European Journal of Cardio-thoracic Surgery 36 (2009) 1037—1044

EUROPEAN JOURNAL OF CARDIO-THORACIC SURGERY

www.elsevier.com/locate/ejcts

Recommended changes for T and N descriptors proposed by the International Association for the Study of Lung Cancer — Lung Cancer Staging Project: a validation study from a single-centre experience☆

Enrico Ruffini [a,*], Pier Luigi Filosso [a], Maria Cristina Bruna [a], Francesco Coni [b], Riccardo Carlo Cristofori [a], Claudio Mossetti [a], Paolo Solidoro [b], Alberto Oliaro [a]

[a] *Department of Thoracic Surgery, University of Torino and S. Giovanni Battista Hospital, Turin, Italy*
[b] *Department of Pneumology, University of Torino and S. Giovanni Battista Hospital, Turin, Italy*

Received 28 August 2008; received in revised form 28 April 2009; accepted 19 May 2009; Available online 18 August 2009

Abstract

Objective: The International Association for the Study of Lung Cancer (IASLC) recently recommended changes for T and N descriptors for the next TNM (Tumour, Node, Metastasis) edition. We re-classify our operated patients to evaluate the effectiveness of the IASLC suggestions. **Methods:** IASLC proposals include: (1) a subdivision of T1 into T1a (≤2 cm) and T1b (2—3 cm); (2) a subdivision of T2 into T2a (3—5 cm) and T2b (5—7 cm); (3) a re-assignment of T2 >7 cm to T3; (4) a re-assignment of intrapulmonary metastasis in the primary lobe (PM1) and in ipsilateral different lobes (PM2) from T4 to T3 and from M1 to T4, respectively; and (5) a classification of N descriptor by the number of involved lymph node zones into: N0; single-zone N1 (N1a); multiple-zone N1/single-zone N2 (N1b/N2a) and multiple-zone N2 (N2b). From 1994 to 2007, 1805 patients were operated on for non-small-cell lung carcinoma (NSCLC); survival analysis was performed using Cox proportional hazard model to assess the prognostic significance of the T and N descriptors. **Results:** Stratification by T descriptor was: T1a (362 patients), T1b (286), T2a (536), T2b (154), T2 >7 cm (58), T3 (243), PM1 (50) and PM2 (36). Stratification by N descriptor was: N0 (1150 patients), N1a (289), N1b/N2a (200) and N2b (67). A significant survival difference was found between T1a and T1b (hazard ratio (HR) 1.45, 95% confidence interval (CI): 1.10—1.90, p = 0.006) but not between T2a and T2b (HR: 1.11, 95% CI: 0.86—1.43, p = 0.38). Tumours >7 cm and PM1 had a survival similar to other T3 tumours (HR: 1.05, 95% CI: 0.97—1.14, p = 0.2 and HR: 0.99, 95% CI: 0.81—1.21, p = 0.94). An excellent patient stratification was provided with the proposed four-category nodal grouping, with significant survival differences between N0 and N1a (HR: 1.81, 95% CI: 1.50—2.21, p = 0.0000001), N1a and N1b/N2a (HR: 1.54, 95% CI: 1.21—2.00, p = 0.02) and between N1b/N2a and N2b (HR: 1.61, 95% CI: 1.14—2.27, p = 0.02). **Conclusions:** Our experience confirms the IASLC recommendations to subdivide patients by tumour size at 2, 3 and 7 cm, to re-assign PM1 tumours to T3 and to group patients according to the number of involved lymph nodal zones are valid and provide excellent survival stratification.

Keywords: Non-small-cell lung cancer; TNM staging system; Tumour size; Nodal metastasis; Intrapulmonary metastasis; IASLC

1. Introduction

The current sixth edition of the Union Internationale Contre le Cancer (UICC) and the American Joint Committee on Cancer (AJCC) staging system for lung cancer is the accepted tumour, node and metastasis (TNM) staging system since 2002 [1]; it has basically confirmed the fifth edition published in 1997 [2]. The patients' database, which formed the basis of the 1997 edition, was relatively small, consisting of 5319 cases accumulated since 1975. It has become progressively clear among the medical community that a formal process of periodical update of the TNM classification of lung cancer is needed as the introduction of new diagnostic techniques, staging procedures and more effective treatment options are introduced in the clinical practice and in research.

For this purpose, in 1998 the International Association for the Study of Lung Cancer (IASLC) established a Lung Cancer Study Project to collect databases from a large number of institutions worldwide in order to propose recommendations for the seventh edition of the TNM staging system for lung cancer expected by the end of 2009. By the end of 2005, more than 100 000 patients treated for primary lung cancer from 1990 to 2000 from different geographic areas were submitted for review by the Cancer Research and Biostatistics (CRAB), a non-profit organisation in Seattle, WA, USA, who provided an internal validation and used the Surveillance, Epidemiology and End Results (SEER) database from 1998 to 2000 as

☆ Presented at the 22nd Annual Meeting of the European Association for Cardio-thoracic Surgery, Lisbon, Portugal, September 14—17, 2008.

* Corresponding author. Address: Section of Thoracic Surgery, University of Torino, Ospedale Molinette, 3, Via Genova 10126, Turin, Italy.
Tel.: +39 0 11 6705380; fax: +39 0 11 6705365.
E-mail address: enrico.ruffini@unito.it (E. Ruffini).

