Perspective

Clinical implications of the innovations in the primary tumour and metastasis of the 8th edition of the TNM classification for lung cancer

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Abstract: The 8th edition of the tumour, node and metastasis (TNM) classification for lung cancer introduced two new categories to accommodate adenocarcinoma in situ (AIS)—Tis(AIS)—and minimally invasive adenocarcinoma—T1mi; subdivided T1 into T1a (≤1 cm), T1b (>1–2 cm) and T1c (>2–3 cm); and T2 into T2a (>3–4 cm) and T2b (>4–5 cm); reclassified tumours >5–7 cm as T3, and those >7 cm as T4; reclassified endobronchial location <2 cm from the carina and total atelectasis/pneumonitis as T2a; and reclassified invasion of the diaphragm as T4. Regarding metastasis, the 7th edition M1a category remained the same, but M1b is now redefined to include single extrathoracic metastasis; and a new category, M1c, has been created for multiple extrathoracic metastases in one or in several organs. Tumours with worse prognosis than that assigned in previous editions, such as T3-4N2M0 and T3-4N3M0, were grouped in stages IIIB and IIIC, respectively. Stage IV was subdivided into IVA, for intrathoracic and single extrathoracic metastasis (M1a and M1b, respectively) and IVB, for multiple extrathoracic metastases (M1c). From the clinical point of view, these innovations will demand a more precise registration of tumour size, a thoughtful assessment of locally advanced tumours at multidisciplinary discussions, and a thorough search of extrathoracic metastases because the number of the metastatic sites has prognostic relevance and may influence therapy.

Keywords: Lung cancer; lung cancer staging; primary tumour; metastasis; tumor, node and metastasis classification (TNM classification)

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Introduction

The 8th edition of the tumour, node and metastasis (TNM) classification was based on the analyses of 77,156 evaluable patients with non-small cell lung cancer and of 6,189 with small cell lung cancer diagnosed from 1999 to 2010 around the world and registered in the International Association for the Study of Lung Cancer (IASLC) database (1). The innovations in the new edition concerned the T and the M components of the classification, were accepted by the Union for International Cancer Control and the American Joint Committee on Cancer, and were eventually published in the 8th edition TNM manuals of both agencies and in the 2nd edition of the IASLC staging manual and handbook on staging (2-5). There were no changes in the N component, although the importance of the quantification of nodal disease based on the number of involved nodal stations was emphasized (6).

The present concise review highlights the clinical implications of the changes introduced in the T and in the M components of the 8th edition of the TNM classification of lung cancer (7-9).

Primary tumour

Newcomers into the system

In 2011, adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma were defined (10); and in 2015, the World Health Organization included them in its book of classification of thoracic malignancies (11). AIS is now coded in the TNM classification as Tis(AIS) and grouped in stage 0 with squamous cell carcinoma in situ—Tis(SCIS)—because these tumours never spread to lymph nodes or distantly. It is important to add AIS and SCIS to their Tis category to differentiate both carcinomas, because they may coincide in the same patient (8). The new T category for minimally invasive adenocarcinoma is T1mi. It is grouped in stage IA1, with T1aN0M0, if there is no nodal or distant spread, which is the rule in these early carcinomas (8).

The inclusion of these new two categories in the TNM classification will increase their awareness in clinical practice. These early lesions are seen more often now than a decade ago and raise diagnostic, therapeutic and follow-up questions that need to be addressed as more evidence is produced.

Measurement of tumour size

For the first time in the history of the TNM classification of lung cancer, there are specific rules to measure tumour size. The TNM classification requires the registration of the greatest dimension of the tumour, both at clinical and pathologic classifications, but up to now there were no rules on how to measure it. In the 8th edition, for solid tumours, the recommendation is to use the lung window of the computed tomography in the projection that provides the greatest dimension of the tumour (8). Lung window measurements correlate better with pathologic size (12). On the other hand, for part-solid non-mucinous adenocarcinomas, the rule is to use the greatest dimension of the solid part on computed tomography or of the invasive component on pathologic study to assign a T category based on tumour size. For mucinous adenocarcinomas, the general rule applies, that is, the size of the whole tumour is the one that counts for the T category (8).

Measurement of tumour size after induction therapy requires special attention. When there is considerable objective tumour response, the size of the tumour is calculated by multiplying the percentage of viable tumour cells by the total size of the residual mass (8).

More T categories based on tumour size

The analyses of tumour size centimetre by centimetre have shown that every centimetre counts and has prognostic relevance from one centimetre or less to 5 centimetres in size. These findings allowed the subdivision of the T1 category into three subcategories (T1a, ≤1 cm; T1b, >1 cm but ≤2 cm; and T1c, >2 cm but ≤3 cm) and the subdivision of T2 into two (T2a, >3 cm but ≤4 cm; and T2b, >4 cm but ≤5 cm). Tumours >5 cm but ≤7 cm are categorized as T3; and those >7 cm as T4, in the 8th edition TNM (7). Tumour size is a T descriptor in all T categories and care should be taken when measuring it, because small variations in size may affect prognosis, both at clinical and pathologic staging (7).

