Induction chemoradiation therapy followed by surgical resection for non-small cell lung cancer (NSCLC) invading the thoracic inlet

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Received 14 September 2007; received in revised form 20 February 2008; accepted 4 March 2008; Available online 14 April 2008

Abstract

Objective: The role of induction therapy for non-small cell lung cancer (NSCLC) invading the thoracic inlet is unclear. We reviewed our experience with induction chemoradiation followed by surgical resection for NSCLC invading the thoracic inlet.

Methods: We performed a retrospective review of 44 consecutive patients with NSCLC invading the thoracic inlet, treated with induction chemoradiation (two cycles of cisplatin and etoposide concurrently with 45 Gy of radiation) followed by surgical resection between 1996 and 2007.

Results: All patients underwent chest wall resection (1–5 ribs, mean 3) with resection of the first rib through an anterior (n = 15), a posterior (n = 18), or a combined approach (n = 11). Lobectomy was performed in 40 cases (90%), pneumonectomy in two (5%), and wedge resection in two (5%). Resection of subclavian vessels or portions of vertebrae was performed in five (11%) and 15 (34%) patients, respectively. Hospital mortality was 5% (n = 2). R0-resection was achieved in 39 patients (89%). On pathologic examination, 13 patients (30%) showed complete response (pCR) to induction therapy, and 15 (34%) showed minimal microscopic residual disease (90–99% tumor necrosis). The median follow-up was 2 years (range, 2 months–10 years) with an overall cumulative 5-year survival of 59%. Sixteen patients (36%) developed recurrence, which was local in five cases and distant in 11 patients. The 5-year survival in patients with pCR was 90%; 69% in those with minimal residual disease, and 12% in patients with no relevant response (p = 0.0005). Conclusions: Resection of NSCLC invading the thoracic inlet can be performed safely after induction chemoradiation therapy. The response rate after induction therapy is a strong predictor of survival.

Keywords: Superior sulcus tumor; Pancoast; Neoadjuvant therapy; Vertebral resection; Subclavian artery

1. Introduction

The role of induction chemoradiation therapy in the treatment of non-small cell lung cancer (NSCLC) invading the thoracic inlet is unclear. Although several investigators have published their experience in the treatment of superior sulcus tumors, few reports have only analyzed the results of surgery after induction chemoradiation therapy [1–3]. Rusch and colleagues recently reported the long-term experience from the Southwest Oncology Group Trial 9416 (Intergroup Trial 0160) on induction chemoradiation therapy followed by surgery for superior sulcus tumors [4]. This study unfortunately was hindered by the lack of description of the surgical procedure performed. Thirteen out of the 88 patients (15%) undergoing surgical resection had no chest wall resection suggesting that these tumors may not have been invading the thoracic inlet despite their radiological appearance [3,4].

In this study we review our experience with induction chemoradiation therapy followed by radical surgical resection in patients with NSCLC invading the thoracic inlet. Involvement of the thoracic inlet was defined by the preoperative radiological appearance of the tumor and by resection of at least the first rib as a component of the thoracic inlet involvement.

2. Patients and methods

Between January 1996 and March 2007, 44 consecutive patients with NSCLC invading the thoracic inlet underwent

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doi:10.1016/j.ejcts.2008.03.008
induction chemoradiation therapy followed by radical surgical resection. All patients received two cycles of cisplatin and etoposide concurrently with 45 Gy of radiation. Induction chemotherapy and radiation began within 24 h of each other. Chemotherapy consisted of cisplatin 50 mg/m² on days 1, 8, 29, and 36, and etoposide 50 mg/m² on days 1 through 5 and 29–33. The total radiation dose was 45 Gy administered in 1.8-Gy daily fractions during 5 weeks. The radiation field was defined by CT scan and included the primary tumor and ipsilateral supraclavicular region, but not the mediastinum or hilum if the mediastinoscopy was negative.

All patients were staged with brain magnetic resonance imaging (MRI), bone scan, abdominal and chest CT scanning. MRI of the thoracic inlet was performed in patients with suspected invasion of the vertebra and/or neural foramen. Mediastinoscopy was performed in all patients before induction chemoradiation therapy. Patients with a positive mediastinoscopy were usually treated with radical chemoradiation therapy without surgery. One exception was performed in this series of patients. One patient intentionally underwent induction chemoradiation followed by surgery despite a positive mediastinoscopy. The radiation field covered the mediastinum in addition to the primary tumor and supraclavicular ipsilateral lymph node in that particular case.

