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A population-based evaluation of the seventh edition of the TNM system for lung cancer

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ABSTRACT: Our study describes the new seventh edition of the TNM system for lung cancer in a national population and its clinical implications.

We classified 1,885 operated patients with lung cancer, reported to the Cancer Registry of Norway (Oslo, Norway) from 2001 to 2005, according to the sixth and the seventh edition of the TNM system. We compared survival differences adjusting for known prognostic factors. Furthermore, we evaluated the overall predictive ability of both editions using Harrell's concordance index.

Survival curves by stage for each of the editions were similar; however, a better description of stage IIIB was observed in the seventh edition. Survival rates of T1b and T2a tumours were similar (log rank p=0.94). The concordance index was 0.68 for both editions, indicating no overall difference in their predictive accuracy. In the seventh edition, 211 (29%) stage IB patients migrated to stage II and 161 (48%) patients migrated from stage IIB to IIA. Stage migrations could change the treatment for up to 326 (17.3%) of the study patients.

The seventh edition did not improve the overall predictive ability of the TNM system; however, the new classification implies changes in treatment for nearly one-fifth of the cases. The implications of the seventh TNM edition for the outcomes of patients should be studied further.

KEYWORDS: Evaluation, lung cancer, population based, seventh edition, TNM

The new seventh edition of the TNM staging system for lung cancer was recently approved by the International Union against Cancer and the American Joint Committee on Cancer [1]. The lung cancer staging project, under the auspices of the International Association for the Study of Lung Cancer (IASLC), assembled more than 100,000 cases of lung cancer. 46 registries in 20 countries contributed cases diagnosed from 1990 and 2000 [2]. Finally, 67,725 cases with nonsmall cell lung cancer (NSCLC) formed the base for the current revision.

This database is a major extension compared to the 5,319 cases diagnosed during 1977 to 1988 from the University of Texas, MD Anderson Cancer Center (Houston, TX, USA) [3] and which were the basis for the fifth and sixth editions. A revised system based on such a large and representative database should better support clinicians in determining the treatment and prognosis of their patients.

The Norwegian Cancer Registry contributed 2,154 surgical cases diagnosed from 1993 to 2000 from its lung cancer quality registry to the seventh edition. These data were considered an important contribution because they were population based, complete and detailed [2].

The stage groupings of the new TNM system must be validated to become internationally accepted. To date, the system has been validated internally using one-third of the included patients and external cases from the Surveillance and End Results (SEER) database in the USA as controls [4]. External independent evaluation has only been performed to a limited extent. Apart from evaluations based on case series from single centres [5, 6], there is only one population-based study of advanced NSCLC from the Cancer Registry of California (Sacramento, CA, USA) [7]. Thus, the system has not been validated externally against representative populations of patients in Europe, and its clinical implications are unknown.

For editorial comments see page 237.

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Therefore, further evaluations are necessary to validate and further refine the system.

We performed an external validation of the revised TNM system, adjusted for established risk factors using the population-based lung cancer registry of Norway.

MATERIAL AND METHODS

The Cancer Registry of Norway receives clinical and pathological reports on all patients with cancer in the country, and the completeness of the registry is estimated to be 99% [8, 9]. This registry comprises a detailed retrospective database of all surgically treated lung cancer patients in the country diagnosed from 1993 to 2007 (>5,000 patients).

The present study includes all surgically resected patients with lung cancer (International Classification of Disease 10: C34) diagnosed from 2001 to 2005, which is after the inclusion period for the IASLC study for the seventh TNM edition. During this period a total of 11,202 patients were diagnosed with lung cancer in Norway. Adjuvant chemotherapy was introduced in Norway around 2005. An experienced thoracic surgeon (H. Rostad) classified each case according to the sixth and seventh TNM editions based on detailed information for all aspects of the pathological TNM classification from pathology and clinical reports. Tumour size was registered with the largest diameter as measured by the pathologists. Patients who underwent a second operation for lung cancer during the period were only considered the first time. Bronchioloalveolar carcinoma was coded as adenocarcinoma in the dataset. Other histological types, including carcinoma without further classification, were grouped as unspecified. We performed all analyses on the complete dataset and on NSCLC cases only. Survival data were updated as of December 31, 2008.

