

Factors Affecting the Prognosis of non-Small Cell Lung Cancer with Chest Wall / Parietal Pleural Invasion (T3) Following Resection

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ABSTRACT

Chest wall involvement occurs in approximately 5% of all patients with newly diagnosed non-small cell lung cancer (NSCLC). In the absence of metastatic spread, en bloc anatomic surgical resection of the involved lung and chest wall is the primary treatment for most of these patients. The aim of our study was to investigate the possible factors that could affect long-term survival after surgery in a homogenous group of patients affected by NSCLC invading the chest wall/parietal pleura (T3). NSCLC patients with chest wall/ parietal pleural invasion who underwent surgical treatment between February 1996 and December 2005 were included in this study. A total of 50 male patients with a mean age of 60.9 years were included in the study. The follow-up period for these patients was 26.1 months, the median survival was 17.8 months, and the 5-year survival rate was 45.1%. The survival rate was better in patients who underwent a pneumonectomy than a lobectomy, patients with no residual disease than those with residual disease, and patients with complete resection than those with incomplete resection. Operative mortality was 9.6%; 3 (25.0%) pneumonectomy and 2 lobectomy (5.6%). Survival was not affected by age, extrapleural dissection or chest wall resection, size of the tumor, tumor histology and differentiation, invasion of the chest wall or parietal pleura, N status, stage, neoadjuvant therapy, administration of adjuvant therapy, procedure of adjuvant therapy, and dimension of the chest wall.

Surgical resection is an effective treatment in non-small cell lung cancer with chest wall or parietal pleural invasion (T3). The absence of concomitant diseases, pneumonectomy, and complete resection are good prognostic factors.

Keywords: Lung cancer, Parietal pleura, Chest wall, Pneumonectomy, Lobectomy, Complete resection

ÖZET

Göğüs Duvarı / Paryetal Plevra İnvazyonlu (T3) Küçük Hücreli Dışı Akciğer Karsinomunda Rezeksiyon Sonrası Prognozu Etkileyen Faktörler

Göğüs duvarı tutulumu, yeni teşhis konulmuş küçük hücreli dışı akciğer kanser (KHDAK)'li hastaların yaklaşık %5'inde görülmektedir. Metastatik yayılım olmadığında, tutulan akciğerin ve göğüs duvarının anblok anatomik cerrahi rezeksiyonu, hastaların çoğunda primer tedavidir. Çalışmanın amacı, göğüs duvarı / paryetal plevra tutulumu (T3) olan homojen bir grup KHDAK'li hastalarda cerrahi sonrası uzun dönemli yaşam süresini etkileyen muhtemel faktörleri araştırmak idi. Şubat 1996 – Aralık 2005 tarihleri arasında cerrahi tedavi uygulanan, göğüs duvarı/paryetal plevra invazyonlu KHDAK hastaları çalışmaya alındı. Yaş ortalaması 60,9 yıl olan toplam 50 erkek hasta çalışmaya alındı. Takip süresi 26.1 ay, median sağkalım 17.8 ay ve 5 yıllık sağkalım %45.1 idi.

Pnöminektomi yapılanlar lobektomi yapılanlardan, rezidüel hastalığı olmayanlar olanlardan ve komplet rezeksiyon yapılanlar inkomplet olanlardan anlamlı derecede daha iyi sağkalım oranına sahip idi. Operatif mortalite %9,6 idi: 3 (%25) pnöminektomi ve 2 lobektomi (%5,6). Yaş, ekstraplevral diseksiyon veya göğüs duvarı rezeksiyonu, tümör boyutu, tümör histolojisi ve diferansiasyonu, göğüs duvarı veya paryetal plevra invazyonu, N durumu, evre, neoadjuvan tedavi, adjuvan tedavi alıp alınması, adjuvan tedavi yöntemi ve göğüs duvarı rezeksiyon genişliği sağkalımı etkilemedi. Göğüs duvarı veya paryetal plevra invazyonlu (T3) küçük hücreli dışı akciğer kanserinde cerrahi rezeksiyon etkili bir tedavidir. Eş zamanlı bir ek hastalığın olması, pnöminektomi ve komplet rezeksiyon uygulanması iyi prognostik faktörlerdir.