1010-7940/$ — see front matter © 2009 European Association for Cardio-Thoracic Surgery. Published by Elsevier B.V. All rights reserved.
doi:10.1016/j.ejcts.2009.05.051

external validation. The impressive work and the results of the IASLC International Staging Committee (ISC) and the CRAB have been recently published [3—5] and some suggestions for the next revision of the UICC and AJCC staging system have been proposed.

In the present retrospective study, we adopted the IASLC proposed changes to the T and N descriptors and re-classified all our patients submitted to surgery for primary non-small-cell lung cancer (NSCLC) from 1994 to 2007 according to the new recommendations and compared our results with those published by the IASLC ISC/CRAB in order to confirm the validity of the IASLC proposals for T and N descriptors.

2. Materials and methods

From January 1994 to December 2007, a total of 1805 patients with primary NSCLC underwent curative resection at our institution and complete pathologic staging was available for analysis; the patients had not been previously included in the IASLC dataset. All patients received resection of the primary tumour along with a complete mediastinal and hilar lymph node dissection. Patients with neuroendocrine tumours, those receiving induction chemo- and/or radiotherapy, patients with incomplete resection or microscopic or macroscopic residual disease were excluded from the analysis. Our service performs about 130 lung resections for primary NSCLC per year. Adjuvant chemotherapy was employed exclusively in N1 disease and in combination with radiotherapy (on a sequential basis) in N2 disease. Patients with ipsilateral pulmonary metastases (PMs) at the time of operation, either in the same lobe (PM1) or in different lobe(s) (PM2) received resection of the associated PM obtained by resection of the lobe in case of PM1 or by one or more wedge resections in case of PM2.

Demographics, types of intervention and histology are shown in Table 1. For the definition of bronchiolo-alveolar carcinoma (BAC), we adopted the 1999 WHO/IASLC definition (subsequently revised in 2004 [6]) in the WHO classification of lung adenocarcinomas; tumours operated before 1999 were re-classified according to the new classification.

Table 1
Demographics, types of intervention and histology of the patient population.

	No (%)
Patients	1805
Male	1498 (83%)
Female	307 (17%)
Age (range)	64 (32—87)
Pneumonectomy	381 (21%)
Right	119
Left	262
Lobectomy	1172 (65%)
Bilobectomy	50 (2.8%)
Segmentectomy	40 (2.2%)
Wedge	162 (9%)
Adenocarcinoma	802 (44.4%)
Squamous	745 (41.2%)
Large cell	89 (4.9%)
Adenosquamous	38 (2.1%)
BAC	131 (7.2%)

BAC: Bronchiolo-alveolar carcinoma.

Table 2
IASLC proposed definitions for T descriptors.

T	(Primary tumour)
TX	Primary tumour cannot be assessed, or tumour proven by the presence of malignant cells in sputum or bronchial washing but not visualised by imaging or bronchoscopy
T0	No evidence of primary tumour
Tis	Carcinoma in situ
T1	Tumour < = 3 cm in greatest dimension surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus) **T1a Tumour ≤2 cm in greatest dimension** **T1b Tumour >2 cm but ≤3 cm in greatest dimension**
T2	Tumour >3 cm **but ≤7 cm** or tumour with any of the following features (T2 tumours with these features are classified T2a if ≤5 cm): involvement of the main bronchus ≥2 cm distal to the carina; visceral pleura invasion; atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung **T2a Tumour >3 cm but ≤5 cm in greatest dimension** **T2b Tumour >5 cm but ≤7 cm in greatest dimension**
T3	**Tumour >7 cm** or one that directly invades any of the following: chest wall (including superior sulcus tumours); diaphragm; phrenic nerve; mediastinal or parietal pleura; parietal pericardium; or tumour in the main bronchus <2 cm distal to the carina but without involvement of the carina; atelectasis or obstructive pneumonitis of the entire lung; **separate tumour nodule(s) in the same lobe (PM1)**
T4	Tumour of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, **separate tumour nodule(s) in a different ipsilateral lobe (PM2)**

Bold characters indicate a change from the TNM-6 staging category.

The patient population was pathologically staged according to the most recent (sixth) edition of TNM staging system (TNM-6). Pathological staging included all the information available from clinical staging plus the pathology report from specimens obtained at surgery. The number of resected lymph nodes ranges from 11 to 25 (mean 15). The Mountain—Dresler modification of the American Thoracic Society (MD-ATS) lymph node map [7] was used for lymph nodal classification. For the present study, the patients were re-classified according to the proposals of the Staging Committee of the IASLC. Tables 2 and 3 illustrate the current TNM staging system (TNM-6) and the IASLC proposed definitions for T, N and M descriptors.

For the purpose of the analysis, five changes were identified among the recommendations of the IASLC Staging committee in the T descriptor and evaluated in the present study: change 1: subclassify T1 as T1a and T1b by size (T1a $\leq$2 cm; T1b $>2 \leq 3$ cm); change 2: subclassify T2 as T2a and T2b by size (T2a $>3 \leq 5$ cm; T2b $>5 < 7$ cm); change 3: re-classify T2 tumours larger than 7 cm as T3; change 4: re-classify T4 tumours by additional nodules in the primary lobe (PM1) as T3; change 5: re-classify M1 tumours by additional nodules in the ipsilateral lung (different lobe) (PM2) as T4. In addition, the N descriptor was re-classified as suggested by the IASLC in N0 (no nodal metastasis), N1a (single N1 zone), N1b (multiple N1 zones), N2a (single N2 zone) and N2b (multiple N2 zones); of these, four prognostic categories were selected, N0, N1a, N1b/N2a and N2b as suggested by the IASLC Committee [5]. An additional group considering

Table 3
IASLC proposed definitions for N, and M descriptors.

