Comparison of seventh TNM and eighth TNM staging system in stage III non–small cell lung cancer patients treated with concurrent chemoradiotherapy

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Introduction

Stage classification of a cancer is important as it provides a nomenclature for description and grouping of the patients and helping clinicians for selecting treatment options and predicting the probable outcomes. It enables the comparison and classification of patients with different size and extent of disease. TNM classification is used for staging of lung cancer, according to the definitions regarding primary tumor for T, nodal stations for N, and metastatic lesions for M.[1] The eighth edition of TNM lung cancer staging and proposals has been introduced in 2015 and implemented through January 2017 in countries beside United States of America.[2]

Lung cancer staging is unique as it is based on a statistical analysis of an international database of more than 100,000 patients from 19 countries which was developed by International Association for the Study of Lung Cancer for the seventh revision of TNM staging.[3] Like the staging of tumors other than lung cancer, this staging system develops a language for defining the anatomical extent of disease, which is one aspect that affects prognosis. Like the seventh edition, eighth revision of TNM staging of lung cancer constitutes information from a large patient

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database in the following ten year period. Ninety-four thousand seven hundred eight patients from 16 countries were included in the database.[4]

The differences from the former seventh TNM classification are mostly regarding the T stage of the tumor.[5] Tumor size is determined by the largest dimension of the solid portion by 1 mm slice thickness of computed tomography (CT) with lung window settings clinically, or invasive portion considering the solid parts of tumor pathologically. Tumor size is subdivided into 1 cm increments up to 5 cm, and tumors >5 cm and ≤7 cm are classified as T3, and tumors exceeding 7 cm are classified as T4. The distance of tumor to carina or presence of total or partial atelectasis are not regarded for classification, and tumors involving main stem bronchus and causing atelectasis or obstructive pneumonitis are classified as T2 disease. Diaphragm involvement is classified as T4. Also other than T staging, tumors with involvement of more than one distant sites are classified as M1c.[6] N-stage categorization remained the same as the seventh edition.[7]

The dataset of eighth edition of TNM for lung cancer is mostly composed of surgically treated patients. While 57.7% of the patients were treated with surgery alone, another 27% were surgically treated together with chemotherapy or radiotherapy.[4] Patients treated with concurrent chemotherapy only form 4.7% of dataset. Thus, the utility and discriminative power of this system would be more limited in these subset of patients.

In this study, we aimed to evaluate the stage changes and prognostic discriminative features after the application of eighth TNM in a subset of non–small cell lung cancer (NSCLC) patients, with stages of IIIA and IIIB according to the seventh TNM criteria, and treated with concurrent chemoradiotherapy (CRT) alone.

Materials and methods

This multicenter, retrospective cohort study was carried out at the two hospitals from two different provinces of Turkey. The patients with unresectable stage III NSCLC treated with concurrent CRT between 2008 and 2015 were reviewed for this analysis. Unresectable stage III disease was defined by multiple and/or bulky N2 or N3 mediastinal lymph nodes and T4 disease detected on the initial staging work-up. All patients underwent conventional staging including with CT of the chest and upper abdomen, contrast enhanced-brain magnetic resonance or CT imaging, 18F-Floro deoxy glucose positron emission tomography (PET)/CT imaging, bronchoscopy, endobronchial ultrasonography-transbronchial needle biopsy or mediastinoscopy. The patients who had the following criteria were treated with definitive (radiation dose ≥ 60 Gy) concurrent CRT (1) histologically diagnosed NSCLC, (2) Eastern Cooperative Oncology Group (ECOG) performance status of 0-1, (3) weight loss of <5% in the previous 3 months. Patients with N3 disease due to supraclavicular lymph node involvement were not treated with concurrent CRT. Adjuvant chemotherapy was not allowed. Patients treated with surgery of lung were excluded from analysis.

Chemotherapy

All patient cohort received cisplatinum 50 mg/m^2 intravenously on days 1, 8, 29, and 36 with etoposide 50 mg/m^2 intravenously on days 1-5 and 29-33. Hydration and antiemetic regimen were used for all patients. Concurrent chemotherapy was applied on the first day of radiotherapy (RT).

