

## Key points

- In TNM7, there are five groups of tumours of different size and significantly different prognosis: T1a:  $\leq 2$  cm; T1b:  $>2-3$  cm; T2a:  $>3-5$  cm; T2b:  $>5-7$  cm; T3:  $>7$  cm.
- In TNM7, the N descriptors remain unchanged, but the quantification of regional nodal involvement according to the newly described nodal zones helps in the assessment of prognosis.
- In TNM7, metastatic disease is subdivided into M1a (intrathoracic) and M1b (extrathoracic).
- TNM7 applies to small and non-small cell lung cancer and to broncho-pulmonary carcinoids

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# The new TNM classification of lung cancer in practice

## Educational aims

- › To describe the changes in the 7th edition of the TNM classification of lung cancer
- › To discuss the clinical implications of the incorporation of the new TNM classification in everyday practice
- › To emphasise the key points for a proper pathologic classification

## Summary

The 7th edition of the TNM (tumour, node, metastases) classification of lung cancer incorporates the proposals of the International Association for the Study of Lung Cancer, whose database included more than 100,000 patients from Asia, Australia, Europe, and North America. The changes affect the T and the M components of the classification, and the stage grouping. The N component remained unaltered, although the present descriptors were validated both in the clinical and pathologic settings. This new TNM classification applies to non-small cell lung cancer, small cell lung cancer and, for the first time, to broncho-pulmonary carcinoids. The innovations allow for a better separation of tumours with significantly different prognosis, and imply a more careful determination of tumour size.

## Introduction

The 7th edition of the tumour, node and metastasis (TNM7) classification of lung cancer was officially enacted on January 1, 2010, and applies to non-small cell and small cell carcinomas and to bronchopulmonary carcinoids (table 1) [1]. It incorporated the latest revision of the classification, which was based on the analyses of the International Association for the Study of Lung Cancer (IASLC) database. The IASLC database included 100,869 patients with lung cancer (table 2), of whom 81,495 fulfilled the inclusion criteria and were available for analyses [2]. The results of these analyses originated several proposals to modify the 6th edition of the TNM

classification (TNM6). These proposals were published in the *Journal of Thoracic Oncology* [3–9], were internally and externally validated [10], were accepted by the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC), and were eventually published in their respective staging manuals [11, 12]. The TNM7 applies to non-small cell lung carcinomas, to small cell carcinomas [7, 8] and, for the first time, to bronchopulmonary carcinoids [9].

After more than one year of practical use, the innovations in the 7th edition have raised questions, the answers to which are not always easy. This review will emphasise the most relevant aspects of the introduction of the new TNM classification in clinical practice.

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None declared.

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**Table 1. Seventh edition of the tumour, node and metastasis (TNM) classification of lung cancer**

TNM components and categories	Definitions
<b>T: Primary tumour</b>	
TX	Primary tumour cannot be assessed; or tumour proven by the presence of malignant cells in sputum or bronchial washings but not visualised by imaging or bronchoscopy
T0	No evidence of primary tumour
Tis	Carcinoma <i>in situ</i>
T1	Tumour $\leq 3$ cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus ( <i>i.e.</i> not the main bronchus) <sup>#</sup>
T1a	Tumour $\leq 2$ cm in greatest dimension
T1b	Tumour $> 2$ cm but $\leq 3$ cm in greatest dimension
T2	Tumour $> 3$ cm but $\leq 7$ cm or tumour with any of the following features (T2 tumours with these features are classified T2a if $\leq 5$ cm): Involves main bronchus, $\geq 2$ cm distal to the carina Invades visceral pleura Associated with atelectasis or obstructive pneumonitis that extend to the hilar region but does not involve the entire lung
T2a	Tumour $> 3$ cm but $\leq 5$ cm in greatest dimension
T2b	Tumour $> 5$ cm but $\leq 7$ cm in greatest dimension
T3	Tumour $> 7$ cm or one that directly invades any of the following: chest wall (including superior sulcus tumours), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumour in the main bronchus $< 2$ cm distal to the carina <sup>#</sup> but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung; or separate tumour nodule(s) in the same lobe
T4	Tumour of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina; separate tumour nodule(s) in a different ipsilateral lobe
<b>N: Regional lymph nodes</b>	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph nodes
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
<b>M: Distant metastasis</b>	
M0	No distant metastasis
M1	Distant metastasis
M1a	Separate tumour nodule(s) in a contralateral lobe; tumour with pleural nodules or malignant pleural (or pericardial) effusion <sup>†</sup>
M1b	Distant metastasis

