

## Comparison of the Effects of the Sixth and Seventh TNM Staging on Survival in Operable Non-Small Cell Lung Cancer

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### BACKGROUND/AIMS

In our study, cases who have been operated due to the diagnosis of non-small cell lung cancer (NSCLC) were staged by the 7<sup>th</sup> edition of the tumor, node, and metastasis (TNM) staging system and analyzed with respect to the survival association between previous and novel TNM systems.

### MATERIAL and METHODS

The study included 136 patients operated with a diagnosis of NSCLC between January 1, 2000 and January 1, 2010 at our clinic. Patients comprised 9 (6.62%) females and 127 (93.38%) males. The age range and mean age of the cases were 30-76 years and 59.4 years, respectively.

### RESULTS

Histopathological examination detected squamous cell carcinoma, adenocarcinoma, adenosquamous cell carcinoma, bronchioalveolar carcinoma, and large cell carcinoma in 88 (64.8%), 41 (30.2%), 4 (2.9%), 1 (0.7%), and 2 (1.4%) cases, respectively. No statistically significant association was found between mortality and tumor type ( $p=0.184$ ). According to the 7<sup>th</sup> edition of the TNM staging system, of the cases, 18 (13.2%), 40 (29.4%), 22 (16.2%), 33 (24.3%), and 23 (16.9%) were stage IA, stage IB, stage IIA, stage IIB, and stage IIIA, respectively. There was a statistically significant association between mortality and tumor stage in our study ( $p=0.028$ ). In addition, applying the 6<sup>th</sup> edition of the TNM staging revealed a statistically significant association between mortality and tumor stage ( $p=0.017$ ).

### CONCLUSION

Tumor stage was found to be the most important factor affecting survival in our study group. No statistically significant difference was determined between the subgroups when the previous and novel staging systems were compared.

**Keywords:** Tumor, node, and metastasis staging, non-small cell carcinoma of lung, survival

### INTRODUCTION

Lung cancer is the most common cancer in the world in terms of both incidence and mortality, accounting for 12.4% of newly diagnosed cancers. The incidence of lung cancer in Turkey is 75.8 per 100,000 among men and 9.6 per 100,000 among women (1, 2).

Tumor, node, and metastasis (TNM) staging was first proposed by Denoix in 1946 and was adapted to lung cancer by the Union for International Cancer Control (UICC) in 1968 and the American Joint Committee on Cancer (AJCC) in 1973. These two different approaches were re-examined in 1986 at the annual meeting of AJCC and UICC and converted into a single system under the name of the International Staging System for Lung Cancer (3).

Changes in TNM stage were made at the annual meetings, and the International Association for the Study of Lung Cancer (IASLC) proposed changes in the 7<sup>th</sup> TNM staging of malignant lung tumors, which was published in the *Journal of Thoracic Oncology* in 2007 (4). The TNM staging system was discussed, and a number of changes were proposed in the 12<sup>th</sup> World Lung Cancer Conference held in South Korea in September 2007; some updates were im-

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plemented in the T and M descriptors, whereas no significant change was made in the N identifier (5). Thus, the pathological stage of many patients has shifted to an upper or lower group. This situation was statistically significant when survival analysis was performed. The published 7<sup>th</sup> TNM staging system has been started to be used in daily clinical practice since 2009 (6).

The aim of the present study was to re-stage patients who underwent resection with the diagnosis of non-small cell lung cancer (NSCLC) according to the 7<sup>th</sup> TNM staging system and to determine the effect of the new system on survival.

## MATERIAL and METHODS

The clinicopathological stages of 136 patients who underwent resection due to NSCLC between January 1, 2000 and January 1, 2010 in our clinic were retrospectively reviewed and re-classified according to the 7<sup>th</sup> TNM staging system to investigate its effect on survival. Of the patients, 9 (6.6%) were females, and 127 (93.4%) were males. The mean age of the patients was 59.4 (min-max: 30-76) years. Age, gender, type and location of the tumor and its diameter, clinical stage of the disease according to the 6<sup>th</sup> TNM staging system, and resection type were noted from the patient files, and the survival data were obtained from the outpatient clinic records and telephone interviews. Oral consent was obtained from the relatives of all the patients who participated in the study.

Ethics committee approval was received for this study from the ethics committee of Trakya University School of Medicine. (TUBADK 2011/46, 23.02.2011)

The mean ages of the patients were 54.0 (min-max: 38-66) years in female cases and 59.8 (min-max: 30-76) years in male cases when the age distribution of cases was examined according to sex.

