were operated in the same institution by two experienced surgeons working in close collaboration with one of the radiotherapists. The SST was resected by means of a high extended posterolateral approach. In three patients with an anterior mediastinal localization, a hemi-clamshell incision was carried out.18 The goal was a radical resection (R0) of at least the upper lobe en bloc with the chest wall. Only in the anterior chest wall resection, an artificial layer was used for reconstruction. For the posterior localization, the scapula was considered to be sufficient as a firm chest wall coverage. Postoperative mortality was defined as death within 4 weeks after surgery.

Intraoperative Radiotherapy

Instead of using catheters (which have to be fixed separately), a so-called flexible intraoperative template (FIT) was used to deliver a homogenous dose to a surface to which the shape of the mold is adapted.16 This is a flexible 5-mm-thick silicone mold in which afterloader catheters are inserted parallel to each other at a fixed distance of 1 cm (Fig 2). The tumor bed was clipped by the surgeon, and the FIT was shaped and fixed to the target area. After inserting dummy catheters, orthogonal x-rays are made of the implant and loaded into the planning system. The treatment plan is generated with the indicated active dwell positions of the catheters. The radiation is delivered during remote-controlled anesthesia. A single radiation fraction of 10 Gy was administered, specified in a plane parallel to the surface of the FIT at 1-cm

Table 1—Selection Criteria for Patients Participating in the Current SST Study

<table>
<thead>
<tr>
<th>Selection Criteria for Patients Participating in the Current SST Study</th>
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<tbody>
<tr>
<td>1) World Health Organization pathologic stage ≤ 2.</td>
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<tr>
<td>2) The criteria for SST were fulfilled, ie, tumors arising in the pulmonary apex with invasion of the first, second, or third rib and pain in dermatomes C8, Th1, or Th2.</td>
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<td>3) Cytologically or histologically proven non-small cell lung carcinoma stage T3N0-1M0 (IB–IIA) or T4N0-1M0 (IIB). Mixed forms with small cell lung cancer were excluded. For T4, extensive destruction of the vertebral body was considered as nonresectable (as seen on MRI).</td>
</tr>
<tr>
<td>4) No evidence of metastatic disease as assessed by physical examination, CT scan of the thorax and upper abdomen (liver and adrenals), bone scan, investigation of liver and adrenals by ultrasound, no longer than 4 wk before start of the treatment.</td>
</tr>
<tr>
<td>5) Cervical mediastinoscopy was required for mediastinal lymph node staging within 4 wk of definitive start of treatment.</td>
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<td>6) Informed consent was obtained.</td>
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<td>7) No CNS involvement.</td>
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<tr>
<td>8) Horner syndrome is not a contraindication for surgery.</td>
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Downloaded From: http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/22000/ on 04/29/2017
distance (1.25 cm from the catheters) with the MicroSelectron high-dose rate ¹⁹²Ir afterloader (Nucletron; Veenendaal, the Netherlands).

Postoperative Radiotherapy

External radiotherapy (12 × 2 Gy) was administered for those patients who proved to be unresectable during thoracotomy.

Results

After the external beam radiotherapy course, three patients dropped out of the protocol because of progressive disease resulting in an nonresectable tumor. We planned for the thoracic inlet resection in combination with intraoperative radiotherapy in 23 patients. Thoracotomy revealed that two patients had no chest wall invasion; these patients only had adhesions to the chest wall not requiring a chest wall resection, and therefore intraoperative radiation was considered not beneficial and thus not performed.

Finally, 21 patients (12 women and 9 men) underwent the entire planned treatment schedule, including resection and intraoperative radiotherapy. Their mean age was 58 years (range, 38 to 78 years). The preoperative clinical staging was stage IIB (all T3N0M0) in 18 patients, and stage IIIB (all T4N0M0) in 3 patients.

The pathologic diagnosis of the SST was as follows: squamous cell carcinoma (n = 12), adenocarcinoma (n = 4), and large-cell undifferentiated carcinoma (n = 5). Three patients entered the protocol without definitive pathologic diagnosis before starting treatment, but the fine-needle aspiration showed malignant cells. In two patients after resection, only necrosis could be found in the surgical specimen; in the third patient, residual squamous-cell carcinoma was present.