N	(Regional Lymph nodes)
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in ipsilateral peribronchialand/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph nodes
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene or supraclavicular lymph nodes
M	**(Distant metastasis)**
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	**Separate tumour nodule(s) in a contralateral lobe; tumour with pleural nodules or malignant pleural or pericardial effusion**
M1b	**Distant metastasis**

Bold characters indicate a change from the TNM-6 staging category.

skip nodal metastases (N2 disease in the absence of N1) was added for the analysis and considered separately.

Follow-up information on all patients was obtained through clinic follow-up notes, direct patient or family contact or contact with the patient's primary care physician; follow-up was complete in more than 85% of the patients. Our routine follow-up protocol consists of a chest-radiograph examination performed every 3 months for the first 2 years and every 6 months thereafter, and a computed tomography (CT) scan (chest + upper abdomen) performed on a yearly basis.

Cumulative survival rates were calculated by the Kaplan—Meier method, using the date of surgical resection as the starting point and the date of death or the latest follow-up date as the end-point. The survival differences were determined by log-rank analysis. Calculation of the relative hazards and the relative 95% confidence intervals using the Cox proportional hazard model was employed. A p value less than 0.05 was considered statistically significant. All statistical analysis was undertaken using software packages (STATISTICA, release 7.1, 2005, Statsoft, Italy).

The study was approved by our institutional review board. Individual patient consent was waived.

3. Results

3.1. Patient stratification according with the IASLC proposals

Staging stratification according with either the TNM-6 or the IASLC proposed staging system is illustrated in Table 4.

Overall, 648 patients (37%) had T1 descriptor (either T1a or T1b), 690 (38%) had T2 descriptor (T2a or T2b), 301 (16%) had T3 descriptor (>7 cm or other T3). PM1 and PM2 made up 5% of our series (PM1 2.7%, 50 patients; PM2 2.2%, 36 patients), while T4—other causes and M1 together accounted for about 4% of the entire patient population. When reclassified by the IASLC proposal, T3 patients including PM1 and T4 patients including PM2 accounted for 19% (351 patients) and 5% (93 patients) of our population. The same

Table 4
Stratification of the patient population by the T and N descriptors of the IASLC proposed classification and of the current edition of the TNM classification.

T descriptor	No (%) any pN	No. (%) pN0
	(N = 1805)	(N = 1150)
IASLC		
T1a	362 (20%)	294 (25%)
T1b	286 (16%)	214 (18%)
T2a	536 (30%)	328 (28%)
T2b	154 (9%)	88 (8%)
>7 cm	58 (3%)	30 (3%)
T3	243 (13%)	123 (11%)
PM1	50 (3%)	22 (2%)
T4 other	57 (3%)	18 (2%)
PM2	36 (2%)	19 (2%)
M1	23 (1%)	14 (1%)
TNM-6		
T1	648 (37%)	508 (45%)
T2	748 (42%)	446 (39%)
T3	243 (14%)	123 (11%)
T4	107 (6%)	40 (4%)

N descriptor	No (%) (N = 1805)
IASLC	
N0	1150 (64%)
N1a	289 (16%)
N1b/N2a	200 (11%)
N2b	67 (4%)
Skip	99 (5%)
TNM-6	
N0	1150 (64%)
N1	325 (18%)
N2	328 (18%)
N3	3 (0.2%)

PM1: additional nodule(s) same lobe; PM2 additional nodule(s) other lobe(s) ipsilateral. M1: distant spread/pleural dissemination. N1a: N1 single station; N1b:N1 multiple stations; N2a: N2 single station; N2b: N2 multiple stations. Skip: N2 without N1.

patient stratification according with the TNM-6 produced 648 T1 patients (36%), 748 T2 (43%), 243 T3 (14%) and 107 T4 (6%) out of 1746 patients (PM2 and M1 patients were excluded from the T descriptor analysis).

Patient stratification by N descriptor included 1150 patients (64%) without nodal involvement (N0) in both staging systems (IASLC and TNM-6). Single-station hilar station (N1a according to IASLC) either peribronchial or hilar was observed in 289 patients (16%); multiple N1 stations or single-station mediastinal node involvement (N1b/N2a according with IASLC) was observed in 200 patients (11%) and multiple-station mediastinal node involvement occurred in 67 patients (4%). By contrast, N1 and N2 involvement according to TNM-6 was observed in 325 (18%) and 328 (18%) patients. A skip metastasis (i.e., mediastinal node involvement without hilar node involvement) was observed in 99 patients (5%); of these, 80 were N2-single station and 19 N2-multiple station metastases.

3.2. Survival analysis

The validity of the IASLC proposals was tested by comparing survival rates, median survival times in years (MSTs) and HR with 95% CI in the proposed subgroups.

