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Prognostic significance of surgical-pathologic multiple-station N1 disease in non-small cell carcinoma of the lung☆

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Abstract

Objectives: The surgical outcome of pathologic N1 disease in resectable non-small cell lung carcinoma (NSCLC) is controversial. The prognosis of the patients with multiple/bulky N2 disease was invariably dismal. However, the prognostic significance of tumor involvement in more than one hilar or intralobar lymph node station has not been fully described. **Methods**: From 1996 to 2002, 181 patients with NSCLC had complete resection. Four levels of N1 nodes and N2 nodes were identified using the new regional lymph node classification for lung cancer staging. There were 67 patients (37%) with no nodal disease (N0), 43 patients (24%) with N1 and 71 patients (39%) with N2 disease. The N1 subgroup cases were reviewed. The prognostic significances of single and multiple N1 diseases were tested. **Results**: The cumulative postoperative survival at 3 and 5 years was 57 and 29%, respectively. The survival associated with single-station N1 disease was significantly better than that of multiple-station N1 disease (45 vs 32% at 5 years; $P = 0.03$). Five-year survival was similar in patients with multiple N1 disease and patients with single-station N2 involvement (32 vs 31% at 5 years; $P = 0.84$). However, no patient survived when tumor was detected in more than one mediastinal station (i.e. multiple N2 disease). **Conclusions**: It was suggested that N1 disease is a compound of two subgroups: one involving in one node and the other (multiple N1 disease) in which the postoperative prognosis was not statistically different from that of N2 disease.
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Keywords: Non-small cell lung cancer; Nodal involvement; Multiple-station N1, N2; Surgical resection

1. Introduction

Survival curves and clinical observations confirm that generally similar patterns of biological behavior will prevail for groups of patients with lung cancer having the same disease stage and histologic type [1–3]. The prognostic significance of this information has proved useful for physicians to select treatment, estimate prognosis, and compare the results of different therapies. As a source of the current staging system, revisions in the international system for staging lung cancer was proposed by Mountain [3]. According to the accepted tumor, node, metastasis (TNM) staging [3], N1 status of lung cancer is encountered in stage IIA (T1N1), IIB (T2N1), IIIA (T3N1) and IIIB (T4N1). Five-year surgical-pathologic (p) survival rates are, respectively, 55, 39, and 25% for the first three stages, and the IIIB group is reported to offer a 7% 5-year survival rate, which is not published. If only N status is considered, N1 5-year survival rate becomes 47%, an intermediate value between those of N0 (56%) and N2 (20%) [3].

N1 disease may involve one or more node [3] levels in the lung. Different types of pN1 status in T1 and T2 tumors (direct extension of metastases in lobar or hilar nodes) were described [4,5] and it was concluded that 5-year survival was highly related to type of nodal involvement.

The purpose of this study was to evaluate the significance of N1 disease discovered in more than one station and better understand its place as compared with N0 and N2 involvement.

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2. Patients and methods

Between January 1996 and November 2002, 181 consecutive patients with histological evidence of non-small cell lung cancer (NSCLC) were enrolled in the study after complete pulmonary resection and lymph node dissection. Routine blood tests included hemoglobin, alkaline phosphatase and serum calcium estimations. All patients underwent postero-anterior and lateral chest radiographs and bronchoscopy. CT scans of the thorax, abdomen (or abdominal ultrasonography), and cranium, all body bone scintigraphies were done in all patients for pretreatment staging.

Mediastinal lymph node sampling consisted of stations 2, 4 (both left and right), and 7 in the recent mapping system [6] from the lymph nodes using cervical mediastinoscopy were carried out in all patients. The mediastinal exploration was supplemented by a left anterior mediastinotomy or extended mediastinoscopy in patients whose tumor lay in the left upper lobe or left main bronchus and in patients with enlarged (>1 cm) anterior mediastinal and/or aortico-pulmonary lymph nodes (i.e. stations 5 and 6). The following patients were excluded: (1) patients who underwent partial resection or segmentectomy; (2) patients with multiple lung tumors; (3) patients with low-grade malignancy, such as bronchial carcinoid; (4) patients who were found to have mediastinal nodal tumor involvement and underwent neoadjuvant therapy and (5) patients who had metastatic carcinoma.