Lobectomy was performed in 81 (59.6%) cases, pneumonectomy in 44 (32.4%) cases, wedge resection in 7 (5.1%) cases, and mediastinal lymph node sampling concomitant with bilobectomy in 4 (2.9%) cases with NSCLC diagnosis.

Cases were followed up for 1-60 (average: 30.7) months. Of the cases, 56 (41.2%) died within this follow-up period.

## Statistical Analysis

Results were expressed as mean. Statistical analysis of data was made using the STATISTICA 7.0 (serial no.: AXF003C-775430FAN2) software (StatSoft; TIBCO Software, CA, USA). The Kaplan-Meier method was used to determine the mean life span and the log-rank test statistic for comparison of life span in different variables. The Cox regression model was used to determine the effects of independent variables on survival. A  $p < 0.05$  was accepted as statistically significant.

## RESULTS

According to histopathological examination, squamous cell carcinoma was determined in 88 (64.7%) cases, adenocarcinoma in 41 (30.1%) cases, adenosquamous cell carcinoma in 4 (2.9%) cases, large cell carcinoma in 2 (1.5%) cases, and bronchoalveolar

TABLE I. Change table between old T and new T

		New T						
		T1a	T1b	T2a	T2b	T3	T4	Total
T	T1	10	11	0	0	0	0	21
	T2	0	4	56	14	14	1	89
	T3	0	0	0	0	23	0	23
	T4	0	0	0	0	2	1	3
Total		10	15	56	14	39	2	136

carcinoma in 1 (0.8%) case. There was no statistically significant relationship between survival and histopathological type of tumor ( $p=0.184$ ). In addition, there was no significant relationship between tumor resection type and survival ( $p=0.169$ ).

Cases were followed up for 1-60 (average:30.7) months. Of the cases, 56 (41.2%) died within this follow-up period, with 54 of them males. No statistically significant relationship was found between gender and survival ( $p=0.323$ ).

When the patients were re-classified according to the 7<sup>th</sup> staging system, 21 (15.4%) cases were T1 according to the 6<sup>th</sup> staging system, whereas 25 (18.4%) cases were T1 according to the 7<sup>th</sup> staging system; 89 (65.4%) cases were T2 according to the 6<sup>th</sup> staging system, whereas 70 (51.5%) cases were T2 according to the 7<sup>th</sup> staging system; 23 (16.9%) cases were T3 according to the 6<sup>th</sup> staging system, whereas 39 (28.7%) cases were T3 according to the 7<sup>th</sup> staging system; 3 (2.2%) cases were T4 according to the 6<sup>th</sup> staging system, whereas 2 (1.4%) cases were T4 according to the 7<sup>th</sup> staging system. Changes in the T stage were statistically significant ( $p < 0.01$ ) (Table I).

The number of cases with stage 1a was 17 (12.5%), and there was no change. There were 56 (41.2%) cases in stage 1b according to the 6<sup>th</sup> staging system, 41 (30.1%) of which remained as stage 1b when they were re-classified according to the 7<sup>th</sup> staging system. Nine of the remaining 15 cases shifted into stage 2a, and 6 of them to stage 2b according to the 7<sup>th</sup> staging system. The most obvious change was observed in the stage 2a group. Three (2.2%) cases were classified as stage 2a according to the 6<sup>th</sup> staging system, whereas 22 (16.2%) cases were classified as stage 2a according to the 7<sup>th</sup> staging system. Ten cases had shifted from stage 2b group into stage 2a, and 9 cases from stage 1b. The number of cases in stage 2b decreased to 33 (24.3%) from 41 (30.1%) with the 7<sup>th</sup> staging system. In the stage 3a group, the number of cases increased from 15 (11%) to 23 (16.9%) with the 7<sup>th</sup> staging system.

There were a total of 3 (2.2%) cases in stage 3b and 4 cases in the 6<sup>th</sup> staging system, whereas no cases were classified in these stages according to the new staging system. Changes between stages were statistically significant ( $p < 0.01$ ) (Table 2).

When the relationship between the 6<sup>th</sup> staging system and survival was analyzed, as the disease stage increased, survival decreased significantly ( $p=0.017$ ) (Figure 1). Similarly, it was determined that the disease stage according to the 7<sup>th</sup> staging system was statistically significantly related with survival ( $p=0.028$ ) (Figure 2).