<sup>#</sup>: the uncommon superficial spreading tumour of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is classified as T1a; <sup>†</sup>: most pleural (and pericardial) effusions with lung cancer are due to tumour. In a few patients, however, multiple cytopathologic examinations of the pleural (pericardial) fluid are negative for tumour, and the fluid is nonbloody and is not an exudate. Where these elements and clinical judgement dictate that the effusion is not related to the tumour, the effusion should be excluded as a staging element and the patient should be classified as M0.

## Changes in TNM descriptors and stages

### Measurement of the greatest tumour dimension

Table 3 shows the changes introduced in the TNM7 compared with the TNM6. A look at the table shows that there are changes that demand more effort from us. All changes related to

tumour size require precise measurements of the greatest tumour dimension. However, the remaining changes, those in the classification of additional tumour nodules, pleural dissemination, metastases and stages require only that we apply a different descriptor.

The identification of five tumour size groups with significantly different prognosis was first based on the selected population of patients with T1–T2 N0 M0 completely resected tumours

**Table 2. Geographic distribution of patients with lung cancer submitted to the International Association for the Study of Lung Cancer database**

Continent	Number of patients
Australia	9,416
Asia	11,622
North America	21,130
Europe	58,701
Total	100,869

who had received no induction therapy, but was also confirmed in patients with tumours with nodal disease, incomplete resection, and in those with clinically staged tumours [3, 10]. To measure tumour size, the greatest dimension must be registered, but the TNM classification does not tell us how to measure it. Computed tomography (CT) is the most common imaging technique to study lung lesions, but in measuring tumour size several conditions may yield different measurements: a) window setting: for lung parenchyma or for mediastinum; b) projection: axial, sagittal or coronal; and c) breathing cycle: inspiration or expiration. In patients who also have positron emission tomography (PET) scans, the PET image may help define the tumour mass in an atelectatic lobe or lung and improve the precision of tumour size measurement. In any case, especially

when multiple measurements are anticipated, as in those patients who will be treated with induction therapy and whose tumours will be measured before and after treatment to assess the objective tumour response, it is important to ensure consistency that all tumour size measurements be carried out in the same conditions. The UICC recommends that one consult with the attending radiologist, who will know which window setting and which condition provide the most accurate measurement in one's institution [13].

### Clinical impact of additional tumour nodules

The downstaging of T4 tumours by additional tumour nodule(s) in the same lobe of the primary tumour to T3, and of M1 tumours by additional tumour nodule(s) in another ipsilateral lobe or lobes to T4 was based on differences in survival in pathologically staged tumours. There were fewer clinically staged tumours with these conditions, which reflects the difficulty to obtain histopathologic diagnosis in the clinical staging [3, 10], but the findings were consistent when the Surveillance, Epidemiology and End Results (SEER) database was analysed [10]. The IASLC database did not allow us to differentiate in these T3 and T4 conditions according to number or size of the additional tumour nodule(s). This raises prognostic and therapeutic doubts in clinical practice. One of these situations is described

**Table 3. Changes in the 7th edition of the tumour, node and metastases (TNM) classification of lung cancer compared with the 6th edition**

