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Prognostic stratification of patients with T3N1M0 non-small cell lung cancer: which phase should it be?

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Abstract In the 1997 revision of the TNM staging system for lung cancer, patients with T3N0M0 disease were moved from stage IIIA to stage IIB since these patients have a better prognosis. Despite this modification, the local lymph node metastasis remained the most important prognostic factor in patients with lung cancer. The present study aimed to evaluate the prognosis of patients with T3N1 disease as compared with that of patients with stages IIIA and IIB disease. During 7-year period, 313 patients with non-small cell lung cancer (297 men, 16 women) who had resection were enrolled. The patients were staged according the 2007 revision of Lung Cancer Staging by American Joint Committee on Cancer. The Kaplan–Meier statistics was used for survival analysis, and comparisons were made using Cox proportional hazard method. The 5-year survival of patients with stage IIIA disease excluding T3N1 patients was 40%, whereas the survival of the patients with stage IIB disease was 66% at 5 years. The 5-year survival rates of stage III T3N1 patients (single-station N1) was found to be higher than those of patients with stage IIIA disease (excluding pT3N1 patients, $P = 0.04$), while those were found to be similar with those of patients with stage IIB disease ($P = 0.4$). Survival of the present cohort of patients with T3N1M0 disease represented the survival of IIB disease rather than IIIA non-small cell lung cancer. Further studies are needed to suggest further revisions in the recent staging system regarding T3N1MO disease.

Keywords Lung cancer · Neoplasm staging · Lymphatic metastasis · Survival · Carcinoma · Non-small cell

Introduction

Surgical-pathologic stage N2 (pN2) disease involving the mediastinal lymph nodes at the advanced stage is associated with a poor surgical outcome with a 5-year survival ranging from 7 to 23% [1–5]. Patients with pN1 disease can be considered an intermediate group with respect to disease progression between patients with pN0 and pN2 diseases. However, the surgical outcome of pN1 disease is controversial. In a collected series that included 1.524 previously untreated patients with non-small cell lung cancer (NSCLC), Mountain reported [1] that 5-year surgical-pathologic stage survival was 23% for stage IIIA patients (all patients with pT1-2-3N2M0), while it was reported to be 25% in patients with only pT3N1M0 disease. Similarly, Inoue et al. [3] and Jassem et al. [5] reported 5-year survival of T3N1M0 patients to be 38 and 35%, respectively.

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We previously evaluated the significance of N1 involvement in multiple- or single stations and reported that 5-year survival was significantly higher in patients with single-station N1 disease [6]. Theoretically, it could be suggested that reclassification of T3N0M0 patients as stage IIB could have led this stage of patients with worse prognosis than previously reported in 1997.

The present study aimed to evaluate the prognosis of patients with T3N1M0 disease as compared with that of patients with stage IIIA and IIB diseases. This information should help to reconsider the classification of patients with T3N1M0 disease.

Materials and methods

Study design and patients

This was a retrospective study in which patients who had received their primary surgical treatment for NSCLC are examined. Three hundred and thirteen consecutive patients (297 men, 16 women) diagnosed as NSCLC histopathological after complete pulmonary resection and lymph node dissection between January 1997 and December 2004 were enrolled in the study. Routine systematic sampling of the hilar and mediastinal lymph nodes was performed in each case, even if the preoperative evaluation was N0 or N1. All patients underwent posteroanterior and lateral chest radiography and bronchoscopy. All patients' hemoglobin, serum alkaline phosphatase, and calcium levels were determined preoperatively.

Preoperative and postoperative staging

Computed tomographical or ultrasonographical imagings of the thorax, abdomen, and cranium with whole-body bone scintigraphical imagings were performed in all patients for pretreatment staging. In the years, the patients were operated, positron emission tomography scan (PET/CT) was rarely used in our country, and thus it was used only in a small number of patients for preoperative staging. Since we did not have the opportunity for PET/CT and we had ample clinical experiences in the past, mediastinal lymph node samplings using cervical mediastinoscopy were performed in all patients. The mediastinal exploration was achieved by a left anterior mediastinotomy or an extended mediastinoscopy in tumors located in the left upper lobe or in the left main bronchus and in tumors associated with enlarged (>1 cm) anterior mediastinal and/or aorticopulmonary lymph nodes. Staging was determined according to the New International Staging System for Lung Cancer in construction of a final surgical-pathologic stage (pTNM) [7]. A systematic lymph node dissection was performed following resection. Data obtained from thoracotomy and pathological examinations were used.