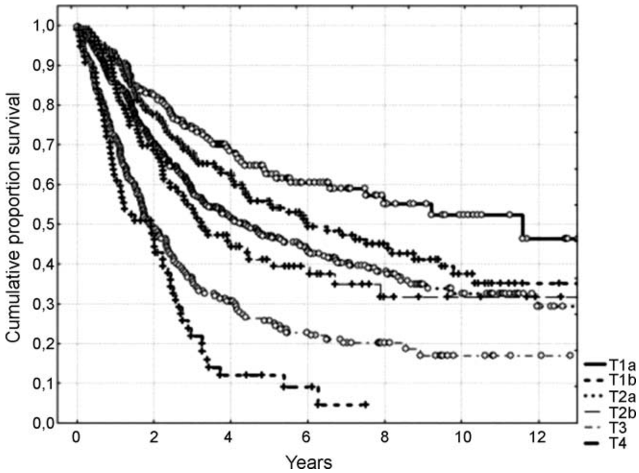

Fig. 1. Survival curves of our patient population stratified by the IASLC proposed T subgroups.

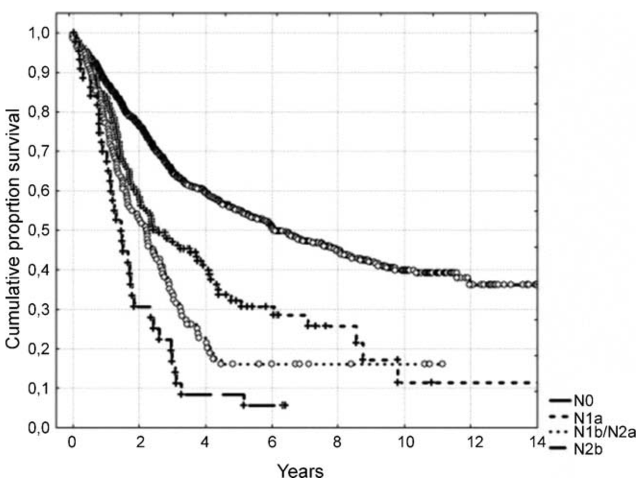

Fig. 2. Survival curves of our patient population stratified by the IASLC proposed N subgroups.

Figs. 1 and 2 show the survival curves of the subsets of patients stratified by the proposed IASLC T and N descriptors. Tables 5 and 6 illustrate the results of the survival analysis for the different subgroups.

As for the T1 subclassification, a significant survival difference was found between T1a and T1b, which was associated with a significant HR ($p = 0.006$). Five-year survival rates were 65% and 55%, respectively. MSTs (years) were 10.1 and 7.0.

As for the T2 subclassification, no significant survival difference was observed in our patient population between T2a and T2b ($p = 0.38$). Five-year survival rates were 48% and 42%, respectively. MSTs (years) were 6.5 and 5.4. There was, however, a significant difference between T2a and T1b using the standard 3-cm cut-point of the current TNM staging ($p = 0.05$).

In the subgroup of T2 tumours, T2 tumours smaller than 7 cm had a significant survival advantage over those larger than 7 cm in greatest diameter ($p = 0.01$). Survival rates were 45% and 32%, respectively; MSTs (years) were 6.3 and

Table 5
Results of survival analysis in our patient population according to the IASLC proposed T subgroups.

T descriptor	Median survival[a]	Five-year survival	HR (95% CI)	*p*
T1 (TNM-6)	7.9	60%		
T1a	**10.1**	**65%**	**1.45 (1.10—1.90)**	**0.006**
T1b	**7.0**	**55%**		
T2 (TNM-6)	6.32	45%		
T2a	6.48	48%	1.11 (0.86—1.43)	0.38
T2b	5.37	42%		
T2 >7 cm	**3.2**	**32%**	**1.25 (1.05—1.50)**	**0.01**[b]
T3 (TNM-6)	2.7	28%		
T2 >7 cm	3.2	32%	1.05 (0.97—1.14)	0.2
T3 all causes	2.7	33%		
T4 invasion	**1.4**	**15%**	**0.75 (0.62—0.98)**	**0.05**
PM1	**2.1**	**28%**		
PM1	2.1	28%	0.99 (0.81—1.21)	0.94
T3	2.7	33%		
PM2	1.6	28%[c]	0.97 (0.82—1.14)	0.75
T4 invasion	1.4	15%[c]		
M1 PM2	1.6	28%[c]	0.96 (0.70—1.33)	0.83
M1 distant	1.0	12%[c]		

PM1: additional nodule(s) same lobe; PM2: ipsilateral additional nodule(s) different lobe(s).
Bold characters represents T or N descriptors with statistical significance.
[a] Median survival in years.
[b] T2 versus T2 >7 cm.
[c] 3-year survival.

Table 6
Results of survival analysis in our patient population according to the IASLC proposed N subgroups.

N descriptor	Median survival (years)	Five-year survival	HR (95% CI)	*p*
N0	6.05	55%	**1.81 (1.50—2.21)**[a]	**0.0000001**
N1a	2.43	35%	**1.54 (1.21—2.00)**[b]	**0.02**
N1b/N2a	2.20	25%	**1.61 (1.14—2.27)**[c]	**0.02**
N2b	1.44	8%		
Skip	1.74	20%	0.71 (0.47—1.96)[d]	0.14
			0.98 (0.83—1.16)[e]	0.53

Bold characters represents T or N descriptors with statistical significance.
[a] N0 versus N1a.
[b] N1a versus N1b/N2a.
[c] N1b/N2a versus N2b.
[d] Skip versus N1b/N2a.
[e] Skip versus N2b.

