Editorial Commentary

The 8th UICC/AJCC TNM edition for non-small cell lung cancer staging: getting off to a flying start?

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Comment on: Koul R, Rathod S, Dubey A, *et al.* Comparison of 7th and 8th editions of the UICC/AJCC TNM staging for non-small cell lung cancer in a non-metastatic North American cohort undergoing primary radiation treatment. Lung Cancer 2018;123:116-20.

Submitted Jun 26, 2019. Accepted for publication Jun 28, 2019.
doi: 10.21037/atm.2019.07.02
View this article at: http://dx.doi.org/10.21037/atm.2019.07.02

Non-small cell lung cancer (NSCLC) represents the primary cause of cancer death in both men and women (1). Proper disease staging at diagnosis is crucial in providing an accurate prognosis and guiding towards the most appropriate treatment strategy. The Union for International Cancer Control (UICC)/American Joint Committee on Cancer (AJCC) TNM classification has evolved through the years and is the golden standard for solid tumor staging. In comparison with the 7th edition of the staging system for NSCLC, significant revisions have been proposed for the 8th edition (2). At this regard, the International Association for the Study of Lung Cancer (IASLC) Staging and Prognostic Factors Committee collected an enormous database of 94,708 cases and compared the performance of the two versions (3). One of the major drawbacks was the geographically inhomogeneous distribution: Asia provided for nearly 80% of tumors (while it was almost 50% in the previous database). Moreover, most of the data for the N descriptor were obtained from Japan, representing a nodal categorization based upon the Japanese Naruke map (4); a further validation was therefore advisable according to Mountain-Dressler modification of the American Thoracic Society map, considering the small quote of data representing western countries patients' cohort; another critical issue was the tiny percentage of non-surgical patients (only 563 cases).

The most significant changes introduced by the 8th edition concerned the T parameter: T1 is now sub-classified into (I) T1a (<1 cm); (II) T1b (between 1 and 2 cm) and (III) T1c (between 2 and 3 cm), which correspond to three new different stage subgroups in patients without lymph node involvement (stage IA1, IA2 and IA3, respectively); T2 now includes T2a (between 3 and 4 cm) and T2b (ranging from 4 and 5 cm). T3 stage now corresponds to a tumor between 5 and 7 cm of diameter (or separate nodules in the same lobe or chest wall, pericardium of phrenic nerve invasion), while T4 refers to tumors larger than 7 cm or invading mediastinal structures or to different nodules in a different ipsilateral lobe.

Koul *et al.*, in a recent article published on Lung Cancer, reported on the results of an interesting study comparing the performance of the seventh and eighth editions among a cohort of non-surgical patients treated with primary radiotherapy (5). As very few data are currently available on the prognostic performance of the TNM staging system for non-surgical patients, their study was undoubtedly original, and the results might be beneficial, especially for the design of new trials. The Authors analyzed data from 295 stage I-III NSCLC patients who underwent RT; they were staged preferably with Positron Emission Tomography (PET), and-or computed tomography (CT) chest—abdomen and cranial imaging (CT or MRI). Demographic parameters, tumor characteristics, and survival data were collected. Patients were followed up with a clinical and radiological assessment and were eventually re-classified according to the 8th edition after individual review of imaging.

As expected, the Authors found a redistribution primarily involving T1a, T2a, T3, and T4. Considering stage group distribution, initial stage IA was subgrouped as IA2 (n=16) and IA3 (n=28) respectively. Significant redistribution was

also noted for stage IIIA and IIIB, as long as 128 patients were redistributed as IIIA (n=85) and IIIB (n=43) according to 8th edition changes. Similarly, 75 patients with stage IIIB according to the 7th edition were re-classified as IIIB (n=55) and IIIC (n=20).

The 8th edition T1b, T1c, T2a, T2b, and T4 patients had a higher Hazard Ratio (HR) of death when compared to T1a; stages IA3, IB, IIA, IIB, IIIA, IIIB, and IIIC showed a progressive increase in the death HR compared to stage IA2.

The Authors then measured the homogeneity of the direct comparison of the two different editions using the Akaike information criterion (AIC), a quantitative parameter which estimates model fit and model complexity. A smaller AIC value indicated better goodness of fit. Both the 8th edition T descriptors and stage grouping had smaller AIC when compared to the 7th edition, suggesting an improved performance.

The work by Koul and colleague is of interest because it acknowledges the need for evaluating the 8th TNM staging edition performance in an under-represented cohort, a group of patients receiving primary RT. While surgery still represents a mainstay in the treatment of localized lung cancer and remains the best therapeutic option for patients with early-stage disease, latest guidelines recognize stereotactic radiation therapy as the first non-surgical choice for early-stage NSCLC (6). For unresectable stage III NSCLC, multi-modality therapy has a crucial role, and the recently completed phase III PACIFIC study showed the superiority of combined chemo-radiation followed by the anti-PD-L1 agent durvalumab over standard chemoradiotherapy alone (7).

In this context, there is a need for the recognition of new prognostic and predictive factors which could identify patients who will, or will not, benefit from specific treatments. Many attempts are therefore ongoing to improve the performance of the TNM staging system, developing new models integrating genetic mutations, expression profiles, and clinicopathological features with radio-genomics and radiomics, towards the definition of a personalized therapeutic approach (8).

What Koul and colleagues showed in their work—despite limitations mainly related to the heterogeneity of the analyzed cohort—is that the new staging system is applicable among non-surgical patients, and maintains its prognostic validity, while also revealing some possible intrinsic differences among surgical and non-surgical cohorts (limited in their exact evaluation by the relatively small sample size). In congratulating Koul and co-Authors for their research work, we might reasonably expect that the new TNM staging system will be further implemented, by different singles academic Institutions and by the joint efforts of the IASLC and UICC/AJCC task groups.

Acknowledgments

None.

Footnote

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

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Lancia A, Merizzoli E, Filippi AR. The 8th UICC/AJCC TNM edition for non-small cell lung cancer staging: getting off to a flying start? Ann Transl Med 2019;7(Suppl 6):S205. doi: 10.21037/atm.2019.07.02

