Results of en bloc resection for bronchogenic carcinoma with chest wall invasion

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Objective: Lung cancer invading the chest wall without lymph node metastasis has recently been downstaged to stage IIb. To validate this reclassification, we reviewed our experience with en bloc lung and chest wall resection for bronchogenic carcinoma.

Methods: From February 1985 to November 1999, 95 en bloc lung and chest wall resections were performed on 94 patients (62 men and 32 women). The median age was 66 years (range, 38-93 years). Pancoast tumors were excluded. Factors that may affect survival were analyzed with univariate analysis, and factors found to be significant univariately were analyzed multivariately to determine whether the significant association remained after adjusting for other significant factors.

Results: Presenting symptoms included chest wall pain in 42 patients, cough in 17 patients, and "other" in 16 patients. Twenty patients were asymptomatic. Ninety-two patients were current or former smokers (median pack-years, 50; range, 8-150 pack-years). Seventy-five lobectomies, 12 pneumonectomies, 5 bilobectomies, 2 wedge excisions, and 1 segmentectomy were performed. The number of ribs resected ranged from 1 to 5 (median, 3). Sixty-one patients required chest wall reconstruction (prostheses in 60 and bovine pericardium in 1). Operative morbidity and mortality were 44.2% and 6.3%, respectively. Sixty-five cancers were classified as T3 N0 M0, 16 as T3 N1 M0, and 14 as T3 N2 M0. Squamous cell carcinoma was present in 56 tumors, adenocarcinoma in 25, large cell carcinoma in 11, and "other" in 3. Follow-up was complete in 86 (96.6%) of 89 operative survivors and ranged from 1 month to 15 years (median, 19 months). Overall 5-year actuarial survival was 38.7%. Five-year survival for patients with stage IIb disease (T3 N0 M0) was 44.3% compared with only 26.3% for those with stage IIIa disease (T3 N1 M0 or T3 N2 M0, $P = .0082$). Women had a better 5-year survival than men (52.9% vs 31.0%, $P = .0122$). The best 5-year survival was observed in women with stage IIb disease (61.2%). All other variables (age, tumor size, histopathology, forced expiratory volume in 1 second, extent of operation, depth of invasion, and adjuvant therapy) did not significantly affect survival.

Conclusions: En bloc resection of lung cancer invading the chest wall is safe but associated with significant morbidity. Long-term survival is stage and sex dependent. The best survival is observed in women who have T3 N0 M0 disease (stage IIb).

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Lung cancer remains the most common cause of cancer deaths in the United States. Unfortunately, most patients have advanced disease at the time of diagnosis and are not candidates for surgical resection. Chest wall invasion historically has been considered unresectable; however, recent studies have demonstrated that invasion does not have an adverse effect on survival if lymph node metastases have not occurred.¹⁻³ As a result, T3 N0 M0 lung cancers invading the chest wall have been downstaged to stage IIb.⁴ To validate the reclassification, we have reviewed our most recent experience with en bloc lung and chest wall resection for lung cancer.

Materials and Methods

Between February 1985 and November 1999, 94 patients underwent 95 en bloc lung and chest wall resections at the Mayo Clinic in Rochester, Minnesota, for bronchogenic carcinoma. During this same period of time, from February 1985 to November 1999, 5666 patients underwent pulmonary resection for bronchogenic carcinoma. Metastatic, T4, and Pancoast tumors were excluded. Medical records were reviewed for patient demographics, preoperative symptoms, pulmonary function, operative procedures, tumor cell type and stage, and survival. Follow-up was obtained by means of office visits, telephone interviews, or both.