**TABLE 2.** Change table between old stage and new stage

		New stage					
		1a	1b	2a	2b	3a	Total
Stage	1a	17	0	0	0	0	17
	1b	0	41	9	6	0	56
	2a	0	0	3	0	0	3
	2b	0	0	10	26	5	41
	3a	0	0	0	0	15	15
	3b	0	0	0	1	2	3
	4	0	0	0	0	1	1
	Total	17	41	22	33	23	136

**DISCUSSION**

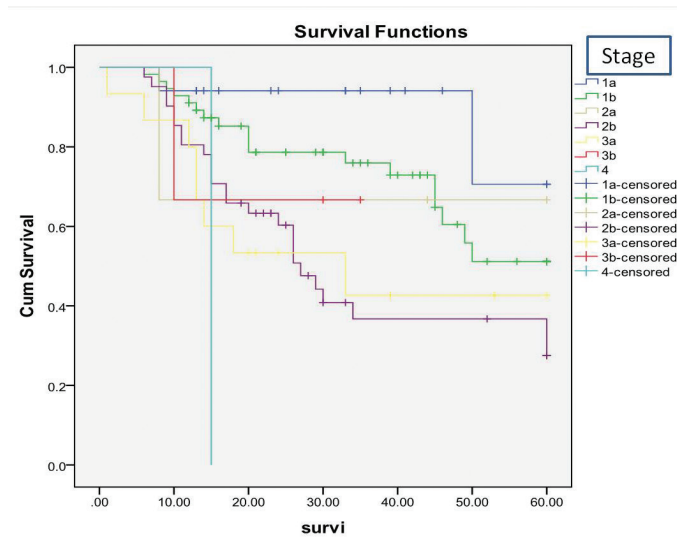
A convenient staging system in lung cancer is essential to determine the prognosis and decision in treatment strategy. The 6<sup>th</sup> TNM staging system, which was revised in 1997, was not suitable for evaluating all patients with lung cancer because it included a limited number of patients. Patients were composed of only one geographical region, and only surgical treatment was applied to the majority of the patients. Since tumors of similar clinical and pathological characteristics were included in this staging system, tumor subgroups could not be studied, and the validity of the classification was not investigated. Then, IASLC carried out a project named "Lung Cancer Staging Project" and performed survival analysis for different cases of T, N, and M descriptors, and their effects on prognosis were determined. The established 7<sup>th</sup> staging system was introduced in 2009 (1, 5-7).

The most important changes in the new staging system were in the T and M evaluations. Statistical evaluation of the obtained data on survival revealed that a tumor size of 2, 3, 5, and 7 cm affected the prognosis significantly. Tumors were classified as T1a ( $\leq 2$  cm), T1b ( $>2$  cm- $\leq 3$  cm), T2a ( $>3$  cm- $\leq 5$  cm), T2b ( $>5$  cm- $\leq 7$  cm), and T3 ( $>7$  cm) according to their size; meanwhile, the prognosis of the satellite nodules in the same lobe was shown to be better than that of the other T4 tumors, thus these tumors were considered as T3. According to the same data, T4 tumors with malignant pleural effusion had been demonstrated to have worse prognosis than others, thus these tumors were classified as M1a (6, 7).

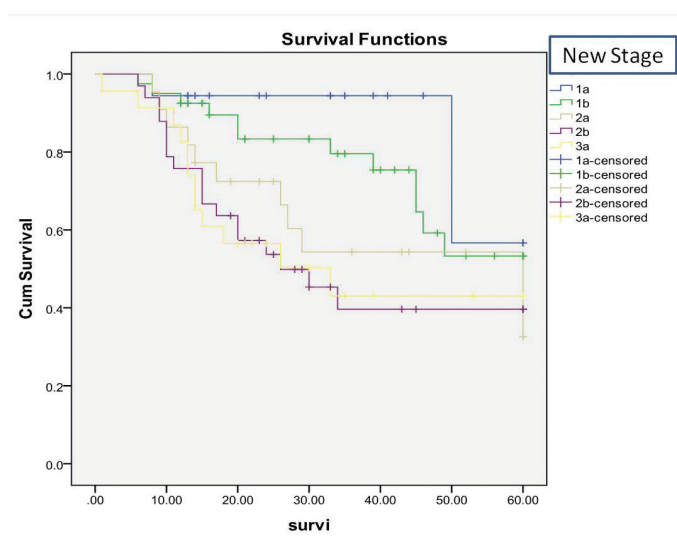
During the new staging trials, though the effects of single zone N1 and multiple zone N1 or single zone N2 involvement on survival had been shown to be different, there was no proposal for change in the N classification since validity assessment could not be performed (6, 7). Considering the case migrations between the old and new staging systems, Strand et al. (8) showed that most migrated cases are in the stage 2a and 3a groups, and in their study, the number of stage 2a cases in the patient population changed from 4.1% to 20.4%, and cases in stage 3a changed from 8.4% to 16.4%. The decrease in the number of cases was mostly observed in the stage 1b and 2b groups. The number of cases decreased from 38.6% to 27.4% in stage 1b and from 17.8% to 11.9% in stage 2b. The only group with no change was identified as stage 1a.

