Surgery after neoadjuvant treatment for non-small cell lung cancer: Decision making and patient outcome
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Citation for published version (APA):

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Results of combined modality treatment in patients with non-small cell lung cancer of the superior sulcus and the rationale for surgical resection

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Abstract

Objectives
Superior sulcus tumours (SST) or Pancoast tumours are preferably treated with chemoradiotherapy (CRT) followed by surgical resection. However, when followed by surgery, it is associated with an increased complication rate. The aim of this study was to evaluate the efficacy and safety of a concurrent induction protocol of 66 Gy radiotherapy with cisplatinum and evaluate the rationale for subsequent surgery.

Methods
Patients with SST treated in our institute from 1994-2006 were identified. The preferred induction treatment consisted of accelerated radiation (66 Gy in fractions of 2.75 Gy) with concurrent daily cisplatinum 6 mg/m². Surgical resection was planned 4-6 weeks thereafter. Performance status, comorbidity, clinical and pathological tumour stage, (response to) treatment and survival were reviewed. Survival analysis was performed using the Kaplan-Meier method.

Results
Over these 12 years, 85 patients with Pancoast tumours, 57 men and 28 women, were referred. Mean follow-up was 42 months (range 2-120 months). Twenty-five patients had stage IIB (29%), 7 stage IIIA (8%), 32 stage IIIB (38%) and 21 stage IV (25%). Of the 64 patients presenting with stage II or III disease, 38 medically operable patients with potentially resectable tumours received induction therapy. After restaging, 22 patients underwent resection. All resections were complete and local recurrences were not observed. In 13 patients (62%) a pathologic complete response was found. In most cases, pathologic response was not evident from radiological imaging. The morbidity of surgery after induction treatment was acceptable. There was no fatal toxicity or treatment-related mortality. The 2- and 5-year overall survival of this selected group was 70% and 37%, respectively.

Conclusion
This schedule of induction therapy with high-dose radiation and concurrent cisplatinum was safe and highly effective in fit patients. At this time, pathologic complete response cannot be reliably recognized preoperatively and better tools for response assessment are critical for more tailored treatment of patients with SST.
Superior sulcus tumours: the rationale for surgery

Introduction

The outcome of recent combined modality trials in patients with locally advanced non-small cell lung cancer (NSCLC) has limited the indications for radical surgical approaches\(^1\). At the same time, the role of surgery for tumours growing into the superior sulcus remains important. Complete en-bloc pulmonary resection with adjacent thoracic wall is considered to be the main step towards local control and long-term survival for T3/T4 non-small cell lung cancer of the superior sulcus (SST or Pancoast tumours)\(^3\).

Pancoast tumours, although first described by Hare in 1838, became generally recognized when radiologist Henry Pancoast drew attention to its clinical and radiographic features in 1932\(^4\). The location of these “Pancoast tumours” near vital structures such as spine, brachial plexus and subclavian vessels demands a combined modality approach to achieve optimal local control. Combined modality treatment was introduced by Shaw and Paulson in 1961, when they observed that, after radiotherapy with palliative intent, the tumour could become resectable\(^5\). More recent phase II experience confirms that better local control can be obtained with surgery following (chemo) radiotherapy\(^6-8\). Induction chemoradiation (CRT) increases the probability of a complete resection, and may even sterilize the tumour complex. Strategies to increase the impact of induction treatment include higher doses of radiotherapy. However, this may also increase toxicity and the complication rate associated with chemoradiotherapy followed by surgery\(^9-11\).

The objective of this study was to evaluate the efficacy and safety of induction chemoradiation of 66 Gy with concurrent low-dose cisplatin preceding surgery, and to review the rationale for surgery in the era of chemoradiotherapy for NSCLC of the superior sulcus.

Patients and Methods

Three institutional databases were used to identify all patients with pulmonary tumours invading the superior sulcus, referred to the Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital (NKI-AVL), Amsterdam, the Netherlands, between 1994 and 2006.

Diagnostic strategies

All patients had received at least one CT scan and bronchoscopy at diagnosis and were evaluated by the multidisciplinary thoracic oncological team to assess tumour stage.
and decide on the treatment strategy. MRI was used to determine tumour involvement of the vertebrae, brachial plexus, and subclavian vessels in patients who were candidates for surgery. Positron emission tomography (\(^{18}\text{F}\)-FDG-PET) was regularly used since its introduction in the year 2000, but only became part of the standard staging procedure in the year 2002. Mediastinoscopy was performed if pathological lymph nodes in the mediastinum were suspected on CT, unless PET was available and negative for mediastinal nodes. Since the year 2002 endoscopic and endobronchial ultrasonography with fine needle aspiration (E(B)US-FNA) were used to replace or add up to mediastinoscopy in staging of the mediastinum.