Cancers were staged according to the revised international staging system.⁴ The depth of chest wall invasion was grouped into 3 levels on the basis of the pathology report: parietal pleura only; parietal pleura and soft tissue; and parietal pleura, soft tissue, and bone. Survival statistics were performed with the Kaplan-Meier method, with the day of operation as the starting point.⁵ Operative mortality included all deaths within 30 days of operation and those deaths that occurred later but during the same hospitalization. Survival curves were compared with the log-rank test. Factors that affected survival significantly with univariate analysis were analyzed multivariately with the Cox proportional hazards model.⁶

Results

There were 62 men and 32 women in the study. One man had 2 separate operations for different metachronous primary lung cancers, both of which involved the chest wall. Median age was 66 years and ranged from 38 to 93 years. Ninety-two patients were current or former smokers (median, 50 pack-years; range, 8-150 pack-years). Presenting symptoms are shown in Table 1. Chest pain was the most common presenting symptom and occurred in 42 patients. Other symptoms included cough in 17 patients, pneumonia in 5, dyspnea in 4, malaise in 4, and "other" in 3. Twenty patients were asymptomatic.

Rib destruction was observed on chest roentgenography in 12 patients and on chest computed tomography in 17 patients. Pulmonary function tests were available in 88 patients. The median forced expiratory volume in one second (FEV₁) was 2.19 L (range, 0.81-3.8 L). Four patients had severe respiratory impairment (FEV₁ <40%). The me-

TABLE 1. Presenting signs and symptoms

Presenting signs/symptoms	Number of patients
Chest pain	42
Cough	17
Pneumonia	5
Dyspnea	4
Malaise	4
Other	3
Asymptomatic	20

TABLE 2. TNM staging

Stage	TNM stage (4)	No. of tumors
IIb	T3 N0 M0	65
IIla	T3 N1 M0	16
	T3 N2 M0	14

dian percentage of predicted diffusion capacity for carbon monoxide and maximum voluntary ventilation were 74% (range, 36%-119%; n = 67 patients) and 79% (range, 32%-141%; n = 81 patients), respectively. Preoperative radiation therapy was administered to 4 patients, chemotherapy to 2 patients, and both to 3 patients.

Mediastinoscopy was performed in 45 patients and showed no evidence of lymph node metastasis in all patients. A posterolateral thoracotomy approach was used in all patients. A lobectomy was performed for 75 of the tumors, a pneumonectomy for 12, bilobectomies for 5, wedge excision for 2, and segmentectomy for 1. All patients had full-thickness en bloc chest wall resection. Our intraoperative approach for patients who may have chest wall invasion is to open the chest cavity away from the site of attachment and to assess the degree of invasion by means of manual palpation. If the tumor is invading the chest wall, we resect the chest wall with a free margin of approximately 1.0 to 2.0 cm. Extrapleural resections are performed only if there are flimsy adhesions to the chest wall. The median number of ribs resected was 3 and ranged from 1 to 5. No patient had resection of the sternum. All patients had complete mediastinal lymph node dissection. All cancers were completely resected (R0), and the chest wall margins were histologically negative in all patients. The bony chest wall was reconstructed in 61 patients with a polytetrafluoroethylene soft-tissue patch in 60 and a bovine pericardium in 1. Reconstruction of the chest wall was performed if there was a sizable defect that would not be covered by the scapula. This usually meant a defect of at least 4.0 cm in diameter or one on which the tip of the scapula might catch. Nineteen patients received postoperative adjuvant therapy (chemotherapy in 3 patients, radiation therapy in 8, and both in 8).

The TNM classification of the tumors is shown in Table 2. Sixty-five tumors were T3 N0 M0. Depth of invasion was

Figure 1. Actuarial cumulative probability Kaplan-Meier estimates of survival after en bloc lung and chest wall resection. Zero years on the abscissa represents the date of the operation. Numbers in parentheses represent patients at risk.

Figure 2. Actuarial cumulative probability Kaplan-Meier estimates of survival after en bloc lung and chest wall resection compared by postsurgical stage. Zero years on the abscissa represents the date of the operation. Numbers in parentheses represent patients at risk.

