Extended Abstract

Tumor-node-metastasis (TNM) update (pathological)—extended abstract

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Background

The 9th tumor-node-metastasis (TNM) staging classification is based on the analysis, performed by the Cancer Research and Biostatistics (CRAB) organization, of over 9,000 cases of thymic epithelial tumors (TETs) collected in the new International Association for the Study of Lung Cancer (IASLC) database, and on the extensive discussion among members of IASLC Staging and Prognostic Factors Committee (SPFC)-Thymic Domain (TD). Some choices of the SPFC-TD were determined by the peculiar TET biology: a single TNM stage classification for all TET types [thymoma, thymic carcinoma (TC), thymic neuroendocrine neoplasms] was maintained (for simplicity and for the existence of "combined" carcinoma-thymoma cases); moreover, thymomas are frequently locally invasive rather than metastatic and the spread is observed in advanced stages. Therefore, the precise definition of the anatomical T extension, in a region so complex such as the mediastinum, cannot be overemphasized. A "T" subcommittee, in the SPFC-TD, was specifically encharged to propose solutions for the "T"-related problems. The T indicator in the TNM system provides important information on tumor size (Tsize) and on surrounding tissues/organs invasion. Clinical (c) and pathological (p)T are strictly interrelated. However, some problems in the discussion concerned more the pathological workup than the clinical side of patient evaluation.

Statistical methodology

To assess the impact of Tsize on survival indicators, "T" analysis was performed separately for TC and thymoma, both for c and p Tsize, and cases were allocated in a training and in a validation set. The allocation in the 2 sets was stratified by geographical region, age (<65 *vs.* ≥65 years), sex, Eastern Cooperative Oncology Group (ECOG) performance status (0/1 *vs.* ≥2), resection status (R), and T category, to ensure that invaded anatomical structures were similarly distributed among datasets. The complete list of methods and results were reported in the original paper (1).

Results

As a general rule, microscopic confirmation of invasion is required for the "p" staging; therefore, the pT is determined after primary tumor removal, completely (R0) or incompletely (R1R2).

- Tsize: the impact of Tsize on survival was among the main unresolved issues of the TET 8th TNM (2), investigated in order to determine if size could be relevant for prognostic evaluation. Among TET, Tsize ranged from less than 1 cm to over 20 cm, and the median p Tsize was 5.4 cm in thymomas and 6 cm in TC. Although a single definite cut point was not determined, 5 cm was found within the range of optimal cut points, approximated the median Tsize for both thymomas and TC, seemed to have the broadest application in both thymoma and TC, and allowed a prognostic stratification of T1 patients in 2 groups, having Tsize of 5 cm or less *vs.* more than 5 cm. Both overall survival (OS) and freedom from recurrence (FFR) were statistically significantly different in the 2 groups.

Therefore, T1 was changed in T1a and T1b in relation to Tsize (T1a: 5 cm or less) (T1b: >5 cm).

- Mediastinal pleura (MP) invasion: the SPFC-TD acknowledged the difficulty in recognizing and reporting MP invasion both preoperatively (by imaging) and by pathological examination. Moreover, in patients with tumors classified as pT1 according to the 9th TNM proposals, different models were tested including contemporarily Tsize and MP invasion, however the results were not statistically significant. Therefore, for the 9th TNM, MP was dropped from relevant to the T1 indicator; however, MP was recommended as "additional histologic descriptor", to be recorded when available.
- Re-assessment of T3 level structures: FFR and cumulative incidence of recurrence (CIR) in T3N0M0 patients with TC and with thymoma—undergoing R0 resection with involvement of the lung or phrenic nerve—appeared to be similar to that of T2N0M0 R0 cases. Therefore, the proposal of the SPFC-TD was to downstage T3-lung and T3-phrenic nerve invasion to T2 in the 9th TNM. Concerning phrenic nerve invasion, it was proposed to include either pretreatment diaphragm elevation or pathological invasion of the perineurium without nerve function loss. The Committee is aware that the new IASLC database does not contain detailed information allowing a precise definition of pathological/clinical lung invasion with prognostic relevance.

Therefore, for the T component, the SPFC-TD proposals were as it follows: T1 category is divided into T1a (≤5 cm) and T1b (>5 cm Tsize) irrespective of MP invasion; T2 includes direct invasion of pericardium, lung or phrenic nerve, at variance with the 8th TNM; T3 includes direct invasion of the brachiocephalic vein, superior vena cava, chest wall, or extrapericardial pulmonary arteries and veins; and T4 category remained the same as in the 8th TNM.

No changes have been made to the N and M categories (3), nor to the International Thymic Malignancy Interest Group (ITMIG) nodal map, other than some added clarifications (4).

Discussion

Tsize, one of the most important prognostic indicators in most tumor systems, was now introduced as staging criterium in the 9th TNM. It should be noted that there are several recent papers dealing with the impact of TET's Tsize on survival, e.g., Cangir *et al.* (5) found better OS in thymomas <5 cm in Tsize measured both in the longest and mean diameters. For the 8th TNM, the Japanese Association for Research on the Thymus (JART) data included systematically the MP invasion, which showed a prognostic relevance. In the new IASLC database Tsize >5 cm was more frequent in T1 cases with MP invasion compared to those without MP involvement. In TC, most patients with T1 tumors with MP invasion had a pathological Tsize >5 cm, whereas less than half of T1 cases without MP involvement had a p Tsize >5 cm. Also, in thymomas, >5 cm Tsize was seen in 57% of T1 cases with MP invasion versus 44% of T1 cases with no MP involvement. Thus, MP, although recorded when available, was dropped from the TNM system and replaced by Tsize.

Unresolved issues that remain for the next 10th TNM edition (6,7), in particular for the "T" indicator include:

- More "granular" data should be collected for the next 10th TNM, in order to better define invasion criteria of anatomical structures. In particular a precise definition—both clinical and pathological—of lung invasion should be reached.
- More details for the cT in nonsurgical (more advanced) cases are needed.

Beside this, we need standardized specimen work up and reporting of relevant pathologic details such as Tsize, characteristics of the specific organ invasion, and uniform and accepted definitions of invasion. It should be pointed out that the recent 3rd edition of expert consensus of the International Collaboration on Cancer Reporting (ICCR) dataset defined and proposed most of the essential data to be investigated and reported for TET (8). The joint collaboration of radiologists, surgeons and pathologist is required to achieve an improved level of TET knowledge for the next 10th TNM.

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