Editorial Commentary

TNM in non-small cell lung cancer: a staging system for all oncologists or just for surgeons?

David Ball

Department of Radiation Oncology, Peter MacCallum Cancer Centre, Melbourne, Australia

Correspondence to: David Ball. Department of Radiation Oncology, Peter MacCallum Cancer Centre, Locked Bag 1, A'Beckett St., Melbourne, Victoria 8006, Australia. Email: david.ball@petermac.org.

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 Apr 22, 2019. Accepted for publication Apr 28, 2019.
doi: 10.21037/atm.2019.04.84
View this article at: http://dx.doi.org/10.21037/atm.2019.04.84

The TNM staging system is a shorthand method of describing the anatomical extent of a cancer. Primarily it sorts patients into different prognostic categories, but it is also useful for guiding treatment and creating a common international language so that comparable groups can be analysed when evaluating the effect of interventions.

The TNM system is revised on a regular basis using the most recent new information. The 2nd edition of TNM for lung cancer dates back to 1973, and was based on the work of the thoracic surgeon Clifton Mountain using a database of 2,155 cases (1). It remained essentially unchanged until the appearance of the 7th edition in 2009 (2). In the evolution of TNM, the work of the Staging Committee of the International Association for the Study of Lung Cancer (IASLC) in preparing the 7th edition revisions is regarded as a landmark. Under the leadership of thoracic surgeon Peter Goldstraw, 100,869 cases were sourced from all over the world and the association of survival and tumor size and extent was analysed by statisticians led by Goldstraw *et al.* at Cancer Research and Biostatistics in Seattle (3).

Primary tumor size emerged for the first time as a key prognostic factor in the 7th edition (4). Intuitively this makes sense, as increasing size is associated with a greater likelihood of the metastatic phenotype, dissemination of disease and less probability of local therapies eradicating all disease. In the 7th edition, the effect of T stage was primarily evaluated in surgically treated patients with node negative (pN0) disease who had a complete resection and no evidence of distant metastases. Exclusion of patients with positive nodes would have selected out some patients with a worse prognosis because of higher risk of subclinical disease spread, nevertheless the adverse effect of increasing size was there even in N0 patients. We can speculate that this is likely due to hematogenous spread bypassing regional nodes. The biological implications of T stage for patients treated non-surgically with radiation therapy are in theory different to the surgical population. T4, implying technical unresectability, for example invasion of vertebra or great vessels, is not a contraindication to radical radiotherapy. The relationship between tumor size and metastatic risk is the same as for surgical patients, but where the surgeon can eradicate the primary with the same operation regardless of size, larger tumors are more difficult to eradicate with a given dose of radiation because of increasing burden of tumorigenic cells and greater likelihood of hypoxia with its associated radioresistance (5). Other factors which might affect outcomes in radiation treated patients include clinical rather than pathologic nodal staging with the latter favoring the surgical population.

If these considerations are correct, TNM might perform differently in patients receiving high dose radiotherapy compared with the surgical patients in the IASLC database. There is some evidence to suggest that this is indeed the case.

An analysis of the IASLC 7th edition database restricted to 868 patients treated with radical radiotherapy or radiochemotherapy revealed longer survival in patients with tumors 3 cm in diameter or smaller (T1); however, unlike the surgical population, evidence of an effect of tumor size on survival above this was weak (6). The T descriptor

represents the size of the primary tumor in one dimension only, so two tumors with the same T stage could have very different sizes if measured by volume. In a prospective study of the Trans-Tasman Radiation Oncology Group (TROG 99.05), tumour volume was prospectively measured in 509 patients having radical radiotherapy or chemoradiotherapy for locoregional non-small cell lung cancer (7). Survival was measured according to volume grouped in four quartiles. As in the IASLC analysis, the longest survival was seen in the quartile with the smallest volumes. Tumor volume did not however provide additional prognostic information beyond TNM (6th edition). Particularly interesting was the observation that in the first 18 months after registration, there was a strong relationship of tumor volume to survival, but after that, the relationship disappeared. At five years the survival was similar at around 20% in all quartiles. Why should there be long term survivors in patients with the largest tumors, supposedly the group in whom radiotherapy is likely to be least effective? Clearly the total number of tumorigenic cells is not the only determinant of outcome. Tumor volume tells us nothing about what proportion is stroma, necrosis or inflammation, and nothing about intrinsic radiosensitivity, oxygenation or metastatic propensity. It seems likely that some tumors can only grow to a very large size for the reason they do not possess the metastatic phenotype, thus removing a major competing risk for death.