TABLE 3. Postoperative complications

Complication	Number of patients
Atrial fibrillation	16
Pneumonia	9
Prolonged air leak	5
Chylothorax	3
Postoperative bleeding	3
Cerebrospinal fluid leak from dural tear	1
Bronchopleural fistula	1
Middle lobe torsion	1

able to be determined in 95 specimens. The depth of invasion was into the parietal pleura only in 29 tumors, the parietal pleura and soft tissue in 43 tumors, and the parietal pleura, soft tissue, and bone in 23 tumors. Lymph node metastases occurred in 30 patients (16 with N1 and 14 with N2 disease). Squamous cell carcinoma was present in 56 cancers, adenocarcinoma in 25, large cell carcinoma in 11, and small cell, undifferentiated, and sarcomatoid carcinoma in 1 each. The median diameter of the tumor was 6.0 cm and ranged from 1.2 to 14.0 cm.

The median hospitalization was 10 days (range, 4-105 days). Forty-two patients had postoperative complications, as shown in Table 3, and included atrial fibrillation in 16, pneumonia in 9, prolonged air leak in 5, chylothorax in 3, postoperative bleeding in 3, a cerebral spinal fluid leak from a dural tear in 1, bronchopleural fistula in 1, and middle lobe torsion in 1. Eleven patients required prolonged mechanical ventilation, 9 of whom required tracheostomy. There were 6 operative deaths (mortality, 6.3%). Cause of death was myocardial infarction in 2 patients and pneumonia, pulmonary emboli, multisystem organ failure caused by sepsis, and a cerebrovascular accident in 1 each. Mortality was 5.3% (4 patients) for lobectomy and 8.3% (1 patient) for

pneumonectomy. Operative mortality was 4.6% (3 patients) for T3 N0 M0 tumors, 6.2% (1 patient) for T3 N1 M0 tumors, and 14.3% (2 patients) for T3 N2 M0 tumors.

Follow-up was complete in 86 (96.6%) of the 89 operative survivors and ranged from 1 month to 15 years (median, 19 months). Twenty-three patients are currently alive. The overall 5-year actuarial survival was 38.7% (95% confidence interval [CI], 29.4%-50.7%; Figure 1). Survival was stage dependent (Figure 2). Five-year survival for patients with stage IIB cancers (T3 N0 M0) was 44.3% (95% CI, 32.9%-59.1%) compared with 26.3% (95% CI, 13.7%-50.5%) for patients with stage IIIa cancers (T3 N1 M0 or T3 N2 M0, $P = .0082$).

Univariate analysis revealed that women had a better 5-year survival than men (Figure 3). The overall 5-year survival for women was 52.9% (95% CI, 37.5%-74.6%) compared with only 31.0% (95% CI, 20.6%-46.0%) for men ($P = .0122$). The best 5-year survival was observed in women with stage IIB disease (61.2%; 95% CI, 42.1%-88.9%). The 5-year survival for men with stage IIB disease was 36.4% (95% CI, 23.8%-54.8%), and that for men with stage IIIa disease was 16.0% (95% CI, 4.8%-54.0%). The 5-year survival for women with stage IIB disease was 61.2% (95% CI, 42.1%-88.9%), and that for women with stage IIIa disease was 38.1% (95% CI, 17.9%-81.1%). Survival varied by depth of invasion. The 5-year survival for tumors that invaded the parietal pleura only was 49.9% (95% CI, 33.6%-74.1%), that for tumors that invaded soft tissue and the parietal pleura was 35.0% (95% CI, 22.6%-53.5%), and that for tumors that invaded bone was 31.6% (95% CI, 15.7%-60.5%; Figure 4). These differences were not statistically significant. Survival was not affected by age, tumor size, cell type, FEV₁, or preoperative or postoperative adjuvant therapy.

Sex remained significantly associated ($P = .008$) with

Figure 3. Actuarial cumulative probability Kaplan-Meier estimates of survival after en bloc lung and chest wall resection compared by sex. Zero years on the abscissa represents the date of the operation. Numbers in parentheses represent patients at risk.

survival after adjusting for stage of disease (risk ratio for male patients was 2.2 times that for female patients; 95% CI, 1.2-3.9). Stage of disease also remained significantly associated ($P = .005$) with survival after adjusting for sex (risk ratio for patients with stage IIIa disease was 2.2 times that of patients with stage IIb disease; 95% CI, 1.3-3.6).