3.2. T2 tumours larger than 7 cm had a similar survival to T3 tumours ($p = 0.2$).

As for PM1, a significant survival difference was observed between PM1 and T4—other causes ($p = 0.05$). Five-year survival rates were 28% and 15%, respectively, MST (years) 2.1 and 1.4. Indeed, survival was similar in PM1 and T3 tumours ($p = 0.94$).

As for PM2, in our patient population no survival difference was observed between PM2 and M1 ($p = 0.83$) and between PM2 and T4—other causes ($p = 0.75$). Survival rates at 3 years for PM2, T4—other causes and M1 were 28%, 15% and 12%, respectively. MSTs (years) were 1.6, 1.4 and 1.0, respectively.

We also analysed the significance of non-size-based T descriptors (visceral pleura invasion, hilar atelectasis, obstructive pneumonitis and main bronchus involvement >2 cm from the carina) in our Stage IB T2N0M0 patients in comparison with our Stage IA T1N0M0 population. Using the Cox proportional hazard model, tumour size (< and >3 cm) was a significant prognostic factor (HR: 1.14, 95% CI: 1.01—1.30, $p = 0.03$) while non-size-based T2 descriptors were not (HR: 0.90, 95% CI: 0.68—1.20, $p = 0.50$), and they appear to be linked to size criteria rather than being independent criteria.

To summarise, we found a significant match with the IASLC proposals for a T1 subclassification by size using the 2 and 3 cm cut-points (T1a vs T1b; T2a vs T1b) and for inclusion of tumours >7 cm and PM1 in the T3 group. Conversely, we were not be able to confirm with a statistical significance the proposals for a T2 subclassification by size around the 5 cm landmark (T2a and T2b), and for inclusion of PM2 tumours in T4 group.

We further analysed the IASLC proposal about the N descriptor into four categories according to the number of involved lymph nodal zones: N0, N1 single-station (N1a), N1 multiple-stations/N2 single-station (N1b/N2a) and N2 multiple stations (N2b). Further, the prognostic significance of skip metastases was analysed and compared with the other categories.

Fig. 2 shows the survival curves of the four categories of patients stratified by the proposed IASLC N descriptor. Table 6 illustrates the results of the survival analysis performed on the N subgroups.

An excellent stratification resulted using the IASLC-proposed categories. HR values for the different categories were N0 versus N1a ($p = 0.0000001$); N1a versus N1b/N2a ($p = 0.02$); N1b/N2a versus N2b ($p = 0.02$). Five-year survival rates were 55%, 35%, 25% and 8%, respectively. MSTs (years) were 6.05, 2.43, 2.20 and 1.44.

Five-year survival rates of patients with skip metastases was 20% (MST (years) 1.74), with a significant difference with N1a category but not with either N1b/N2a or N2b category ($p = 0.02$, $p = 0.14$ and $p = 0.53$, respectively).

4. Discussion

The purpose of the present study was to apply to our patient population of resected NSCLCs over the last 14 years, the IASLC proposals for a change of the current lung cancer TNM staging T and N descriptors.

The results of our study indicate that: (1) the proposal to include additional size thresholds to the current 3-cm one resulted in a better survival stratification in our patient population. However, we found a significant survival difference for tumours smaller and greater than 2 cm (T1a vs T1b) and 3 cm (T2a vs T1b) and for tumours larger than 7 cm, although we were not able to demonstrate a significant survival difference for tumours smaller or greater than 5 cm (T2a vs T2b); (2) the proposal to downstage PM1 tumours to T3 was confirmed in our patient population, but we were not able to confirm the downstaging of PM2 to T4; and (3) the proposal to re-classify the N descriptor into four categories of decreasing prognosis based upon the number of nodal stations involved was confirmed in our patient population.

The TNM system for cancer staging was first developed in 1946 and since then a constant modification process has progressed with periodical updates. The most recent edition (TNM-6) dates back to 2002 [1] and no changes were made to the 1997 edition [2]. All the previous editions of the TNM classification contained very little internal and no external validation information. As new technologies became available, numerous articles appeared in the literature suggesting deficiencies in the current staging system, which have not been addressed by the TNM-6. It should be noted, however, that the validity of all the studies is limited and only a large multi-institutional effort being able to collect databases from different geographical areas and different institutional categories might be of value to provide sufficient information for a change of the staging system.

For this purpose, in 1998, the IASLC established its Lung Cancer Staging Project, and nominated the ISC, which oversaw the conduct of the study in collaboration with the Cancer CRAB in Seattle, WA, USA, which provided the statistical support. In total, more than 100 000 patients were submitted to the CRAB and, after a screening process, more than 80 000 patients met the inclusion criteria for analysis. The time period chosen was between 1990 and 2000 and data acquisition involved 46 sources from 19 countries. The geographical distribution covered Europe (which provided the vast majority of data), North America, Asia and Australia. Unfortunately, several significant geographic areas were not represented, including Russia, South America, Africa and China. The results of this considerable effort have been the object of several articles [3—5] and included some recommended changes in T and M descriptors. As for the N descriptor, the ISC Committee tested the potential impact of the number of involved lymph node zones on survival, by identifying four categories: N0, N1 single-zone, N1multiple-zones/N2 single-zone, and N2 multiple-zones. Even if they found a satisfactory survival stratification among the groups, the number of patients available in each subset was too small to yield statistically valid analysis, and therefore the Committee suggested that the current categories of N descriptors be maintained.

