Postoperative morbidity and mortality after induction chemoradiotherapy for locally advanced lung cancer: an analysis of 350 operated patients

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Abstract

Objective: The purpose of this study was to evaluate the frequency and risk of postoperative cardiopulmonary and bronchial complications in patients with locally advanced lung cancer after induction chemoradiotherapy and definitive surgery. Methods: We reviewed the charts of 350 patients who underwent thoracotomy in the course of two phase II and one phase III studies with preoperative chemotherapy (three cycles of split-dose cisplatin/etoposide in 261 patients and cisplatin/paclitaxel in 89 patients) followed in all 350 patients by concurrent chemoradiotherapy (one cycle cisplatin/etoposide combined with 45 Gy hyperfractionated accelerated radiotherapy) and operation from March 1991 to December 2000. Univariate and multivariate analysis was used to identify predictors of complications. Results: Of 350 consecutive patients 278 (79%) had a non-small cell lung cancer (154 stage IIIA and 124 IIIB) and 72 (21%) a small cell lung cancer (12 stage IIA/B, 35 stage IIIA and 25 stage IIIB). Resections included 125 pneumonectomies (35%), 15 bilobectomies (4.3%), 37 sleeve lobectomies (11%), 157 lobectomies (45%), and two segmentectomies (0.6%); 14 patients (4%) had an exploration only. Additionally to pulmonary resection 32 patients underwent a partial chest wall resection. One hundred and fifty-four patients (44%) developed early or late complications; the hospital mortality rate was 4.9% (17 patients). The causes of death were sepsis (n = 5), pneumonia and respiratory failure (n = 4), adult respiratory distress syndrome (n = 3), cardiac failure (n = 3) and lung embolism (n = 2). Multivariate analysis extracted increased age, lower Karnofsky status, abnormal echocardiographic findings and no bronchial stump covering technique to be risk factors for perioperative morbidity. Lower Karnofsky status and increased age were significant risk factors for postoperative mortality. Conclusion: This retrospective analysis demonstrates that in patients with locally advanced lung cancer and induction chemoradiotherapy, surgery can be feasible with acceptable mortality but increased morbidity. Accurate cardiopulmonary evaluation before surgery and standard operative techniques with protection of bronchial stump or anastomosis can contribute to a reduced complication rate with this intensive approach. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Locally advanced lung cancer; Induction chemoradiotherapy; Postoperative morbidity; Postoperative mortality

1. Introduction

Lung cancer remains one of the most common malignancies among men and women in Europe [1]. Long-term prognosis for this disease is generally poor, with an overall five-year survival rate of less than 15% [2]. In non-small cell lung cancer (NSCLC), the main curative therapeutic approach is surgery for early disease stages IA to IIB. However, these early stages constitute only a minority (20–25%) of all NSCLC patients, whereas the majority of patients initially present with locally advanced stages IIIA and IIIB or even with metastasized disease. Only few patients of stage III are today remaining as accepted indications for surgery alone [3,4]. This includes a small subset of patients with minimal disease in mediastinal nodes – so-called minimal N2-disease – with only one or two nodes microscopically involved. It is also widely accepted that some subgroups of T4-disease can be potential candidates for surgical approaches (T4-carina, T4-satellite nodes), while others are generally not considered for any inclusion of surgery (T4-malignant pleural effusion) [5,6]. In the vast majority of stage III patients upfront surgery is no longer

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appropriate due to early locoregional or/and systemic relapse. Therefore, treatment that includes a combination of local and systemic modalities has become a popular approach, and several investigators have tested the value of different induction strategies in extended phase II trials and a small number of randomized trials [7,8]. Chemotherapy or chemoradiotherapy are used to downstage tumors and render them completely resectable [9,10]. Even if response rates between 60 and 70% have been reported, the randomized trials were based on too small patient numbers so that patient heterogeneity of the staged groups makes interpretation of published phase II and phase III trials data rather difficult. Additionally, certain studies suggest postoperative risks with an increase of morbidity and mortality after induction therapy as compared to historical groups.

The aim of this monoinstitutional study was to evaluate the frequency and risk of postoperative cardiopulmonary and bronchial complications in patients with locally advanced lung cancer following induction chemoradiotherapy and definitive surgery.

