**Original
Article**

Unification of T2a and T2b Tumors to T2 Tumors in Non-Small Cell Lung Cancer Staging

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Introduction: We investigated the validation of the seventh edition of the TNM staging (2009) system for lung cancer, retrospectively.

Methods: From January 1990 to March 2004, 1629 patients who underwent lung resection with systemic lymph node dissection for non-small cell lung cancer at Nippon Medical School and Saitama Cancer Center were included. The overall survivals after surgery by each pathological stage according to the 1997 and 2009 systems were statistically analyzed using Kaplan-Meier estimated survival curves, and the significance of the difference was analyzed by the log-rank test.

Results: The 2009 system had significant prognostic distinction between each T descriptor except for T2a and T2b, and between each M descriptor. The 2009 system had better prognostic distinction between each pathological stage except for stages IB and IIA, and stages IIIB and IV. In the simulation, we unified T2a and T2b tumors into T2 tumors, and T2bN0M0 and T2bN1M0 were moved to stages IB and IIA, respectively. This proposed system had significant prognostic distinction between the proposed IB, IIA, and IIB stages.

Conclusions: The 2009 system provides better patient selection for surgery and prognostic distinction between each stage except for stages IB and IIA, and stages IIIB and IV, compared with the 1997 system. Unification of T2a and T2b tumors to T2 tumors can improve prognostic distinction between stages IB and IIA.

Keywords: non-small cell lung cancer, TNM staging system, pathological stage, survival, prognosis, surgery

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Introduction

The seventh edition of the TNM staging (2009) system for lung cancer has come into effect in 2009.¹⁾ This system is the first classification to be based on data on lung cancer cases from around the world treated by all modalities^{2–7)} and has been validated internally and externally by the International Association for the study of Lung Cancer (IASLC).⁸⁾ However, the 2009 system has considerably complex refinements that are difficult to remember for clinicians involved in the management of lung cancer.⁹⁾

The aim of this study was to evaluate merits and

drawbacks of the 2009 system in the surgical patient population, retrospectively, and to suggest solutions to drawbacks in order to obtain a more simplified and precise staging system.

Materials and Methods

From January 1990 to March 2004, 1648 patients who underwent lung resection with systemic lymph node dissection for non-small cell lung cancer consisting of squamous cell carcinoma, adenocarcinoma, large cell carcinoma, and adenosquamous carcinoma were available for the present study. All patients were staged according to Naruke lymph node map, adopted by the Japan Lung Cancer Society as the official staging map.¹⁰⁾ Nineteen patients were excluded from the present study because their metastatic station 10 lymph nodes in Naruke lymph node map could not be converted to exact station in the Mountain-Dresler lymph node map.¹¹⁾ Therefore, 1629 patients were finally included.

Seven hundred and eighty-nine patients (48.4%) and 840 patients (51.6%) underwent lung resection at the Division of Thoracic Surgery, Department of Surgery, Nippon Medical School and the Department of Thoracic Surgery, Saitama Cancer Center, respectively. These patients consisted of 1,119 males (68.7%) and 510 females (31.3%), ranging in age from 29 to 90 years old (median age: 66 years). Clinically, 4 patients (0.2%) had stage 0 disease, 635 (39.0%) had stage IA disease, 367 (22.5%) had stage IB disease, 143 (8.8%) had stage IIA disease, 122 (7.5%) had stage IIB disease, 297 (18.2%) had stage IIIA disease, 43 (2.6%) had stage IIIB disease, and 18 (1.1%) had stage IV disease based on the 2009 system. Of these patients, 1,478 patients (90.7%) underwent lobectomy, 126 (7.8%) underwent pneumonectomy, and 25 (1.5%) underwent segmentectomy. One thousand, thirty-nine patients (63.8%) had adenocarcinoma, 498 (30.6%) had squamous cell carcinoma, 50 (3.0%) had large cell carcinoma, and 42 (2.6%) had adenosquamous carcinoma. Preoperative and postoperative adjuvant therapies were employed in 56 (3.4%) and 503 (30.9%) patients, respectively.