Radiotherapy

RT was delivered using conventional fractionation (1.8-2.0 Gy/day, 5 days/week) with a total dose of 60-66 Gy using 6-18 MV photon beams. All patients received three-dimensional (3D)

conformal RT. The gross tumor volume (GTV) consisted of the primary tumor and the regional lymph nodes considered positive (SUVmax > 2.5) on PET scan even if not involved by CT scan. Any intrathoracic lymph nodes with a diameter >10 mm in the short axis were included in GTV regardless of the PET scan. For GTV definition on CT, pulmonary window settings were used to contour the pulmonary tumor and hilum, and the predefined mediastinal window settings were used to contour the mediastinal lesions. Margins for GTV to clinical target volume (CTV) were 5-7 mm for squamous cell carcinoma and 6-8 mm for other histologic types. To generate the planning target volume (PTV) 5-10 mm margin was added to the CTV to compensate setup errors and target motion. Thoracic radiotherapy (TRT) was delivered to this volume at a daily dose of 1.8-2.0 Gy to a total dose of 45-46 Gy over 5 weeks. The sixth and seventh weeks of TRT were delivered to a smaller target volume encompassing the primary tumor and lymph nodes known to be involved with disease. Dose volume histograms for the PTV, normal lung, esophagus, and heart have been calculated to gain full knowledge of the 3D dose distribution. The total dose to the spinal cord was restricted to 48 Gy or less. For the heart, dose (D) mean and percentage volume receiving a dose of 40 Gy or more (V40) was calculated. For the lungs, percentage of lung volume receiving a dose of 20 Gy or more (V20) and mean lung dose was calculated. Mean lung dose was defined as the average dose to total normal lung volume. For the esophagus, mean esophageal dose was calculated. Coverage of the CTV by the 95% isodose line was mandatory. PTV coverage with 95% isodose line was not achievable in some patients due to critical organ dose constraints. Treatment was delivered using a linear accelerator. TRT was interrupted for grade 3 or greater nonhematologic toxicity or grade 4 hematologic toxicity.

Patient's follow-up

Patients underwent response evaluation with CT of chest through the upper abdomen in the 4 weeks of completing treatment and follow-up continued every 3 months for the first 2 years, every 6 months for third year, and yearly thereafter, with repeat CT of chest through the adrenals on each visit. Response was assessed according to the response evaluation criteria in solid tumors criteria. Toxicities were analyzed using the Common Toxicity Criteria for Adverse Events (version 3.0).

Stages were classified according to seventh TNM based on clinical stage. For the purpose of comparison, seventh TNM stages were reclassified and regrouped according to eighth TNM for each patient.

Statistical analysis

This study was designed as a retrospective, multicenter cohort study. Overall survival (OS) and progression-free survival (PFS) were defined as the interval between the first day of CRT day and the date of death/last visit and date of progression, respectively. Locoregional relapse or distant progression was defined as any type of local/regional or distant metastasis of the disease. Survival was analyzed by using the Kaplan-Meier method. Survival analyses were performed in both staging systems, according to the T category, N category, and stage groupings. Log-rank test was used for comparison of survival differences between staging systems. All analyses were performed using SPSS software (version 18.0; SPSS, Inc., Chicago, IL). *P* value < 0.05 was considered as statistically significant.

Table 1
Patient characteristics.

Characteristics		Number of patients
Age (years)		Median 58 (35-74)
Sex	Male	96 (93.2)
	Female	7 (6.8)
Weight loss	<5%	22 (21.4)
	None	81 (76.8)
Histological type	Squamous cell	69 (67)
	Adenocancer	24 (23.3)
	Non–small cell	10 (9.7)
Performance status	ECOG 0	53 (51.5)
	ECOG 1	50 (48.5)
Treatment response	Total	15 (14.6)
	Partial	45 (43.7)
	Stable	33 (32)
	Progression	9 (8.7)
	Unidentified	1 (1)

Results

Patients

A total of 103 patients with a median age of 58 (range 35-74) were included in the study. Males constituted 93.2% ($n = 96$) of the study population, and squamous cell carcinoma was the prominent histological subtype (67%, $n = 69$). Five percent weight loss was present in 21.4% of the patients. Performance status was either ECOG 0 (51.5%) or ECOG 1 (48.5%). Patient characteristics are seen in Table 1. All patients were treated with curative concurrent CRT alone. The median follow-up duration for patients in life was 51 (range 17-111) months. Eighty patients (77.7%) died during the follow-up period, and progressive disease was evident in 87 (84.5%) patients.