Anahtar Kelimeler: Akciğer kanseri, Paryetal plevra, Göğüs duvarı, Pnöminektomi, Lobektomi, Tam rezeksiyon

INTRODUCTION

Surgery remains the cornerstone of treatment for lung cancer. Invasion of the chest wall is quite common, occurring in 5% to 8% of all patients with resected non-small cell lung cancer (NSCLC).¹⁻³ Despite all of the available investigative tools, the diagnosis of chest wall invasion cannot always be determined pre-operatively. CT scanning is sometimes unable to discriminate between tumor invasion, adhesions, or simple contact between the tumor and the chest wall. Therefore, the likelihood of chest wall invasion must always be taken into account during thoracotomy or thoracoscopy.⁴

Although neoplastic invasion of chest wall has never been considered to be evidence of unresectability, early reports stated a very low long-term survival.¹⁻³ In 1947, Coleman⁵ reported the first important findings regarding the resection of tumors invading the chest wall. The most recent clinical findings since 1985^{1,2,6,7} have revealed an improvement of almost 50% in survival rates of patients with stage T3N0M0 tumors. Some prognostic factors have been reported in NSCLC patients with chest wall/parietal pleural involvement (T3) who underwent surgical resection.

We aimed to reveal the prognostic factors related to the surgery in patients with NSCLC invading the chest wall or parietal pleura. A ten year experience was reviewed.

MATERIAL AND METHODS

Patient Selection

A total of 393 patients at The Department of Thoracic Surgery underwent surgical resection due to NSCLC between February 1996 and December 2005. Of these patients, 52 (13.2%) had T3 tumors due to chest wall (CW) or parietal pleural (PP) in-

vasion, and underwent surgical resection. Two patients who were not monitored dropped out from the study. Eventually, a total of 50 patients were included in the study.

Surgical treatment was not administered to the subjects with recent cardiac ischemia, congestive heart failure, unstable angina pectoris, malignant arrhythmia, and severe pulmonary insufficiency. Patients with abnormal pulmonary function tests (FEV₁ < 60% of predicted; DLCO < 60%; MW < 50%) were evaluated by lung perfusion scintigraphy and cardiopulmonary testing.

Diagnosis and Staging

Patients were evaluated by physical examination, routine blood tests, contrast-enhanced thoracic computerized tomography, fiberoptic bronchoscopy, abdominal ultrasonography, pulmonary function tests, and contrast-enhanced brain computerized tomography during the pre-operative period as indicated. In the case of the presence of symptoms or the enhancement of serum phosphate/alkaline phosphate levels, bone scintigraphy was performed. Pre-operative mediastinoscopy was performed when a mediastinal lymph node (in five patients) existed with a short diameter of > 1 cm in the thorax computerized tomography. The international staging system was used to evaluate patient staging.⁸ Induction chemotherapy was administered to six patients (three chemotherapy, two radiotherapy, and one concurrent chemoradiotherapy).

Surgical Intervention

A posterolateral thoracotomy was performed on all patients. During exploration, extrapleural dissection was performed starting from the non-adhesive area, in which the tumor was determined to be ad-

herent to the parietal pleura and chest wall. In cases, in which no tumor was identified on the chest wall with frozen section analysis, extrapleural resection was considered to be sufficient. On the other hand, in cases in which identification was difficult during dissection, en bloc surgical resection of the chest wall was performed. During this procedure, macroscopic complete resection was the goal. At least 2 cm of intact area on 4 sides of the lesion remained in appropriate cases. After the procedure, frozen section analysis of the suspected soft tissue areas were performed, and the margins of the resection were expanded in invasive cases. This was followed by surgical resection of the lung, and mediastinal lymph node dissection. All mediastinal nodes (Naruke stations 2, 4, 7, 8, 9, and 10 in right-sided resections and stations 5, 6, 7, 8, 9, and 10 in left-sided resections) were systematically dissected (systematic lymph node dissection).