The study was approved by the regional ethics committee (Regional Ethics Committee South/East, Oslo, Norway) in November 2008 (reference 449-08618c 2008/17501) and the Norwegian Social Science Data Services in September 2008 (reference 19671).

Statistical analysis

We calculated 1-, 3- and 5-yr survival percentages using life tables and compared differences according to the T descriptor and TNM stages with the log-rank test. We further visually compared survival curves according to the sixth and seventh edition of the TNM system with Kaplan–Meier plots. Hazard ratios were calculated using the Cox proportional hazard model for the different tumour stages with and without adjustment for known risk factors, such as sex, age (continuous variable), localisation (side) of tumour, morphology, resection margins and procedure [10]. Furthermore, we computed Harrell's concordance index (c-index) of the two editions of the TNM classification [11]. The c-index is a measure of the predictive accuracy of a Cox regression model. A value of 0.5 indicates that the set of variables in the model does not discriminate the survival of patients better than chance, while the maximum value of 1 indicates perfect prediction of their survival. We performed re-sampling validation of the fitted models and adjusted for optimism. Finally, we explored the possibility of interactions or co-linearity among different variables in the regression model and explored whether the assumption of proportional hazards in the regression model was present.

The statistical analyses were carried out using SPSS 17.0 (SPSS Inc., Chicago, IL, USA) and R version 2.9.1 (R Foundation for Statistical Computing, Vienna, Austria). The level of significance was set to 0.05.

RESULTS

We identified 1,885 patients, nine of whom underwent surgical procedures twice during the study period. Four patients had emigrated so we censored their follow-up at the last date that they were known to be alive. Cases diagnosed from 2001 to 2003 had complete data on 5-yr survival, and 831 cases were censored. The median follow-up time was 3.5 yrs. The mean (range) age at diagnosis was 65.1 (19–88) yrs. Patient characteristics are presented in table 1 and TNM characteristics are presented in table 2.

Figure 1 shows the distribution of cases according to the sixth and seventh TNM editions. Table 3 describes the migration of cases and probable clinical consequences for the choice of treatment. Migrations could potentially lead to changes in treatment for 326 (17.3%) patients, mainly by crossing the limit between surgery alone (stages IA and IB) and surgery with adjuvant chemotherapy (stage II; n=211).

The 1-, 3- and 5-yr survival rates for all patients were 78.5%, 55.9% and 44.6%, respectively. The corresponding figures according to TNM stage in the sixth and seventh editions are summarised in table 4. Survival for all T, N and M descriptors is given in table 2. In comparison, the survival curves by stage of the sixth and the seventh editions were quite similar (fig. 2). The only exception was stage IIIB, which was better differentiated from stages IIIA and IIB in the seventh edition.

TABLE 1 Patient characteristics and prognostic factors

Male	1109 (59)
Histology	
Squamous cell carcinoma	635 (34)
Adenocarcinoma	842 (45)
Large cell carcinoma	122 (6)
Carcinoid	92 (5)
Small cell carcinoma	31 (2)
Unspecified carcinoma	163 (9)
Localisation of the tumour	
Left side	846 (45)
Peripheral	1226 (65)
Procedure	
Sublobar resection	122 (7)
Lobectomy and bilobectomy	1380 (73)
Pneumonectomy	383 (20)
Resection margin	
Free	1789 (95)
Involved	74 (4)
Possibly involved or unknown	22 (1)

Data are presented as n (%).