The methodology for the preparation of the 8th edition was similar to that for the 7th edition, but included prospectively collected data. The majority of the cases came from Asia, and the analyses were based on patients who had complete surgical resection. The 8th edition expanded the number of T stage size descriptors from five to seven (8). In addition to size, other T category descriptors remain, legacies of Dr. Mountain's 2nd edition. Some still appear to have prognostic significance, such as diaphragmatic invasion; for others there are insufficient data to determine if they should be left in or out (for example vertebral invasion). It seems unlikely, with his limited database, that Dr. Mountain had strong evidence for some of his descriptors one way or the other. Apart from technical resectability, there seems no biological rationale, as there is for tumor size, why some of these descriptors should carry an adverse prognosis.

There were insufficient patients treated by radiotherapy or chemotherapy alone to test the generalizability of the 8th edition beyond the surgical population. Recently Koul and colleagues have compared the performance of the 8th with the 7th edition in a relatively small cohort of 295 North American patients treated by primary radiation therapy (9). The details of radiotherapy were not provided. For example, we do not know if any patients were treated with stereotactic ablative body radiotherapy or what proportion of patients received concomitant chemotherapy. Since the N classification did not change between the 7th and 8th editions, the comparison was effectively between T categories (not the individual descriptors) and the derived stage groupings. Using the 8th edition T categories, there was no consistent increase in the hazard ratio with progressive increase in T stage and with small numbers in each category, the confidence intervals were wide. With the stage groupings, there was however evidence of worsening hazard ratio with higher stage, as would be expected since it is driven largely by nodal status. For both comparisons (T stage and stage group) the Akaike information criterion, corrected for age and sex, showed a small improvement in performance for the 8th edition, but the numbers are not particularly convincing.

So how much more can we get out of TNM? Probably not a lot. It is only one of a number of tumor related prognostic factors and is restricted to anatomical extent rather than biological behaviour of the disease. Recognising the importance of patient related prognostic factors and emerging biological determinants of response and outcome, the IASLC has expanded the remit of the Staging Committee so that it is now named the Staging and Prognostic Factors Committee. It seems likely that in the future TNM will be subsumed into a multifactorial prognostic index. Our own group has developed such an index incorporating the most important prognostic and predictive factors, including mutation status, sex, age as well as TNM (10). The prognostic index provided much greater separation between groups than TNM alone.

In the modern era of big data there is no question this is the way forward, but the biggest hurdle appears to be a lack of resources to prospectively collect potential prognostic factors from multiple populations in as many different geographic locations as possible. The proportion of patients from North America constituted a disappointing 5% of the database used for the 8th edition, compared with 49% from Europe and 44% from Asia (11). Over 80% were treated with surgery, either alone or in conjunction with other treatments. Only 1.5% were treated with radiotherapy alone, and 4.7% with chemotherapy and radiotherapy. As an international community we can and must do better than that.

Acknowledgments

None.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

References

1. Mountain CF, Carr DT, Anderson WA. A system for the clinical staging of lung cancer. Am J Roentgenol Radium Ther Nucl Med 1974;120:130-8.
2. Sobin LH, Compton CC. TNM seventh edition: what's new, what's changed: communication from the International Union Against Cancer and the American Joint Committee on Cancer. Cancer 2010;116:5336-9.
3. Goldstraw P, Crowley JJ. The International Association for the Study of Lung Cancer international staging project on lung cancer. J Thorac Oncol 2006;1:281-6.
4. Rami-Porta R, Ball D, Crowley J, et al. 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. Dubben HH, Thames HD, Beck-Bornholdt HP. Tumor volume: a basic and specific response predictor in radiotherapy. Radiother Oncol 1998;47:167-74.
6. Ball D, Mitchell A, Giroux D, et al. 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;8:315-21.
7. Ball DL, Fisher RJ, Burmeister BH, et al. The complex relationship between lung tumor volume and survival in patients with non-small cell lung cancer treated by definitive radiotherapy: a prospective, observational prognostic factor study of the Trans-Tasman Radiation Oncology Group (TROG 99.05). Radiother Oncol 2013;106:305-11.
8. Rami-Porta R, Bolejack V, Crowley J, et al. 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;10:990-1003.
9. 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.
10. Alexander M, Wolfe R, Ball D, et al. Lung cancer prognostic index: a risk score to predict overall survival after the diagnosis of non-small-cell lung cancer. Br J Cancer 2017;117:744-51.
11. Rami-Porta R, Bolejack V, Giroux DJ, et al. 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;9:1618-24.

Cite this article as: Ball D. TNM in non-small cell lung cancer: a staging system for all oncologists or just for surgeons? Ann Transl Med 2019;7(Suppl 3):S103. doi: 10.21037/atm.2019.04.84