Condition	Descriptor in 6th edition	Descriptor in 7th edition
Tumour size ≤2 cm	T1	T1a
Tumour size >2 cm but ≤3 cm	T1	T1b
Tumour size >3 cm but ≤5 cm	T2	T2a
Tumour size >5 cm but ≤7 cm	T2	T2b
Tumour size >7 cm	T2	T3
Additional tumour nodule(s) in the same lobe of the primary tumour	T4	T3
Additional tumour nodule(s) in another ipsilateral lobe	M1	T4
Pleural dissemination (malignant pleural effusion and separated pleural nodules)	T4	M1a
Intrathoracic metastases	M1	M1a
Extrathoracic metastases	M1	M1b
T2b N0 M0	Stage IB	Stage IIA
T2a N1 M0	Stage IIB	Stage IIA
T4 N0–N1 M0	Stage IIIB	Stage IIIA
Small cell carcinomas	Included	Included; use of TNM favoured over "limited versus extended" classification
Broncho-pulmonary carcinoids	Excluded	Included

in a real case: a 76-year-old woman is found to have a nodule on the left upper lobe. Bronchoscopy and mediastinoscopy were negative. Left upper lobectomy and systematic nodal dissection were performed. At pathologic examination, the nodule was a 1.6 cm adenocarcinoma, but a 2 mm adenocarcinoma a few millimetres from the main tumour was identified. There was no nodal involvement. In this case, the tumour would be pathologically staged as pT1a by primary tumour size, but the presence of an additional tumour nodule upstages it to pT3. The expected 5-yr-survival rate decreases from 77 to 28% [3]. Adjuvant therapy might even be considered for this stage IIB tumour. Well, the clinical questions are: 1) will this small nodule really affect prognosis the way the analysis of the IASLC database suggests?; and 2) is adjuvant therapy really indicated for this tumour? Intuitively, one is tempted to assume that the presence of any additional tumour nodule is a more advanced stage, but the fact is that there is no evidence to support this in a particular case. The prospective phase of the IASLC Lung Cancer Staging Project will try to answer this question by collecting detailed information on the number, size and distance from the primary tumour of the additional tumour nodule(s) in the same lobe and in other ipsilateral lobe(s) [14]. In the era of data-driven classification, this is the only way to answer such a relevant clinical question on staging. Regarding treatment, in the era of evidence-based medicine, new randomised clinical trials designed with stratification by TNM subsets will provide evidence on the best therapeutic option for these tumours. At the present time, accurate prognosis for an individual patient escapes our capacity to prognosticate. Prognosis is based on results from large numbers of patients with similar tumours. In this particular case, time will tell us whether the prognosis of this pT3 tumour, so classified by strictly following the letter of the TNM classification, will indeed have a pT3 or a pT1 prognosis. The decision to indicate adjuvant therapy requires thoughtful clinical judgement and the consideration of co-morbidity, postoperative course, extent of intraoperative lymph node assessment, serum CEA level, maximum standardised uptake value, and the presence of histopathologic features associated with worse prognosis: vascular invasion, perineural invasion or lymphatic permeation [15, 16]. It is appropriate to emphasise that the evidence for benefit of adjuvant chemotherapy after complete resection of stage II NSCLC came from trials in which this stage was associated with N1 disease,

not more advanced N0 cases [17]. In discussing adjuvant treatment, the patient must understand the uncertainty of the prognosis and the uncertainty of the benefit of therapy. With all this information in mind, the multidisciplinary team in charge will be in the condition to decide on the convenience of administering adjuvant treatment or not.

Only seven patients out of 369 with contralateral lung nodules registered in the IASLC database underwent surgical treatment and, therefore, their tumours had a pathologic classification [5]. This reflects the generalised practice of denying surgical intervention to patients with lung cancer associated to contralateral nodules. A contralateral nodule may be a benign condition, a second primary tumour, a metastasis from the known lung cancer or a metastasis from an unknown second primary. It is important to bear in mind that to classify a lung cancer as M1a by the presence of contralateral lung nodule(s), according to the letter of the TNM classification, the nodule must have been proven to be a tumour nodule. The M1a descriptors are: separate tumour nodule(s) in a contralateral lobe; tumour with pleural nodules or malignant pleural or pericardial effusion. As in T3 and T4 by additional tumour nodule(s) in the lobe of the primary tumour and in another ipsilateral lobe(s), respectively, the key word is tumour. Not any nodule qualifies classification of a primary lung cancer as T3, T4 or M1a, but only those that are of neoplastic nature. Even with this confirmation, if both the primary tumour and the additional tumour nodule(s) are of the same histopathological cell type, it will be difficult to determine whether they are synchronous primaries or metastases. To classify them as synchronous primaries, the pathologist must determine that they are different sub-types of the same histopathological cell type based on differences in morphology, immunohistochemistry and/or molecular studies. In the particular case of squamous cell carcinomas, they should be associated with carcinoma *in situ*. Additionally, there should be no evidence of mediastinal nodal metastases or of nodal metastases within a common nodal drainage [1]. Recent retrospective evidence has shown that the differences in standardised uptake value of PET scans are significantly higher in patients with second primary cancers than in those with metastases [18]. Differences in epidermal growth factor gene status may also differentiate one from the other [19]. Although these findings should be prospectively validated, they may help determine