The main finding from the IASLC study was the recognition of the importance of size as a major prognostic determinant. The study, using the running log-rank analysis to identify the best cut-points, suggested three more cut-points at 2, 5 and 7 cm in addition to the current 3-cm landmark, with five resulting size groups showing statistically significant differences in survival rates. They therefore recommended to stratify patients by tumour size into T1a (≤2 cm), T1b (2—3 cm), T2a (3—5 cm), T2b (5—7 cm) and T2c (>7 cm).

The IASLC conclusions were not unexpected, since in the past decade several reports have emphasised the prognostic importance of tumour size in lung cancer and most authors called for a modification of the TNM classification. Several cut-points were proposed, including 1.5 cm [8], 2 cm [9,10], 4 cm [9,11], 5 cm [10,12,13] and 7 cm [11]. All these authors found decreased survival rates for larger tumours, although the thresholds varied among the different series. The statistical methods used the different patient numbers and the heterogeneity for different geographical areas and type of databases may account for the different cut-points. Addressing the issue of 'size matters' from a different view, a recent article from the Washington University [14] retrospectively analysed a series of 292 patients with clinical Stage IA NSCLC and found that a size increase of 1 cm increases the risk of nodal metastases by a factor of 3.5 with a significant decrement in survival. In contrast to these series, two influential articles from the Duke University dispute these conclusions: Patz and colleagues in 2000 [15] in a series of more than 500 patients with pathologic Stage IA concluded that there was no statistical relationship between tumour size and survival; the same authors confirmed their results in a revision of their series in 2001. Similarly, Takeda and colleagues in 2005 [16] in a population of more than 600 patients with nodal-negative NSCLC found that no significant prognostic differences were seen among tumours up to 5 cm; they however found a significantly worse prognosis in patients with tumours larger than 5 cm.

In the present study, we were able to demonstrate a statistically significant size landmark at 2, 3 and 7 cm but not at 5 cm, possibly because of the relatively small number of patients which obviously reduced the power of the analysis. We, however, may confirm the IASLC suggestion about the 2-cm cut-point with the consequent subdivision of a T1 tumour into T1a and T1b, and the upstaging of tumours larger than 7 cm to a T3 descriptor.

With the recognised crucial importance of tumour size as a prognostic indicator, some issues need to be addressed in the future TNM classifications, including the way the tumour size is measured and the fixation process after resection: indeed, it has been found that tumours tend to shrink after being left in formalin overnight [17], while no shrinkage has been observed in fresh specimens. In the present study, tumour size was measured whenever possible on the fresh specimen and calculated on the longest diameter. A TNM classification in which tumour size is so crucial might theoretically falsely downstage about 10% of the patients depending upon which fixation process is used.

Although the major focus of the IASLC project was the prognostic impact of tumour size, the TNM-6 staging system also recognises the importance of the airway location of the tumour and its extent of local invasion, which are denoted as non-size-based descriptors. The IASLC staging project did not incorporate recommendations regarding non-size-based descriptors because they could not be evaluated due to the small number of patients, inconsistent clinical and pathologic results or lack of validation, and the final recommendation of the ISC was to maintain the current non-size-based descriptors. In a recent report, however, Ou and colleagues [18] investigated the prognostic significance of non-size-based AJCC T2 descriptors including visceral pleura invasion, hilar atelectasis or obstructive pneumonitis and main bronchus involvement >2 cm from the carina in a population of more than 10 000 patients with stage IB NSCLC. The authors conclude that size is an important prognostic indicator (using the standard 3 cm cut-point), consistent with the recommendation of the IASLC Committee; however, the authors also demonstrate that patients staged as T2 on the basis of non-size-based T descriptors with tumours <3 cm have a prognosis similar to Stage IA patients. The authors conclude that, in future, considering the changes in the T2 descriptor in the AJCC staging system for NSCLC, the non-size-based criteria should be linked to size criteria rather than be considered as independent determinant. Our results over more than 900 Stage I patients are in accordance with the study of Ou and surely the issue deserves consideration for future studies.

The second issue addressed in the present study was the downstaging of intrapulmonary metastases (PM) either in the same lobe (PM1) or in different ipsilateral lobe(s) (PM2) from T4 to T3 and from M1 to T4, respectively. The presence of additional foci of cancer in the ipsilateral lung parenchyma separate from the primary mass has been a considerable matter of controversy over the past decades. A reasonable amount of data suggest that an additional focus in the same lobe represents a form of local spread, hence the inclusion of this patients in the T4 descriptor in the last TNM-6 classification; a second focus of tumour in a different lobe, however, raises the question whether it represents a second primary, an unusual form of aerogenic spread or a haematogenous spread in the lung. For these reasons, this form of tumour diffusion has customarily been considered a form of distant (M) spread, and patients are classified as M1. The IASLC suggestions include downstaging of PM1 to T3 and PM2 to T4 with a consequent relocation of PM1 and PM2 without nodal metastases (N0) into Stage IIB and IIIA. This is a critical issue, since it has fundamental implications in therapeutic strategies. The authors correctly stated that the limitations of the database suggest caution about the appropriateness of these re-assignments in case of multiple additional nodules or other T4 tumours. Again, the IASLC considerations did not come unexpectedly. During the last 10 years many authors have addressed this contradictory issue reporting controversial results. Most authors indeed confirmed the impression that PM1 and PM2 tumours behave differently from their T4 and M1 counterparts, although there are other series who still maintain that the current TNM-6 attributions are correct [19—21]. The most recent contribution to the issue from Lee and colleagues in 2008 [22], including more than 1200 operated patients with NSCLC, concludes that patients with PM1 should be staged as T3 or designated as upstaging co-parameter of T stage, while PM2 patients can be staged as T4.

