Factors affecting long-term survival after en-bloc resection of lung cancer invading the chest wall

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Abstract

Objective: Several reports emphasize the importance of en-bloc resection as the optimal surgical treatment of lung cancer with chest wall invasion. We investigated possible factors which could affect long-term survival following radical resection of these tumors. Methods: Between 1981 and 1998, 100 patients (90 male; ten female), with a median age of 60 years (36–84), underwent radical en-bloc resection of non-small cell lung cancer (NSCLC) with chest wall involvement. Patients with superior sulcus tumors invading the thoracic inlet were excluded from this series. There were 43 squamous and 57 non-squamous tumors. The median number of resected ribs was three (1–5). Lung resection included 73 lobectomies, two bilobectomies, 18 pneumonectomies and seven segmentectomies. Chest wall resection also extended to the sternum in one patient, the transverse process in one, the costotransverse foramen and hemivertebrae in two. All patients had a complete resection. Sixty-three patients received postoperative radiotherapy and 12 received chemotherapy. Histological data, including differentiation and depth of chest wall invasion, were carefully reviewed. The effect of various factors on survival were studied. Results: There were four in-hospital deaths. Lymph node involvement was negative on surgical specimens in 65 patients, and 28 patients had positive N1 nodes; the final histology revealed seven N2 diseases. Chest wall invasion was limited to the parietal pleura in 29 patients and included intercostal muscles, bones and extrathoracic muscles in 67, 24 and seven cases, respectively. The overall 2-year survival rate was 41%. The 5-year survival for patients with N0, N1 and N2 disease was 22, 9 and 0%, respectively. A local recurrence occurred in 13 patients, with four having a new resection and 45 patients developing systemic metastases. The nodal status (N0±1 vs. N2; \(P \approx 0.02\)) and the number of resected ribs (<2 vs. \(\geq 2; P = 0.03\)) were survival predictors in univariate analysis. By multivariate analysis, the two independent factors affecting long-term survival were the histological differentiation (well vs. poorly differentiated; \(P = 0.01\)) and the depth of chest wall invasion (parietal pleura vs. others; \(P = 0.024\)). Conclusions: Histological differentiation and depth of chest wall involvement were the main factors affecting long-term survival in this series. The role of induction chemotherapy for tumors with poor prognosis should be investigated.

Keywords: Lung cancer; Chest wall involvement; En-bloc resection; Nodal status; Histological differentiation; Long-term survival

1. Introduction

Between 2 and 8% of patients undergoing resection for non-small cell lung cancer (NSCLC) have direct involvement of the chest wall [1]. Lung cancer with chest wall invasion is considered potentially resectable since a 5-year survival of 15 to 30% may be anticipated [2]. The likelihood for an ultimate cure can be expected for patients without N2 disease and in whom a complete resection can be accomplished.

Several reports emphasize the importance of an en-bloc resection of the lung and chest wall as the optimal surgical treatment in order to prevent tumor spillage [3,4]. In the present study, we investigated possible factors, which could affect the long-term survival following radical resection of these tumors.

2. Patients and methods

Between 1981 and 1998, 100 patients (90 men; ten women), with a median age of 60 years (range, 36–84), underwent radical en-bloc resection of lung cancer with
chest wall involvement. Patients with superior sulcus tumors invading the thoracic inlet were excluded from this series, because their pathological process have different clinical and therapeutic implications [5].

2.1. Preoperative assessment

Every patient had a bronchoscopy. An endobronchial lesion was present in 31 cases. Chest pain was the most common symptom and occurred in 62 patients.

The precise location of the tumor and the extent of suspected chest wall involvement were assessed by computed tomography scan. The tumors were on the right side in 60 cases and on the left in 40. They were located on the posterior part of the chest wall in 66 cases, on the lateral in 23, and on the anterior in 11. There was rib destruction noted on the chest X-ray in five patients. Mediastinoscopy, performed in ten patients for the elimination of N2 disease, was negative in every case. An increased carcinoembryonic antigen (ACE) blood level was observed in 35 patients. A CT scan of the brain was systematically done, and none of these patients had extrathoracic metastases at the time of evaluation. Pulmonary function tests and quantitative perfusion lung scans were routinely done to assess the patient’s ability to withstand operation. The forced expiratory volume in 1 s was above 70% of the theoretical value in 85 patients.