the probable nature of an accompanying nodule. In the particular case of contralateral nodules considered synchronous lung cancers, resection of both lesions is associated to 5-yr survival rates of 38–63% in recently published series [20–22]. These results suggest that resection of both tumours is a therapeutic option that should not be denied to operable patients if both lesions are deemed completely resectable.

### MX is not used any more

The analyses of the IASLC database provided enough evidence to separate intrathoracic (M1a) from extrathoracic (M1b) metastases [5]. In the best-staged group of tumours, the 5-yr survival rate of 771 patients with pleural dissemination was 6%, which was not significantly different from the 3% of 369 patients with contralateral lung nodules. However, the 5-yr survival rate of 1% in the group of 4,350 patients with distant metastases was significantly different from the other two. Prognosis of metastases to single sites was not different, with median survival of 6 months. However, there were not enough data to analyse single *versus* multiple sites in any extrathoracic organ [5].

An innovation in the M component of the classification was the removal of the MX category. It used to indicate that the presence of metastatic disease could not be assessed. It is now considered inappropriate, because the assessment of metastases can be based, at least, on clinical examination, which is the minimum examination any patient should have [1, 23].

### How to treat patients whose tumours are stage shifters

The modifications in the T and M components of the TNM classification originated some changes in stage grouping, with the relocation of certain TNM subsets in different stages (table 3). The result is that the stages of TNM7 better separate groups of tumours with significantly different prognosis compared with the stage grouping of TNM6. In TNM7, stage IIA is numerically larger than in TNM6, and its survival curve is properly located between those of stages IB and IIB [6]. These changes, however, already have raised questions on the optimal therapy for those tumours that changed from one stage to another. Large T2 tumours (T2bNOM0) have been upstaged from stage IB to stage IIA, a stage for which there is evidence that adjuvant therapy improves postoperative prognosis. However, these tumours were scantily represented in

the clinical trials that provided evidence for the benefits of adjuvant chemotherapy. Should they now be treated according to the guidelines for treatment of stage IIA? The answer is they should not. As with the case of an additional tumour nodule in the same lobe of the primary tumour described above, new randomised clinical trials are needed to answer this question. Contrary to the perceptions recently reported [24, 25], in principle, a change in stage does not automatically mean a change in therapy [26]. Each case must be considered individually by the multidisciplinary team, assessing all possible factors in addition to tumour stage, to indicate adjuvant treatment or not.

## Quantification of regional lymph node involvement

Regional nodal involvement in lung cancer is described by its absence (N0) or its presence, and the latter is further qualified by anatomic location of the involved lymph nodes, as follows. N1: ipsilateral intrapulmonary, peribronchial and/or hilar lymph nodes; N2: ipsilateral mediastinal and/or subcarinal lymph nodes; and N3: contralateral mediastinal and/or hilar, and ipsilateral and/or contralateral scalene and supraclavicular lymph nodes. These categories could be reliably validated with the IASLC data in the clinical and pathologic settings (table 4) [4]. The prognosis of nodal disease depending on the involvement of the different individual nodal stations was analysed and the result was that no nodal station had a significantly better or worse prognosis than another. However, when neighbouring nodal stations were amalgamated into nodal zones, three different prognostic groups were identified depending on the extent and location of nodal involvement: single pathologic N1 zone, with a 5-yr survival rate of 48%, had the best prognosis; multiple pathologic N1 zones and single pathologic N2 zone, with 5-yr survival rates of 35 and 34%, respectively, had similar prognosis; and multiple pathologic N2 zones, with a 5-yr survival rate of 20%, had the worst prognosis. Figure 1 shows the new IASLC lymph node map with the nodal stations and newly described nodal zones [27]. For descriptive purposes, this nodal involvement was coded as N1a, N1b, N2a and N2b, respectively, but could not be used to modify the present N descriptors because the findings were based on a selected population of nearly 2,000 patients who had