Endobronchial location and atelectasis/pneumonitis

The identification of endobronchial tumour in the main bronchi at any distance from the carina, but with no invasion of the carina, is now a T2 descriptor. The analyses of survival of the 8th edition data have shown that those tumours located less than 2 cm from the carina have the same prognosis as those beyond 2 cm. This is a new finding of the 8th edition TNM for lung cancer. Therefore, it will not be so important to measure the distance from the carina to classify these endobronchial tumours. In the previous editions, this posed a problem, especially at pathologic staging, because the pathologist could not know the distance of the tumour to the carina in the resected specimens, unless it was described at clinical staging (7).

Most atelectasis and pneumonitis occurring in patients with lung cancer are due to tumour obstruction of the bronchial lumen. As with endobronchial tumour location, total atelectasis/pneumonitis (T3 in the 7th edition) was found to have the same prognosis as partial atelectasis/pneumonitis (T2 in the 7th edition). Therefore, in the 8th edition, both are grouped in the T2a category if tumour size is >3 cm but ≤4 cm or if tumour size cannot be determined, which is common when there is atelectasis or pneumonitis (7).

Visceral pleura invasion

There are no changes in the definition of visceral pleura invasion proposed for the 7th edition, that is, the invasion of the elastic layer of the visceral pleura (13). However, in the analyses of 8th edition data, it was found that the two types

of visceral pleura invasion (PL1, or invasion of its elastic layer, but not the lung surface; and PL2, or invasion of the lung surface) had different prognosis, PL2 being associated with worse prognosis than PL1 (7). It is, therefore, important to use elastic stains to determine the invasion of the visceral pleura and its type, if the invasion is not clearly seen with standard hematoxylin and eosin stains, because visceral pleura invasion is a bad postoperative prognostic factor (13).

Tumours with worse prognosis

From the clinical point of view, it is relevant to emphasize the bad prognosis of T3 and T4 tumours with nodal disease beyond N1. In the absence of distant metastasis, T3–T4 N2 tumours are now staged as IIIB; and T3–T4 N3, as IIIC, a new 8th edition stage created to accommodate these locally advanced tumours. In addition, tumours invading the diaphragm (T3 in the 7th edition) were upstaged to T4 (14). Exercising clinical judgement in the multidisciplinary discussions about the management of these tumours is of paramount importance because they require precise pathology-proved staging and intensive multimodality therapy.

Metastases

For the study of distant metastases, the subset of patients whose data had been registered prospectively through the electronic data capture (EDC) online system established by Cancer Research And Biostatistics (CRAB) was used. This smaller database consisted of a total of 3,905 patients whose data were rich in the detail of number and location of metastases (1,9).

Intrathoracic metastasis

The survival analyses of the intrathoracic metastases (M1a), that is, malignant pleural and pericardial effusion, malignant pleural and pericardial nodules, and contralateral separated tumour nodules, all had similar prognosis. Therefore, for the 8th edition there was no need to modify the M1a descriptors (9).

Extrathoracic metastases

In the analyses of extrathoracic metastases, there were clinically relevant findings that prompted some changes to the 7th edition. Firstly, all organ locations of metastatic sites had similar prognosis. Secondly, single extrathoracic metastasis had significantly better prognosis than multiple extrathoracic metastases, but similar to intrathoracic metastases. And thirdly, multiple extrathoracic metastases in one organ or in several organs had similar prognosis. Therefore, the 7th edition M1b category was redefined to include a single extrathoracic metastasis, and the new M1c category was created to include multiple extrathoracic metastases in one or in several organs (9).

M1a and M1b categories have the same prognosis, but they represent different types of anatomic spread. It makes sense, then, to keep them in different categories in the M component, but they are together in the new stage IVA, because they have better prognosis than M1c, which is stage IVB (9,14).

The separation of single extrathoracic metastasis from multiple extrathoracic metastases and the redefinition of M1b category to classify the former may help refine the definition of oligometastasis and oligoprogression. This is clinically relevant because, in contradistinction with the treatment of polymetastases, which mainly is palliative, the treatment of oligometastasis and oligoprogressive disease is intended to be radical with whatever means are available: resection, standard radiotherapy, stereotactic radiotherapy, radiofrequency, microwave or ultrasound ablation, chemotherapy and targeted therapy, either alone or, more commonly, in combination.

Despite the detailed analyses performed for the 8th edition, it is clear that the last word on the M component has not been said. Shortly after the publication of the article describing the findings of the analyses of metastases, a single institution study validated the proposed innovation, but also found that the prognosis of one or two extrathoracic metastases was the same (15). This has to be taken into account for future analyses of the new IASLC database that is now being collected to inform the 9th edition of the TNM classification due to be published in 2024.

Conclusions

All the innovations of the T and the M components of the 8th edition of the TNM classification for lung cancer are clinically relevant. The newcomers, Tis(AIS) and T1mi, will call more attention now that they have a specific category in the TNM classification. The determination of tumour size will have to be as precise as possible, because small variations in size have an impact on prognosis. Larger,

locally advanced tumours will require thoughtful clinical judgement to decide on therapy, because their prognosis is worse than indicated in previous TNM editions. The number of extrathoracic metastases counts, not only from the prognostic point of view, but because a single extrathoracic metastasis has more possibilities of radical treatment. Overall, the innovations of the 8th edition increase our capacity to indicate prognosis, both at clinical and pathologic staging, and therefore, fulfil one of the most important objectives of the TNM classification.

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