The 2009 system includes several changes in T and M descriptors.^{3, 5)} Accordingly, in the T descriptors, T1 is sub-classified into T1a (2 cm or less in greatest dimension) and T1b (more than 2 cm but not more than 3 cm), and T2 into T2a (more than 3 cm but not more than 5 cm) and T2b (more than 5 cm but not more than 7 cm). Tumors more than 7 cm are classified as T3. Separate tumor nodule in the same lobe as the primary tumor is classified

as T3, separate tumor nodule in a different ipsilateral lobe to that of the primary tumor as T4, and separate tumor nodule in a contralateral lobe as M1a. Tumors with pleural dissemination or malignant pleural or pericardial effusion are classified as M1a. Distant metastasis is classified as M1b. N0, N1, N2, and N3 descriptors are maintained as in the 1997 system.⁴⁾ In addition, the 2009 system includes changes in the TNM stage grouping as follows⁶⁾; T2bN0M0 cases are moved from stage IB to stage IIA, T2aN1M0 cases from stage IIB to stage IIA, and T4N0-1M0 cases from stage IIIB to stage IIIA.

Survival analysis

The overall survivals after surgery by pathological stages according to the 1997(1) and 2009 (2) systems for lung cancer were statistically analyzed using Kaplan-Meier estimated survival curves, and the significance of the difference was analyzed by the log-rank test. The statistical analysis was performed using SPSS 10.0 software package (SPSS, Inc, Chicago, IL, USA). $p < 0.05$ was considered significant.

Results

Comparisons of 5-year survival by each T, N, and M descriptor according to the 1997 and 2009 systems are shown in **Tables 1** and **2**, respectively. There were significant differences between each T descriptor except for T3 and T4 ($p = 0.1526$), between each N descriptor except for N2 and N3 ($p = 0.2214$), and between each M descriptor according to the 1997 system (**Table 1**). On the other hand, based on the 2009 system, there were significant differences between each T descriptor except for T2a and T2b ($p = 0.7234$), and between each M descriptor (**Table 2**). The 5-year survival rates for T2a N0 M0 and T2b N0 M0 were 69.3% and 78.0%, respectively ($p = 0.2043$). The 5-year survival rates for T2a N1 M0 and T2b N1 M0 were 54.9% and 56.7%, respectively ($p = 0.9993$). The 5-year survival rates for T2a N2, 3 M0 and T2b N2, 3 M0 were 28.8% and 38.1%, respectively ($p = 0.975$). The 5-year survival rates for T2a N0 M1 and T2b N0 M1 were 10.7% and 30.0%, respectively ($p = 0.7502$).

The 5-year survival rates by each pathological stage according to the 1997 system were as follows: 83.9% for stage IA ($n = 568$), 69.6% for stage IB ($n = 369$), 73.6% for stage IIA ($n = 41$), 49.0% for stage IIB ($n = 164$), 36.3% for stage IIIA ($n = 269$), 21.2% for stage IIIB ($n = 175$), and 13.7% for stage IV ($n = 39$). There is a significant difference in survival between stage IA and IB

Table 1 Comparisons of 5-year survival by each T, N, and M descriptor according to the 1997 system

T, N, and M descriptors in the 1997 system	Deaths/Number	5-Year survival (%)	Median survival time (mo)	p value
Tis	0/4	-	Not reached	-
T1	104/666	80.4	Not reached	-
T2	249/645	57.0	Not reached	0.0000 *
T3	88/148	33.4	28	0.0000 *
T4	111/166	21.1	26	0.1526
N0	240/1071	73.7	Not reached	-
N1	78/182	50.3	60	0.0000 *
N2	219/355	30.6	24	0.0000 *
N3	15/21	19.1	16	0.2214
M0	526/1590	62.3	Not reached	-
M1	26/39	13.7	17	0.0000 *

*: Statistical significance

Table 2 Comparisons of 5-year survival by each T and M descriptor according to the 2009 system