Stages

Staging procedures included PET/CT imaging results in all patients. Only 6 of 103 patients underwent invasive mediastinal staging. T-stage distribution according to the seventh TNM was 0 (0%), 4 (3.9%), 17 (16.5%), 3 (2.9%), 22 (21.4%), 57 (55.3%) patients, respectively, for T1a, T1b, T2a, T2b, T3, and T4. According to the eighth TNM, number of patients in T1a, T1b, T1c, T2a, T2b, T3, and T4 groups were, respectively, 0 (0), 2 (1.9%), 3 (2.9%), 13 (12.6%), 9 (8.7%), 10 (9.7%), and 66 (64.1%). In total, T stage was changed in 24 patients (23.1%). TNM status of the study population according to the seventh and eighth TNM staging is seen in Table 2.

Study population was composed of 52 (50.5%) stage IIIA and 51 (49.5%) stage IIIB patients regarding seventh TNM. After restaging according to the eighth TNM criteria, 15 patients (14.6%) were reclassified to have stage IIIC disease, and 30 patients (29.1%) had stage IIIA disease, while 58 patients (56.3%) had stage IIIB disease. In total, reclassification changed the stage groups of 41 patients (39.4%), 39 patients (37.5%) were upstaged (24 patients [23.1%] from IIIA to IIIB and 15 patients [14.4%] from IIIB to IIIC) and 2 patients (1.9%) were downstaged from IIIB to IIIA. Changes of the T-stage categories and stage groups of study population are seen in Table 3.

Survival

Median survival of the study group was 25.1 months (95% confidence interval; 19.08-31.12) and median PFS was 12.5 months (95% confidence interval; 9.22-15.78). Eighty patients (77.7%)

Table 2
Stage groupings of the study population according to the seventh TNM (a) and eighth TNM (b) staging systems.

	N0	N1	N2	N3
(a)				
T1a	IA	IIA	IIIA	IIIB
T1b	IA	IIA	IIIA (3)	IIIB (1)
T2a	IB	IIA	IIIA (15)	IIIB (2)
T2b	IIA	IIB	IIIA (2)	IIIB (1)
T3	IIB	IIIA (1)	IIIA (15)	IIIB (6)
T4	IIIA (14)	IIIA (2)	IIIB (31)	IIIB (10)
	N0	N1	N2	N3
(b)				
T1a	IA1	IIB	IIIA	IIIB
T1b	IA2	IIB	IIIA (2)	IIIB
T1c	IA3	IIB	IIIA (1)	IIIB (2)
T2a	IB	IIB	IIIA (12)	IIIB (1)
T2b	IIA	IIB	IIIA (7)	IIIB (2)
T3	IIB	IIIA (1)	IIIB (7)	IIIC (2)
T4	IIIA (14)	IIIA (2)	IIIB (37)	IIIC (13)

Table 3
Changes of T categories and stage groups after application of eighth TNM staging system.

(a) T categories

		8-TNM							Total
		T1a	T1b	T1c	T2a	T2b	T3	T4	
7-TNM	T1a	-	-	-	-	-	-	-	-
	T1b	-	2	2	-	-	-	-	4
	T2a	-	-	-	12	5	-	-	17
	T2b	-	-	-	-	1	2	-	3
	T3	-	-	1	2	2	8	9	22
	T4	-	-	-	-	-	-	57	57
Total		-	2	3	14	8	10	66	103

(b) Stage groups

		8-TNM			Total
		IIIA	IIIB	IIIC	
7-TNM	IIIA	28	24	-	52
	IIIB	2	34	15	51
Total		30	58	15	103

died during the follow-up period and 1 year, 3 years, and 5 years survival rates were 75.7%, 36.1%, and 20.8%, respectively. Disease-free survival was 50.4% for 1 year, 21.2% for 3 years, and 14.9% for 5 years.