Defects covered by scapula or small ones were directly repaired in patients who had been performed rib resection. When it was not possible (n= 18), defect was reconstructed by using prolene mesh. The resected specimens were examined histopathologically.

A resection was designated as complete when all gross disease was excised and the margins of the resection displayed a clean zone when examined microscopically. Operative mortality was defined as the postoperative (<30 days) deaths related to the surgery.

The Department of Oncology determined the indications of postoperative adjuvant treatment as N2 node-positivity, incomplete resection, and T3N0-1M0 disease. Local recurrence was defined as any recurrence in the ipsilateral hemithorax. The follow-up period for each patient began on the day of surgery until the last visit or death of the patient.

Statistics

Statistica, version 5.1 (StatSoft, Inc., USA) software was used for statistical analysis. For the comparison of frequencies Fisher's exact test or Pearson chi-square test was used. In analysis of survival, death because of the disease was concerned and the operative mortality was excluded. For survival analyses and rates, Kaplan-Meier survival analysis

Table 1. The general characteristics of the patients

Parameter		n
Age, years (p= 0.79)	≤60	19
	>60	31
	Mean	60.9±1.3 (38-79)
Gender	Male	50
	Female	0
Symptom	(+)	47
	(-)	3
History of Smoking	Smoker	26
	Stopped smoking	22
	Never smoked	2

and the log-rank test were used, respectively. A P value < 0.05 was accepted as statistically significant.

RESULTS

The general characteristics of the 50 patients included in the study are shown in Table 1. Pre-operative mediastinoscopy was applied to five patients with whom lymphadenopathies with a short diameter of >1 cm were detected by thorax computerized tomography. Lymph node metastasis was not demonstrated histopathologically in these patients.

Surgical procedures performed on the patients and post-operative data were shown in Tables 2 and 3. Resection was incomplete in 6 patients who had microscopic tumor invasion at the surgical border of chest wall. In 38 patients who underwent rib resections, 2.7±0.96 (1-5) ribs were resected. The patients were followed for a mean of 26.1±26.6 (1.9-119.2) months during the post-operative period. There was a median survival of 17.8 months, and 5-year survival rate of 45.1% (Figure 1).

The survival rate was statistically better in the patients who underwent pneumonectomy than the patients who underwent lobectomy (p= 0.048), patients with no residual disease than those with residual disease (p= 0.014), and patients with complete resection than those with incomplete resection (p= 0.046). Survival was not affected by extrapleural dissection or chest wall resection, size of the tumor,

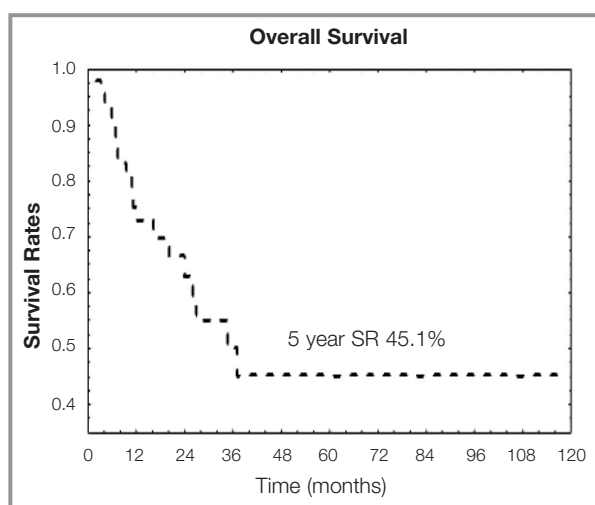


Figure 1. Overall survival

tumor histology and differentiation, invasion of the chest wall or parietal pleura, N status, stage, neoadjuvant therapy, administration of adjuvant therapy, type of adjuvant therapy, and diameter of resection (Table 2, Table 3) (Figures 2-4).