Two to 6 weeks after induction therapy all patients were re-staged with CT scan of the chest and abdomen, bone scan, and brain MRI. Surgery was performed 3–6 weeks after the end of induction therapy. Six patients presenting with local (n = 1) or distant (n = 5) progression of their tumors during induction therapy did not undergo surgery and were not included in this study.

The surgical approach, anterior, posterior, or combined, was decided by the operating surgeon according to the location and morphology of the tumor. An anterior approach either alone or in combination with a posterior approach was usually performed when the subclavian vessels were involved and/or if resection of T1 vertebrae was required. The anterior approach was performed either through a hemi-clamshell incision with the thoracotomy in the fourth intercostal space, or through an anterior transclavicular approach with the thoracotomy in the second intercostal space (Fig. 1). The posterior approach was performed through a large posterolateral thoracotomy extending up to C7 (Fig. 2). All patients underwent chest wall resection with at least a resection of the first rib. Mediastinal lymph node dissection of all accessible nodal stations was performed during thoracotomy.

The pathologic response to induction chemoradiation therapy was assessed by the degree of tumor necrosis and divided into three categories. Pathologic complete response (pCR) was defined as no residual microscopic tumor seen, minimal microscopic residual disease was defined by the presence of few scattered tumor foci involving less than 10% of the residual necrotic mass, and no significant response was defined by the presence of residual disease in more than 90% of the tumor mass.

Patient demographic and treatment details are reported using descriptive statistics. Student’s t-test was used to calculate differences between continuous variables, and chi-square was used for categorical variables. Survival rates were calculated by life-table analysis. Kaplan–Meier curves were plotted and compared using the log-rank test. Graphpad software (San Diego, CA) was used for all analyses. Differences were considered significant when p was less than 0.05.
3. Results

A total of 23 men and 21 women with a median age of 61 (range, 32—75) years underwent surgery (Table 1). The tumor originated from the right lung in 24 patients. Most patients were staged clinically as IIB (cT3N0) and IIIB (cT4N0).

All patients underwent chest wall resection (1—5 ribs, mean 3) with resection of the first rib through an anterior (n = 15), a posterior (n = 18), or a combined approach (n = 11). Lobectomy was performed in 40 cases (90%), pneumonectomy in two cases (5%), and wedge resection in two cases (5%). Resection of the subclavian vessels was performed in five patients (11%). A polytetrafluoroethylene (PTFE) ring graft was used for reconstruction of the subclavian artery in three cases (Fig. 1). Portion of the vertebrae was resected in 15 patients (34%) with hemi-vertebrectomy of 2—4 vertebrae (median 3) in 11 cases (Fig. 2) and resection of the transverse process in four cases.

Duration of hospital stay ranged between 4 and 112 days (median 11 days). Two patients died postoperatively after 92 and 167 days from pulmonary emboli (n = 1) and pneumonia (n = 1), respectively, for an in-hospital mortality of 5%. No patient died within 30 days of surgery. A total of 20 patients (45%) developed at least one complication during their hospital stay (Table 2). The main complications were pneumonia and respiratory failure, which occurred in 10 patients. The rate of pneumonia/respiratory failure was independent of the surgical approach and occurred in four patients after an anterior approach (27%), in four patients after a posterior approach (22%), and in two patients after a combined approach (18%). Two patients had partial dehiscence of their posterior incision, requiring a muscle flap to close the wound.

R0-resection was achieved in 39 patients (89%). Five patients had an incomplete resection because of residual tumors along the brachial plexus, the paravertebral margin, or within the spinal canal. On pathologic examination, 13 patients (30%) showed complete response (pCR) to induction therapy, and 15 (34%) showed minimal microscopic residual disease (90—99% tumor necrosis). Pathologic stage is presented in Table 1. Five patients had metastatic nodal disease to N1 nodes, one patient had metastasis to ipsilateral mediastinal nodes (N2 nodes), and one patient had metastasis to ipsilateral supra-clavicular nodes (N3 nodes).

