Editorial Commentary

Comment on an external validation of the 8th edition of the TNM classification for lung cancer staging in patients treated with chemoradiation

Ramón Palmero[1,2], Arturo Navarro-Martin[3], Ernest Nadal[1,2]

[1]Department of Medical Oncology, Catalan Institute of Oncology, L'Hospitalet, Barcelona, Spain; [2]Clinical Research in Solid Tumors (CReST) Group, Bellvitge Biomedical Research Institute, L'Hospitalet, Barcelona, Spain; [3]Department of Radiation Oncology, Catalan Institute of Oncology, L'Hospitalet, Barcelona, Spain

Correspondence to: Ernest Nadal. Department of Medical Oncology, Catalan Institute of Oncology, Avinguda de la Gran Via de l'Hospitalet, 199-203, 08908 Hospitalet de Llobregat, Barcelona, Spain. Email: esnadal@iconcologia.net.

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More than half a century ago, Dr. Pierre Denoix devised the tumor, node, and metastasis (TNM) staging system of classifying cancer patients into distinct categories based on the anatomical extent of the tumor. Ever since, it has been adopted as the basis for estimating prognosis and selecting treatment in solid tumors. The Union for International Cancer Control (UICC) and the American Joint Committee for Cancer (AJCC) initially developed independent TNM classifications which were unified in 1987 for a single, consistent stage classification system.

The initial editions of the TNM classification of lung cancer were based on a relatively small database from a single institution, but the need to develop an international database to improve the external validity of future TNM editions was already envisioned in 1996 during a workshop on lung cancer staging sponsored by the International Association for the Study of Lung Cancer (IASLC) (1). Since IASLC has led the revisions of the TNM lung cancer classification, two editions have been published. The 7th edition was published in 2009 based on retrospective data of 81,496 patients collected in the 1990s. This edition had some caveats, such as the lack of a prospective design which precluded validation of some descriptors, an inadequate worldwide representation, or the reduced use of positron-emission tomography (PET) during that period.

To overcome these and other limitations, IASLC launched an initiative for the 8th version of the TNM lung cancer staging including data from more than 100,000 patients from over 19 countries aiming for worldwide representation. Data were collected and analyzed by the Cancer Research and Biostatistics (CRAB) between 1999 and 2010 and, for the first time, also included prospective data (2). Distinct key features among the 8th and 7th edition are the use of the solid or invasive portion of the lesion to determine tumor size, the tumor descriptor (T) is further subdivided with 1 cm increments up to 5 cm, reclassification of >5 but <7 cm as T3 and >7 cm as T4, and the change in the staging value of T descriptors regarding main stem bronchus, lung atelectasis, obstructive pneumonitis and diaphragm invasion. In the 8th edition, for metastatic disease, a new M1b category was defined for patients with a single metastasis in one distant organ, whereas M1c indicates multiple extrathoracic metastases. There were no changes in the nodal descriptor (N), but further subdivision of N1 and N2 was proposed. All these modifications are clinically relevant because they are associated with different prognosis. However, the 8th version of the TNM classification still has the limitations that only a few cases were prospectively collected (5%) and most patient data came from Europe (49%) and Asia (44%), while North America was underrepresented. Moreover, several databases contributing to the 8th edition were derived from surgical patients and were not specifically designed to assess the TNM classification (3).

Table 1 External validations of the 8th edition of the TNM classification for lung cancer in cohorts of patients from regions relatively underrepresented in the 7th and 8th editions (North America and Asia) or treated with radiotherapy

Publication	Country	Period	N	Stage	Treatment	Performance of 8th *vs.* 7th TNM edition
Koul *et al.* 2018 (4)	Canada	2011–2014	295	I–III	RT	Improved
Choi *et al.* 2017 (5)	Korean	2010–2015	64	I–III	cCRT	Improved
Yılmaz *et al.* 2019 (6)	Turkey	2008–2015	103	III	cCRT	Not improved
Shin *et al.* 2017 (7)	US (SEER)	1998–2013	7,732	N3	Chemotherapy +/– radiotherapy	Slightly improved
Chansky *et al.* 2017 (8)	US (NCDB)	2000–2012	780,294	Any	Any	Improved
Yang *et al.* 2017 (9)	US (NCDB)	2004–2013	858,909	Any	Any	Improved
Yin *et al.* 2017 (10)	China	2001–2010	225	IIB	Surgery	Improved
Chen *et al.* 2017 (11)	China	2006–2015	2,043	I–III	Surgery	Improved
Jin *et al.* 2016 (12)	China	2008–2009	408	Any	Surgery	Improved
Sui *et al.* 2017 (13)	China	2005–2012	3,599	I–III	Surgery	Improved