Operative mortality was 9.6% (n= 5) including 3 (25.0%) pneumonectomy and 2 lobectomy (5.6%) (p= 0.056). A total of 21 complications occurred

during the post-operative period in 17 of 45 patients remained. The complications included pleural space (n= 7), atelectasis (n= 3), empyema (n= 3), prolonged air leakage (n= 2), pneumonia (n= 2), wound infections (n= 2), an arrhythmia (n= 1) and a chylothorax (n= 1).

DISCUSSION

The management of NSCLC with chest wall involvement remains a subject of interest, owing particularly to issues under the following three headings: factors that may influence the odds for cure and long-term survival⁹, indications and techniques of repair of the chest wall defects¹⁰, and the role for additional therapies.² The prognosis is determined by the completeness of resection and the patient's lymph node status.¹¹ T3N0 disease (i.e., stage IIB) has a 5-year survival rate of 35% to 50%.^{2,10} The patients with the highest survival rate in all periods were those with stage IIB disease who underwent rib resection for a tumor infiltrating the parietal pleura, but not invading the rib.¹²

Five years survival in the presence of N(+) disease is markedly reduced, ranging from 11% to 39% for N1 disease to zero for N2 disease.^{13,14} According to Matsuoka et al.¹⁵, prognosis in these patients is mostly assessed by the completeness of resection

Table 2. The median survival and 5-year survival rates according to the surgical procedures performed

Parameter	Finding	n	Median survival (95% Confidence interval) (months)	5-year survival rate ± standard error (%)	p
Surgical Operation	Pneumonectomy	12	23.9 (13.3-60.8)	80.2±17.9	0.048
	Lobectomy	36	15.4 (14.3-32.4)	35.5±11.2	
	Wedge resection	2	23.8 (0-117.9)	50.0±35.4	
Surgical Resection	Chest wall	38	16.4 (15.6-31.4)	53.4±15.5	0.94
	Extrapleural dissection	12	22.6 (10.2-56.3)	42.6±11.7	
Resection	Parietal pleura	12	22.6 (10.2-56.3)	53.4±15.5	0.90
Diameter	1-2 ribs	16	14.2 (7.6-38.1)	31.2±23.4	0.046
	3-5 ribs	22	17.8 (14.6-33.4)	43.5±13.9	
Complete Resection	(+)	44	23.4 (19.2-37.8)	51.3±10.5	0.046
	(-)	6	13.7 (8.3-17.5)	0	
Invasion	Parietal pleura	13	23.9 (13.0-55.2)	57.7±14.6	0.73
	Soft tissue and bone	37	15.4 (14.8-30.9)	38.9±12.1	

Table 3. The median survival and 5-year survival rates according to the postoperative pathology and patients' characteristics