Discussion

Patients with lung cancer and contiguous chest wall invasion represent less than 8% of all patients with primary lung cancer.⁷ Controversy persists regarding optimal treatment of these patients. Historically, lung cancer invading the chest wall was considered unresectable. However, 50 years ago, Coleman⁸ described 2 long-term survivors who underwent en bloc lung and chest wall resection. Since that initial report, there have been several larger series that have demonstrated that survival after en bloc resection approaches that of patients with T2 cancers if lymph node metastases have not occurred.⁹ This observation has resulted in T3 N0 M0 lung cancer being downstaged from IIIa to IIb. This report examines our most recent experience with en bloc lung and chest wall resection for lung cancer and reconfirms the efficacy of resection.

The absence of lymph node metastasis in our study was a significant predictor of long-term survival. Others have reported this similar finding.^{3,7,10} Given the poor 5-year survival and increased morbidity encountered in patients with positive N2 lymph nodes, we would not recommend surgical resection for these patients. They should be treated, however, as part of a clinical trial. Female sex was also a predictor of improved survival. Other reports have demonstrated improved survival in women.¹¹⁻¹⁴ In 1985, our institution reported a 45-year prevalence study of lung cancer in Olmsted County, Minnesota.¹¹ Women had a better 5-year survival for all lung cancer cell types, except small cell

Figure 4. Actuarial cumulative probability Kaplan-Meier estimates of survival after en bloc lung and chest wall resection compared by depth of invasion. Zero years on the abscissa represents the date of operation. Numbers in parentheses represent patients at risk.

carcinoma. When compared by stage, Ouellette and colleagues¹⁴ demonstrated that women lived 12 months longer than men. This finding of prolonged survival in women may be a statistical aberration; however, it is present in 3 separate studies. If it is a real finding, the reasons this occurs are unclear at present and await further examination.

Little information exists regarding adjuvant chemotherapy for lung cancers invading the chest wall. Although preoperative chemotherapy has recently been demonstrated to improve resectability and overall survival in patients with Pancoast tumors,¹⁵ no comparable data exist to suggest that preoperative chemotherapy improves survival for lung cancer invading the chest wall. Radiation therapy has been used more often but still remains controversial. Several studies have analyzed the advantages and disadvantages of radiation therapy administered both preoperatively and postoperatively. The potential benefits of preoperative radiation therapy include improving resectability by downstaging the tumor, reducing the chance for seeding at the time of resection, and reducing the amount of radiation required postoperatively. In 1982, Patterson and associates¹ demonstrated a 5-year survival of 56% for patients receiving radiation therapy postoperatively compared with only 30% for those who did not. However, their results were not statistically significant. More recently, Facciolo and colleagues⁷ observed a 5-year survival of 74.1% after radiation therapy compared with only 46.7% for patients who did not receive radiation therapy ($P = .023$). However, other series, including our previous report, the Massachusetts General Hospital's report, Memorial Sloan-Kettering Cancer Center's report, and a recent series from France have not demonstrated any improvement in survival with the use of radiation therapy.^{2,3,10,16} One report did demonstrate an increased operative mortality with the administration of preoperative radiation therapy.¹⁷

As with other series, complications occurred in nearly half of our patients, and pulmonary and cardiovascular complications accounted for most of these complications.^{7,10} Our operative mortality was 6% and compared favorably with our past experience and that reported by others.^{2,7,10} Prevention of complications is best accomplished by selecting the appropriate procedure for a given patient, meticulous surgical technique, and dedicated perioperative care.

