Prognostic value of visceral pleura invasion in non-small cell lung cancer

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Received 3 November 2002; received in revised form 1 February 2003; accepted 20 February 2003

Abstract

Objectives: The purpose of this study was to clarify the prognostic significance of visceral pleura invasion in T2 non-small cell lung cancer (NSCLC). Materials and methods: Between 1990 and 2001, 439 consecutive patients with T2 NSCLC underwent curative surgical resection. The subjects included 234 patients with stage IB, 95 with stage IIB, and 110 with stage III A and B disease. The patients were divided into two groups according to the existence of visceral pleura invasion (group I without, group II with). Both groups were compared with regard to tumor size, histology, associated mediastinal lymph node involvement, and survival rates. Results: Visceral pleura invasion (group II) was identified in 114 patients (26%), and was present in 22% of patients with NSCLC with a tumor size of 3 cm or less and in 27% of those with a tumor larger than 3 cm ($P = 0.37$). Visceral pleura invasion was associated with a higher frequency of mediastinal lymph node involvement (group I = 22%, group II = 34%, $P = 0.009$). Five- and 10-year survival rates were 50 and 45% in group I, and 36 and 22% in group II ($P = 0.0006$). In stage IB, visceral pleura invasion was identified in 53 patients (23%), and 5- and 10-year survival rates were 63 and 60% in the visceral pleura non-invasion group, and 44 and 28% in visceral pleura invasion group ($P = 0.0018$). By multivariate Cox model analysis, age at intervention (relative risk $= 1.03$, $P = 0.0017$), N status (relative risk $= 1.53$, $P < 0.0001$), tumor size (relative risk $= 1.83$, $P = 0.0452$) and visceral pleura invasion (relative risk $= 1.42$, $P = 0.0291$) were independent predictors of poor prognosis. Conclusions: We were able to demonstrate that visceral pleura invasion was a factor of poor prognosis in T2 NSCLC. It was found to correlate with more extensive mediastinal lymph node involvement and a decreased survival rates. Therefore, the patients with visceral pleura invasion should be closely followed up especially.

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Keywords: Visceral pleura; Non-small cell lung cancer; Prognostic factor

1. Introduction

Lung carcinoma causes the greatest number of cancer deaths in Korea; more than 10,000 patients die each year from lung cancer.

Visceral pleura invasion by non-small cell lung cancer (NSCLC) is known to be one of the most important prognostic factors in patients who undergo complete resection for lung cancer [1–3]. Visceral pleura invasion appeared in the mid 1970s as a specific entity in the TNM classification, which has remained unchanged until now: a tumor of any size that invades the visceral pleura is classified as T2 [1]. In 1995, Ichinose and associates [3] confirmed visceral pleura invasion to be a predominant prognostic factor in stages I and II NSCLC. In 2001, Manac’s and associates [4] reported visceral pleura invasion by NSCLC to be an underrated poor prognostic factor.

We attempted to evaluate the significance of visceral pleura invasion in completely resected NSCLC, with a special emphasis on T2 lung cancer, to better understand its role as a prognostic factor and to target adjuvant treatment.

2. Materials and methods

The medical records of all patients who underwent lung resection for a pathologic T2 NSCLC, as defined by the new International Classification System [1], were reviewed retrospectively for the 12-year period from 1990 to 2001. Seven-hundred and twenty consecutive patients underwent pulmonary surgical resection for NSCLC in the department of Thoracic Surgery at Yonsei University. The surgical...
procedure was a potentially curative complete resection with extensive mediastinal lymph node dissection, similar to that described by Martini and Flehinger [5]. Among the included patients, 439 patients presented with T2 disease and formed the basis of this study. There were 352 men and 87 women aged 10–79 years (mean, 59.9 years).