Parameter	Finding	n	Median survival (95% Confidence interval) (months)	5-year survival rate \pm standard error (%)	p
Tumor size	\leq 3 cm	6	29.6 (0-88.9)	80.3 \pm 17.9	0.12
	3-5 cm	24	24.8 (20.6-46.3)	50.7 \pm 12.9	
	>5 cm	20	10.2 (7.7-19.0)	25.6 \pm 14.1 (4 years)	
Histology	Squamous cell carcinoma	26	20.7 (15.3-33.6)	42.6 \pm 16.2	0.24
	Adenocarcinoma	19	15.4 (13.4-39.9)	46.5 \pm 12.9	
	Other	5	8.4 (0-93.3)	37.5 \pm 28.6	
Differentiation	Good	5	27.0 (1.7-52.1)	0	
	Moderate	18	24.2 (19.2-47.9)	64.4 \pm 13.1	
	Poor	20	10.3 (7.4-26.6)	31.6 \pm 15.5	
N status	N 0	38	20.6 (17.4-34.1)	49.1 \pm 11.5	0.12
	N 1	9	20.7 (4.0-67.2)	40.1 \pm 20.3	
	N 2	3	4.1 (0-11.0)	0	
Stage	II B	38	20.6 (17.4-34.1)	49.1 \pm 11.5	0.22
	III A	12	14.4 (3.8-50.6)	31.9 \pm 17.0	
Adjuvant therapy	(-)	29	20.0 (14.4-30.2)	36.0 \pm 12.9	0.45
	Radiotherapy	13	16.8 (8.7-47.0)	61.9 \pm 15.6	
	Chemotherapy + Radiotherapy	5	14.0 (6.9-21.1)	60.0 \pm 21.9	
	Chemotherapy	3	61.5 (0-185.0)	66.7 \pm 27.2	
Comorbid disease	(+)	8	16.4 (3.3-31.1)	0	0.014
	(-)	42	19.5 (18.3-36.1)	54.8 \pm 10.2	
Neo-adjuvant therapy	(+)	6	19.0 (0-72.0)	100	0.09
	(-)	44	17.8 (17.1-33.3)	40.0 \pm 9.7	
Recurrence	(-)	28			
	Local	9			
	Distant	10			
	Distant + Local	3			

and nodal involvement, instead of the depth of chest wall invasion and the type of resection. The survival of patients after complete resection of a tumor invading the chest wall, but not involving mediastinal lymph nodes has been reported to range from 8% to 78.5%.^{6,12} Survival is certainly related to nodal involvement; even patients with involved N1 nodes have a 5-year survival as high as 39%.¹⁶ On the other hand, involvement of mediastinal (even N2) lymph nodes in a patient with a T3 primary tumor portends a poor prognosis, and this subgroup

of patients with N2 disease should be operated rarely, in a combined modality setting, only if they have excellent performance status.¹⁷ The results of our study unexpectedly demonstrated pneumonectomy as a good prognostic factor. Apart from the good survival results obtained from pneumonectomy, the high operative mortality and morbidity properties of this procedure should also be taken into consideration. The good survival results of our series may be associated with good pre-operative patient selection and exclusion of early postoperative