2. Material and methods

Between March 1991 and December 2000 all patients with lung cancer who underwent elective thoracotomy after induction chemoradiotherapy at the Ruhrlandklinik, Essen were retrospectively reviewed. There were 350 patients (245 men and 105 women) treated in the course of two phase II and one phase III studies with preoperative chemotherapy (three cycles of split-dose cisplatin 60 mg/m2 days 1,7 and etoposide 150 mg/m2 days 3,4,5 in 261 patients and cisplatin 50 mg/m2 days 1,8 and paclitaxel 175 mg/m2 day 1 in 89 patients) followed in all 350 patients by concurrent chemoradiotherapy (one cycle cisplatin 50 mg/m2 days 2.9 and etoposide 100 mg/m2 days 4,5,6 combined with 45 Gy hyperfractionated accelerated radiotherapy to the primary tumor and mediastinal nodes). Furthermore, from 1993 onwards all patients were routinely offered a prophylactic cranial irradiation of 30 Gy in 2-Gy fractions given over 3 weeks (‘PCI’). Median age of the patients was 56 ± 9 (range 28–74 years), Karnofsky status [11] was 79 ± 9% (range 60–100%). Two hundred and seventy-eight (79%) patients had NSCLC (154 stage IIIA and 124 IIIB) and 72 (21%) SCLC (12 stage II/A/B, 35 stage IIIA and 25 stage IIIB). All 350 patients had been staged by cervical mediastinoscopy before induction treatment; for those with initially proven positive mediastinal nodes repeat mediastinoscopy was performed before surgery. Patients with NSCLC still having contralateral nodes involved at repeat mediastinoscopy were excluded from surgery. Also were excluded all patients with SCLC and remaining positive ipsilateral or contralateral nodes. Additional to staging investigations, to rule out metastasis patients underwent a preoperative cardiovascular risk assessment including cardiopulmonary function testing. Patients were ineligible due to a predicted postoperative forced expiratory volume at 1 s of less than 1 liter (quantitative ventilation–perfusion lung scanning), cardiac infarction or unstable angina pectoris in the 6 months before study entry or cardiac failure of class III or greater (NYHA criteria). If re-evaluation showed continuing medical/functional operability patients were taken to thoracotomy 3–5 weeks following the end of radiation treatment.

Two hundred and six (59%) patients had a right-sided and 144 (41%) a left-sided thoracotomy; the operative time was 171 ± 49 min (range 28–342 min). Fourteen patients (4%) had an exploration only. The causes were infiltration of esophagus (n = 2), trachea (n = 1) and heart (n = 1) on the right and aortic arch (n = 4), pulmonary truncus (n = 4) and heart (n = 2) on the left side. Resections included 58 pneumonectomies on the right and 67 on the left side (35%), 15 bilobectomies (4.3%), 32 sleeve lobectomies on the right and five on the left side (11%), 103 lobectomies on the right and 54 on the left side (45%), two left-sided segmentectomies (0.6%). Additional to pulmonary resection, a resection of pericardium in 84 patients (24%), parietal pleura in 79 (23%), chest wall in 32 (9.1%), left atrium in 24 (6.8%), diaphragma in 12 (3.4%), carina in five (1.4%), aortic adventitia and esophageal muscle in four patients each (1.1%), superior vena cava and vertebral body in two patients each (0.6%) and the subclavian vessels in one patient (0.3%) was necessary. Lymphadenectomy included interlobar, hilar and ipsilateral mediastinal nodes. Contralateral nodes were usually not resected.

Bronchial stump was closed hand-sutured in all patients. We used the Overholt technique both after lobectomy/bi-lobectomy and after pneumonectomy. From 1996 onwards the bronchial stump after pneumonectomy was routinely sutured with 2-0 monofilament, nonabsorbable continuous horizontal mattress suture, running the length of the stump. After water testing with a pressure of 40 cm H2O, a second layer with four or five single sutures was followed. From 1993 we started to reinforce individually, and from 1996 obligatorily, the bronchial stump with viable tissue. In patients after pneumonectomy a reinforcement was performed with intercostal muscle flap (n = 8), diaphragmatic muscle (n = 6) and thymus/mediastinal fat (n = 54). To reduce tissue edema prednisolone 1 mg/kg body weight was given for 3 days starting in the operating room. The blood loss was 360 ml (range 110–1720 ml); overall 114 patients had intraoperatively (n = 22) or postoperatively (n = 92) at least one blood transfusion (median 2.4 U, range 2–9 U).