The median follow-up was 2 years (range, 2 month—10 years) with an overall cumulative 5-year survival of 59 ± 11% (Fig. 3). Thirteen patients (33%) developed recurrent disease after complete resection (R0). Recurrence was local in four cases (10%) and distant in 9 (23%). The primary site of distant recurrence was localized in the brain (n = 3), in the contralateral lung (n = 3), in the bone (n = 2), and in the kidney (n = 1). The 5-year survival in patients with pCR was 90%; 69% in those with minimal residual disease (90—99% tumor necrosis), and 12% in patients with no relevant response (Fig. 4). Except for the pathological stage, there was no significant difference between responders (≥90% tumor necrosis) and non-responders (<90% tumor necrosis) to

### Table 1

| Age (years) | Median | Range 32—75 |
| Gender | Male 23 (52%) | Female 21 (48%) |
| Side | Right 24 (52%) | Left 20 (48%) |
| Clinical stage | cT3N0 25 (57%) | cT3N1 4 (9%) | cT3N2 1 (2%) | cT4N0 14 (32%) |
| Pathological stage | ypT0N0 13 (30%) | ypT3N0 18 (41%) | ypT3N1 5 (11%) | ypT3N2 1 (2%) | ypT4N0 6 (14%) | ypT4N3 1 (2%) |

### Table 2

| Postoperative complications | | |
| Pneumonia/respiratory failure | 10 | |
| Atrial fibrillation | 6 | |
| Empyema | 2 | |
| Wound dehiscence | 2 | |
| Chylothorax | 2 | |
| Pulmonary emboli | 1 | |
| Seizure | 1 | |

Fig. 3. Overall 5-year survival of 44 consecutive patients undergoing induction chemoradiation therapy followed by surgery.

Patients at risk 44 29 19 13 13 13

Fig. 4. Survival according to the pathologic response after induction therapy.
Table 3
Characteristics of responders and non-responders to induction therapy

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Fig. 5. Survival according to pathological staging (ypTNM) after completion of trimodality therapy.

induction chemoradiation therapy (Table 3). Survival according to the postinduction TNM stage is presented in Fig. 5.

4. Discussion

The first descriptions of tumors invading the thoracic inlet were published by Pancoast and Tobias in 1932 [5,6] and Hare in 1938 [7]. In 1946 it was agreed that this disease, which was characterized by pain, Horner’s syndrome, destruction of the first rib and atrophy of hand muscles was uniformly fatal [7,8]. The first long-term survivor was reported in 1956 by Chardack and MacCallum who treated a 54-year-old man with surgery and radiation [9]. Following the report from Shaw and Paulson and colleagues in 1961 and 1962 [10,11], the standard therapy for tumors invading the superior sulcus became preoperative radiation therapy followed by surgical resection. A large posterolateral thoracotomy extending up to C7 was usually used to approach these tumors until 1990s. Dartelle and colleagues in 1993 described an innovative anterior approach for resection of superior sulcus tumors involving the cervical structures of the thoracic inlet [12]. This approach was particularly useful when the subclavian vessels and/or the spine was involved by the tumor at the thoracic inlet [13,14].

In our institution, an anterior approach was preferred for resection of tumors invading the subclavian vessels, as shown in a representative picture in Fig. 1. Tumors in a more posterior location were usually approached through a posterior incision. However, if vertebral resection of T1 was required a combined anterior and posterior approach was required to achieve en bloc resection of the tumor.

It has been suggested that the anterior approach as described by Dartelle et al. might lead to malfunction of the shoulder due to resection of the proximal portion of the clavicle. However, this approach offers the ability to access the spine and the chest through the same incision and obviates the need for a posteroserolateral thoracotomy even if a vertebral resection is required. In our experience, resection of the inner part of the clavicle did not cause significant shoulder dysfunction if the scapulothoracic junction was preserved [15].

Since the report by Ginsberg and colleagues in 1994 demonstrating that the long-term outcome was significantly improved in patients undergoing en bloc resection of superior sulcus tumor with a lobectomy, there is general agreement that a lobectomy rather than a lung sparing resection should be performed [16]. In our experience, all patients but two had a lobectomy or a pneumonectomy with en bloc resection of the chest wall, spine, and/or subclavian vessels.