TABLE 2 Survival by the pathological TNM descriptors in the seventh edition of the TNM system for lung cancer

Descriptor	Subjects n	Survival %		
		1 yr	3 yr	5 yr
T descriptor				
Surrounded by lung tissue	425	81.2	63.0	48.9
Surrounded by visceral pleura	863	76.1	52.5	41.7
Involves lobe bronchus	199	83.4	61.6	52.8
Involves main bronchus ⩾2 cm distal to the carina	45	73.3	44.4	39.4
Invades visceral pleura	677	74.4	47.5	36.4
Associated with partial atelectasis	27	74.1	59.3	48.9
Invades chest wall (including superior sulcus tumours)	78	62.8	33.3	29.7
Invades phrenic nerve	0			
Invades mediastinal pleura	22	63.6	36.4	15.6
Invades parietal pericardium	12	50.0	16.7	8.3
In the main bronchus <2 cm distal to the carina	4	75.0	75.0	75.0
Associated atelectasis or obstructive pneumonitis of the entire lung	1	0	0	0
Invades mediastinum	7	57.1	28.6	28.6
Invades heart	2	50.0	0	0
Invades great vessels	3	33.3	0	0
Invades trachea	0			
Invades recurrent laryngeal nerve	0			
Invades oesophagus	3	66.7	33.3	0
Invades vertebral body	0			
Invades carina	0			
Separate tumour nodule(s) in the same lobe	58	70.7	44.8	21.9
Separate tumour nodule(s) in a different ipsilateral lobe	49	59.2	26.5	23.9
N descriptor				
No regional lymph node metastasis	1307	83.3	65.7	53.5
Metastasis or involvement by direct extension in ipsilateral peribronchial lymph node(s)	152	70.4	40.7	22.3
In ipsilateral hilar lymph node(s)	329	66.5	33.3	26.6
Metastasis in ipsilateral mediastinal nodes(s)	143	60.1	23.1	13.3
Subcarinal lymph node(s)#	39	59.0	23.1	16.5
Contralateral mediastinal lymph node(s)	0			
Contralateral hilar lymph node(s)	0			
Ipsilateral or contralateral scalene or supraclavicular lymph node(s)	1	0	0	0
M descriptor				
Separate tumour nodule(s) in a contralateral lobe	4	75.0	50.0	0
Tumour with pleural nodules or malignant pleural (or pericardial) effusion	5	20.0	20.0	0
Distant metastasis	12	41.7	25.0	16.7

Each descriptor is presented irrespective of the status of the other descriptors. #: not included with mediastinal nodes.

In the seventh edition, the survival rates of cases with T1bN0M0 (>2–3 cm) and T2aN0M0 (>3–5 cm) were almost equal (log rank p=0.62). We did not find significant survival differences between cases with T4 (central invasion or nodules in other ipsilateral lobes) and T3 (log rank p=0.88) (table 5). Meanwhile, the new cut-off point between T2a and T2b (>5–7 cm) (log rank p=0.029) clearly added prognostic information. Furthermore, the changes to T3 (>7 cm or invasion or separate nodules in same lobe or <2 cm from carina) (log rank p=0.016 *versus* T2b) contributed to better differentiation. When we adjusted T descriptors for the risk factors previously mentioned in a separate analysis the results were essentially unchanged.

Stepwise deteriorations of hazard ratios across stages were slightly more linear for the revised classification with or without adjustment for prognostic factors. Furthermore, the reversed hazard ratios of stages IIIB and IV in the sixth edition were corrected in the seventh edition (table 6). The validated and optimism-adjusted c-index was 0.68 for the sixth and seventh TNM editions, suggesting no difference in the prediction of survival between the two models. The p-value for trend of both editions in the full model was p<0.001 in univariate analysis with stage coded as a continuous variable. We did not find significant interactions by formal test or violation of the proportional hazard assumption for any of the variables, as reviewed by inspection of the plots for each variable.

In the subgroup analysis of NSCLC, the 1-, 3- and 5-yr survival rates were 77.0%, 53.8% and 42.1%, respectively. The validated and optimism-adjusted c-indices based exclusively on NSCLC