2.2. Operative procedure

As a rule, tumors were approached through a standard posterolateral thoracotomy. For posterior and superior chest wall involvement, the vertical incision was extended to the C7 spinous process; the scapula was then fully mobilized from the chest wall and retracted upward. A lateral approach was performed in only two cases of anterior tumors; an additional posterior midline approach was necessary for vertebral resection in two cases.

After the thorax was entered and the cancer was found by the naked eye to be invading at least the parietal pleura, a wide en-bloc resection of the chest wall with attached lung was performed, without any extrapleural dissection. Resection of the involved ribs with the related intercostal muscles included one segment of intact rib above and below the gross margin of the tumor, and if possible, at least 3 cm laterally. The median number of resected ribs was 3, with a range of 1–5 in this series (Table 1).

The resected portion of the chest wall attached to the lung was then dropped into the pleural cavity and the pulmonary resection performed. Lung resection included 72 lobectomies (upper, 67; lower, five), two bilobectomies and one sleeve upper lobectomy. Eighteen pneumonectomies were performed for tumors of the upper (n = 17) or lower (n = 1) lobe. Indication of pneumonectomy was required mostly for large tumors, because of a proximal pulmonary arterial invasion or a hilar nodal involvement. Three segmentections and four wedge resections were done for patients with a peripheral tumor and poor respiratory function.

Chest wall resection also extended to the superior vena cava in one patient, to the sternum in one and the transverse process in one. In two cases, the intervertebral foramen was involved, and required resection of three hemivertebrae followed by spinal fixation through a combined median posterior approach. Resection included the lower root of the brachial plexus in five patients. Frozen histology sections were done in every case and only concerned the soft tissue margins. All patients had a complete resection. At thoracotomy, we performed nodal dissection of all visible nodes and sampling, but not a routine extensive mediastinal lymphadenectomy.

The majority of patients had no chest wall reconstruction. In seven cases of large anterior or lateral chest wall defect, reconstruction was done with prosthetic material, using Marlex Mesh in three patients, Polyglactin in three and polytetrafluoroethylene in one. Muscle transpositions (one latissimus dorsi, one pectoralis major) were associated in two cases.

2.3. Pathology

There were 43 squamous cell carcinomas and 57 non-squamous tumors (43 adenocarcinomas, 13 undifferentiated and one sarcomatoid). Histological features were carefully reviewed at the time of the study with emphasis on the differentiation and the depth of chest wall invasion.

2.4. Adjuvant therapy

Preoperative chemotherapy was given to six patients and radiotherapy to two, with large tumors. Postoperative radiotherapy was administered to 63 patients, including the borders of the resected chest wall in 50 and both the chest wall and mediastinum in 13. Although there were no strict criteria, adjuvant radiotherapy was given in cases with large tumors. Radiotherapy was also given to patients with close margins of the resected chest wall and for patients with proximal N1 or N2 diseases. In recent years, postoperative chemotherapy alone was given to six patients, and six others received both radiotherapy and chemotherapy, based on the high grading of the tumor.

2.5. Statistical analysis

Survival was calculated from the date of surgery until...
death or the date of last follow-up. Only two patients were lost in the follow-up. Survival was estimated by the Kaplan–Meier product-limit method [6]. The effect of various factors on survival was evaluated via the log rank test, for univariate analysis, and by Cox’s proportional hazards step-wise model [7], for multivariate analysis. The a priori level of significance was 0.05.

3. Results

3.1. Mortality and morbidity

There were four in-hospital deaths (4%) in this series; two patients died of pneumonia (one after a pneumonectomy and one after a lobectomy), one patient died after a reoperation for an acute bowel obstruction following a lobectomy, and one as a result of a cerebral vascular accident after a pneumonectomy. There was a 5% incidence of prolonged air leak. Pneumonia developed in two patients. There were two wound infections, one empyema, one chylothorax, one pulmonary embolism and one myocardial infarction. Three patients developed a bronchopleural fistula in the follow-up (two after a pneumonectomy and one after a lobectomy). All required surgery.