We recently published our experience about the prognostic significance of PM in our patients [23] and we found that the presence of PM represents a survival advantage over other T4/M1 patients, although the difference was not significant at that time. In the present study, on a longer follow-up, we found that patients with additional nodule(s) in the same lobe of the primary tumour (PM1) did have a significant reduced risk of death as measured by the HR than other T4 patients, and they had a HR similar to other T3 tumours. Conversely, we were not able to confirm the IASLC results about patients with ipsilateral additional nodule(s) in different lobe(s) (PM2), which in our series had HR similar to other M1 patients, possibly due to the small number of patients.

The third result of our study was that patients could be prognostically stratified according to the number of involved lymph node zones, thus confirming the IASLC results. Since the last TNM edition, N descriptor has defined the anatomic location of the lymph nodes by dividing them in N1 (peribronchial, interlobar or hilar), N2 (ipsilateral mediastinal) or N3 (contralateral mediastinal or supraclavicular).

Over the past years, however, it has become increasingly evident that many patients may have different prognosis even in the same nodal group, especially in the N2 group [24]. For this reason, many authors started to examine the pattern of lymphatic drainage of the lung and tried to subdivide the N1 and N2 determinants into more precise prognostic groups. The results of these studies showed that the number of metastatic involved nodes is an important prognostic indicator, as already known for breast, gastric and colon malignancies where it has been included in the TNM staging system. In a recent report, Lee and colleagues [25] divided their patient population of more than 1000 patients into four groups, according to the number of metastatic lymph nodes (0, 1—3, 4—14 and more than 15) and they found that the number of involved lymph nodes was a significant prognostic factor. The IASLC Committee therefore tested the prognostic significance of a 4-category classification of the nodal spread into N0, N1 single-zone, N1 multiple zones/N2 single zone, and N2 multiple zones. It is unfortunate that, out of their large database of more than 28 000 patients, only 1992 cases had sufficient data for this survival analysis, and further correlation of these nodal groups with other covariates could not be performed. Indeed, the analysis did demonstrate a stepwise decremental prognosis along the four nodal groups, thus suggesting that the overall disease burden, other than just the anatomical location of the lymph node involvement, might have an influence on the outcome. Unfortunately, the results could not be validated and the ISC prudentially accepted to maintain the current N descriptors [5] until future analysis on larger and more homogeneous databases will become available.

Our study confirmed the IASLC results, and we found that the stratification according to the number of involved lymph nodal zones is prognostically valid and deserve future studies. The issue of skip metastasis, that is, the presence of metastasis in the N2 stations without involvement of N1 station has been marginally addressed in the present study, although our results demonstrate that survival rates in this subset of patients are better than the overall N2 population (20% vs 15%).

In conclusion, our study on a patient population of over 1800 patients pathologically staged after resection of NSCLC largely supports the IASLC recommendations about changes in the current TNM-6 staging system, including the identification of the 2- and 7-cm cut-points for tumour size in addition to the standard 3-cm landmark, the re-assignment of PM1 to T3 and the stratification of the nodal involvement by the number of metastatic lymph node zones. Thanks to the extraordinary effort of the IASLC in re-assessing and validating the current staging system, the forthcoming revision of the TNM classification will surely be a major step forward to provide more accurate prognostic information, to guide appropriate therapy and to support future research among patients with lung cancer.

References

[1] Sobin LH, Wittekind C, editors. International Union Against Cancer (UICC) TNM Classification of malignant tumours. 6th edition, New York: Wiley-Liss; 2002. p. 99—103.

[2] Mountain CF. Revisions in the international system for staging lung cancer. Chest 1997;111:1710—7.

[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;2:706—14.

[4] Rami-Porta R, Ball D, Crowley J, Giroux DJ, Jett J, Travis WD, Tsuboi M, Vallieres E, Goldstraw P. The IASLC Lung Cancer Staging Project: proposals for the revision of the T descriptors in the forthcoming (seventh) edition of the TNM classification for lung cancer. J Thorac Oncol 2007;2:593—602.

[5] Rusch VW, Crowley J, Giroux DJ, Goldstraw P, Im JG, Tsuboi M, Tsuchiya R, Vansteenkiste J. 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—12.

[6] Colby TV, Noguchi M, Henschke C, Harris CC. Adenocarcinoma. In: Travis WD, Brambilla E, Muller-Hermelink HK, Harris CC, editors. World Health Organisation classification of tumours. Pathology and genetics of tumours of the lung, pleura, thymus and heart. Lyon: IARC Press; 2004. p. 35—44.

[7] Mountain CF, Dresler CM. regional lymph node classification for lung cancer staging. Chest 1997;111:1718—23.

[8] Gajra A, Newman N, Gamble GP, Abraham NZ, Kohman LJ, Graziano SL. Impact of tumour size on survival in Stage IA non-small cell lung cancer: a case for subdividing stage IA disease. Lung Cancer 2003;42:51—7.

[9] Mulligan CR, Meram AD, Proctor CD, Wu H, Zhu K, Marrogi AJ. Lung cancer staging: a case for a new T definition. Ann Thorac Surg 2006;82:220—6.