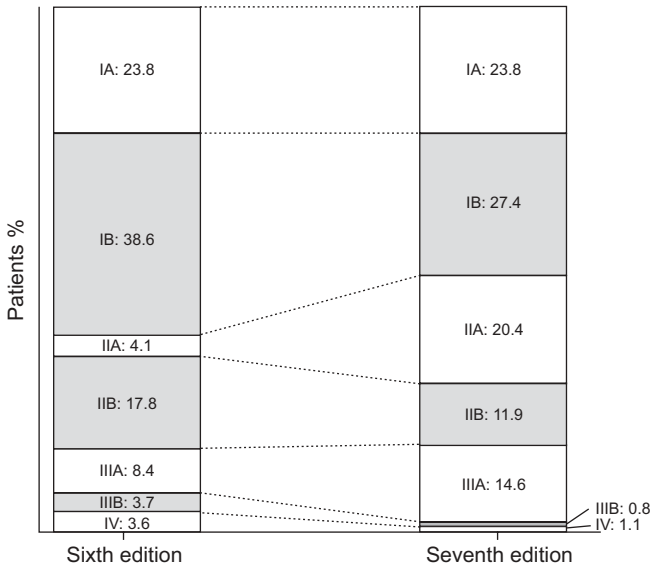

FIGURE 1. Distribution of pathological TNM stages according to the sixth and seventh editions of the TNM system for lung cancer.

cases were 0.66 for both editions. Apart from this the subgroup differed only marginally from the whole study population.

Lung cancer surgery was performed at 22 hospitals during the study period. There were five hospitals treating <10 patients and three hospitals treating >200 patients (range 1–312 patients) during the whole study period. The 5-yr survival of patients who underwent operations at one of the eight hospitals treating >100 patients during the whole period was 46.1% (n=1,416) compared to 40.2% (n=469) in hospitals treating fewer patients.

DISCUSSION

The sixth edition of the TNM system for lung cancer has been revised to improve its representativeness, methodological accuracy and validity. The current study evaluated the new seventh edition of the TNM system using a complete national registry of surgical cases [12]. Our registry included patients studied over a period of time after the inclusion of cases for the IASLC revision (2001–2005). This period was stable with regard to the treatment of lung cancer. The revised edition of the TNM system better discriminates stage IIIB from IIB and IIIA and yields a slightly clearer distribution of survival curves. The overall predictive accuracy of the two editions of the TNM system, however, was unchanged. Importantly, the reclassification in the seventh edition altered the stage of nearly one-fifth of the patients in a way that could potentially affect treatment plans.

The selection of patients for different treatment categories requires clear distinctions between prognostic groups; thus, an important aim of the current revision is to reduce overlaps between TNM stages. Several studies have highlighted overlaps of the survival curves between stages IB/IIA and IIIB/IV in the sixth edition [13–15], which were not confirmed in the current study for either edition. While stages IIB and above were better differentiated on visual inspection, we did not find significant stepwise differences of survival between the higher

TABLE 3 Stage migrations of patients and potential clinical implications of the seventh revision of the TNM system for lung cancer

TNM6	TNM7	Subjects n	Implications for treatment
IB	IIA	146	Adjuvant chemotherapy
IB	IIB	65	Adjuvant chemotherapy
IIB	IIA	161	None
IIB	IIIA	42	None
IIIB	IIB	27	Surgery a more likely option
IIIB	IIIA	40	Evaluation for surgery/radical thoracic radiation therapy
IV	IIIA	35	Evaluation for surgery/radical thoracic radiation therapy
IV	IIIB	13	Evaluation for radical thoracic radiation therapy/surgery

stages, most probably because we had relatively few cases in these groups. Finally, the migration of patients with satellite tumours in the same or ipsilateral lobe in the seventh edition probably corrected the inverted survival curves of stages IIIA and IIIB in the sixth edition. Thus, the new classification contributes to a slightly more adequate distribution of survival curves at the higher stages.

Overall, the application of the seventh edition of the TNM system in our population did not yield better discrimination of the survival of patients than the sixth edition, as evaluated by means of Harrell's concordance index. The concordance index is a measure of the prognostic information of the variables in a Cox regression model and has become more widely used in studies of different types of cancer [16, 17]. We included known prognostic factors such as sex, age, side of tumour, morphology, resection margins and procedure in our model [18]. Tumour size was not included because of the association with stage, and we were not able to adjust for lung function, smoking habits, comorbid conditions or molecular characteristics of tumours since these data were not available in our registry. Adding these factors to the models would probably have improved the prognostic accuracy of both editions and, thus, yielded higher c-indices for both editions. A possible explanation for why the c-index was not higher in the seventh than in the sixth edition could be that the patients in our study were treated within the paradigm of the sixth edition. It remains to be seen whether staging and treating patients within the paradigm of the current revision leads to better outcomes of patients. It is also possible that the antidromic up- and down-staging of cases in the two models counterbalance each other and keep the overall predictive accuracy at the same level. Taking all these issues into consideration, the nearly identical predictive accuracy of the two TNM editions is a relevant finding that should be studied further.

