Problems related to TNM staging: Patients with stage III non-small cell lung cancer

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Objective: Many reports have raised certain problems concerning the current TNM classification of lung cancer, namely that there is no sufficient difference in prognosis between patients with pathologic stage IIIA and IIIB disease. For clarifying this problem, the present study was constructed in light of T3 and T4 classifications.

Methods: Among 429 patients with non-small cell lung cancer who underwent resection, those with stage IIIA (n = 73) and stage IIIB (n = 79) disease were enrolled in this study, and their prognostic factors were compared.

Results: No difference in the survivals between patients with T3 and T4 disease was observed, and this seemed to affect the prognoses of patients with stage IIIA and IIIB disease. However, when those with T3 and T4 disease were classified into different groups on the basis of TNM descriptors, differences in the survivals became evident. The T3 bronchial invasion group showed a better prognosis than the T3 extrapulmonary invasion group. The T4 tracheal invasion group and T4 pulmonary metastasis group showed a significantly better prognosis than that in the T4 extrapulmonary invasion group and the T4 malignant pleural exudate group. The surgical curativity of patients with T3 disease was evaluated as curative resection or noncurative resection, and the surgical curativity of T4 was evaluated as R0 resection or R1 or R2 resection. The T3 bronchial invasion group included more curative resection cases. The T4 tracheal invasion group and T4 pulmonary metastasis group included more R0 resection cases. Furthermore, when patients with T3 to T2 bronchial invasion and patients with T4 tracheal invasion and T4 pulmonary metastasis were reclassified as having T3 disease, the survivals of the patients reclassified as having T3 and T4 disease, as well as the resultant subsets having stage IIIA and IIIB disease, were significantly different.

Conclusion: Tumor status should be reviewed by taking into account the surgical curativity.

There have been many reports that the current TNM classification of lung cancer, revised in 1997,¹ fails to sufficiently differentiate between the prognoses of patients with pathologic stage IIIA and IIIB disease.²⁻⁴ This might be attributable to the classification method of tumor status, especially T3 and T4. Both these groups comprise patients with significantly different degrees of surgical curativity. The heterogeneity of the disease stages within the T3 and T4 groups causes difficulties in determining patient prognosis in these groups. In the present study we reviewed the revised TNM classification, with emphasis on patients with non-small cell lung cancer classified as having stage IIIA and IIIB disease, as well as patients with tumors designated as T3 and T4.

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Figure 1. Postoperative survival curves of patients with stage IIIA and IIIB disease. There is no tendency toward difference between the prognosis of patients with stage IIIA and IIIB disease.

Methods

From November 1983 to the end of December 2000, 604 patients underwent resection of primary lung cancer at our department. Of these, 429 with non-small cell lung cancer that could be classified according to the TNM evaluation method into pathologic stages ranging from I to III were enrolled in the study. Those who died of other diseases were excluded. Of the 429 patients, 168 had squamous cell carcinoma, 221 had adenocarcinoma, 17 had large cell lung cancer, and 23 had other types of cancer. Staging of disease in these patients was as follows: 222 patients had stage I, 55 had stage II, and 152 had stage III disease (Table 1). Any separate tumor nodule was considered as intrapulmonary metastasis (PM). PM in the same lobe of the primary tumor was defined as PM1, and PM in a different lobe was defined as PM2. Resection was considered as R0 when there was no residual tumor microscopically, macroscopically, or both,¹ and resection was considered as curative when (1) the tumor did not extend beyond the visceral pleura or the resection line of the bronchus, (2) no mediastinal lymph node metastasis was detected, and (3) pulmonary resection with complete dissection of mediastinal lymph nodes was performed.⁵ Survivals on the basis of the TNM classification were analyzed by using the Kaplan-Meier method,⁶ and the differences in survivals were tested with a log-rank test.⁷ The prognostic factors were analyzed with the Cox proportional hazards regression model.⁸ Any difference between 2 factors was tested with the χ^2 or Fisher exact tests.