Mediastinal lymph node involvement seems to be associated with a particularly poor outcome in patients with superior sulcus tumors [16,17]. Most recent series have included a mediastinoscopy as part of the staging process and patients with mediastinal lymph node involvement have typically been excluded from surgery. Hence, better staging also contributed to improvement in long-term survival in recent surgical series. The role of PET scans, and EBUS have yet to be clarified for mediastinal staging in patients with NSCLC. In our practice, mediastinoscopy has remained the gold standard.

Rusch and colleagues have recently reported a resectability rate of 76% after induction chemoradiation therapy for superior sulcus tumors and a 54% 5-year survival for patients with complete surgical resection [4]. However, 15% of the patients undergoing surgical resection had no chest wall resection, suggesting that these patients may have been upstaged clinically. There is also no mention of the type of chest wall resection required. Resection of tumors involving the first rib presents particular challenges because of the proximity of the spine, the brachial plexus, and the subclavian vessels. Hence, in this single center retrospective review, we only included patients with NSCLC that required at least resection of the first rib as part of their chest wall resection. All of our patients were treated with a similar protocol to the intergroup trial, namely induction chemoradiation therapy with cisplatin—etoposide concurrently with 45 Gy of radiation. We observed that 64% of our patients had an excellent response to induction therapy regimen with
minimal residual tumor (≥90% necrosis) on final pathology examination. These patients had excellent long-term survival with 90% 5-year survival in patients with complete response and 69% 5-year survival in patients with 90—99% tumor necrosis. Patients with large residual disease (<90% tumor necrosis) after induction chemoradiation therapy had significantly worse survival with a 5-year survival of 12% only. Future studies looking at PET scan before and after one cycle of chemotherapy may be beneficial to determine metabolic responders and select which patients should be offered induction therapy prior to surgery [18].

Our study has limitations inherent to its retrospective nature, the limited length of follow-up after surgery, and the inclusion of a selected group of patients who completed trimodality therapy. However, this study offers the advantage of being a single center study with a homogenous therapeutic approach to a consecutive series of patients with NSCLC invading the thoracic inlet.

This study demonstrates that induction chemoradiation therapy leads to a favorable outcome after surgical resection in patients with NSCLC invading the thoracic inlet. Approximately 64% of the patients had near complete necrosis of their tumor and only 11% of the patients had local recurrences. Survival strongly correlated with the pathologic response of the tumor to induction therapy.

Acknowledgements

The authors would like to acknowledge Jonathan Yeung and Sandra Tomaszek for their help in retrieving the data and performing some of the analysis.

References


Appendix A. Conference discussion

Dr L. Lang-Lazdunski (London, United Kingdom): Dr de Perrot has presented an 11-year experience of surgery for Pancoast tumors at the Toronto General Hospital. Forty-five percent of patients had T4 disease and all patients received a classical induction regimen involving two cycles of cisplatin and etoposide with concurrent radiotherapy. Eighty-nine percent of patients had an R0 resection. Most patients had a good response to induction treatment, with 30% of patients having complete pathological response and 34% of patients having only minimal microscopic disease left. These patients had an impressive 90% and 69% survival rate at 5 years, respectively.

I have noticed that 56% of your patients had been operated on in the last 2 years. Therefore, it is likely that you have some interim analysis effect in this study and you will have to wait another 3 years, at least, for the data to mature before drawing a conclusion. However, your results taken together with the data published by Dr Valerie Rusch and the South Western Oncology Group earlier this year suggest a significant association between complete response and long-term survival and also between marginal response and poor survival. Should these data be confirmed by the proof of time, we may have to change our surgical indication in Pancoast tumors.

I have four questions for you. First, why did you perform the mediastinoscopy before the induction treatment and not after? Now, PET/CT or EBUS can screen patients before induction treatment and mediastinoscopy can be performed 3 or 4 weeks after completion of the induction treatment to stage your mediastinal nodes.

Second question, what is the best imaging modality to assess the pathological response, is it MRI or PET/CT, which ones tell you best if the tumor has turned necrotic or if there is a large viable tumor component left?

Third question, what is the percentage of patients turned down for surgery because of poor response over this period of time?

And the last question: how do you assess the tumor necrosis. With H&E staining or immunohistochemistry or any other techniques?