A pneumonectomy was performed in 81 patients, a lobectomy (sleeve or non-bronchoplastic) was done in 85 patients. Fifteen patients underwent bilobectomy. All patients underwent a uniform staging protocol (UICC's, TNM classification revised in 1997) [3] in construction of a final surgical-pathologic stage (pTNM) using information obtained at thoracotomy and supplemented by pathological examination. Informed consent was not required because it was an observational study.

All patients who were discovered to have single or multiple-station N2 disease after surgery were referred to adjuvant chemotherapy and radiotherapy.

2.1. Pathological evaluation

The specimens were evenly planed with a cryostat. Sections of 3–4 mm were taken followed by hemotoxylin and eosin staining. All resected lymph nodes were formalin fixed. The sections were taken similarly and examined microscopically by standard hematoxylin–eosin stain. Special attention was paid to N1 and N2 stations according to the recent revision of lymph node mapping [6]. 'Single-station metastasis' was defined as when only one station in the N1 or N2 region was involved (i.e. 'single-station N1' and 'single-station N2', respectively) whereas 'multiple-station metastasis' was defined as when more than one station in the N1 or N2 region was involved ('multiple-station N1' and 'multiple-station N2' respectively). Sixty-seven patients (37%) were found to have no nodal disease, whereas 43 patients (24%) had N1 tumor involvement and 71 patients (39%) were found to have N2 disease. The total number of resected mediastinal lymph nodes was 2117 (mean 11.8/patient).

2.2. Statistical analyses

Patient survival was expressed by analysis according to the method of Kaplan and Meier, using time zero as the date of thoracotomy and death as the end point. The mean survival time and its 95% confidence interval (CI) were given in nodal stages. The prognostic predictors were studied by univariate (age, gender, clinical and surgical-pathologic T and N status, histologic type of tumor, grade of differentiation and multivariate analyses using Cox proportional hazard regression model. SPSS software for Power Macintosh computers was used on a personal Apple computer for statistics. If the P-value was below 0.05, the result was considered significant.

3. Results

The main clinical and pathological characteristics of the 181 patients enrolled are summarized in Table 1.

For the entire group, the median follow-up period was 20 months (range 1–80 months) and median survival time, 63 months (95% CI, 45–80 months). The 1- and 3-year survival rates were 82 and 53%, respectively (Fig. 1). The T factor has been found to be a significantly important prognosticator ($P = 0.02$).

Table 1
Clinical and surgical characteristics of patients

	N (%)
Male	172 (95)
Female	9 (5)
Histology	
Adenocarcinoma	41 (23)
Squamous cell carcinoma	124 (69)
Large cell neuroendocrine carcinoma	2 (1)
Adenosquamous cell carcinoma	12 (7)
NOS*	2 (1)
Stage (pTNM)	
IA	14 (8)
IB	23 (13)
IIA	5 (3)
IIB	43 (24)
IIIA	78 (43)
IIIB	18 (10)
pN	
N0	67 (37)
N1	43 (24)
N2	71 (39)

*NOS, not otherwise specified.

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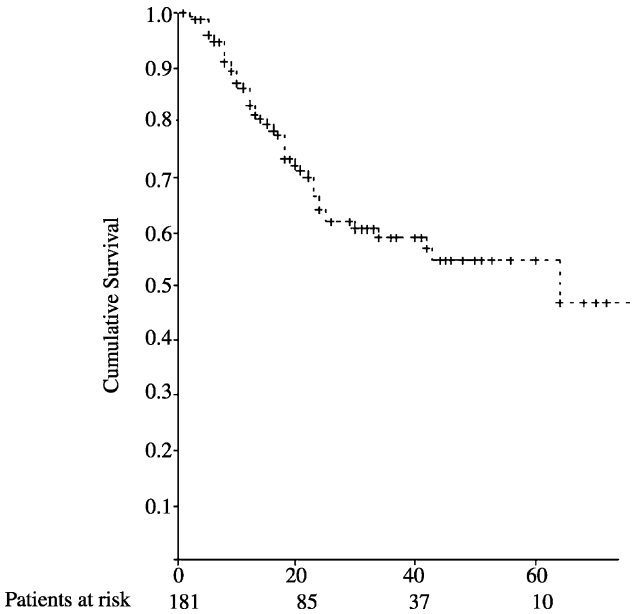

Fig. 1. Survival curve of all patients.