Results

The 5-year survivals of the patients classified according to pathologic stages I, II, and III were 71.2%, 44.0%, and 23.5%, respectively. Significant differences were observed between patients with stage I and II disease and between patients with stage II and III disease ($P < .001$ and $P = .010$, respectively). When disease was subclassified into

stages IA, IB, IIA, IIB, IIIA, and IIIB, the 5-year survivals of the patients with stage IA and IB disease were 82.1% and 57.8%, respectively, indicating a significant difference in the prognosis ($P < .001$). The 5-year survivals of the patients with stage IIA and IIB disease were 58.3% and 39.6%, respectively. There was a tendency to produce a significant difference in the prognoses, but statistical significance was not obtained ($P = .175$). This might be caused by the small number of patients with IIA disease ($n = 12$). The 5-year survivals of the patients with stage IIIA and IIIB disease were 25.2% and 22.5%, respectively, and no significant difference was observed between these 2 groups ($P = .114$, Figure 1).

The survival curves of the patients classified according to the tumor status showed that the 5-year survivals of patients with T1, T2, T3, and T4 disease were 71.8%, 47.2%, 26.1%, and 21.5%, respectively. Significant differences in prognosis were observed between the patients with T1 and T2 disease, as well as between the patients with T2 and T3 disease. However, there was no significant difference between the patients with T3 and T4 disease (Figure 2). The survival curves of the patients classified according to the nodal status showed that the 5-year survivals of patients with N0, N1, N2, and N3 disease were 62.9%, 50.0%, 19.4%, and 16.7%, respectively. The patients with N0 and N1 disease showed a tendency to exhibit a prognostic difference ($P = .084$). Significant differences were observed between the patients with N1 and N2 disease, as well as between the patients with N2 and N3 disease ($P < .001$ and $P = .002$, respectively). These findings suggest that the absence of a significant difference between the prognoses of

TABLE 1. Characteristics of the 429 patients with non-small cell lung cancer

Characteristics	No. of patients	Percentage
Age (y)		
<60	115	26.8
≥60	314	73.2
Sex		
Male	286	66.7
Female	143	33.3
Histologic type		
Squamous cell carcinoma	168	39.2
Adenocarcinoma	221	51.5
Large cell carcinoma	17	4.0
Others	23	5.3
Tumor status		
T1	160	37.3
T2	157	36.6
T3	40	9.3
T4	72	16.8
Nodal status		
N0	283	66.0
N1	37	8.6
N2	97	22.6
N3	12	2.8
Pathologic stage		
Stage I	222	51.7
Stage II	55	12.8
Stage III	152	35.4
Curativity		
R0	377	87.9
R1 or R2	52	12.1
Total	429	100.0

Curativity was considered as R0 when there was no residual tumor microscopically, macroscopically, or both.

patients with stage IIIA and IIIB disease might be due, at least in part, to the tumor status, T3 and T4 in particular.

Analysis was further carried out with the Cox proportional hazards regression model to find out which factors indicated poor prognosis. The patients' age (<60 years and ≥60 years), sex, surgical curativity, and tumor and nodal status were used as covariates. The tumor status was significant in indicating poor prognosis for patients with stage I to III disease, with a hazard ratio of 1.545 (Table 2). Nevertheless, the tumor status was not recognized as a significant poor prognostic indicator for stage III disease alone (Table 3).

Patients with T3 and T4 tumors were subjected to further study. T3 tumors, classified according to invasion or metastasis sites, were divided into patients with bronchial invasion and patients with extrapulmonary invasion. One patient with both bronchial invasion and extrapulmonary invasion was excluded. Patients with T4 tumors were divided into patients with tracheal invasion, patients with PM1, patients with extrapulmonary invasion, and patients with malignant pulmonary exudate, including pleural dis-

TABLE 2. Cox proportional hazards regression model in predicting survival of 409 patients

Variables	Assigned score	Hazard ratio	(95% CI)	P value
Age (y)				
<60	0	1.706	(1.185-2.458)	.004
≥60	1			
Sex				
Male	0	1.584	(1.121-2.237)	.009
Female	1			
Curativity				
R0	0	1.622	(1.012-2.597)	.044
R1 or R2	1			
Tumor status				
T1	1	1.545	(1.295-1.843)	<.001
T2	2			
T3	3			
T4	4			
Nodal status				
N0	0	1.794	(1.543-2.085)	<.001
N1	1			
N2	2			
N3	3			