Exclusion criteria

Patients with multiple lung tumors or low-grade malignancy such as bronchial carcinoid, mediastinal node or T3 involvement, and chest wall invasion and patients who underwent partial resection or segmentectomy and got neoadjuvant therapy were excluded from the study.

Ethics

All patients were informed before the operation by "patient consent form." Informed patient consent forms could not be obtained from the patients since the study was conducted retrospectively.

Pathological examination

Resection materials of primary tumor or resected lymph nodes were fixed in 10% formalin. Samples were sliced using cryostat and treated in the standard manner. Lymph nodes that could potentially alter the borders of resection were examined by frozen section. Afterward, routine follow-up and histopathological examinations of paraffin sections were carried out. The pathologist sampled lymph nodes on resection material and did paraffin blocks, routine follow-up, and microscopic examination. There were no disconcordances observed between frozen examinations and routine follow-up. Sections were stained with hematoxylin–eosin and then examined. Limited numbers of immunohistochemical examinations were being carried out in our center during the period when patients were operated. Immunohistochemical examinations were carried out when necessary and in doubt. Patients with histologic subtype of adenocarcinoma, squamous cell carcinoma, and large cell neuroendocrine carcinoma were included in the study. Tumors like adenosquamous cell carcinoma comprised of mixed cells histopathologically were named as "not otherwise specified (NOS)." Special attention was paid to N1 and N2 stations according to the recent revision of lymph node mapping. "Single-station N1 metastasis" was considered if only one station in the N1 region was involved, whereas "multiple-station N1 metastasis" was considered if more than one station in the N1 region was involved.

Follow-up

All patients discovered to have single- or multiple-station N2 disease postoperatively were referred to adjuvant chemotherapy and radiotherapy. Patients had been followed by

different centers and oncology experts. Follow-ups and treatment data were not homogenous in this retrospective study. Therefore, the relation between survival and treatment modalities with disease-free survival times was not defined as study goals.

Statistical evaluation

Survival analysis was performed by the method of Kaplan and Meier, using time zero as the date of thoracotomy and time death as the end point. The mean survival time with 95% confidence intervals (CI) was given for patients with different nodal stage classification. Initially, a univariate analysis was performed and the factors identified as significant were included in a multivariate analysis. Univariate analysis for the prognostic variables (age, gender, co- morbidity, smoking, clinical and surgical-pathologic T and N status, histological type of tumor, stage, resection type, and curability) was performed using a Cox proportional hazard regression model. All analyses were performed using the statistical program for social sciences (SPSS) version 11. Results were evaluated in 95% confidence intervals (CI). P values < 0.05 were considered significant.

Results

The clinical and surgical characteristics of 313 patients enrolled in the study are presented in Table 1. According to the postoperative pathologic evaluation, there were 32 (10%), 67 (21%), 18 (6%), 93 (30%), 83 (27%), and 20 (6%) patients with stages IA, IB, IIA, IIB, IIIA, and IIIB diseases, respectively (Table 1).

For the entire patient population, the mean follow-up period was 24 months (range 1–102 months) and the median survival time was 49 months (95% CI 24–67 months). The 1-, 3-, and 5-year survival rates were 79, 59, and 53%, respectively. The median survival times were 77, 44, 46, and 21 months in patients with surgical-pathologic stages I, II, IIIA and IIIB, respectively (Fig. 1).

Table 1 Demographic, surgical and pathologic characteristics of patients

Variables	Features	Patient count (n)	%
Age (all patients, year)	57 ± 33	313	–
Gender	Men	297	95
	Women	16	5
Smokers/non-smokers	Men	211/86	71/29
	Women	2/14	12/88
Comorbidity (present/absent)	Men	16/281	5/95
	Women	2/14	12/88
Histology	Adenocarcinoma	61	19
	SCC	199	64
	LCNEC	9	3
	NOS	44	14
Postoperative T status	T1	57	18
	T2	148	47
	T3	88	28
	T4	20	7
Postoperative N status	N0	147	47
	N1	108	34
	N2	58	19
Stage	Stage IA	32	10
	Stage IB	67	21
	Stage IIA	18	6
	Stage IIB	93	30
	Stage IIIA	83	27
	Stage IIIB	20	6
Operation	Pneumonectomy	124	40
	Bilobectomy	29	9
	Lobectomy	160	51
Curability	Complete	278	89
	Incomplete (R1, R2)	35	11

SD: SCC squamous cell carcinoma, *LCNEC* large cell neuroendocrine carcinoma, *NOS* not otherwise specified (the patient group includes mixed pathologies such as adenosquamous carcinoma)