The 5-year survival rate of pN0, pN1 and pN2 disease patients were 75, 45 and 31%, respectively. The N status had a statistically important impact on survival ($P = 0.0011$). The type of operation and histologic type (squamous vs non-squamous) had no impact on survival ($P = 0.29$, $P = 0.056$, respectively). Fifteen patients had N1 involvement at more than one station. The patients with multiple-station N1 disease had a 44 and 32% of 3-year and 5-year survivals, respectively. Patients with single-station N1 disease had a significantly lower survival than those with multiple-station N1 disease (Fig. 2; $P = 0.03$). The mean survival times were 66 (95% CI 58–74 months), 52 (95% CI 39–64 months), 33 (95% CI 21–45 months), 35 (95% CI 24–46 months) and 28 (95% CI 22–35 months) in patients with N0, single-station N1, multiple-station N1, single-station N2 and multiple-station N2 diseases, respectively. Moreover, there was no significant difference in survival between multiple-station N1 and single-station N2 diseases (Fig. 2; $P = 0.1$). No patient with multiple-station N2 metastasis ($n = 39$) survived beyond 5 years (i.e. 0% 5-year survival) and the difference was found to be significantly worse comparing those of single-station N2 disease and single-station N1 diseases ($P = 0.03$, $P = 0.015$, respectively).

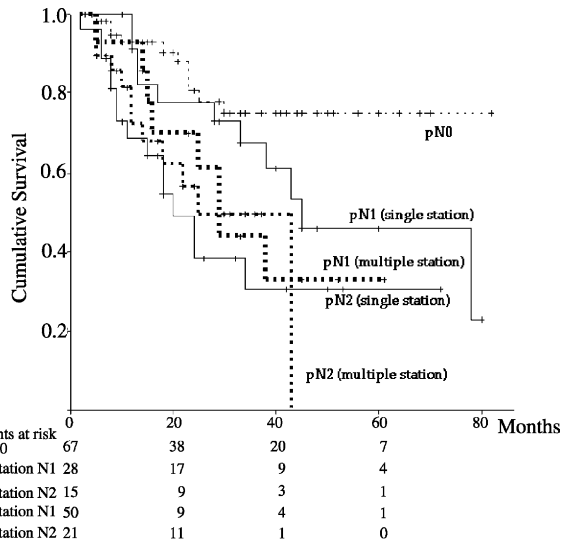

Fig. 2. Survival curves for patients with pN0, pN1 (single station), pN1 (multiple station), pN2 (single station), pN2 (multiple station).

No significant difference was found in survival between patients with hilar vs lobar metastasis ($P = 0.81$). In patients with multiple-station N1 disease, involved lymph node stations were #10 in five patients, #11 in seven patients, #12 in three patients and #13 in four patients. The median of involved N1 stations was 2 and there was a total of 34 N1 node in these patients.

4. Discussion

Assigning patients to a particular pTNM subset and stage will allow the most appropriate individual therapeutic decision. Like previous staging systems, the recent one has been established on a large database [3]. The power of this large database in prognosis is self-evident. Nevertheless, the inherent inaccuracy of the staging process should be brought to attention. The new revision defines the nodal tumor involvement (i.e. N1, N2, N3) as a most effective prognosticator. The patients with N3 disease had no chance to survive beyond 5 years [3]. According to the recent TNM system, the predicted 5-year survival after complete resection for T1N0M0 NSCLC is only 67% [3].

Martini and associates proposed the number of involved N1 nodes to be a significant prognostic factor [7]. However, Asamura et al. reported that no difference in survival was observed between patients with single station and multiple-station N1 metastasis although the boundary between N1 and N2 stations was debated [8]. On the other hand, Naruke and associates claimed better survival with intrapulmonary or peribronchial lymph node metastases [9]. Van Velzen et al. reported that, in patients with N1 hilar nodes, the most common pattern was distant metastases and direct extension from tumor seemed to have better prognosis compared to those who had non-tumor neighboring N1 disease [5].