OS curves were evaluated according to the T-stage and stage grouping for both seventh TNM and eighth TNM. Differences in survival according to the T-stage factors was not significant for both seventh TNM and eighth TNM classifications ($P = 0.32$ for seventh TNM and $P = 0.43$ for eighth TNM). Differences of survival in stage IIIA and IIIB groups according to the seventh TNM was not significant ($P = 0.52$). OS of stage groups in eighth TNM did not reveal a significant survival difference between stages IIIA and IIIB, IIIA and IIIC, IIIB and IIIC ($P = 0.21$, $P = 0.41$, and $P = 0.72$, respectively). N-stage definition is not different between seventh TNM and eighth TNM classification systems, but also there was not a significant difference between N-stage groups of study population ($P = 0.91$). OS curves for T category, N category, and stage groups are shown in Figs 1 and 2.
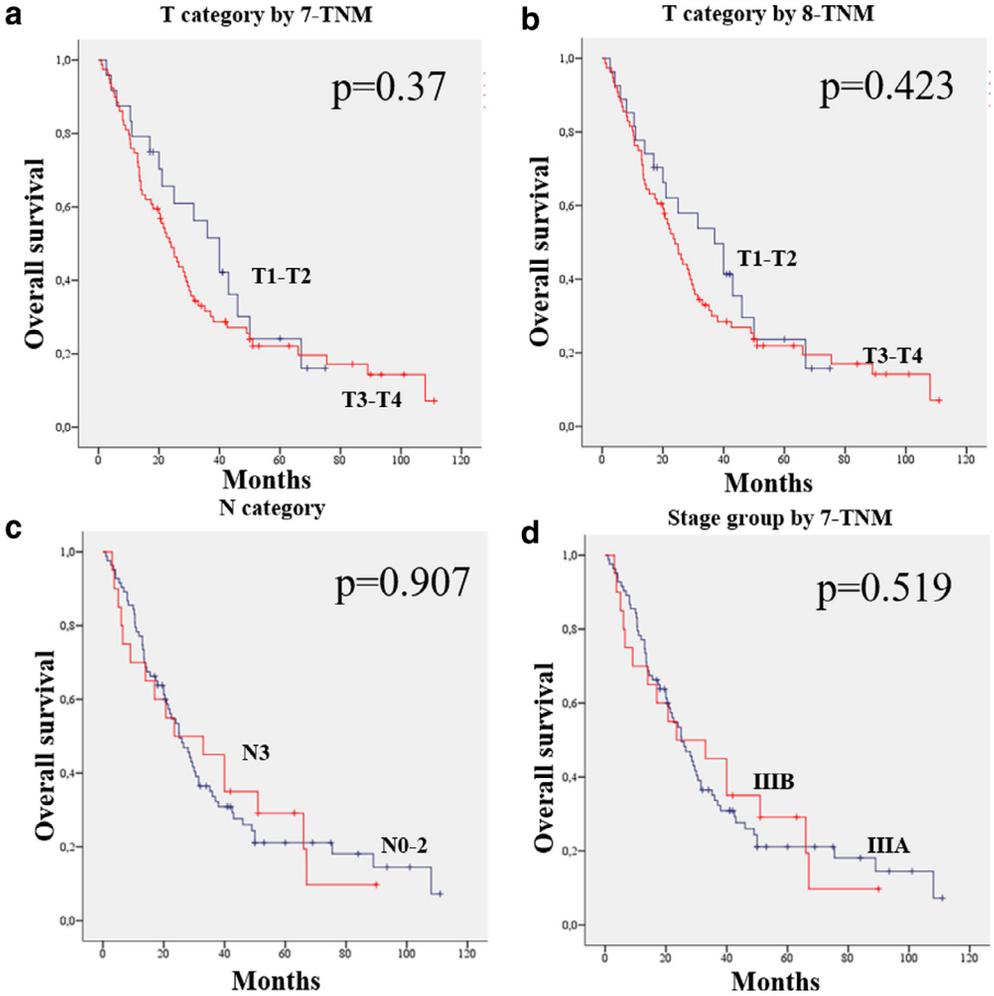
Fig. 1. OS curves of patients according to (a) T category by seventh TNM staging system, (b) T category by eighth TNM staging system, (c) N category, (d) Stage groupings by seventh TNM staging system, and (e) Stage grouping by eighth TNM staging system.
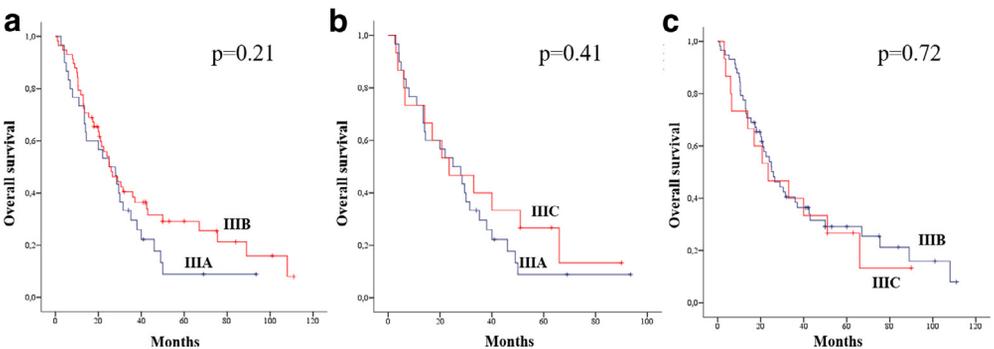