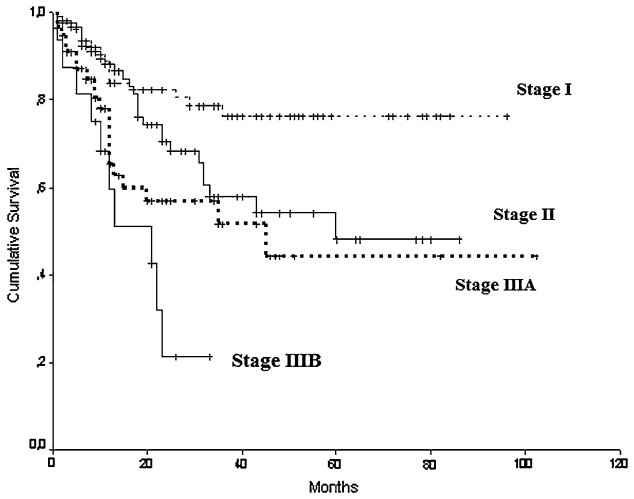

Fig. 1 The median survival curves according to the stages (the median survival times were 77, 44, 46, and 21 months in patients with surgical- pathologic stages I, II, IIIA, and IIIB, respectively)

There were significant differences between patients with stage IA and IB disease ($P = 0.04$), patients with stage IB and IIA disease ($P = 0.03$), and patients with stage IIA and IIB disease ($P = 0.01$) with respect to cumulative survival. In addition, a significant difference was found between patients with stage IIIA and IIIB ($P = 0.02$) with respect to cumulative survival.

Initially, univariate analysis was performed to enable identification of the factors that were significant for survival. The variables that showed significance in the analysis were as follows: surgical-pathologic nodal status ($P = 0.002$), histologic type ($P = 0.013$), stage ($P = 0.048$), and T status ($P = 0.02$). Patients with histopathological subtype adenocarcinoma histopathology were defined to have worse prognosis than patients with squamous cell carcinoma ($P = 0.041$). NOS group had the best survival among all histologic types ($P = 0.043$). The type of resection was found to be a significant prognostic factor, and the outcome of lobectomy/bilobectomy was a better survival compared with those who had pneumonectomy ($P = 0.039$). Incomplete resection (R1 or R2) resulted in a lower survival rate ($P = 0.0012$).

The following factors were found to be non-significant: age ($P = 0.497$), smoking ($P = 0.235$), and comorbidity ($P = 0.458$; Table 2).

After grouping the variables in steps, multivariate analysis was performed. Presence of metastatic lymph nodes (N0/N1 vs. N2) was found to be an independent prognostic factor ($P = 0.0013$, Hazard ratio 26.71 95% CI 2.09–98.82). Multivariate analysis resulted that histopathology type, T status, stage, operation type, and incomplete resection had no effects on survival (Table 2).

There were 34 patients (11%) who were found to have T3N1 NSCLC. The 5-year survival rate of these patients

Table 2 Univariate and multivariate analyses of the factors for overall survival

	Hazard ratio (95% CI)	*P* value
Univariate factors		
Age	1.52 (0.39–5.99)	0.497
Comorbidity	1.56 (0.41–6.01)	0.458
Smoke	1.74 (0.58–4.06)	0.235
Histology	0.31 (0.12–0.79)	0.013*
T status	0.28 (0.09–0.86)	0.025*
N status	24.06 (4.72–76.15)	0.002*
Stage	1.04 (1.00–1.08)	0.048*
Resection type	3.47 (1.14–9.78)	0.039*
Curability	0.42 (0.14–16.08)	0.012*
Multivariate factors		
Histology	1.03 (0.95–1.17)	0.434
T status	2.33 (0.30–9.78)	0.420
N status	26.71 (2.09–98.82)	0.013*
Stage	0.29 (0.02–5.06)	0.395
Resection type	2.34 (0.41–11.42)	0.701
Curability	2.55 (0.34–9.78)	0.424

Cox proportional hazards model of overall survival

The variables that showed significance in the analysis were; surgical-pathologic nodal status ($P = 0.002$), histologic type ($P = 0.013$), stage ($P = 0.048$), T status ($P = 0.02$), resection type ($P = 0.039$), and curability ($P = 0.012$). Presence of metastatic lymph nodes (N0/N1 vs. N2) was found to be independent prognostic factor ($P = 0.0013$)

*P values < 0.05 were considered significant

(single-station and multiple-station N1 patients) was 58%, and the mean survival time was 66 ± 12 months (95% CI, 45–88 months). Of these patients, five had multiple-station N1 disease. The 5-year survival rate of the remaining T3N1 patients ($n = 29$, single station) was calculated to be 65%, and the mean survival time was 69 ± 12 months (95% CI = 48–91 months). The number of patients with hilar (station 10), interlobar (station 11), lobar (station 12), segmental (station 13), and subsegmental (station 14) metastases were 5, 16, 2, 1, and 5, respectively. In the present study, the median number of examined N1 nodes (removed from resected material by both the surgeon and the pathologist) was eight.