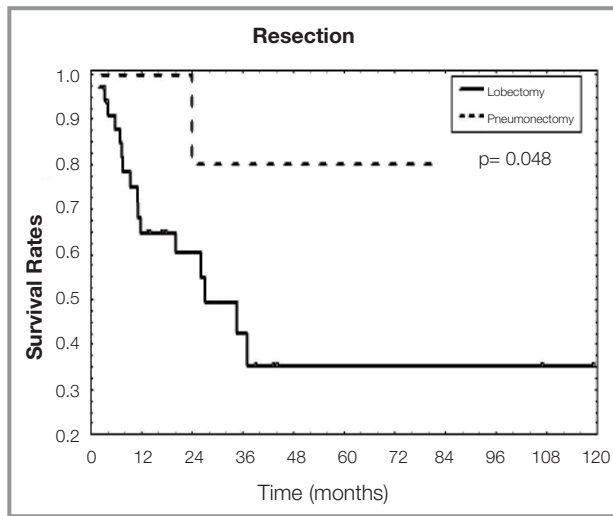


Figure 2. Survival according to the type of resection

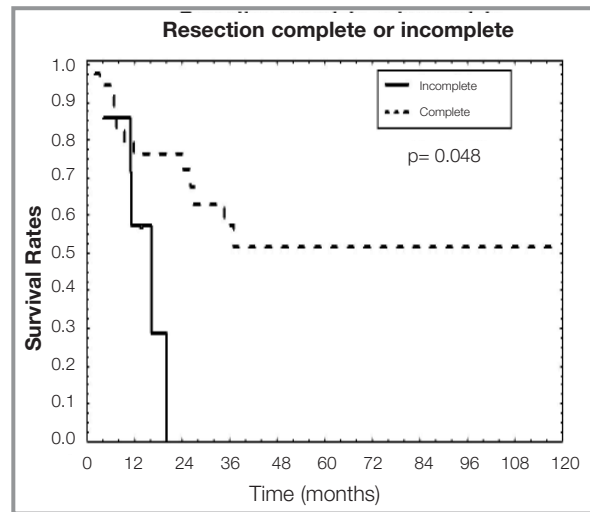


Figure 3. Survival according to the completeness of resection

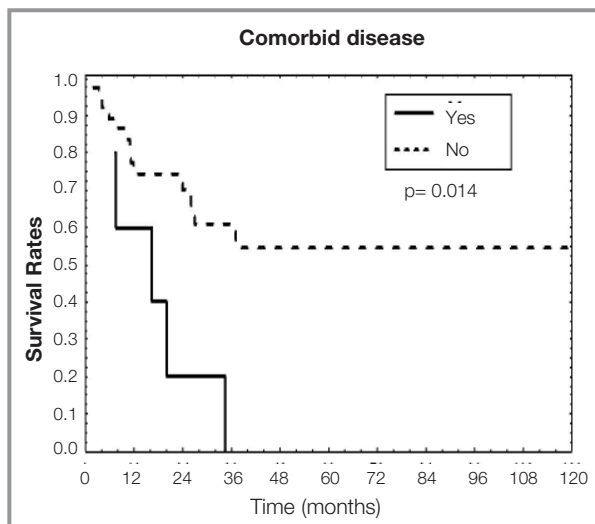


Figure 4. Survival according to the presence of comorbid disease

ve mortality. Although there is no identified relation between N positivity and survival, this condition may be explained by the fact that patients with N2 status comprise only a very small group (n= 3).

In stage IIB patients with complete resection of T3 chest wall invasion, male gender and large tumor size are considered as independent poor prognostic factors, and in stage IIIA, resected ribs and adjuvant parietal and mediastinal RT are the factors affecting prognosis. In en bloc resection, the 5-year survival (63%) is higher than extrapleural resection

(39.1%; 18). In these series, no relation was found between the resection shape, resection dimension, the presence of post-operative adjuvant therapy, and the type of adjuvant therapy and the survival.

In some series, chest wall invasion¹⁹ and histologic differentiation³ are considered as prognostic factors, but in our series, these parameters were not shown to be associated with survival. In a similar study, the operative mortality rate was 3.4% with parietal pleural invasion and 1.8% with chest wall invasion. In these patients, local recurrences were 7.4% and 24%, mean survival was 27 and 16 months, and the 5-year survival rates were 33% and 14%, respectively.²⁰ Voltolini et al.²¹ reported the 30-day mortality as 4% and the cause of mortality was myocardial infarctions and bronchopleural fistulas. In isolated T3 tumors with pleural involvement, the 5-year survival rate was 43%, and in patients with chest wall involvement this was reduced to 8.7%. In this study, the depth of chest wall invasion and nodal involvement were considered as poor prognostic factors. In addition, surgical procedures did not affect the prognosis. In a series in which the mortality was 19% (due to pneumonia), emphasis was placed on the poor surgical results in old and weak patients with respiratory dysfunction²² In our study, patients who registered operative mortality were excluded from the study. Survival after resection was markedly low in patients with concomitant additional disease.

Today, surgical resection can easily be performed with low morbidity and mortality in NSCLC patients with chest wall or parietal pleural invasion (T3) and the 5-year survival rate is reported as 45.1%. The absence of concomitant additional diseases and the presence of a complete resection are considered as good prognostic factors. This study, with a limited number of patients, also revealed that survival had not been affected by age, depth of chest wall invasion, resection shape and dimension, tumor size, tumor histology and differentiation, stage of the disease (stages IIB and IIIA), presence of neo-adjuvant or adjuvant therapy, and the procedure of adjuvant therapy.

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