CI, Confidence interval.

semination (Table 4). Seven patients involved in 2 or more categories were excluded. The survival curves showed that the 5-year survivals of the patients with T3 bronchial invasion and the patients with T3 extrapulmonary invasion were 43.8% and 22.2%, respectively, indicating a tendency to exhibit a difference (Figure 3, A). The 5-year survivals of the patients with T4 tracheal invasion, patients with T4 PM1, patients with T4 extrapulmonary invasion, and patients with T4 malignant exudate were 57.1%, 57.4%, 13.4%, and 5.0%, respectively. Patients with tracheal invasion and PM1 had prognoses different from those of patients with extrapulmonary invasion or malignant exudate (Figure 3, B). Surgical curativity was also investigated. Among the patients with T3 disease, the bronchial invasion group contained a significantly larger number of curative resections than the extrapulmonary invasion group (Table 5). Among the patients with T4 disease, the tracheal invasion group and the PM1 group contained significantly larger numbers of R0 resections (Table 6).

On the basis of these findings, patients with T3 bronchial invasion who exhibit a relatively good prognosis were reclassified as having T2 disease, and patients with T4 tracheal invasion, as well as patients with T4 PM1, were reclassified as having T3 disease. After this reclassification, the 5-year survivals were again determined, and the results were 34.4% for patients with T3 disease and 7.3% for patients with T4 disease, showing a significant difference between the prognoses of the 2 groups (Figure 4, A). When the 5-year survivals of the different pathologic stages were determined by using this new classification, survivals for patients with stage IIIA disease and patients with stage IIIB

Figure 2. Postoperative survival curves on the basis of tumor status. There are significant differences in the prognoses between T1 and T2 groups and between T2 and T3 groups, but there is no tendency of difference between T3 and T4 groups.

TABLE 3. Cox proportional hazards regression model in predicting survival of patients with stage III disease

Variables	Assigned score	Hazard ratio	(95% CI)	P value
Age (y)				
<60	0	1.572	(1.013-2.439)	.044
≥60	1			
Sex				
Male	0	1.241	(0.807-1.909)	.325
Female	1			
Curativity				
R0	0	2.312	(1.297-4.122)	.005
R1 or R2	1			
Tumor status				
T1	1	1.266	(0.967-1.656)	.086
T2	2			
T3	3			
T4	4			
Nodal status				
N0	0	1.815	(1.377-2.393)	<.001
N1	1			
N2	2			
N3	3			

CI, Confidence interval.

disease were 23.1% and 10.2%, respectively, with the difference being statistically significant (Figure 4, B).

Discussion

The TNM classification was revised and adapted by the International Union Against Cancer (UICC) in 1997 to address the problems of heterogeneity of end results within stage groups and a need for greater specificity in stage

classification.¹ This study was conducted after this revision. Studies evaluating this revised classification have shown that the prognoses of patients with pathologic stages IA and IB and the prognoses of patients with stage IIA and IIB disease are distinct from each other.⁹ It has often been reported, however, that no difference was observed between the prognoses of patients with stage IIIA and stage IIIB disease according to this classification.^{3,4} This might be attributable to the tumor status, T3 and T4 in particular. The tumor status classifies the tumor according to size and the extent of invasion. If the nodal status is not taken into consideration, the surgical curativity should be notably different as you go from T1 to T4 disease. That is to say, it is expected that patients with T1 and T2 disease include many curative resection cases, that patients with T3 disease include many R0 resection cases, and that patients with T4 disease include many R1 or R2 resection cases. The sites of invasion and metastasis of tumors in patients with T3 and T4 disease vary widely and consequently, and surgical curativity also differs. This leads to a diversity of results within the same T subsets. Curative cases and noncurative cases exist in R0 cases of T3 disease. Therefore, the surgical curativity of T3 disease was evaluated as curative or noncurative. Although this classification is not common, it was unavoidable for explanation of the surgical curativity in the patients with T3 disease. On the other hand, R0 cases and R1 or R2 cases exist in patients with T4 disease, and the surgical curativity of T4 disease was evaluated as R0 or R1 or R2. In addition, the curativity has been reported as the only prognostic factor that had a significant effect in all pathologic stages.² If patients with T3 and T4 disease were

Figure 3. Postoperative survival curves on the basis of the T3 and T4 categories. **A**, Patients with bronchial invasion had a tendency to have better prognoses than those with extrapulmonary invasion. **B**, Patients with tracheal invasion or PM1 had better prognoses than those with extrapulmonary invasion or malignant exudate.

reclassified on the basis of the surgical curativity, differences should become evident between their prognoses.