**Primary therapeutic strategies**

Patients with stage II or III who were ineligible for surgery were offered radiotherapy (RT) and/or chemotherapy (C). Intended doses of RT ranged from 66-88 Gy, depending on performance status, spinal cord involvement in the radiation field, and participation in a phase II dose escalation trial\(^{12}\). Radiation treatment included the primary tumour and all lymph node levels with (suspicion of) metastatic nodal disease. For patients diagnosed with distant metastatic disease (stage IV), no uniform schedule was used. They received palliative radiotherapy, chemotherapy or a combination of both. When surgical resection was considered feasible, the preferred induction regimen was concurrent chemoradiotherapy (CRT): accelerated RT, using a concomitant boost technique to a total dose of 66 Gy in 24 fractions of 2,75 Gy within 32 days\(^{13}\), and daily low dose Cisplatin 6 mg/m\(^2\), given intravenously 1 to 2 hours before each fraction of RT. This regimen has been extensively studied in two trials (Uitterhoeve 2000 and Belderbos 2007\(^{13;14}\)). Contraindications for this concurrent CRT scheme were a performance status of WHO > 2, weight loss of > 10% of the original weight, or insufficient renal function. When patients had already started induction chemotherapy in a referring hospital they received either sequential chemoradiation or chemotherapy alone.

**Restaging and surgical (contra)indications**

Three to four weeks after completion of the induction treatment, CT and MRI examinations were performed to evaluate resectability and response. Exclusion criteria for surgical intervention were progressive disease (PD), persisting N2/N3 disease, (extensive) tumour invasion in neural foramina, vertebral bodies, brachial plexus, or greater vessels, WHO ≥ 2, weight loss of >10% of the original weight, or insufficient cardiopulmonary reserve. Radiological response was not a prerequisite for resection. Restaging of the mediastinum was done with mediastinoscopy, esophageal ultrasound,
or EBUS if (persisting) N2 disease was suspected on CT scan, but re-mediastinoscopy was avoided. Surgery was scheduled 4 to 6 weeks after completion of induction treatment, and generally consisted of en-bloc resection of the affected lobe and chest wall structures. Mediastinal lymph node sampling was routinely performed.

**Data collection**

Age, gender, smoking status, performance status, pulmonary function, type of treatment, clinical and pathological tumour stage, date and site of first relapse, and clinical and pathological response to treatment were retrieved from the patient charts. Toxicity was assessed using the WHO Toxicity Criteria. Follow-up information was retrieved from the original patient records. Incidence, type and date of recurrence or death were recorded. In case of missing follow-up information, general practitioners were contacted.

**Statistical analysis**

All statistical analyses were performed using the statistical software package SPSS (SPSS, Chicago, Il). Survival was calculated with the Kaplan-Meier method from the date of diagnosis. For the analysis of (disease-free) survival, events were defined as recurrent disease – due to distant metastasis or locoregional recurrence – or death of any cause. Survival was compared using the log-rank test (pCR versus non-pCR, no comparison was made between treatment groups because of selection bias).

**Results**

**Patient group**

From 1994 to 2006, 85 patients with Pancoast tumours were referred to our institute. There were 57 men and 28 women, with a mean age of 57 years (range 32-82 years). Follow-up was complete until January 2007 for all patients except one, who was lost to follow-up after 2 months. The mean follow-up time was 42 months (range 2-120 months). Histological subtypes were adenocarcinoma in 38 patients (45%), unspecified large cell carcinoma in 36 patients (42%), and squamous cell carcinoma in 11 patients (13%). In 21 patients (25%) distant metastases were found at further diagnostic work-up (stage IV). They were treated with palliative intent and will not be discussed in this report.

Of the remaining 64 patients, 25 patients had stage IIB (29%), 7 patients stage IIIA (8%), and 32 patients stage IIIB (38%), including 33 cT3 and 31 cT4 tumours, on pre-treatment staging. Mediastinoscopy was performed in 22 patients.
Primary treatment strategies

The applied treatment combinations are shown in Figure 1. According to the multidisciplinary thoracic oncological team, 39 of these 64 stage II and III patients were judged eligible for (combined) induction treatment. Stages of these patients are shown in Figure 1. One patient refused induction treatment, and underwent surgery only. Several patients received additional treatment after induction chemotherapy (conc CRT n=1; seq RT n=4) and after induction radiotherapy (seq CT n=4). The other 25 patients were considered medically inoperable by the multidisciplinary team, and were treated either with concurrent CRT (n=10), or radiotherapy only (n=15). In all, 63 patients received some form of CT and/or RT, either with or without surgery. These different regimens were generally well tolerated. In irradiated patients, pulmonary toxicity occurred in 10 patients (grade 3 in 2 patients), oesophageal toxicity was observed in 28 patients, (grade 3 in 8 patients) and one patient developed a tracheo-oesophageal fistula. There were no fatal toxicities.
Table 1: Radiological versus pathological response.