T, N, and M descriptors in the 2009 system	Deaths/Number	5-Year survival (%)	Median survival time (mo)	p value
Tis	0/4	-	-	-
T1a	33/346	87.7	Not reached	-
T1b	70/321	73.4	Not reached	0.0000 *
T2a	199/504	56.2	Not reached	0.0000 *
T2b	38/105	60.8	Not reached	0.7234
T3	175/296	31.0	30	0.0000 *
T4	37/53	16.8	14	0.0010 *
M0	532/1599	62.7	Not reached	-
M1a	9/14	29.0	25	0.0051 *
M1b	11/16	0	16	0.0229 *

*: Statistical significance

($p = 0.0000$), between IIA and IIB ($p = 0.0114$), between IIB and IIIA ($p = 0.0045$), and between IIIA and IIIB ($p = 0.0241$). There is no difference between IB and IIA ($p = 0.6731$) or between IIIB and IV ($p = 0.0577$) (**Fig. 1**). Adjuvant therapy did not affect survival in the 1997 system (data not shown). The 5-year survival rates by each pathological stage according to the 2009 system were as follows: 83.9% for stage IA ($n = 568$), 69.3% for stage IB ($n = 300$), 67.9% for stage IIA ($n = 155$), 44.0% for stage IIB ($n = 144$), 30.9% for stage IIIA ($n = 381$), 15.9% for stage IIIB ($n = 47$), and 18.7% for stage IV ($n = 30$). There is a significant difference in survival between stage IA and IB ($p = 0.0000$), between IIA and IIB ($p = 0.0001$), between IIB and IIIA ($p = 0.0016$), and between IIIA and IIIB ($p = 0.0049$). There is no difference between IB and IIA ($p = 0.6391$) or between IIIB and IV ($p = 0.4476$) (**Fig. 2**). Adjuvant therapy did not affect survival except for pathological stage IV in the 2009 system (data not shown). The 2009 system had better prognostic distinction between each pathological stage except for stages IB

and IIA ($p = 0.6391$), and stages IIIB and IV ($p = 0.4476$), compared with the 1997 system.

In the simulation, T2a and T2b tumors were unified as T2 tumors according to the results of our analyses of TNM descriptors in the 2009 system. Therefore, T2a N0 M0 and T2b N0 M0 were unified as T2N0M0 and T2aN1M0 and T2bN1M0 were unified as T2N1M0. All other TNM descriptors did not have a change. As for staging group, T2bN0M0 was moved from stage IIA to stage IB, and T2N0M0 was restaged as proposed stage IB. T2bN1M0 was moved from stage IIB to stage IIA, and T1a, bN1M0 and proposed T2N1M0 were restaged as new stage IIA. Only T3N0M0 was restaged as proposed stage IIB. All other TNM staging group did not have a change. The number of patients with proposed stage IB disease ($N = 350$) increased, but the number of patients with proposed stage IIA ($N = 125$) and proposed stage IIB ($N = 124$) disease decreased. The 5-year survival rates by each pathological stage according to the proposed system were as follows: 83.9% for stage IA ($n = 568$),

Fig. 1 Survival curves by each pathological stage according to the 1997 system.

Fig. 2 Survival curves by each pathological stage according to the 2009 system.

70.7% for stage IB ($n = 350$), 61.4% for stage IIA ($n = 125$), 41.9% for stage IIB ($n = 124$), 31.3% for stage IIIA ($n = 377$), 16.5% for stage IIIB ($n = 46$), and 15.5% for stage IV ($n = 35$) (**Fig. 3**). There is a significant difference in survival between stage IA and IB ($p = 0.0000$), between stage IB and IIA ($p = 0.0302$), between IIA and IIB ($p = 0.0034$), between IIB and IIIA ($p = 0.0065$), and between IIIA and IIIB ($p = 0.0049$). There is no difference between IIIB and IV ($p = 0.4476$). The proposed system had significant prognostic distinction in the proposed stages.