Fig. 2. Comparison of overall survival curves of stage III subgroups according to the eighth TNM staging system: (a) Comparison of stages IIIA and IIIB, (b) Comparison of stages IIIA and IIIC, and (c) Comparison of stages IIIB and IIIC.
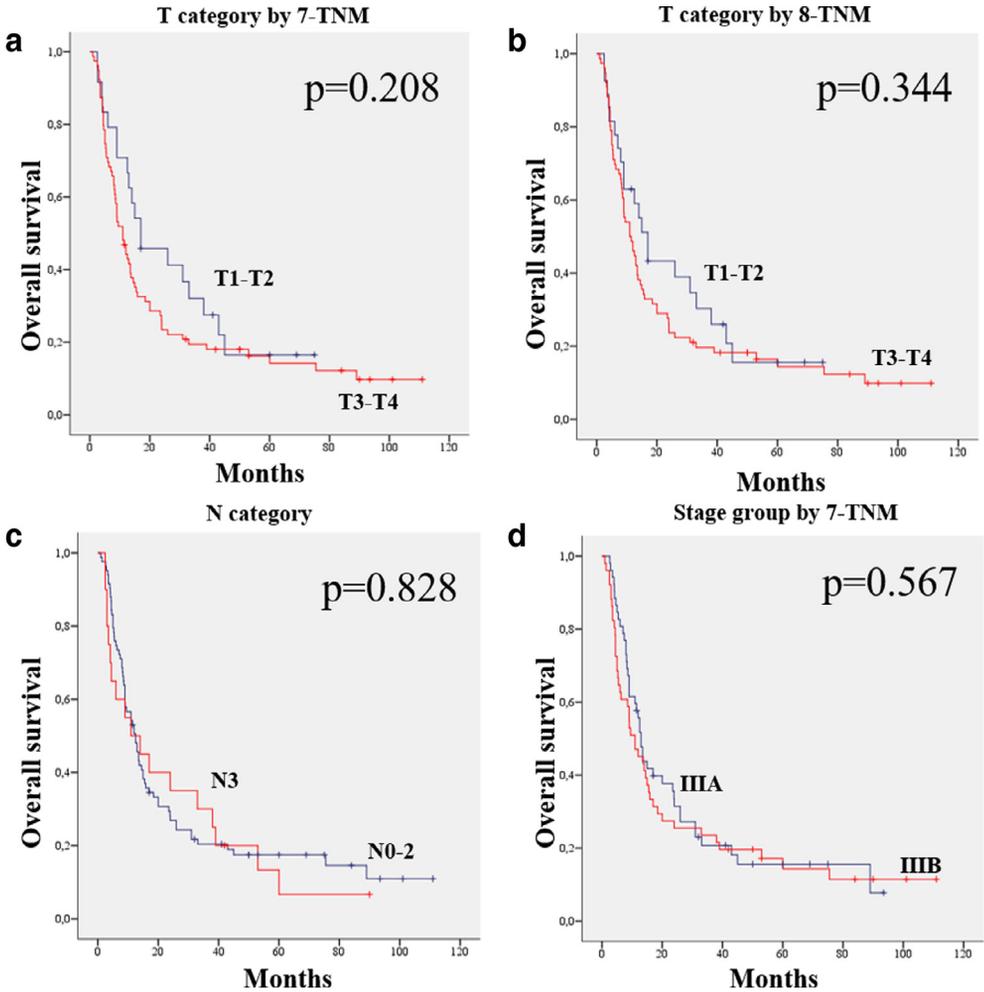
Fig. 3. PFS curves of patients according to (a) T category by seventh TNM staging system, (b) T category by eighth TNM staging system, (c) N category, (d) Stage groupings by seventh TNM staging system, and (e) Stage grouping by eighth TNM staging system.