For the statistical analysis data are presented as the mean ± standard deviation. The primary end points of analysis were rates of complications and mortality. The effect of risk factors on these endpoints were evaluated with univariate analysis first. Categorical variables were analyzed by χ² test. Continuous variables were assessed
with unpaired t-tests, or with Mann–Whitney rank sum test when the data did not fit into a Gaussian distribution. Variables were selected for multivariate analysis if their P-values were less than 0.10 by univariate analysis. Multiple logistic regression was performed for multivariate analysis of risk factors. All tests were two-tailed and performed by Statview version 5.0 statistical software (SAS Institute Inc., Cary, NC). Differences were considered significant with \( P < 0.05 \).

3. Results

The overall hospital mortality rate was 4.9% (\( n = 17 \)) 7.2% after pneumonectomy and 3.8% after lobectomy/bilobectomy. The causes of death were sepsis (\( n = 5 \)), pneumonia and respiratory failure (\( n = 4 \)), adult respiratory distress syndrome (ARDS) (\( n = 3 \)), cardiac failure (\( n = 3 \)) and lung embolism (\( n = 2 \)). Univariate analysis demonstrated that increased age (\( P = 0.03 \)) and lower Karnofsky status (\( P < 0.0001 \)) adversely affected incidence of mortality. Multivariate analysis identified lower Karnofsky status (\( P = 0.0008 \)) to be a significant risk factor for mortality. There was no significant difference (\( \chi^2 \) test) in regard to the side (12 right and five left \( P = 0.35 \)), to the type of resection (nine pneumonectomies and eight lobectomies \( P = 0.66 \)), also to the amount of blood transfusion (\( P = 0.25 \)).

One hundred and fifty-four patients (44%) developed one or more early or late complications (Fig. 1). The most common complications were arrhythmia, in 45 patients (13%), air leakage longer than 7 days in 34 (16% after lobectomy/bilobectomy), pneumonia in 18 (5.1%), atelectasis with more than one bronchoscopic intervention in 15 (4.3%) and septic complication as bronchopleural fistula (BPF) in 14 (4.1%), and empyema without BPF in six (1.7%). Arrhythmias occurred in all patients within the first 72 h and were treated with digoxin and verapamil. Abnormal findings in echocardiography prior to surgery were a risk factor for postoperative arrhythmia with statistical significance (\( P < 0.0001 \)). Air leakage from lung parenchyma was more common than in historical controls without induction therapy and resulted in a longer hospital stay, 16 ± 10 days (range 7–163 days). The fact that 94% of the patients were smokers before induction therapy and an unknown number of them during the chemoradiotherapy resulted in postoperative complications such as pneumonia and atelectasis with mucus retention requiring bronchoscopy. We observed 18 cases of postoperative pneumonia, four of them with fatal outcome. Univariate and multivariate analysis identified increased age (\( P = 0.0005 \), \( P < 0.0001 \)) and a lower Karnofsky status (\( P = 0.032 \), \( P < 0.0001 \)) to be significant risk factors for postoperative pneumonia. There was no statistical difference between right- and left-sided thoracotomies and between pneumonectomy and lobectomy. Postoperative bleeding requiring rethoracotomy occurred in nine patients, five after lobectomy and four after pneumonectomy. The cause was found only in four cases (one bronchial, two intercostal and one esophageal artery bleeding, respectively); in the remaining five patients hemotherax developed following diffuse bleeding after extended adhesiolysis.