<table>
<thead>
<tr>
<th>Radiological response</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td></td>
<td>6</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>PR</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease

Restaging
Response evaluation with CT (and MRI) imaging in the 38 patients who received induction treatment revealed partial response (PR) in 10 patients, stable disease (SD) in 24 patients and progressive disease (PD) in 4 patients. Twenty-one patients (55%) (concurrent iCRT n=19; sequential iCT/RT n=2) completed combined modality treatment (median dose given 66 Gy; range 61-67 Gy) with subsequent surgical resection. For 17 patients with stable or progressive disease surgery was cancelled, as the selection criteria for surgery were not met. In the 21 patients who underwent induction treatment and resection, the radiological response was compared to the pathological response (Table 1). In 13 patients (62%) no vital tumour was found at pathological examination. Interestingly, these pathological complete responses (pCR) were not recognized by repeated CT (6 PR and 7 SD; Table 1). After induction treatment with concurrent CRT and surgery downstaging was seen in 14 patients, of which 10 patients had no vital tumour rest at all (59%).

Surgical data
In all patients who underwent resection, a high-posterior or extended posterolateral approach was used. Twenty-one lobectomies and one bilobectomy were performed with en-bloc resection of the involved thoracic wall. Partial resection of the subclavian artery, vertebral bodies or brachial plexus were necessary in 5 patients. All resections were microscopically complete (R0). Postoperative morbidity included pneumonia in 6 patients, chylothorax in 1 patient, atelectasis of the remaining lobe in 1 patient, and postoperative bleeding in 1 patient. There was no surgery-related mortality (<30-days postoperative).
Table 2: Recurrences after (chemo)radiotherapy only and induction treatment + surgery.

<table>
<thead>
<tr>
<th>Type of recurrence</th>
<th>(C)RT n = 42</th>
<th>(induction +) surgery n = 22</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local only</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Distant</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>Local + distant</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>No recurrence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Of which alive</td>
<td>12</td>
<td>12</td>
</tr>
</tbody>
</table>

Follow-up

Local tumour control was 100% in the surgery group (Table 2). However, in 17 out of the 42 patients of the non-surgery group (40%) locoregional recurrence was detected. Eight of them suffered from isolated locoregional recurrent disease (of whom 4 patients were medically inoperable at primary evaluation); in 9 patients distant metastases were found at the same time.

The 2- and 5-year overall survival in the 22 patients who underwent surgical resection were 77% and 37%, respectively (Figure 2). Patients treated by CRT only had 2- and 5-year survival rates of 42% and 19%, respectively (n=19). Patients treated with sequential or single modality radiotherapy and chemotherapy (n=23) had 2- and 5-year survival rates of 19% and 5%, respectively.

By the end of January 2007, 19 patients of 64 stage II-III patients were still alive. Fifteen of them are free of recurrence, of whom 10 had received trimodality treatment (chemoradiation followed by surgery), as shown in Figure 3. Although survival of patients with pCR at the time of resection was noticeably higher, the statistical level of significance was not reached in this series due to small numbers (5 year survival of 56% vs. 17%, p=0.12).
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Figure 2: Overall survival of patients with superior sulcus tumours stage II or III receiving different forms of combined modality treatment. CRT = chemoradiotherapy.

Legend:
- (Induction and) resection (N=22)
- Concurrent CRT (N=19)
- Sequential CRT (N=23)

Figure 3: Disease-free survival of patients with superior sulcus tumours stage II or III receiving different forms of combined modality treatment. CRT = chemoradiotherapy.

Legend:
- (Induction and) resection (N=22)
- Concurrent CRT (N=19)
- Sequential CRT (N=23)
Discussion

In our study, with a strict selection for surgical resection after high dose radiotherapy with daily cisplatin, long-term survival was obtained in 37% of patients and local tumour control was achieved in all patients with SST. Pathologic complete response was detected in over 60% of surgical specimens, which shows that this induction scheme is a very potent regimen with major impact on tumour tissue. Toxicity of high dose CRT and complications of consecutive surgery were acceptable and no treatment-related deaths occurred.