Also, for PFS rates, there was not any statistically significant survival difference between T-stage groups according to seventh TNM and eighth TNM ($P = 0.21$ and $P = 0.34$, respectively). Again there was not any significant difference of PFS according to the stage groups of seventh TNM and eighth TNM and also according to the N stage of study population ($P = 0.57$, $P = 0.55$, and $P = 0.83$, respectively). PFS of stage groups in eighth TNM did not reveal a survival difference between stages IIIA and IIIB, IIIA and IIIC, IIIB and IIIC ($P = 0.30$, $P = 0.73$, and $P = 0.57$, respectively). Survival curves of PFS are seen in Figs 3 and 4.

Discussion

In this study, we compared the prognostic discrimination of seventh and eighth TNM staging of non–small cell lung cancer in a particular group of patients who were inoperable and treated
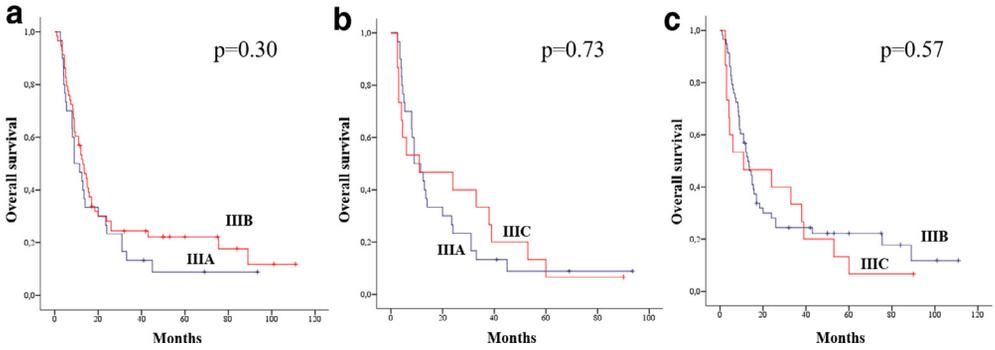
Fig. 4. Comparison of PFS curves of stage III subgroups according to the eighth TNM staging system: (a) Comparison of stages IIIA and IIIB, (b) Comparison of stages IIIA and IIIC, and (c) Comparison of stages IIIB and IIIC.

with concurrent CRT as having stage IIIA or IIIB disease according to the seventh TNM. Neither seventh TNM classification system nor eighth TNM classification system revealed statistically significant difference of overall or PFS curves, regarding T category, N category, or stage groups of these particular patients.

It should be always kept in mind that prognosis of a particular patient is not solely depends on the anatomical extent of the disease defined by staging systems. Many other factors like comorbidities, molecular characteristics of tumors, histological subtypes, or even geographic localizations affect the survival of the patients.[2] Staging systems are important as they create a nomenclature for effective comparison of patients with different tumor extensions, also help clinicians for deciding the appropriate treatment options in a particular patient.

Here, we present a magnification of a group of lung cancer patients, with stages of IIIA and IIIB disease according to the seventh TNM treated with concurrent CRT. All patients were treated with a uniform treatment plan by using 3D conformal radiotherapy and identical chemotherapy regimen.

In their recent study, Choi et al also investigated the application of eighth TNM on 64 patients treated with concurrent CRT, and they showed that survival curves of N category were significantly different.[8] Also further division of stage III into 3 groups by adding IIIC group in eighth TNM also showed significant difference especially between stage IIIB and IIIC groups. However, their study population was more heterogenous than ours, as including stages IB, IIA, and IIB. Also their stage IIIC was mostly composed of N3 disease. N3 disease is excluded in some studies as they have poorer prognostic outcomes.[9,10] Our stage IIIB group was mostly composed of T4 disease with N2 nodal involvement. This distribution of our study population may be one of the reasons of the lack of statistical significant difference of overall and PFS curves among stages and N categories.