3.2. Pathology

The average maximum diameter of the tumor was 6.2 cm. Lymph nodes were negative on surgical specimens in 65 patients; 28 patients had positive N1 nodes (lobar, n = 20; hilar, n = 8), and seven patients had N2 disease. The tumors were well differentiated in 37 cases, poorly in 50 (among them, one was sarcomatoid) and undifferentiated in 13. The chest wall margins were confirmed histologically to be tumor free in all patients except one, but they were close (<2 mm) in six patients.

Histological invasion of the parietal pleura was documented in all patients. Chest wall invasion was limited to the parietal pleura in 29 cases; in the other cases, the tumor extended through the parietal pleura and included the intercostal muscles in 67 cases, the bone of at least one rib in 24, and extrathoracic muscles in seven.

3.3. Recurrence

Recurrence occurred in 58 patients in the follow-up, with a median interval of 10 months (range, 1–95). Local recurrence occurred in 13 patients. The primary tumor was large (>10 cm) in five cases; it was located on the posterior part of the chest wall in nine cases, and among them, the chest wall margins were read as close in six. The patient with a positive margin survived 18 months. Four patients underwent a chest wall re-section with completion pneumonectomy in three cases. Forty-five patients developed systemic metastases (brain, n = 17; hepatic, n = 4; lung, n = 5; bone, n = 4; adrenal, n = 2; others, n = 6; and multiple lesions, n = 7).

3.4. Survival

With a median survival of 18 months (range, 1–144), the 2-year survival rate was 41% and the 5-year survival rate was 18%. No difference was observed between the two groups of patients who had either a lobectomy or a pneumonectomy.

The 5-year survival for patients with N0 and patients with N1 was 22 and 9%, respectively. The seven patients with N2 disease survived between 4 and 37 months (Fig. 1). There was no significant difference between the two groups of N0 and N1 patients. The survival in both those groups was significantly better than in patients with N2 disease (P = 0.026). Postoperative adjuvant radiotherapy had no effect on survival. Adjuvant chemotherapy, used in 12 patients, had no apparent effect on survival. Cell type, tumor size and age were not found to influence survival significantly. The number of resected ribs (<2 vs. >2; P = 0.03) was a survival predictor. The long-term survival was significantly greater for patients having a well differentiated tumor than for those with a poorly differentiated or undifferentiated one (P = 0.005). Extension to the parietal pleura only was associated with a significant increase in long-term survival when compared with deeper involvement (intercostal muscles, bone and extrathoracic muscles; P = 0.02). The histological differentiation and the depth of chest wall invasion were found to be two independent factors affecting long-term survival by multivariate analysis (Table 2).

<table>
<thead>
<tr>
<th>Factors influencing survival</th>
<th>p Univariate analysis</th>
<th>p Multivariate analysis</th>
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<tbody>
<tr>
<td>Number of resected ribs (&lt;2 vs. &gt;2)</td>
<td>0.03</td>
<td>NS</td>
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<tr>
<td>pNodal (N0–1 vs. 2)</td>
<td>0.026</td>
<td>NS</td>
</tr>
<tr>
<td>Histological differentiation (well vs. poorly)</td>
<td>0.005</td>
<td>0.01</td>
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<tr>
<td>Chest wall invasion (parietal pleura vs. others)</td>
<td>0.02</td>
<td>0.024</td>
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Fig. 1. Survival by lymph node involvement.
4. Discussion

The goal of surgery for lung cancer with chest wall invasion is to completely resect the primary tumor with clear surgical margins. The importance of performing a complete resection is stressed by the absence of 2.5-year survivors among incompletely resected (macro- or microscopic residual disease) patients [8].