Complete surgical resection consisted of pneumonectomy (n = 197) and lobectomy (n = 242). The subjects included 234 patients with stage IB, 95 with stage IIB, and 110 with stages IIIA and B disease. Regardless of stage, the patients were divided into two groups according to the existence of visceral pleura invasion. Visceral pleura involvement was classified according to Hammar’s diagram [6]: px and p0 = with no pleural involvement or that reaches the visceral pleura but does not extend beyond its elastic layer; p1 = tumor that extends beyond the elastic layer of the visceral pleura but is not exposed on the pleural surface; and p2 = tumor that is exposed on the pleural surface but does not involve the parietal pleura. P1 and p2 tumor, defined as having visceral pleura invasion, were both included in group II in the present study, whereas px and p0 tumors were classified as group I. Both groups were compared with regard to the size of the tumors, histology, associated lymph node involvement, and survival rates. The patients of stage IB were also divided into two groups and compared for survival according to the existence of visceral pleura invasion.

Patients were grouped into those with a tumor of 3 cm or less in size and those with a tumor larger than 3 cm. Histologic cell types were divided into squamous cell carcinoma and non-squamous cell carcinoma. For regional lymph node involvement we used the classification of Mountain and Dresler [7]. Operative mortality was defined as any death occurring within 30 days of operation or during the initial hospitalization. Late mortality was defined as any death occurring within 30 days of operation or during the initial hospitalization. Follow-up data were obtained from patients’ clinic visits, and when needed, by telephone interview. Follow-up was completed in all patients and ranged from 0.13 to 151.63 months (mean 36.07 months, median 25.23 months).

The χ² test was used to evaluate the significance of the relationship between the positivity of visceral pleura invasion and each of the clinicopathologic factors. Survival curves were calculated using the Kaplan–Meier method [8], and the date of tumor resection at our institution was used as the starting time; statistical comparisons were made using the log-rank test [9]. Univariate analysis was conducted according to each factor, such as, sex, age at intervention, operation procedure, histologic type, N status, tumor size and visceral pleura invasion. Cox’s proportional hazards model was used for the multivariate analysis to evaluate the independent prognostic roles of these factors in overall survival [10]. The level of significance was set at 5% (P < 0.05).

3. Results

NSCLC with a tumor size of 3 cm or less were present in 98 patients (22%) and tumors larger than 3 cm were present in 341 patients (78%). Visceral pleura invasion was present in 22 patients (22%) with a tumor of 3 cm or less in size and in 65 patients (27%) with a tumor larger than 3 cm (P = 0.37).

Concerning histologic type, squamous cell carcinomas accounted for 236 cases (54%) and visceral pleura invasion was present in 54 of these patients (23%). Non-squamous cell carcinomas accounted for 203 cases (46%) and visceral pleura invasion was present in 60 of these patients (30%) (P = 0.11).

The visceral pleura invasion (group II) was identified in 114 patients (26%): group I (n = 325), group II (n = 114). In group I, N2 or N3 involvement was present in 71 patients (22%) and in 39 patients (34%) of group II. Visceral pleura invasion was associated with a higher frequency of N2 or N3 involvement (P = 0.009).

In group I, N1, N2 or N3 involvement was present in 144 patients (44%) and in 61 patients (54%) of group II (P = 0.090).

Nineteen patients (4%) died perioperatively. At the closing date, 167 other patients had died. Five- and 10-year survival rates were 50 and 45% in group I, and were 36 and 22% in group II (P = 0.0006) (Fig. 1).

In stage IB, visceral pleura invasion was identified in 53 patients (23%), 5- and 10-year survival rates were 63 and 60% in the visceral pleura non-invasion group, and 44% and 28% in the visceral pleura invasion group (P = 0.0018) (Fig. 2).

By univariate analysis, sex, age at intervention, operation procedure (lobectomy versus pneumonectomy), tumor histologic type (squamous cell carcinoma versus non-squamous cell carcinoma), N status, tumor size (3 cm or less versus larger than 3 cm) and visceral pleura invasion were evaluated to find predictors of a poor prognosis. As a result, age at intervention (P = 0.0002), operation procedure (P = 0.0073), N status (P < 0.0001), tumor size (P = 0.0091) and visceral pleura invasion (P = 0.0007) were found to be statistically significant predictors of a poor prognosis.

The factors above were evaluated by multivariate Cox model analysis. As a result, age at intervention (relative risk = 1.03, P = 0.0017), N status (relative risk = 1.53, P < 0.0001), tumor size (relative risk = 1.83, P = 0.0452) and visceral pleura invasion (relative risk = 1.42, P = 0.0291) were identified as independent predictors of a poor prognosis (Table 1).