Originally, patients with T3 and T4 disease were classified together as having T3 disease in the UICC TNM classification in 1978.¹⁰ They were subsequently subdivided to better reflect clinical outcomes when the classification was revised in 1987.¹¹ With the latest revision, it seems that clinical outcome is still not sufficiently reflected in the staging, mainly because of heterogeneity of clinical results in the T3 and T4 subsets. Some patients with respiratory tract invasion undergo curative resection, even if they have T3 tumors, or undergo R0 resection, even if they have T4

tumors. Among those with T3 tumors with bronchial invasion in our series, 5 of 8 underwent bronchoplasty, with 3 of the 5 achieving curative resections. This agrees with some observations that the prognosis of patients with T3 bronchial invasion was relatively good.¹² Furthermore, among those with T4 tumors with tracheal invasion in our series, 6 of 7 underwent tracheobronchoplasty, with 4 of the 6 achieving R0 resections.

In the present study the patients with extrapulmonary invasion were classified as one group, but there is a possibility that their prognoses varied with the invasion site. Some investigators have reported that patients with chest

TABLE 4. Original categories of the patients with T3 and T4 disease on the basis of TNM descriptors

Original categories	n	TNM descriptors
T3 Bronchial invasion	8	Tumor in the main bronchus less than 2 cm distal to the carina
Extrapulmonary invasion	31	Tumor-associated atelectasis or obstructive pneumonitis of the entire lung
T4 Tracheal invasion	7	Tumor of any size that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, mediastinal pleura, parietal pericardium
PM1	22	Tumor of any size that invades trachea or carina
Extrapulmonary invasion	16	Tumor with separate tumor nodules in the same lobe
Malignant exudate	20	Tumor of any size that invades any of the following: mediastinum, heart, great vessels, esophagus, vertebral body,
		Tumor with malignant pleural effusion, malignant pericardial effusion, or pleural dissemination

One patient with T3 disease with both bronchial invasion and extrapulmonary invasion was excluded.

Seven patients with T4 disease involved in 2 or more categories were excluded.

TABLE 5. Curativities of the original T3 categories on the basis of TNM descriptors

T3 categories	n	Curative	Noncurative
Bronchial invasion	8	4	4
Extrapulmonary invasion	31	1	30
Total	39	5	34

Resection was considered as curative when (1) the tumor did not extend beyond the visceral pleura or the resection line of the bronchus, (2) no mediastinal lymph node metastasis was detected, and (3) pulmonary resection with complete dissection of mediastinal lymph nodes was performed. Among the patients with T3 disease, the bronchial invasion group contained a significantly larger number of curative resections than the extrapulmonary invasion group ($P = .004$ by Fisher exact test).

TABLE 6. Curativities of the original T4 categories on the basis of TNM descriptors

T4 categories	n	R0	R1 or R2
Tracheal invasion	7	5	2
PM1	22	21	1
Extrapulmonary invasion	16	6	10
Malignant exudate	20	0	20
Total	65	32	33

Resection was considered as R0 when there was no residual tumor microscopically, macroscopically, or both. Among the patients with T4 disease, the tracheal invasion group and the PM1 group contained significantly larger numbers of R0 resections ($P < .001$ by χ^2 test).

wall invasion showed different prognoses, depending on invasion to the parietal pleura, intercostal muscle layer, and ribs.^{13,14} Patients with invasion to the diaphragm have been reported to have a poor prognosis.¹⁵ It is thought that some T4 tumors with invasion to a large artery or the heart can be completely resected because of the advances of extended and combined resection. Consequently, a good prognosis is expected.