Controversy exists as to whether full-thickness resection is necessary in all patients, especially those with invasion limited to the parietal pleura. Although some investigators have reported that the depth of tumor invasion is a prognostic indicator of survival, both the current study and earlier reports from our institution did not demonstrate that tumor depth was a predictor of survival.^{2,3,10,18} We have previously reported that full-thickness chest wall resection had superior survival results compared with those of extrapleural resections, and therefore our practice has been to perform full-thickness chest wall resections for all depths of lung cancers invading the chest wall.¹⁹ Nonetheless, full-thickness resection for all patients remains controversial.

In summary, en bloc resection of bronchogenic carcinoma invading the chest wall is safe but associated with significant morbidity. Long-term survival is stage and sex dependent. The best survival was observed in women with stage IIb disease.

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Discussion

Dr Eric Vallieres (Seattle, Wash). Over the years, it has become accepted that surgical resection is the key component in the management of most patients with non-small cell lung cancer and direct parietal involvement. Controversies, however, remain as to how extensive a resection should be, on what the place of induction therapy may be, and, if so, what type, and, finally, on what the role of adjuvant therapy may be. Most of us answer these questions on the basis of personal opinions that have evolved over the years, either from reviewing our own experiences with the disease or from reviewing published single-institution series similar to this one from the Mayo Clinic in Rochester. There are no randomized data to answer the questions. The Lung Cancer Study Group attempted a study in the early 1980s that closed prematurely owing to poor accrual, and with only 5% to 8% of all non-small cell lung cancers presenting in this manner, it is unlikely that phase III data will ever be available to guide us.

Your results really compare with previously reported series in terms of operative morbidity, mortality, and survival. This 14-year series of 95 resections has its merits in that it is uniform by spanning an era where computed tomographic assessment was available for all patients. In addition, all patients in this series underwent an en bloc chest wall resection, whatever the depth of parietal invasion was judged to be at exploration. This is, to my knowledge, the third or fourth series on the topic by the Mayo group, which has, over the years, contributed significantly to our knowledge of the problem.

I have the following questions. We know from your and others' experiences that completeness of resection is one of the most important predictors of survival with this group of patients. I note that every patient in this series had an R0 resection. Did you restrict your analysis to R0 resected patients, or did you really consecutively achieve such statistics? If so, what preoperative evaluation allowed you such results?

Second, it is my understanding that since Mayo's review of the topic in 1994 by Vic Trastek, it has been your institutional policy to perform en bloc chest wall resection in all patients and never attempt extrapleural resection, whatever the findings are at explo-

ration. This remains a subject of controversy. How many patients treated along those lines were found pathologically to have T2 disease and would have been excluded from this series, and what happened to these patients?

Third, 43% of your patients presented with pain. Twenty-one percent were asymptomatic. Did pain at presentation affect prognosis? Did pain at presentation correlate with depth of chest wall invasion? Did radiologic bone destruction seen preoperatively in 17 patients imply a worse prognosis?

You described that 34 patients required no chest wall reconstruction and that 61 did. Was there a correlation with the presence or absence of a chest wall reconstruction and the occurrence of acute postoperative respiratory difficulties encountered in 11 patients?

Finally, in your conclusion you have noted that, stage for stage, women have a better prognosis than men for this disease. Were these tumors biologically different? Was molecular evaluation of these lesions performed?

Dr Burkhart. Thank you, Dr Vallieres, for your comments. I will take them in order here.

All of the resections that we included in this study were complete resections (R0). Our standard preoperative radiologic evaluation was computed tomography of the chest and upper abdomen. Patients with incomplete resections because of invasion into the spine were not included in this series.

We prefer a full-thickness chest wall resection on any patient who has a cancer that invades the chest wall. For patients that have loose adhesions from the lung to the chest wall, we would resect the pleura locally for those tumors, but these were T2 tumors and not included in this series.

Pain at presentation did not correlate with long-term survival. We looked at it with univariate analysis, and there was no correlation with survival.

We did not examine whether chest wall reconstruction was associated with a higher rate of respiratory difficulty. My impression is that it was not related.

There was no difference in the stage or histologic types of the cancers between men and women. Two thirds of the women had T3 N0 lesions, and two thirds of the men did. We did not perform any molecular evaluations on these tumors.