4. Discussion

In 1977, Brewer reported that lung cancer patients with a subpleural location had a poor prognosis, and proposed
pleural involvement as a poor prognostic factor [11]. Visceral pleura invasion appeared in the mid 1970s as a specific entity in the TNM classification. This assigned a tumor of any size that invades the visceral pleura as T2, in the 1997 ‘Revisions in the international system for staging lung cancer’ by Mountain.

TNM staging in non-small cell lung cancer is recognized as the most important prognostic factor. We compared T2 non-small cell lung cancers with and without visceral pleura invasion.

In our study, visceral pleura invasion was observed in 26% of resected T2 non-small cell lung cancer specimens and in 23% of stage IB non-small cell lung cancers.

Manac’h showed that visceral pleura invasion is correlated with a tumor size larger than 3 cm [4], but we
did not find a correlation between tumor size and visceral pleura invasion.

In terms of the histologic type, we divided patients into a squamous cell carcinoma group and a non-squamous cell carcinoma group. A trend ($P = 0.11$) toward an increased rate of visceral pleura invasion in the non-squamous cell lung cancer patients was observed. The probable reason for this is that most of the non-squamous cell lung cancers were adenocarcinomas, and were located more peripherally than the squamous cell lung cancer, hence increasing the likelihood of visceral pleura invasion.

We observed that visceral pleura invasion was significantly associated with more extensive mediastinal lymph node involvement, an observation in agreement with other studies [4,12]. Its frequent association with extensive mediastinal lymph node involvement supports the hypothesis that exfoliated tumor cells are drained through the pleural lymphatics by the mediastinal lymphatic pathways and then into the bloodstream.

Some debate exists as to whether visceral pleura invasion influences the survival of patients with stage I disease. Martini [13] and Padilla [14] insisted that visceral pleura invasion does not influence the survival of patients with stage I disease; however, Ichinose [3,15] and Manac’h [4] were able to document, by multivariate analysis of survival curves, that pleural involvement is a significant prognostic factor in NSCLC. Deslauriers [16] reported that visceral pleura invasion did not seem to influence the survival of patients with stage I disease in their review article.

Our study shows that the survival rates in T2 NSCLC of the visceral pleura invasion group (group II) and the visceral pleura non-invasion group were different (group I) ($P = 0.0006$). In stage IB, survival rates for the visceral pleura invasion group and the visceral pleura non-invasion group were also different ($P = 0.0018$).

This difference may be explained by the rapidity with which a lung cancer in a subpleural location invades the pleura and disseminates cancer cells throughout the pleural cavity [11]. Once exfoliated in the pleural cavity, preformed stomas that connect subpleural lymphatics with the pleural space could account for the lymphatic and then the systemic dissemination of the tumor cells [17].

Visceral pleura invasion may be regarded as the first step toward a minimal hematogenous tumor cell dissemination, and hence provides a rationale for the selective application of any effective systemic adjuvant treatment in stage IB non-small cell lung cancer with visceral pleura invasion.

We performed multivariate analysis to exclude the effects of other factors, and found by multivariate analysis that the independent prognostic factors of T2 NSCLC were: age at intervention, N status, a tumor size larger than 3 cm and visceral pleura invasion.

To conclude, this study finds that visceral pleura invasion is an independent prognostic factor in T2 non-small cell lung cancer, and that visceral pleura invasion is a potential indication for adjuvant chemotherapy.

### References


### Table 1

<table>
<thead>
<tr>
<th>Factors</th>
<th>UVA ($P$ value)</th>
<th>MVA ($P$ value)</th>
<th>Risk ratio</th>
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<tr>
<td>Sex: male versus female</td>
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<td>0.99</td>
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<td>Age</td>
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<td>Operation procedure: lobectomy versus pneumonectomy</td>
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<td>Histology: squamous cell carcinoma versus non-squamous cell carcinoma</td>
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<td>$0.92$</td>
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<td>N status</td>
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<td>$&lt;0.0001$</td>
<td>1.53</td>
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<td>1.83</td>
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<td>Visceral pleura invasion</td>
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<td>$0.0291$</td>
<td>1.42</td>
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* Univariate (UVA) and multivariate analysis (MVA).