Findings related to clinical and pathologic features of patients at T3N1, stage IIB, and stage IIIA (excluding T3N1 patients) were shown in Table 3.

The 5-year survival rate of patients with stage IIIA disease excluding T3N1 patients was 40%, whereas the survival of the patients with stage IIB disease was 66% at 5 years. The 5-year survival of T3N1 (single-station N1) patients (65%) was found to be higher than that of patients with stage IIIA (excluding T3N1 patients) disease (40%, $P = 0.04$), whereas it was found to be similar to that of patients with stage IIB disease (66%, $P = 0.4$; Fig. 2).

Table 3 Demographic, surgical and pathologic characteristics of patients with stage IIB, stage IIIA (excluding T3N1), and pT3N1 (single-station N1) NSCLC

Variables	pT3N1 (single-station N1)	Stage IIB	Stage IIIA (excluding T3N1)	*P*
Patients (*n*)	29	93	54	
Histology				
ACA	8	12	11	0.253
SCC	17	68	32	
LCNEC	1	2	4	
NOS	3	11	7	
Smoking				
Present	20	63	38	0.198
Absent	9	30	16	
Comorbidity				
Present	4	6	2	0.432
Absent	25	87	52	
Operation				
Lobectomy	10	38	26	0.098
Bilobectomy	3	11	5	
Pneumonectomy	16	45	23	
5-year survival	65%	66%[a]	40%[a]	

ACA adenocarcinoma, *SCC* squamous cell carcinoma, *LCNEC* large cell neuroendocrine carcinoma, *NOS* not otherwise specified (the patient group includes mixed pathologies such as adenosquamous carcinoma)

[a] The 5-year survival rate of T3N1 (single-station N1) patients (65%) was found to be higher than that of patients with stage IIIA (excluding T3N1 patients) disease (40%, $P = 0.04$), whereas it was found to be similar to that of patients with stage IIB disease (66%, $P = 0.4$)

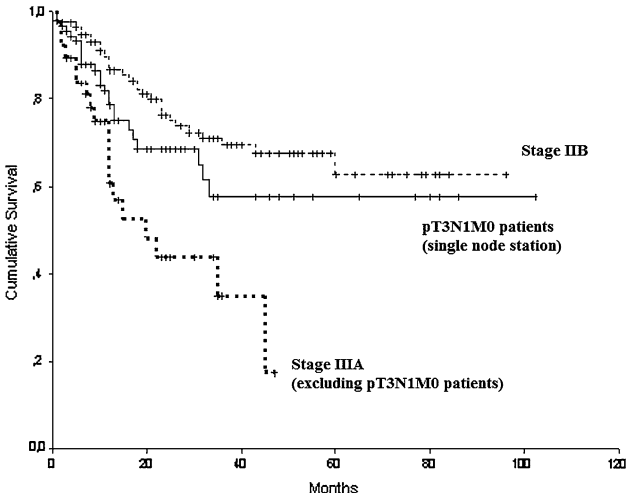

Fig. 2 The 5-year survival curves according to the patients with stage IIB, stage IIIA disease (excluding pT3N1 patients with single station) and pT3N1 (single-station N1) (the 5-year survival rate of patients with stage IIIA disease excluding T3N1 patients was 40%, whereas the survival of patients with stage IIB disease was 66% at 5 years. The 5-year survival rate of T3N1 patients with single-station N1 was 65%)

Discussion

Approximately one in every three cancer deaths occurs due to lung cancer. The proportion of patients with lung cancer who survive longer than 5 years after the diagnosis is only 15% [7]. To determine the best treatment modality in light of recent data, the clinical stage of these patients, who have a poor survival after surgical operation, should be determined. In fact, tumor stage is the most important prognostic factor in patients with lung cancer [7–11]. Thus, TNM (tumor, node, metastasis) staging system used for staging of the malignant tumors was first devised by Pierre Denoix in 1946 and modified for lung cancer by the American Joint Committee on Cancer (AJCC) in 1973 [7]. Of the staging studies to date, the last was published in 2007 as the seventh edition of the TNM classification for malignant tumors [11, 12]. This classification system has provided a precise discussion of tumor size, which was not focused before [11, 12]. Considering the survival of T3N0M0 patients, it was suggested that T3N0M0 patients be moved to stage IIB in the fifth edition of TNM classification, and in the sixth edition, no modification was established with regard to this suggestion. Although this suggestion was not changed in the seventh edition, tumors >7 cm in size was classified as T3 independent from invasion criteria [11]. In the seventh edition of TNM classification, in which no changes was proposed with respect to N descriptors, it was suggested that each T stage and N subgroups should be evaluated together. However, the fact that local lymph node metastasis is the most important prognostic factor in NSCLC patients has not changed [12].