The seventh TNM staging system T categories were evaluated for prognostic difference in a subset of 8099 patients, who had complete resection with node negative disease.[5] Another analysis was made in 868 patients without distant metastasis and with treatment of radiotherapy or CRT.[11] In that analysis, study population was mostly composed of N2 disease (62.8%) and patients with tumors less than or equal to 3 cm had significantly higher survival than patients with tumors of 3-7 cm diameter. There were not any statistically significant difference between T2a, T2b, and T3 disease. Effect of size on prognosis was found to be weak. One possible explanation of this was the masking effect of node involvement on the effect of tumor size. But also N categories were not found to be a prognostic factor in these subset of patients. Also prognostic effect of tumor size may vary according to the treatment given. These factors also may be a confounding factor in our study population.

There are also some other studies investigating the prognostic effect of tumor size in patients treated with radiotherapy with or without chemotherapy.[12-15] But none of these studies investi-

gated the size groups of TNM staging system. In some studies tumor size and lymph node size was considered as a whole. Some also included patients who had induction chemotherapy.

It is also known that, involvement of the nodal zone constitutes a heterogenous group of patients. Differently from other cancer types, the number of involved lymph nodes is not a criterion for discriminating stage groups in lung cancer patients.[16] The categorization of nodal status in lung cancer was not changed in both revisions from sixth to seventh and from seventh to eighth.[17] Beside from the standardization problems of pathologic nodal staging, one reason for this is the lack of precise determination of the involved lymph nodes with available techniques for clinical staging. PET does not clearly separates metastatic nodes for accurate counting.[5] However, in some studies, like the study of Lee et al, it was shown that number of involved lymph nodes reflect prognosis.[18] pN1 and pN2 categories are found to be prognostically heterogenous and multiple N2 was found to have better prognosis than single N2, and the same is true for N1 nodal disease.[19,20] Also skip metastasis of N2 disease share similar prognostic features with multiple N1 disease.[5] As our patient population is mainly composed of N2 and N3 disease, number of nodal stations involved may have affected the outcome of our study population.

The new database of International Association for the Study of Lung Cancer consisted of 94,708 patients diagnoses from 1999 to 2010.[3] Eighty-five percent of the patients in the database were surgically treated either alone or with other modalities. The patients treated with concurrent CRT formed 4.7% of the database. So it may have some limitation in discriminating survival difference especially in locally advanced disease treated with concurrent CRT.

Our study bears the disadvantages of retrospective evaluation of our dataset. Although our study group was homogenous in terms of chemotherapy regimen and radiotherapy technique, the number of patients was limited. These may also influence the statistical power of our study. Also, one limitation of our study is that staging procedures of our study population is mostly PET based, and only in 6 patients invasive mediastinal staging was performed. The comparison of outcomes of patients with or without invasive staging was not eligible, because of the small proportion of invasively staged patients.

Conclusions

In conclusion, we failed to show difference between survival curves of stage IIIA and stage IIIB lung cancer patients treated with concurrent CRT. Subdivision of stage III to stages IIIA, IIIB, and IIIC may not have clinical impact in these subset of patients. In the future, additional features of nodal disease such as the number of metastatic nodes may be taken into consideration for subdivision of locally advanced disease.

References

1. Tsim S, O'Dowd CA, Milroy R, Davidson S. Staging of non-small cell lung cancer (NSCLC): a review. *Respir Med*. 2010 Dec;104(12):1767–1774.
2. Detterbeck FC. The eighth edition TNM stage classification for lung cancer: what does it mean on main street? *J Thorac Cardiovasc Surg*. 2018 Jan;155(1):356–359 Epub 2017 Sep 28.
3. Goldstraw P, Crowley J, Chansky K, Giroux DJ, Groome PA, Rami-Porta R, Postmus PE, Rusch V, Sobin L. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM classification of malignant tumours. *J Thorac Oncol*. 2007 Aug;2(8):706–714 Erratum in: J Thorac Oncol. 2007 Oct;2(10):985.
4. Rami-Porta R, Bolejack V, Giroux DJ, Chansky K, Crowley J, Asamura H, Goldstraw P. The IASLC lung cancer staging project: the new database to inform the eighth edition of the TNM classification of lung cancer. *J Thorac Oncol*. 2014 Nov;9(11):1618–1624.
5. Rami-Porta R, Bolejack V, Crowley J, Ball D, Kim J, Lyons G, Rice T, Suzuki K, Thomas Jr CF, Travis WD, Wu YL. The IASLC Lung Cancer Staging Project: proposals for the revisions of the T descriptors in the forthcoming eighth edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2015 Jul;10(7):990–1003.
6. Eberhardt WE, Mitchell A, Crowley J, Kondo H, Kim YT, Turrisi 3rd A, Goldstraw P, Rami-Porta R. The IASLC Lung Cancer Staging Project: proposals for the revision of the M descriptors in the forthcoming eighth edition of the TNM classification of lung cancer. *J Thorac Oncol*. 2015 Nov;10(11):1515–1522.
7. Asamura H, Chansky K, Crowley J, Goldstraw P, Rusch VW, Vansteenkiste JF, Watanabe H, Wu YL, Zielinski M, Ball D, Rami-Porta R. The International Association for the Study of Lung Cancer Lung Cancer Staging Project: proposals for