The substantial stage migration in the revised edition would clinically affect as many as one-fifth of our cases. Most importantly, 211 (11.2%) patients migrated from stage I to II, where adjuvant chemotherapy is recommended [19, 20]. This finding is in accordance with two studies from Japan [5, 6] which report similar migrations, with increasing numbers of

TABLE 4 Survival by pathological TNM stage group for the sixth and seventh editions of the TNM system

Stage	Sixth edition				Seventh edition			
	Subjects n	1 yr	3 yr	5 yr	Subjects n	1 yr	3 yr	5 yr
IA	449	89.3	73.7	60.3	449	89.3	73.7	60.3
IB	728	82.4	64.7	53.3	517	85.7	68.6	57.9
IIA	77	83.0	47.3	34.6	384	77.6	50.4	37.9
IIB	335	67.8	38.8	30.5	224	65.6	42.9	31.2
IIIA	159	64.2	24.5	16.1	276	62.7	25.7	17.7
IIIB	69	69.6	40.6	18.8	15	60.0	20.0	13.3
IV	68	55.9	27.9	20.8	20	45.0	30.0	14.4

Data are presented as %, unless otherwise stated.

cases in stages IIA and IIIA along with decreasing numbers in stages IB, IIB and IIIB. Our study reproduced these results in a national cohort and we are confident that they can be generalised to other lung cancer populations.

Meanwhile, our finding of no improved overall predictive ability of the seventh edition is in contrast to earlier studies. The studies from Japan [5, 6] carried out a limited evaluation of the new system and concluded that the seventh edition improves the discrimination of prognostic groups. However, one of the studies only showed better differentiation between stage IB and IIA [5] and the other study between IIA and IIB [6], while both found that patients at stage IIIB had a poorer prognosis than those at stage IV. No formal tests for comparing the predictive ability of the sixth and seventh TMN systems were conducted. Furthermore, these studies were performed at single institutions, in younger patients with more adenocarcinomas and lower pneumonectomy rates and the study periods were much longer (including study periods dating back to 1980) and, therefore, more heterogeneous with regard to treatment standards. KAMEYAMA *et al.* [6] studied patients for a period of 5 yrs during which adjuvant chemotherapy was routinely administered; however, in Norway, adjuvant chemotherapy was only introduced after our study period. In a study from the California Cancer Registry, OU *et al.* [7] have so far performed the only population-based evaluation of the seventh TNM edition. They studied 23,583 cases of advanced NSCLC treated with all modalities but their data overlap with those from the SEER database, which the IASLC used in the external validation of the seventh edition. The results support the reclassification of patients with multiple nodules in the same lobe to T3 and multiple nodules in the same lung to T4, as well as the differentiation into M1a (pleural/pericardial dissemination) and M1b (distant metastases) in the seventh edition. Furthermore, OU *et al.* [7] report that stages IIA and IIB were better differentiated in the seventh edition. Notwithstanding the differences in the populations of the currently available studies, our results, which are based on the thorough investigation from

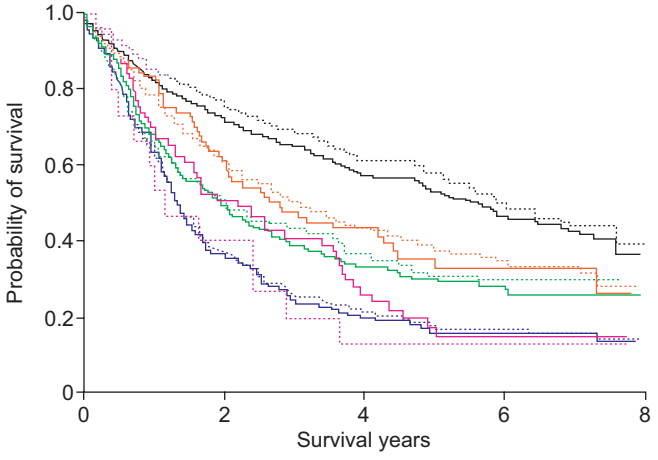

FIGURE 2. Survival for pathological TNM stages IB to IIIB according to the sixth (solid lines) and seventh (dashed lines) editions of the TNM system for lung cancer. Black: stage IB; orange: stage IIA; green: stage IIB; blue: stage IIIA; pink: stage IIIB.