Due to the rareness of the disease, there are no randomized trials on the management of SST patients. Two prospective trials have been reported recently by Rusch and colleagues, 2007, and Kunitoh and coworkers, 2008. Both studies used a regimen of 45 Gy radiotherapy, concurrently with 2 cycles of cisplatin and etoposide. In the North American study 88 of 110 patients (who were enrolled by 76 surgeons from the North American cooperative groups) underwent induction chemoradiation and surgery, and pathologic complete response was seen in 32 of 88 patients (36%). The overall survival was similar to that of the of the present study (44% at 5 years) and locoregional recurrence occurred in 9%. Treatment related mortality was 3%. The Japanese study (76 patients from 19 institutions) reported a pathological response rate of 21% (12 of 57 patients), with an overall survival rate of 56% at 5 years and locoregional recurrence in 12% (after R0 resection). Treatment related mortality was 4%.

Our retrospective study describes all patients referred for treatment and shows that in a pragmatic clinical setting only a selected group can receive combined modality treatment (followed by surgery). Still, the pathologic response rate of 62 % in these patients differs notably from the abovementioned studies with a radiotherapy dose of 45 Gy. Our exclusion criteria for surgical resection (progressive disease (PD), persisting N2/N3 disease, (extensive) tumour invasion in neural foramina, vertebral bodies, brachial plexus, or greater vessels, WHO > 2, weight loss of >10% of the original weight, or insufficient cardiopulmonary reserve) may be rather cautious when compared to those criteria employed by other surgical groups. Other approaches have been described, for example the anterior transclavicular approach described by Dartevelle in 1993 or the cervicothoracic transmanubrial approach described in 1997 by Grunenwald. They can be advantageous when resecting anteriorly located tumours, because they provide good exposure of the brachial plexus and subclavian vessels, but an additional posterior incision is often necessary to complete the lobectomy. Some performed more extensive resections, including reconstructions of vertebrae, vessels or brachial plexus, in limited numbers of patients. However, some critical comments
are warranted. The risk of an incomplete resection at these sites should be considered, since local recurrences are associated with serious pain and, inevitably, short survival. Wider selection criteria for surgical resection could be beneficial for those patients who are at risk for local recurrence after primary non-surgical therapy. However, our data suggest that this group is disappointingly small. Only 4 out of 42 patients could have had a potential benefit from a more extensive surgical approach (medically operable patients with irresectable tumours at primary evaluation, who developed isolated locoregional recurrent disease).

An even more challenging question is, whether the role of surgery in the subgroup of patients with a pathologic complete response should be debated. After all, the rationale for both concurrent CRT and surgery is the achievement of local control. Should surgical resection be abandoned when complete response has already been accomplished by chemoradiotherapy?

There are two issues that prohibit a definite answer to this question. First, the accuracy of pathological examination in assessing a complete response is questionable. Post-chemoradiotherapy effects can be difficult to interpret and, since only a restricted number of pathological sections are examined, routine pathological examination might fail to identify residual cancer. A study on pathologic re-examination of oesophagectomy specimens of complete responders after chemoradiation for oesophageal cancer did not reveal extra residual cancer\textsuperscript{21}, but to our knowledge, this issue has never been studied in lung cancer. Secondly, at present, we cannot adequately predict complete response preoperatively with radiological imaging (Table 1). It is impossible with CT and MRI to distinguish vital tumour cells from radiation induced fibrosis and necrosis. Moreover, preoperative response assessment, usually at 2-4 weeks post-induction treatment, is too early to detect the maximal effect of (chemo)radiation. Although solely based on unsystematic clinical recommendations, it is generally considered undesirable to postpone surgery for more than 4-6 weeks, as radiation fibrosis may hamper the surgical resection after that time\textsuperscript{5}. The optimal response can therefore not be determined by preoperative CT. It is only after surgery and subsequent pathological examination that response to treatment is accurately assessed. Other imaging modalities may gain in importance for more reliable response evaluation. Several studies have already tested the use of \textsuperscript{[18F]}-FDG-PET for evaluation of response, and even prediction of response prior to neoadjuvant therapy\textsuperscript{22-25}. Promising results, (i.e. an almost linear correlations between SUV\textsubscript{max} and pathologic response) were reported in one study\textsuperscript{23}, but results of other studies concerning this issue were less optimistic.
To resume, for patients with superior sulcus tumours it is of primary importance to achieve the best possible local control, since local recurrence is associated with intense pain and discomfort. At present times, this remains a legitimate reason for surgical resection following chemoradiation. The high rate of pathologic complete response that can be achieved with an accelerated concurrent scheme of 66 Gy radiotherapy with daily cisplatin are promising, although in at least 40 % of these patients surgery is essential for locoregional disease control. At this time, pCR cannot be reliably recognized preoperatively and better tools for response assessment are critical for more tailored treatment of patients with SST.
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