[10] Asamura H, Goya T, Koshiishi Y, Sohara Y, Tsuchiya R, Miyaoka E. How should the TNM staging system for lung cancer be revised? A simulation based on the Japanese Lung Cancer Registry population. J Thorac Cardiovasc Surg 2006;132:316—9.

[11] Lopez-Encuentra A, Duque-Medina JL, Rami-Porta R, de la Camara AG, Ferrando P. Bronchogenic Carcinoma Cooperative Group of the Spanish Society of Pneumology and Thoracic Surgery. Staging in lung cancer: is 3 cm a prognostic threshold in pathologic stage I non-small cell lung cancer? A multicentre study of 1,020 patients. Chest 2002;121:1515—20.

[12] Carbone E, Asamura H, Takei H, Kondo H, Suzuki K, Miyaoka E, Tsuchiya R, Motta G. Tumours larger than five centimeters in diameter can be upgraded to T3 in non-small cell lung cancer. J Thorac Cardiovasc Surg 2001;122:907—12.

[13] Cangir AK, Kutlay H, Akal M, Gungor A, Ozdemir N, Akay H. Prognostic value of tumour size in non-small cell lung cancer larger than 5 centimeters in diameter. Lung Cancer 2004;46:325—31.

[14] Veeramachanenia NK, Battafarano JR, Meyers BF, Zoole JB, Patterson GA. Risk factors for occult nodal metastasis in clinical T1N0 lung cancer: a negative impact upon survival. Eur J Cardiothorac Surg 2008;33:466—9.

[15] Patz Jr EF, Rossi S, Harpole Jr DH, Herndon Je, Goodman PC. Correlation of tumour size and survival in patients with stage IA non-small cell lung cancer. Chest 2000;117:1568—71.

[16] Takeda S, Fukai S, Komatsu H, Nemoto E, Nakamura K, Murakami M. Impact of large tumour size on survival after resection of pathologically node negative (pN0) non-small cell lung cancer. Ann Thorac Surg 2005;79:1142—6.

[17] Hsu PK, Huang HC, Hsieh CC, Hsu HS, Wu YC, Huang MH, Hsu WH. Effect of formalin fixation on tumour size determination in Stage I non-small cell lung cancer. Ann Thorac Surg 2007;84:1825—9.

[18] Ou SI, Zell JA, Ziogas A, Anton-Culver H. Prognostic significance of the non-size based AJCC T2 descriptors. Chest 2008;133:662—9.

[19] Port JL, Korst RJ, Lee PC, Kansler AL, Kerem Y, Altorki NK. Surgical resection for multifocal (T4) non-small cell lung cancer: is the T4 designation valid? Ann Thorac Surg 2007;83:397—400.

[20] Rao J, Sayeed RA, Tomaszek S, Fisher S, Keshavjee S, Darling GE. Prognostic factors in resected satellite-nodule T4 non-small cell lung cancer. Ann Thorac Surg 2007;84:934—8.

[21] Trousse D, D'Journo XB, Avaro JP, Doddoli C, Giudicelli R, Fuentes PA, Thomas PA. Multifocal T4 non-small cell lung cancer: a subset with improved prognosis. Eur J Cardiothorac Surg 2008;33:99—103.

[22] Lee JG, Lee CY, Kim DJ, Cgung KY, Park IK. Non-small cell lung cancer with ipsilateral pulmonary metastases: prognostic analysis and staging assessment. Eur J Cardiothorac Surg 2008;33:480—5.

[23] Oliaro A, Filosso PL, Cavallo A, Giobbe R, Mossetti C, Lyberis P, Cristofori RC, Ruffini E. The significance of intrapulmonary metastasis in non-small cell lung cancer: upstaging or downstaging? A re-appraisal for the next TNM staging system. Eur J Cardiothorac Surg 2008;34:438—43.

[24] Keller SM, Vangel MG, Wagner H, Schiller JH, Herskovic A, Komaki R, Marks RS, Perry MC, Livingston RB, Johnson DH. Prolonged survival in patients with resected non-small cell lung cancer and single-level N2 disease. J Thorac Cardiovasc Surg 2004;128:130—7.

[25] 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;85:211—5.

Appendix A. Conference discussion

Dr H.K. Kim (*Seoul, South Korea*): In your study population are there any patients who underwent neoadjuvant therapy, and in those cases what have you done in terms of pathologic staging? Second, have you ever compared the long-term survival between multiple N1 and single N2?

Dr Ruffini: As for the first question, we excluded patients receiving induction therapy because this could have been a confounding variable for the staging. We tried to have as much of a homogeneous population as possible. So that was an exclusion criteria.

Your second question was?

Dr Kim: Have you ever compared the long-term survival between multiple N1 and single N2?

Dr Ruffini: Yes, but the numbers were quite small. Survival was quite similar in the two. So we agreed with the IASLC proposal to group together multiple N1 and single N2. As you know, there are also a lot of problems with the node maps. You know, you Japanese use the Naruke node map and generally the Americans use the Mountain—Dressler node map, and there is some overlapping between the mediastinal nodes. For example, the subcarinal nodes in one node map are considered as N1 and in another as N2, particularly the subcarinal nodes along the main bronchus. So this proposal probably has the effect maybe to unify the two maps.

Dr Kim: So you mean that there were no significant differences between the multiple N1 and single N2?

Dr Ruffini: Yes. We agreed that they should be grouped together.