Bronchopleural fistulas occurred within 6–28 days after resection in 14 patients, ten after pneumonectomy (8%), eight on the right (6.4%) and two on the left side (1.6), and four after lower lobectomy (1.9%), two on each side. Statistical analysis (\( \chi^2 \) test) showed that only the stump-covering technique employing with viable tissue prevented development of BPF with statistical significance (\( P = 0.026 \)) (Table 1). BPF resulted in sepsis and death of five patients, four after pneumonectomy and one after lobectomy. Our attempt to close the fistula with diaphragmatic muscle (\( n = 2 \)) or intercostal muscle (\( n = 3 \)) was of short success duration, so that open thoracostomy was necessary in all cases. Nine patients who survived this complication were definitively treated by partial thoraco-plasty in combination with muscle latissimus dorsi transposition. Empyema without BPF was observed in six patients, four after lobectomy and one each after bilobectomy and pneumonectomy, respectively. Thoracoscopic debridement

Table 1

<table>
<thead>
<tr>
<th>Risk factors affecting occurrence of bronchopleural fistula (BPF)⁳</th>
<th>Yes</th>
<th>No</th>
<th>( P )-value</th>
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<td>Karnofsky status</td>
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<td>80 ± 10</td>
<td>0.034*</td>
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<td>( \chi^2 ) test</td>
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<td>Stump reinforcement vs. BPF</td>
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<td>Multivariate logistic regression analysis</td>
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<tr>
<td>Karnofsky status</td>
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<td>1.007–1.133</td>
<td>0.028*</td>
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<tr>
<td>Stump reinforcement</td>
<td>0.102</td>
<td>0.012–0.832</td>
<td>0.033*</td>
</tr>
</tbody>
</table>

⁴ CI, confidence interval. *Statistically significant. 
⁵ Unpaired t-test, Mann–Whitney test (for Karnofsky status).
was performed and a chest tube was placed, followed by daily irrigation with 1000 ml saline solution.

4. Discussion

Preoperative treatment strategies with chemotherapy or combinations of chemotherapy and radiotherapy are used to downstage locally advanced lung cancer stages IIIA and IIIB and render patients completely resectable. There is a fairly compelling evidence that multimodality treatment offers a clear survival benefit for these patients groups [12–15]. In all these promising reports increased morbidity and mortality rates were observed especially in patients following pneumonectomy, suggesting a higher risk after induction treatment [16–18]. Fowler et al. [16] reported in a small series of 13 patients a perioperative mortality rate of 23% for all patients and of 43% for those after pneumonectomy. Fowler’s group used an aggressive protocol with high dose of concomitant thoracic irradiation of 60 Gy. Abolhoda et al. [17] found that right-sided pneumonectomy was the only predictor of postoperative mortality in a large series of 471 patients. Doddoli et al. [18] reported an ‘in hospital mortality’ of 9% for all patients and 14% for those with right-sided pneumonectomy, based on pulmonary complications in all cases. Contrary to these reports other groups observed lower mortality rates of 5.7% (only after lobectomy) [19] and 5.3% (mainly after pneumonectomy) [20]. In our large investigated series overall hospital mortality rate was 4.9%, 7.2% after pneumonectomy, 12% for the right side and 2.9% for the left side, without significant statistical difference. Even if our patients had a chemoradiotherapy before resection, the mortality of 7.2% after pneumonectomy compares favorably with reports from surgery only approaches in stages IIIA/IIIB under standard conditions [21]. The mortality rate for lobectomy was found to be 3.8%; a comparison with other reports is difficult, because statistical analysis and the number of extended resections in addition to lobectomy vary widely between investigations. The causes of deaths were predominantly septic complications due to BPF and respiratory failure, pneumonia and ARDS. Risk factors such as patient’s age and performance status both leading to a significantly higher incidence of postoperative death must be considered for patient selection before surgery.

Patients who require pulmonary resection for lung cancer often present with chronic obstructive or and cardiopulmonary disease, so that pulmonary and cardiovascular complications were in our series the most frequent ones and accounted for 90% of all complications. Even if smokers and patients with chronic obstructive lung disease participated in an intensive training and inhalative treatment with bronchodilators prior to surgery, complications such as pneumonia and atelectasis requiring bronchoscopic intervention were common. Comparable to other series [18], we found that the incidence of pneumonia is related to the performance status and the age of patients with statistical significance.

Despite meticulous preparation of interlobar fissure or adhesiolysis, the incidence of air leakage after lobectomy or bilobectomy was higher compared with historical collectives without induction, probably related to the tissue damage induced by radiotherapy. Also, changes in the structure of interlobar and hilar nodes after chemoradiotherapy, especially in patients with SCLC, resulted in lung parenchyma injury during their removal with prolonged postoperative air leakage. The hospital stay of 16 days compares well with that published by other authors [22].