Dr de Perrot: The mediastinoscopy was always done before the induction treatment in order to allow the radiation field to cover the mediastinal nodes if they were involved, and, as well, at least initially in our experience, it was a contraindication to surgery. In this series there is one patient with known N2 disease who had induction chemoradiation followed by surgery. But as a general rule, we have been excluding these patients for surgery. For the second question, to assess the response to the treatment, that’s impossible still at the time to determine based on the CT scan and even on the MRI whether they had a response to the treatment or not. It has been clearly demonstrated in several series that CT scan doesn’t allow to determine if there is a response.
This leads to the fourth question, whether there is necrosis or not is impossible to assess radiologically. All these patients had residual disease on their CT scan despite the fact that 30% had a complete response.

Now the third question?

Dr Lang-Lazdunski: How many patients were excluded, were turned down for surgery, over this period because of the response of tumor progression?

Dr de Perrot: There were six patients who progressed on chemoradiation therapy and were not included in this analysis. Five of them were found to have distant metastases on repeat staging after the induction therapy, and one had a local progression, so six patients in addition to the 44 had progression of the disease.

Dr Lang-Lazdunski: Based on your findings, do you think we should still operate on patients who have stable disease or marginal response for induction treatment?

Dr de Perrot: Yes, I think that the main question is whether they have a response or not and this cannot be determined preoperatively. Based on our findings, I was surprised to see that patients who do not respond have only a survival of 12% at 5 years, which is lower than we had anticipated. These patients did not seem to have any benefit from induction chemoradiation prior to surgery. One can wonder if they should have surgery first instead of having induction therapy.

Dr A. Jilaihawi (Glasgow, United Kingdom): A short technical question. You had five patients involving the subclavian artery and vein. Did you reconstitute the vessels or did you rely on collaterals, or what did you do technically for those?

Dr de Perrot: If a subclavian vein is involved, we don’t reconstruct it, we ligate the vein and then the collaterals will be good enough to drain the arm. But if the subclavian artery is involved, we always reconstruct it. You can either do an end-to-end anastomosis. Sometimes by resecting the first two ribs, you are able to reconnect the artery directly, or otherwise we have used the PTFE graft in three patients and one patient had a vein graft. But we always reconstructed the artery.

Dr P. Dartevelle (Paris, France): Why do you give induction therapy? The advantage of induction therapy is not proven. I don’t give induction therapy in these kinds of tumors. And it was never proven that induction therapy has an advantage. It’s only because Paulson said that you have to give radiation therapy before removing this kind of tumor. But with the right approach to remove this kind of tumor, induction therapy is not useful.

Dr de Perrot: I agree it’s certainly never been proven. And I think the main thing is to obtain a complete resection whether you give induction therapy or not. The induction therapy does not allow you to do a less aggressive surgery.

There may be some advantage in giving induction therapy in patients who respond since they tolerate the treatment better and can receive chemotherapy and radiation concurrently. So potentially in that group there is an advantage. But again, complete resection is the key for all these patients.

Dr W. Klepetko (Vienna, Austria): Just to confuse the audience even more, I would like to put the question the other way around. Why don’t you intensify the induction therapy? When I look at your data I think it has a slightly higher local recurrence rate than has been published from other groups like Carson’s group or the group from Essen. Now, the Essen group, they start off with induction chemotherapy followed by concurrent chemoradio. Have you thought about that as an approach or not?

And in addition to that, could you give us some information about the toxicity the patient experienced during your induction regimen?

Dr de Perrot: The data from patients who received 60 Gy of radiation from a few series in the literature suggests that there is an increased response rate up to about 70% instead of the 64% or so that we’ve had.

But the key, I think, is to see who will have a response. I think that’s really what future studies should investigate. It’s impossible to determine preoperatively who is likely to have a response and who is not at this point.

Certainly any induction treatment increases the morbidity of the surgery. By increasing the radiation to 60 Gy that may further increase the morbidity postoperatively. And again, the benefit will be probably for those who respond.

Dr M. Beshay (Bielefeld, Germany): You did wedge resection in two patients and five patients had local recurrence.

The first question, what was the indication to do wedge resection in these patients, and was there any relation between the local recurrence and these patients, did both of them have local recurrence?

Dr de Perrot: The two wedge resections were done early on in the series and clearly we would not recommend to do a wedge resection for these tumors anymore. I don’t exactly know why the wedge resection was done.

One of the patients who had local recurrence did have a wedge resection. But again, we certainly would always recommend to do a lobectomy for these patients.