Of the 21 patients who underwent a resection, three ribs were resected in 10 patients, four ribs in 6 patients, and five ribs in 2 patients. In 16 patients, a lobectomy was performed, 3 patients underwent bilobectomy, and 4 patients underwent pneumonectomy (Table 2).

Because in most cases, the chest wall defect was covered by the scapula, in only seven patients (four patients with a large posterior, and all three patients with an anterior defect) a reconstruction was made.

Figure 1. Staging and treatment algorithm. RT = radiotherapy; LN = lymph nodes; IORT = intraoperative radiotherapy.
using an artificial layer (Composix; Bard/Davol; Cranston, RI) was used to obtain chest wall stability.

**Complication**

One patient died 1 week after the operation because of cardiac failure. The postoperative mortality is 1 of 23 patients (4%). Another patient was readmitted in the hospital with a bronchopleural fistula and sepsis, and died 7 weeks after surgery. Two patients had a prolonged hospital stay of >3 weeks because of ARDS and pleural empyema; both recovered after intensive conservative treatment. In this retrospective analysis, no detailed information was available about functional morbidity and the use of analgesics.

**Follow-up**

In 21 patients, after a median follow-up of 18 months (range, 5 to 58 months), 8 patients were alive (37%), of which 7 had no evidence of disease (median follow-up, 24 months; range, 6 to 58 months). Thirteen patients died, all but one with metastatic disease (63%). The first site of distant relapse was lung (n = 3), bone (n = 2), brain (n = 2), soft tissue (n = 2), and visceral (n = 2). The median survival after treatment of SST for this group of patients was 14 months, and the median survival after distant relapse was 6 months (range, 1 to 15 months). At the end of the study, 18 patients (85%) were free from locoregional relapse (median follow-up of 18 months). All five patients who had a local relapse after 8 to 16 months (median, 11 months) underwent a R1 resection (macroscopic free but not microscopic free margin; R2 = macroscopic no free margin; Adh = only adhesiolysis; Dod = death of disease; Ned = no evidence of disease; Awd = alive with disease).

**Discussion**

Earlier reports of treatment of SST have only historical value because major improvements have been made in staging (CT scan, MRI, (video-)mediastinoscopy and, more recently, positron emission tomography and endoscopic ultrasonography), surgical skills (type of incision), and radiotherapy (treatment planning and delivery). Most surgical series reported in the recent literature show a 5-year survival rate of 10 to 40%, with a calculated median of 32 ± 12% (± SD). There are indications that the prognosis of SST can be improved when the combination of preoperative and/or postoperative radiotherapy and surgery is used whether or not

<table>
<thead>
<tr>
<th>Patient Gender/ Age, yr</th>
<th>UICC Stage</th>
<th>Pathology</th>
<th>Resection</th>
<th>Necrosis, † %</th>
<th>Local Relapse, mo</th>
<th>Distal Relapse, mo</th>
<th>Overall Survival, mo</th>
<th>Status</th>
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<tr>
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<td>Adh</td>
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<tr>
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</table>

*UICC = International Union Against Cancer; Adeno = adenocarcinoma; Squam = squamous-cell carcinoma; Undiff = undifferentiated carcinoma; R0 = microscopic free margin; R1 = macroscopic free but not microscopic free margin; R2 = macroscopic no free margin; Adh = only adhesiolysis; Dod = death of disease; Ned = no evidence of disease; Awd = alive with disease.
†Percentage at pathologic examination of the resected specimen.
with concomitant chemotherapy. In this series of SST, a protocol has been used combining optimal radiotherapy including intraoperative brachytherapy and resection of the apex of the thoracic wall. In delivering external beam radiotherapy, concerns about the tolerance level of the plexus and spinal cord has to be taken into account. To avoid late radiation damage of these structures, it is often impossible to administer a curative dose of radiotherapy only with external fields. Brachytherapy is by nature the most conformational technique of radiotherapy. Boosting the surgical bed, the area with the highest risk of microscopic residual disease gives a high extra dose to a thin layer of tissue, while due to the rapid fall-off of dose, the spinal cord is relatively spared. Therefore, brachytherapy by means of intraoperative high-dose rate afterloading irradiation is an option after approaching the tolerance level (50 Gy) of the spinal cord by external irradiation, a facility available in our institute; however, others could not find any advantage for the use of this technique.