the revision of the N descriptors in the forthcoming 8th edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2015 Dec;10(12):1675–1684.

8. Choi HS, Jeong BK, Jeong H, Lee YH, Ha IB, Song JH, Kang KM. Application of the new 8th TNM staging system for non-small cell lung cancer: treated with curative concurrent chemoradiotherapy. *Radiat Oncol*. 2017 Jul 21;12(1):122.

9. Albain KS, Swann RS, Rusch VW, 3rd TurrisiAT, Shepherd FA, Smith C, Chen Y, Livingston RB, Feins RH, Gandara DR, Fry WA, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. *Lancet*. 2009;374:379–386.

10. Imperatori A, La Salvia D, Rotolo N, Nardecchia E, Bandera M, Toungoussova O, Spanevello A, Dominioni L. Five-year survival of stage IIIA-IIIB (non-N3) non-small cell lung cancer patients after platinum/gemcitabine induction chemotherapy and surgery. *J Chemother*. 2010;22:191–196.

11. Ball D, Mitchell A, Giroux D, Rami-Porta R. Effect of tumor size on prognosis in patients treated with radical radiotherapy or chemoradiotherapy for non-small cell lung cancer. An analysis of the staging project database of the International Association for the Study of Lung Cancer. *J Thorac Oncol*. 2013 Mar;8(3):315–321.

12. Basaki K, Abe Y, Aoki M, Kondo H, Hatayama Y, Nakaji S. Prognostic factors for survival in stage III non-small-cell lung cancer treated with definitive radiation therapy: impact of tumor volume. *Int J Radiat Oncol Biol Phys*. 2006;64:449–454.

13. Bradley JD, Ieumwananonthachai N, Purdy JA, et al. Gross tumor volume, critical prognostic factor in patients treated with three-dimensional conformal radiation therapy for non-small-cell lung carcinoma. *Int J Radiat Oncol Biol Phys*. 2002;52:49–57.

14. Dehing-Oberije C, De Ruysscher D, van der Weide H, et al. Tumor volume combined with number of positive lymph node stations is a more important prognostic factor than TNM stage for survival of non-small cell lung cancer patients treated with (chemo)radiotherapy. *Int J Rad Oncol Biol Phys*. 2008;70:1039–1044.

15. Stinchcombe TE, Morris DE, Moore DT, et al. Post-chemotherapy gross tumor volume is predictive of survival in patients with stage III non-small cell lung cancer treated with combined modality therapy. *Lung Cancer*. 2006;52:67–74.

16. UICC International Union Against Cancer. *TNM Classification of Malignant Tumours*. 7th ed. New York: Wiley-Blackwell; 2009.

17. Rusch VW, Crowley J, Giroux DJ, Goldstraw P, Im JG, Tsuboi M, Tsuchiya R, Vansteenkiste J, et al. The IASLC lung cancer staging project: proposals for the revision of the N descriptors in the forthcoming seventh edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2007;2:603–612.

18. Lee JG, Lee CY, Park IK, Kim DJ, Park SY, Kim KD, Chung KY. Number of metastatic lymph nodes in resected non-small cell lung cancer predicts patient survival. *Ann Thorac Surg*. 2008 Jan;85(1):211–215.

19. Wei S, Asamura H, Kawachi R, Sakurai H, Watanabe S. Which is the better prognostic factor for resected non-small cell lung cancer: the number of metastatic lymph nodes or the currently used nodal stage classification? *J Thorac Oncol*. 2011;6:310–318.

20. Saji H, Tsuboi M, Shimada Y, et al. A proposal for combination of total number and anatomical location of involved lymph nodes for nodal classification in non-small cell lung cancer. *Chest*. 2013;143:1618–1625.