Arrhythmias occurred in 13% of all patients and in 27% of those after pneumonectomy. Because of known toxicity of some chemotherapeutic drugs and radiotherapy to myocardium, all patients were investigated before surgery with echocardiography and in case of abnormal findings with stress electrocardiogram. We found that pathological echocardiography was a significant risk factor for development of postoperative arrhythmia.

Even if our induction protocol included a preoperative chemoradiotherapy for all patients, the incidence of BPF of 4.1% compares favorably with that reported by others [16,18,23,24]. We suppose that aggressive lymph node resection with removal of the surrounding fat tissue and devitalization of peribronchial tissue in addition to a high dose of radiotherapy of more than 45 Gy are important factors favoring bronchial fistulas. We decided in our protocols to give all patients a standard dose of radiation of 45 Gy (1.5 Gy b.i.d. fractionation) and we tried to preserve peribronchial and peritracheal tissue as far as possible. Lymphadenectomy was performed only ipsilaterally, and patients still having N3-disease proven with repeat mediastinoscopy were excluded from definitive surgery. Finally, the analysis of our data identified that the bronchial stump-covering technique is a highly effective procedure to prevent BPF with statistical significance. The use of pleura tissue, pericardium, intercostal muscle, serratus anterior muscle, latisimus dorsi muscle and omentum has been reported [18,23]. In our previous experience with standard resections without induction treatment, pleural flaps showed an insufficient blood supply and necrosis, intercostal muscle developed differently from patient to patient and sometimes mobilization of two intercostal spaces was necessary to adequately cover the bronchial stump. However, calcification of the intercostal muscle was observed in X-rays and chest computed tomography scans 3–6 months after the operation, so that we cannot recommend it as the tissue of first choice. To reinforce bronchial stump after pneumonectomy we favor the use of a flap of mediastinal fat/thymus tissue. The blood supply from the pericardiophrenic artery is excellent and the tissue volume usually sufficient. In a prospective study with 50 patients after preoperative chemoradiotherapy and pneumonectomy, a normal bronchial healing was observed in all cases without BPF.

Reintervention due to postoperative bleeding was
observed in 2.6% of the cases. We tend to reoperate the patients as early as possible so that further complications can be reduced. Statistical analysis showed that postoperative bleeding rates did not affect the morbidity and mortality.

5. Conclusion

Our analysis demonstrates that in patients with locally advanced lung cancer and induction chemoradiotherapy, surgery can be feasible with acceptable mortality but increased morbidity rates. Patient selection for surgery after accurate cardiopulmonary evaluation and standard operative techniques with reinforcement of the bronchial stump or anastomosis with sufficient tissue can contribute to a significantly reduced complication rate.

References


Appendix A. Conference discussion

Dr H. Toomes (Stuttgart, Germany): I want to ask about your policy nowadays in the treatment of advanced non-small cell lung cancer. Do you operate primarily in stage III, IV or N2 or are all these patients treated with neoadjuvant therapy?

Dr Stamatis: I do not have the results, the final results from the randomized study IIB/B disease, but generally the trend for the center is to perform a multimodality treatment in these cases. That means in T3, T4 and N3 disease. For N2 disease, I think the answer is open.
**Dr T. Dosios (Athens, Greece)**: You said that you operate on N3 patients. What are the results of this subgroup of patients? What is the 5-year survival of them?

**Dr Stamatis**: We published these results 2 years ago, especially for N3 disease. It is an 18% 5-year survival for a selected group of patients.

**Dr Dosios**: Also, another question about T4. Are there are patients with pleural effusion or pleural spread which are included in T4? Do you have 5-year survivors in this subgroup of patients?

**Dr Stamatis**: No. In this protocol patients with pleural effusion were excluded.

**Dr W. Budach (Tuebingen, Germany)**: Did you check whether the time of operation after the neo-adjuvant treatment does make a difference in terms of morbidity?

**Dr Stamatis**: We have not compared groups between different times, but I think the best time to operate on these patients is between the fourth and the sixth week after finishing their radiotherapy.