In experienced hands, the complex surgical procedure is feasible without increased morbidity, compared with a lung resection without removing a part of the chest wall even when preoperative radiotherapy has been administered. Only our patient who died after a bronchopleural fistula may be considered as a complication related to the radiotherapy; however, published data on additional complications of radiotherapy are scarce. The complication rate of 1 of 22 patients (4%) is similar to that reported in the literature of extended lung surgery. Operative mortality is only mentioned in 7 of the 13 reviewed articles with a median mortality of 3.5 ± 2.9%. We are now prospectively monitoring functional morbidity and use of analgesics, as these subjects are important parameters related to quality of life. Although the goal of cancer treatment should be tumor control and improvement of survival, optimal locoregional treatment will reflect in better local relapse-free survival. Because the presence of distant metastases reflects the biological behavior of the primary tumor, a reduction of local failure rates does not guarantee a better overall survival rate. In that respect, SST is no exception. The high morbidity of local tumor progression and local treatment failure (pain, nerve damage) does justify aggressive local treatment, and the main target should be local recurrence-free survival, even for those patients with a rather poor prognosis. Palliative radiotherapy alone can give local control of ≥ 50%. Only a few articles give information on the local control rate after combined radiation and surgical treatment for SST; their figures range from 40 to 86%, but neither this information nor the duration of follow-up is always clearly stated. Another point of criticism is that these groups are not homogenous; in some series, N2 status is included, and in others also concomitant chemotherapy. In addition, some patients with probably negative prognostic factors, such as bad performance status, were also treated. In our series of 23 patients with good performance status, no concurrent chemotherapy, high-dose radiotherapy, and resection resulted in a local control rate of 85%. Excluding the two patients with treatment-related mortality, the local control rate is 76%. These figures could probably be further improved with more aggressive surgery, such as vascular or spine resection and reconstruction. In our series, the number of patients is too small to study the positive influence of radiotherapy on resection margins and tumor necrosis, which could be the case. In all our resected specimens necrosis was present, but the original pathology could not be studied because the diagnosis was made by brush or percutaneous fine-needle aspiration. As shown in the present study and confirmed by others, the overall survival of patients with SST remains poor because of the high distant relapse rate. Induction chemotherapy for stage IIIA and IIIB lung cancer seems to improve the survival figures. The ongoing study for SST (Eastern Cooperative Oncology Group S9416, phase II, including the combination of cisplatin and etoposide and radiotherapy [45 Gy] before surgery) addresses this issue. But whether the chemoradiation regimen will improve resectability figures is questionable. Proper preoperative staging is the cornerstone in any patient who is candidate for oncologic surgery. All patients in the present study underwent CT scanning of the whole thorax and the abdomen. The primary tumor was investigated to establish its relationship to the adjacent structures and to exclude ingrowths in the nerve plexus. CT scanning provided anatomic information concerning operability, and the use of IV contrast allowed evaluating compression or ingrowths in the vascular structures. This is important for staging procedures in order to exclude adrenal metastases and pulmonary metastases. Whether MRI is superior to CT scanning for preoperative planning cannot be concluded from our study; in case there is doubt about resectability, we always perform MRI. In a study conducted in 1989, MRI proved superior to CT scanning; because in that study, all R1 resected patients relapsed, it may be important to perform MRI in all cases. However, in the last decades enormous improvements have been made in both modalities and a comparison between multislice CT scanning and MRI has not yet been made.
CONCLUSION

Combined radiotherapy and surgery should always be considered in patients with SSTs. In experienced centers, this treatment does not result in an increased complication rate. In the present study, use of intraoperative radiotherapy resulted in a local relapse-free survival of at least 76%, which probably led to an improvement in quality of life, even in patients with a limited life expectancy. Improvement of overall survival in SST is currently studied in ongoing trials with concomitant radiotherapy and chemotherapy. Also, attention is paid to morbidity, functionality, and analgesic requirements. Improvement of staging and preoperative planning will also improve proper patient selection.

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REFERENCES