Controversy still exists over the management of a tumor found at operation to be only adherent to the parietal pleura. McCaughan [8] showed that extrapleural mobilization was sufficient for a significant number of patients whose tumors invaded the parietal pleura only. On the other hand, Albertucci and associates [9] reported a high incidence of histological evidence of tumor at the margins of the resection after extrapleural dissection and a high incidence of local tumor recurrence. We believe that when a lung cancer invades at least the parietal pleura, a wide resection of the chest wall with attached lung should be performed. To prevent tumor spillage, the entire tumor-bearing area should be resected en bloc [3,4]. It is frequently easier to initially do the chest wall resection and then proceed with the appropriate pulmonary resection. For large involvements, however, it can be easier to do a wedge excision of the tumor-bearing area with a mechanical stapler first, and resect the remainder of the collapsed lobe later. As a rule, a lobectomy or a pneumonectomy is done, the parenchymal resection being limited to a wedge excision or a segmentectomy for patients with poor respiratory function.

In our series, a large chest wall resection was performed in many patients, with a median number of resected ribs being 3. However, there were six patients who had close margins of a posterior lesion and all of them developed a local recurrence. The posterior limit of a radical chest wall resection is the vertebral involvement. Until recently, lung cancer, mostly apical tumors, with direct invasion of the costovertebral angle or the vertebral body, have been considered inoperable. We still believe that massive vertebral invasion or intraspinal extension represent a surgical contra-indication. However, encouraged by the results obtained by DeMeester and colleagues [10] from tangential vertebral resections, we have undertaken vertebral resection for superior sulcus tumors invading the thoracic inlet extended into the intervertebral foramen [11]. We thus performed hemivertebrectomies with reconstructive vertebral fixation, to obtain free margins in two cases in this series. Both these patients died of systemic metastases 9 and 10 months postoperatively. The benefit of such major resection is not yet clear, although long-term survival can be obtained.

Chest wall reconstruction was performed in only seven patients. As in other reports [3,4], the majority of patients did not require prosthetic reconstruction. Most defects are covered by the scapula and the muscles. Large defects, especially when located at the anterolateral aspects of the ribs, may require prosthetic replacement in order to limit paradoxical chest wall motion. Reconstruction can be accomplished using materials like Marlex-mesh or a Gore-Tex patch, and reinforced with a muscle flap [12,13]. The risks of infection should be balanced against the cosmetic and functional benefits of prosthetic replacement.

Our mortality rate was low and compared favorably with those of others [4,14,15]. It might be related to improvements in the perioperative management with a careful patient selection. The incidence of pneumonia, which led to death in two cases, can be explained by a prolonged mechanical ventilation after extended chest wall resection.

After radical resection of lung cancer with chest wall invasion, 5-year survival rates of 15–40% have been reported in the literature [4,15,16]. The long-term survival is predominantly influenced by the completeness of the resection and by the nodal status [17]. None of our seven patients with N2 disease survived beyond 37 months. Most series report no 5-year survivor with positive N2 compared with 5-year survivals from 22 to 56% for N0 patients [3,4,15,16]. A majority of our patients had no lymph node involvement on surgical specimens with a 5-year survival of only 22%. A complete mediastinal lymph node dissection at thoracotomy might have modified the nodal status considering that some N0 and N1 patients could have been understaged N2 diseases. However, some patients in this series underwent primary radical resection taking into account pain relief and without strict preoperative nodal staging. We would now advocate routine mediastinoscopy for patients with lung cancer and chest wall involvement. Those with N2 disease should only be considered for operation as part of a protocol with other modalities of treatment.

The histological differentiation was found to be a major survival predictor in this series, which included a majority of poorly differentiated tumors, and this aspect had not been outlined in other reports. The depth of chest wall invasion was an important survival predictor. Extension to the parietal pleura only was observed in only 29% of our patients and was associated with a significant increase in 5-year survival. Seventy-one patients proved to have invasion beyond the parietal pleura.

Deeper involvements impair the prognosis and this is in accord with a previous report [18]. Since only an accurate histological study of the resected chest wall can prove the integrity of the intercostal muscles, this is therefore another strong argument for en-bloc chest wall resection for all tumors invading at least the parietal pleura. Among various other factors which could affect survival, the extension of the resected chest wall, and not the tumor size, was significant; this suggests a better prognosis for those with a smaller chest wall involvement. A relationship between age and survival, predicting a better prognosis in selected groups of patients younger than 60 has been reported [3]. We did observe as expected, a lower morbidity in younger patients, but age did not significantly influence survival in our series.