In this study we analyzed the effect of the number of tumor-involved N1 nodes on survival. We found that single-station N2 disease was similar to multiple-station N1 disease in terms of survival. Despite the relatively short follow-up period, multiple-station N1 disease resulted in a significantly poorer prognosis than that of single N1 disease. It could be proposed that multiple N1 disease might be an overlooked N2 disease. However, in every patient, a systematic lymph node dissection was made. Nevertheless

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a micrometastasis to the mediastinal nodes was not investigated. Tanaka and associates declared that involvement of the hilar node and aberrant p53 expression were significant factors to predict a worse prognosis in resected T1-2N1M0 NSCLC [10].

In our series, T factor, stage and N factor were also found to be prognosticators whereas histologic type, type of operation were found to have no significant effect on survival in patients.

The purpose of the assessment of additional prognostic markers in the primary tumor is to discriminate, on groups of patients, the early stage disease, the risk of recurrence of which is sufficiently high to justify adjuvant therapy. D'Amico [11] concluded that conventional pathologic prognostic factors had a different impact pattern on the prognosis of patients with disease in each pathologic stage. In this study, we proposed that N1 disease did not seem to be a uniform group in terms of number of involved nodes. Multiple-station N1 disease represented single-station N2 disease. Therefore in the patients with multiple-node N1 metastasis not only radical resection but also adjuvant therapy should be considered. Mountain reported that the 5-year survival of T1-3N2M0 patients was 23% [3]. However, there was no number-of-station based N2 subclassification in his report. It should be noted that the patients with multiple-station N2 disease had the worst survival. Every attempt should be made to unveil the N2 node involvement in more than one station. Despite our routine mediastinsocopy strategy (even for the cN0 patients), multiple N2 disease was a reality in a number of patients. Fernando and Goldstraw [12] and Cetinkaya [13] found that clinical and surgical-pathologic stage coincided in only 47 and 48% of patients, respectively. Intraoperative staging could have diminished the number of those patients.

There was little evidence for the need for adjuvant therapy after complete resection in NSCLC patients. Recently one randomized study has revealed a 4% 5-year survival benefit of adjuvant therapy followed by operation compared with operation alone [14].

The limitations of the present study should also be addressed. We were unable to analyze recurrence pattern in patients with multiple-station N1 and N2 diseases. The number of patients with multiple-station metastasis is also relatively small, however, the statistical power of the observed effect of multiple station was sufficient to be significant. Also, the difference between multiple-station-lobar and multiple-station-hilar N1 disease was not investigated due to the small number of patients in each subset.

In conclusion, we suggested that multiple-station N1 disease behaves like a single-station N2 disease. The confirmation of the impact of multiple-station disease and the necessity of adjuvant therapy in these patients need prospective and larger series with longer follow-up.

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Appendix A. Conference discussion

Dr P. De Leyn (*Leuven, Belgium*): In 39% of your patients you found N2 disease and in about 13% of these patients you found multilevel N2 disease. You told us that since 1998 you have performed mediastinoscopy in every patient. I guess the rate of unforeseen N2 disease has gone down. Do you have any figures on that?

Dr Turna: Yes, it started to fall down, and now it's about 15%.

Dr O. Kshivets (*Siauliai, Lithuania*): According to your report, the lung cancer patients with multiple N1 metastases should be discussed as the patients with stage IIIA?

Dr Turna: N1 metastasis you mean?

Dr Kshivets: I mean the multiple metastasic disease in N1, did you stage these patients as patients with stage IIIA? According to the classical TNM-classification, these patients have stage II.

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Dr Turna: Yes.

Dr Kshivets: If you have multiple N1 lymph node metastases, the patients have stage IIIA. Okay?

Dr Turna: Yes. The patient had T3 disease also.

Dr Kshivets: I mean in terms of prediction, prognosis.

Dr Turna: If the patient had T3 disease and multiple N1 disease, the patient was deemed to have stage IIIA, yes, it's correct, but it's different in T1 and T2 diseases.

Dr S. Margaritora (*Rome, Italy*): I'm sorry, maybe I did not understand. The N2 patients that you showed in your series are false-negative in the CT scan, or are you going to operate patients with a multiple N2 stations involvement? You know that the difference in terms of survival of patients with clinical/pathologic stage N2 is completely different.

Dr Turna: Yes. If you find that any given patient has multiple N2 disease after mediastinoscopy, we don't perform resectional surgery and we refer the patient to neoadjuvant therapy. All these patients with multiple N2 disease were discovered to have multiple N2 disease after surgery, and we don't recommend them for surgery because the survival was very dismal for these patients.

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