cCRT, concurrent chemoradiotherapy; NCDB, National Cancer Database; SEER, Surveillance, Epidemiology, and End Results Program; RT, radiotherapy.

There have been several attempts to validate the 8th edition of the TNM classification in a non-Asian and non-surgical population (*Table 1*). The identification and assessment of prognostic factors, including the TNM classification, in patients with inoperable non-small cell lung cancer (NSCLC) is crucial. Indeed, thoracic radiotherapy is the treatment of choice for non-surgical patients with stage I–II and concurrent definitive chemoradiation is the standard of care for unresectable stage III NSCLC (14).

In a manuscript recently published in *Lung Cancer*, Koul *et al.* studied evaluated the 7th and 8th editions of the TNM lung cancer classification in a cohort of 295 patients with stage I–III NSCLC from North America who were primarily treated with radiotherapy (5). This is a relevant analysis that externally validates the TNM classification in the non-surgical setting. Data were collected from a Canadian Cancer Registry on patients with a histologically or cytologically confirmed NSCLC diagnosis. Remarkably, half the patients were older than 71 years of age, with patients up to 97 years included in the analysis. When re-evaluated with the 8th edition of the TNM, 73% of patients were upstaged and 18% of patients were downstaged, mainly due to the changes in the T3 descriptor. As the authors mentioned, the paper has some limitations due to its retrospective design and reduced sample size. Indeed, patient data were collected from a Canadian Cancer Registry, but the authors did not indicate if the cases were consecutive, there was no stratification according to histology or smoking history, and the information about staging procedure and treatment was apparently limited. In this regard, it is unknown if a PET-CT scan was performed in all patients or whether involvement of mediastinal lymph nodes was confirmed histologically.

The authors compared the performance of the 8th and 7th edition of the TNM classification using the Akaike information criterion (AIC) score to correct for potential biases of comparing distinct classification models. In the survival analysis, the categories defined by the T descriptor and the N descriptor showed distinct survival outcomes. The authors observed that the current 8th edition of the TNM classification had better performance over the 7th edition in terms of prognosis by means of the AIC score. The authors made the interesting observation that the T descriptor retained its prognostic value only below T2, while no differences in survival were seen among T2a, T2b and T3. Tumor size had a similar effect on prognosis in patients treated with radiotherapy or chemoradiotherapy in an internal validation of the previous 7th edition of the TNM (15). In this work, the authors concluded that patients with T1 tumors had longer survival than those with T2 and T3 based on tumor size, but there were no significant differences in survival between the T2a and T2b categories or the T2 and T3 categories. Two recent external validations of the 8th edition of the TNM classification

in patients receiving concurrent chemoradiation also concluded that the T descriptor was not prognostic in this setting (5,6). This suggests that the prognostic value of tumor size is stronger in patients receiving local treatments (surgery or radiotherapy alone) rather than in patients treated with concurrent chemoradiotherapy.

Additional external validations of the 8th edition of the TNM Classification for lung cancer have included patients who received distinct treatment modalities in population-based registries from the United States [Surveillance, Epidemiology, and End Results Program (SEER) and National Cancer Database (NCDB)] (7-9) or consisted of retrospective series of surgical patients from China (10-13) (*Table 1*). These studies have consistently shown that the 8th edition of the TNM overperformed the previous edition at predicting survival.

In conclusion, the work of Koul *et al.* is relevant since external validations of the TNM classification in the non-surgical setting are warranted to expand its clinical utility for patient care. In this sense, to increase the internal and external validity of the forthcoming 9th edition of the TNM classification for lung cancer, it is expected that the following will be included: more prospectively entered patient data, larger geographical representation, increased proportion of non-surgical patients, and clinically staging to include genomic information.

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Footnote

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

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