The role of adjuvant therapy for tumors invading the chest wall remains undefined. Postoperative radiotherapy had been used for nearly 2/3 of our patients, but appeared
to have no effect on survival as previously reported [3,14,15]. Currently, radiotherapy is proposed to reduce the incidence of local recurrence [19], and should be reserved for patients with close surgical margins, or those with hilar or mediastinal nodal involvement. Adjuvant chemotherapy had no apparent effect on survival, but the number of patients was too small to obtain statistically meaningful data.

In our experience, if compared with other potentially resectable locally advanced NSCLC, including superior sulcus tumors invading the thoracic inlet [11], radical resection of lung cancer with chest wall involvement was associated with the lowest long-term survival rate. In the present study, despite aggressive surgical management, many patients progressed rapidly to distant metastatic disease.

We conclude that en-bloc resection of lung cancer invading the chest wall can be done with a low mortality. The factors affecting long-term survival after a complete resection were the extension of resected chest wall, nodal status, and mainly the histological differentiation and depth of chest wall involvement. For tumors with a poor prognosis, this report suggests that the role of induction chemotherapy needs further evaluation.

References


Appendix A. Conference discussion

Dr S. Mattioli (Bologna, Italy): My question relates to the partial resection of the vertebrae, a hemivertebrectomy. In the two cases you presented, did you achieve free margins in the bone?

Dr Chapelier: Yes, we obtained free margins on the surgical specimen in these two cases of vertebral resection. We performed hemivertebrectomies with reconstructive vertebral fixation, using the same technique we have now experienced in 16 cases of superior sulcus tumors invading the thoracic inlet and extended into the intervertebral foramen.

In our early experience, some patients in this series, with posterior tumors close to the costotransversal angle, could have been probably treated by vertebral resection with wide free margins.

Dr P. Vadocz (Budapest, Hungary): What is your proposal and experience with irradiation prior to surgery?

Dr Chapelier: As you have seen, we have only done in two cases, of large tumors.

Mr P. Goldstraw (London, UK): Your 5-year survival for T3, N0 is disappointing, it was only 24%, whereas most people, including ourselves, have achieved 50 or 55% 5-year survival. Equally, your incidence of N2 disease is very low. You had only 7% of N2 disease, and again, we are finding that despite extensive, if selective, use of mediastinoscopy, we are getting about 20% N2 disease. These two factors lead me to ask whether you were perhaps underestimating the proportion of N2 disease. Did you undertake systematic nodal dissection at thoracotomy?

Dr Chapelier: Literature shows survival between 20 and 56% for N0 disease. In this series, we did not systematically undertake a complete mediastinal lymph node dissection. You are right, we have probably underestimated N2 disease in not doing mediastinoscopy as well. Consequently, our 5-year survival for N0 disease has been probably impaired and we were quite disappointed, reviewing these cases, of this survival.

Dr G. Massard (Strasbourg, France): I would like you to elaborate your thoughts about adjuvant radiotherapy as far as local prognosis is concerned in the T3N0 subset. Do you think that radiotherapy does add anything to local control of the disease following complete resection? And on the opposite, if we consider vital prognosis, and if we remember the results of the PORT meta-analysis reported last summer, would you still recommend adjuvant radiotherapy in the T3N0 subset?

Dr Chapelier: We could say that there is a lack of uniformity of opinion regarding the value of radiotherapy postoperatively. We have done it in the majority of patients, but the question remains, what radiotherapy if you have a very large chest wall resection. On the other hand, if the margins are...
close, you have radiotherapy on the borders of the resected chest wall. We will continue to do radiotherapy for this subset of patients.

**Dr M. Koudieh (Riyadh, Saudi Arabia):** I would just ask you, do you screen your patients for preoperative metastases and which way of screening do you use?

**Dr Chapelier:** Complete screening, and none of these patients had metastases at the time of evaluation.

**Dr Koudieh:** The brain, the bone, everything?

**Dr Chapelier:** A systematic CT scan of the brain.