TABLE 5 Survival by pathological T-descriptor in the sixth and seventh editions of the TNM system for lung cancer[#]

TNM stage	Subjects n	Survival %		
		1 yr	3 yr	5 yr
Sixth edition				
I	449	89.3	73.7	60.3
II	728	82.4	64.7	53.3
III	65	61.5	38.5	32.6
IV	33	81.8	57.6	26.3
Seventh edition				
IA	249	92.4	79.9	65.5
IB	200	85.5	66.0	53.8
IIA	517	85.7	68.6	57.9
IIB	146	78.8	59.6	45.8
III	157	66.9	45.9	32.8
IV	27	70.4	40.7	32.6

[#]: only cases without lymph node involvement or distant metastases are included.

TABLE 6 Multivariate analyses of survival by pathological TNM stage for the sixth and the seventh editions of the TNM system for lung cancer[#]

TNM stage	Sixth edition		Seventh edition	
	Subjects n	HR (95% CI)	Subjects n	HR (95% CI)
IA	449	1 (Reference)	449	1 (Reference)
IB	728	1.19 (0.99–1.43)	517	1.08 (0.89–1.32)
IIA	77	1.88 (1.36–2.60)	384	1.74 (1.43–2.13)
IIB	335	2.18 (1.78–2.68)	224	2.15 (1.71–2.68)
IIIA	159	3.13 (2.47–3.96)	276	3.00 (2.44–3.69)
IIIB	69	2.47 (1.81–3.36)	15	3.16 (1.77–5.63)
IV	68	3.18 (2.32–4.37)	20	5.02 (2.99–8.43)

[#]: adjusted for sex, age (continuous variable), side of tumour, morphology, resection margins and procedure.

multiple sources of every patient in Norway, represent an important contradiction to earlier conclusions. Therefore, we believe that our findings should be studied further using the prospective IASLC lung cancer database.

The completeness, reliability and universal national coverage of the Norwegian Cancer Registry and our representative sample from a time period with stable treatment regimens assure a valid and relevant evaluation of the proposed staging system. However, this study is not a complete evaluation of the new TNM system because it only covers surgical patients. Furthermore, it is based on pathological staging data, which are mainly relevant for clinical choices regarding adjuvant chemo- and radiotherapy. Conversely, adjuvant chemotherapy has been the most important curative therapeutic innovation for patients with NSCLC over the last few decades [19, 20], and stage migrations that increase the number of patients being treated with this modality will probably improve the survival of patients. Finally, from a methodological point of view, surgical samples are the most accurate means of staging and, in the seventh edition, the majority of the cases (53%) were surgical [21]. Thus, we are confident that our findings are valid and relevant for the staging of patients with NSCLC.

The implementation of the seventh edition of the TNM system will have substantial clinical implications. Since current treatment algorithms are based on former TNM versions, new randomised studies are needed to assess and confirm algorithms based on the stages of the new seventh edition of the TNM system. Furthermore, it should be considered that clinicians will have to use an even more complicated classification, and it is not known how this will affect the quality of the staging of lung cancer.

In conclusion, the new edition only slightly increased the differentiation of TNM stages without improving its overall predictive ability. These findings are in contrast to all former studies on this topic. Whether the use of the more complicated seventh edition and its clinical implications for as many as one-fifth of the cases will contribute to better outcomes for patients with lung cancer remains a question for future research.

STATEMENT OF INTEREST

A statement of interest for C. von Plessen can be found at www.erj.ersjournals.com/misc/statements.dtl

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