In the study by Suzuki et al. (9), it was shown that the greatest increase in the number of cases is in stage 2a, which increased from 3.1% to 10.2% after re-staging. The group with the most decrease is in stage 3b. The number of cases in this group decreased from 17.4% to 4.6%. It has been determined that the vast majority of cases in this group have been displaced to stage 3a. In their study, stage 1a was the only group with no change.

Similar to other previous studies, there were migrations between the groups observed in our study. The most increase in the number of cases occurred in stage 2a, which increased from 3 (2.1%) in the old system to 22 (16.1%) according to the new staging system that started to be used in 2009. It was seen that the number of cases also increased in the stage 3a group according to the new staging system. The number of cases decreased in both stages 1b and 2b.



**FIGURE 1.** Relationship between stage and survival according to the 6<sup>th</sup> tumor, node, and metastasis (TNM) staging system



**FIGURE 2.** Relationship between stage and survival according to the 7<sup>th</sup> tumor, node, and metastasis (TNM) staging system

The number of cases decreased from 41.2% to 30.1% in stage 1b and from 30.1% to 24.2% in stage 2b. As in all previous studies, there was no change in the number of cases in stage 1a. The case migration between the groups was statistically significant. The main factor affecting the shift between stages was the changes in the T system.

In the study conducted by Chansky et al. (10), the median survival of cases staged according to the new staging system was found as 95 (66%) months for stage 1a, 75 (56%) months for stage 1b, 44 (43%) months for stage 2a, 29 months for stage 2b, and 19 (23%) months for stage 3a. The relationship between disease stage and survival was shown to be statistically significant.

In the study by Rami-Porta et al. (6), a 5 year survival analysis of the patients was conducted according to the pathology results and new staging system, and the 5 year survival rate was found as 73% for patients in stage 1a, 58% for stage 1b, 46% for stage 2a, 36% for stage 2b, 24% for stage 3a, 9% for stage 3b, and 14% for stage 4.

In the study by Strand et al. (8), a similar relationship was found between new staging system and survival of the patients. The 5 year survival rates were 60.3% in stage 1a, 57.9% in stage 1b, 37.9% in stage 2a, 31.2% in stage 2b, 17.7% in stage 3a, 13.3% in stage 3b, and 14.4% in stage 4. Based on the subgroups of the 6<sup>th</sup> and 7<sup>th</sup> TNM staging, many studies have reported that a 5 year survival did not significantly change between the subgroups.

Goldstraw et al. (4) found that the expected 5 year survival rates are 73% for stage 1a, 58% for stage 1b, 46% for stage 2a, 36% for stage 2b, 24% for stage 3a, 9% for stage 3b, and 13% for stage 4. According to the 6<sup>th</sup> TNM staging system, the 5-year survival rates were determined as 50% for stage 1a, 43% for stage 1b, 36% for stage 2a, 25% for stage 2b, 19% for stage 3a, 7% for stage 3b, and 2% for stage 4. They found a 5 year survival for each group to be statistically significant when the 6<sup>th</sup> and 7<sup>th</sup> TNM grading systems were compared within their subgroups with a lower and an upper group.

Detterbeck et al. (11) stated that the new staging system proposed brings many innovations, but that the innovations introduced are still controversial, and that new subgroups created by the new staging system are more prognostic.

In our study, the 5 year survival rate decreased as the stage increased, both in the 6<sup>th</sup> and in the 7<sup>th</sup> grading systems. The relationship between disease stage and survival rate was found to be statistically significant in both staging systems. However, there were no statistically significant migrations between the subgroups.

In conclusion, the 7<sup>th</sup> TNM grading system, which was introduced in 2009, has provided guidance on the correctness of the survival analysis in terms of the T and M classifications and the selection of appropriate patients for surgical treatment. However, no changes have been done in the N classification with regard to surgical decision making or per-operative patient management, thus it still cannot fully meet the expectation. The expectation from the updated advanced staging systems is to reveal the survival differences between the single focus N1 and

the multifocus N1 together with more effective guidance in patient selection by performing survival analyses of multifocus N1, single focus N2, and multifocus N2 patients.

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**Informed Consent:** Oral consent was obtained from the relatives of all the patients who participated in the study.

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**Conflict of Interest:** The authors have no conflicts of interest to declare.

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