Discussion

The TNM staging systems have played a main role in planning treatment, evaluating prognosis and survival, and exchanging information. However, on the background of unsureness as to whether TNM has any relevance in non-surgical cases and the lack of validation of the previous editions, the 2009 system is devised on the basis of 100000 cases treated with all modalities from 1990 to 2000 around the world, and is validated internally and externally.^{1, 6)} The distribution of patients in each stage has

Fig. 3 Survival curves by each pathological stage according to the proposed system.

good balance in the 2009 system. The number of patients with stage IIA and IIIA disease increased, and the number of patients with stage IB, IIB, and IIIB decreased in our and other series.^{9, 12-14)} The number of patients with stage IV disease increased in other series,^{9, 12-13)} but it decreased in our series probably because of a small number of patients with pleural dissemination or malignant pleural effusion. The proportion of patients with stage IIIB and IV disease which were treated non-surgically in general decreased from 13.1% to 4.7% in our surgical series. The 2009 system is also reported to be clinically feasible in non-surgical series.¹⁵⁾ Therefore, the 2009 system seems to provide better optimal patient selection for all modalities.

The 2009 system has good as well as bad points with regard to prognostic evaluation. It has better prognostic distinction between stages IA and IB, stages IIA and IIB, stages IIB and IIIA, and stages IIIA and IIIB, but it shows no significant difference between stages IB and IIA, and the 5-year survival rate of patients with stage IIIB disease is inferior to that of patients with stage IV disease in our series. The 1997 system has been reported to have no significant difference between stages IB and IIA in many reports.¹⁶⁻²²⁾ The 5-year survival rate of patients with stage IB disease is inferior to that of patients with stage IIA disease in our series according to the 1997 system. Prognosis in stage IIA has not been evaluated properly because of small number of the patients.¹⁶⁻²²⁾ The proportion of patients with stage IIA disease in our series increases from 2.5% to 9.5% in the 2009 system,

and the 5-year survival rate of patients with stage IB disease is slightly superior to that of patients with stage IIA disease, but there is no difference between stages IB and IIA. Similar results are reported in another report.⁹⁾ In our analysis, poor prognostic distinction between patients with T2a and T2b tumors leads to poor prognostic distinction between patients with stage IB and IIA disease. Therefore, it is preferable to unify T2aN0M0 and T2bN0M0 as T2N0M0 and T2aN1M0 and T2bN1M0 as T2N1M0. As for staging group, it is preferable that T2bN0M0 is moved from stage IIA to stage IB, and T2N0M0 is restaged as proposed stage IB, and that T2bN1M0 is moved from stage IIB to stage IIA, and T1a, bN1M0 and proposed T2N1M0 are restaged as proposed stage IIA. In the simulation, the proposed system had significant prognostic distinction between the proposed stages. Therefore, T2a and T2b tumors can be unified as T2 tumors, and T2bN0M0 and T2bN1M0 can be moved to stage IB and stage IIA, respectively. Unification of T2a and T2b tumors to T2 tumors can contribute to simplify the 2009 system. Another prognostic problem in the 2009 system is poor prognostic distinction between stage IIIB and IV. The reversal of the 5-year survival rates between stage IIIB and IV is reported in our and other surgical series.^{9, 12-13)} One of the reasons for this seems to be a small number of patients with stage IIIB and IV disease in the surgical series, which did not represent the whole population of these stage groups.⁹⁾ Prospective and non-surgical studies are expected to clarify prognostic evaluation in advanced stages in the future.

Conclusion

The 2009 system provides better optimal patient selection for surgery and prognostic distinction between stages IA and IB, stages IIA and IIB, stages IIB and IIIA, and stages IIIA and IIIB, compared with the 1997 system. Unification of T2a and T2b tumors to T2 tumors improves prognostic distinction between stages IB and IIA, and contributes to simplify the 2009 system.

Conflict of Interest Statement

We, or members of our immediate family, have no relevant financial interests in this manuscript.

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