The patients with PM1 (ie, those with a tumor node in the same pulmonary lobe as the primary focus) are very likely to undergo R0 resection, and therefore evaluating them as

having T4 disease might contribute to the anomalies in staging. Some authors¹⁶⁻¹⁸ recommend upgrading the tumor status, as was done in the supplement of the UICC TNM classification issued in 1993,¹⁹ and others²⁰ propose designating patients with PM1 as having T3 disease. Other investigators report that the prognosis of patients with PM1 was dependent on the nodal spread and should be reevaluated according to the nodal status.^{3,17} It is our belief, however, that the prognosis of patients with PM1 is more accurately reflected if they were classified as having T3 disease, independent of the nodal status. Other questionable points are microscopic PM1, synchronous multiple lung cancer, and metastatic lung cancer, which are detected for the first time during the postoperative pathologic examination. The R0 resection rate of microscopic PM1 cases is thought to be considerably high, with a good prognosis compared with that of PM2, which is detected on the opposite side by means of imaging, and PM2 in the pulmonary lobe of the same side, which is detected by means of perioperative palpation. It is extremely difficult to differentiate synchronic multiple cancer and metastatic lung cancer from PM.

However, in our study the number of patients in each of the subgroups was smaller, and more comprehensive literature reviews of other survival data in these subgroups was examined (Table 7).^{12,16,21} As for bronchial invasion, Pitz and colleagues¹² showed that the mean 5-year survival was greater in 75 patients with tumors located in the main bronchus (40%) than in 32 patients with tumors with invasion of mediastinal structures (25%). Nakahashi and colleagues²² found that a 4-year survival of patients with invasion of the main bronchus was 80% and demonstrated that this subcategory of T3 tumors had a favorable prognosis. As for tracheal or carinal invasion, Mitchell and colleagues²¹ showed that the overall 5-year survival of 60 patients undergoing carinal resection, including operative mortality, was 42%, and patients without lymph node involvement (N0) had a survival of 51%. These patients performed carinal resection were classified as having T4 disease with

Figure 4. Postoperative survival curves on the basis of the reclassified tumor status and pathologic stage. A, There are significant differences of prognoses between T1 and T2 groups, between T2 and T3 groups, and between T3 and T4 groups. B, There is a significant difference between the prognosis of patients with stage IIIA and IIIB disease.

TABLE 7. Five-year survival of the patients with bronchial invasion, tracheal invasion, and PM1+PM2

Categories	Authors	No. of patients	5-year survival (%)
Bronchial invasion	Pitz and colleagues ¹²	32	40
Tracheal invasion	Mitchell and colleagues ²¹	60	42
PM1+PM2	Urschel and colleagues ¹⁶	568	20

the current TNM classification, and their survivals were better than those of other patients with T4 disease. As for same-lobe intrapulmonary satellite or metastasis, Urschel and colleagues¹⁶ retrieved 11 articles and pooled their data for analysis. They showed that a 5-year survival of 568 patients with satellite nodules in general (primary and ipsi-

lateral nonprimary lobes) was 20% and concluded that the survival for resected lung cancer with satellite nodules in a primary lobe was better than that usually observed for T4 (IIIB) disease. All these data might support our present results.

It is our belief that the tumor status, T3 and T4 in

particular, should be reviewed if the TNM classification is revised in the future. A reevaluation of the classification of patients with PM revised in 1997¹ and the classification according to invaded organs is also warranted, the latter having been hardly revised since 1987.¹¹ Surgical curativity should be taken into account in such reevaluation. In the present study attempts were made to reclassify patients with PM1 and respiratory tract invasion, showing relatively good surgical curativity with lower stages of disease. It was found that with the proposed shifts in classification, differences in prognosis between patients with T3 and T4 disease, as well as between patients with stage IIIA and IIB disease, become significant. However, the patients with respiratory tract invasion in our series included many who were eligible for bronchoplasty or tracheobronchoplasty. This might not reflect the general population of patients with respiratory tract invasion. The ability to perform extended and combined resection of other invaded organs also confounds the definition of surgical curativity among various facilities. Consequently, a multicenter study would be a better setting in which to evaluate the TNM classification as far as this characteristic is concerned.

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