In the sixth version of the TNM staging system, N1 tumors were categorized as two stage groups for T1 to T3 tumors without distant disease: stage II (T1N1, T2N1) and stage IIIA (T3N1) [9]. However, in the 1997 revision of the TNM staging system, N1 tumors were divided into three stage groups as stage IIA (T1N1), stage IIB (T2N1), and stage IIIA (T3N1) [1]. In addition, T3N0 disease was reclassified as stage IIB rather than stage IIIA. Thus, it could be speculated that stage IIIA disease now consists of patients who have slightly worse prognosis than it was before 1997. We recently found that N1 disease consisted of two subgroups: one involving single node and the other involving multiple nodes (i.e., multiple-station N1 disease or multiple N1 disease) of which the postoperative prognosis was not statistically different from that of N2 disease [6]. Therefore, we hypothesized that the T3 tumors with single-station N1 involvement must be revisited in terms of staging. We found that the survival of patients with T3N1 disease was similar to that of patients with stage IIB

disease rather than the patients with stage IIIA disease ($P = 0.4$ and $P = 0.04$, respectively).

It is generally accepted that patients with T3N1M0 and T3N2M0 diseases had similar prognoses [1, 2, 13]. However, there are also studies reporting better prognoses for patients with T3N1M0 disease as compared to patients with T3N2M0 diseases [14]. Obviously, a need for reconsideration of stage IIB was declared soon after the new classification [15]. Mediastinal nodal involvement, which is one of the most important prognostic factors, significantly affects survival of patients with lung cancer [1–6]. In an analysis of stage III NSCLC patients by Ichinose et al. [16], 5-year survival rates for N0/N1 and N2 diseases have been reported as 62 and 23%, respectively. As a result, stage III in NSCLC N2 disease was reported to be an independent prognostic factor. T3N1M0 may be another subgroup candidate for stage IIB; however, further studies are required to find the correct classification.

The survival rates of patients with NSCLC in the present study were comparable with the rates reported previously [1, 3–5, 14, 16]. However, the survival rates of patients with stage IIIB disease in the present study was found to be relatively better than the survival rates reported in previous studies [1, 14, 16]. This may be attributed to patient selection criteria, since this group consisted of patients with T4 disease rather than N3 disease, and each institution used its own criteria for the inclusion of selected T4 tumors [5, 14, 16].

It could be suggested that multiple N1 disease might be an ignored N2 disease [17]. It can also be proposed that a more extensive lymph node dissection might provide a more accurate lymph node staging postoperatively. However, we did not analyze time trends in patients undergoing surgical resection for NSCLC. Nevertheless, exclusion of multiple-station N1 disease may lead to decrease in the number of ignored N2 disease.

In the study by Tanaka et al. [18], involvement of the hilar node and aberrant p53 expression was reported to be significant factors predicting a worse prognosis in resected T1-2N1M0 NSCLC. Although its biological meaning remains unclear, nodal status could be an indicator of invasiveness of tumor in terms of lymphatic and/or blood vessel involvement. Thus, multiple-station N1 or N2 disease (e.g., T3N1 vs. T3N2 disease) could be proposed to have more invasive/metastatic carcinoma than those with single-station N1 disease. Therefore, further molecular analysis of biologic differences in different nodal statuses has to be accomplished.

There are some limitations of the present study that must be addressed. The number of patients with T3N1M0 disease is relatively small. Moreover, we did not assess the micrometastatic disease involving mediastinal nodes which may have been overlooked. In addition, the observed statistical difference between the survival curves of patients with stage IIIA and T3N1 was minor in the present study. Moreover, the "single-station N1" entity has not been universally accepted and seemed to depend on the appropriate and adequate effort in the isolation of N1 nodes from the resected material by a pathologist.

In conclusion, we suggest that the prognosis of T3N1 disease among the present cohort of patients is similar to that of stage IIB disease rather than that of stage IIIA NSCLC. As this retrospective study has been carried out in a limited geographic region with a restricted technical set-up, it should be supported by multicenter studies in which more patients are included, different clinical and histopathological features as well as different treatment modalities are compared.

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