**Table 4. Survival according to the nodal (N) descriptors**

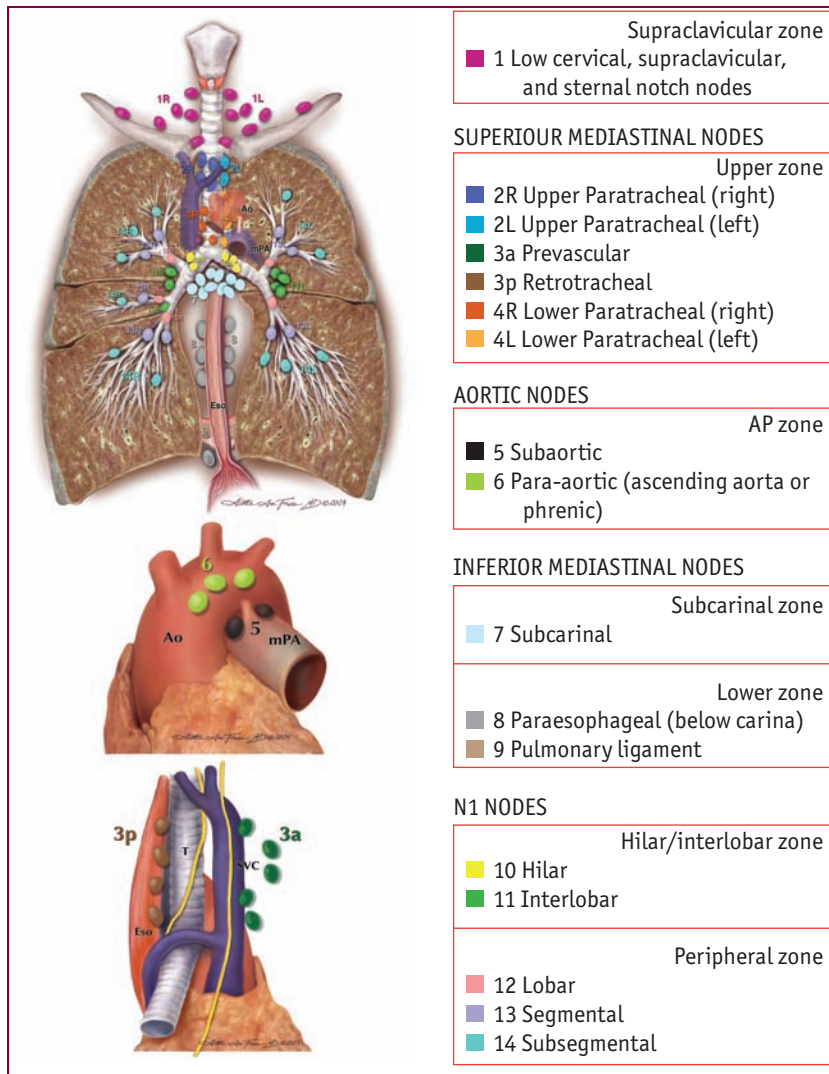
N category	Clinically staged tumours		Surgically treated patients			
	Patients n	5-yr survival rate (%)	Clinically staged tumours		Pathologically staged tumours	
			Patients n	5-yr survival rate (%)	Patients n	5-yr survival rate (%)
N0	19806	42	15711	50	16530	56
N1	3631	29 <sup>#</sup>	2471	39 <sup>#</sup>	5770	38 <sup>#</sup>
N2	11619	16 <sup>#</sup>	4277	31 <sup>#</sup>	5770	22 <sup>#</sup>
N3	3209	7 <sup>#</sup>	356	21 <sup>#</sup>	201	6 <sup>#</sup>

<sup>#</sup>: p<0.0001 compared with preceding row.

undergone lung resection and detailed pathologic N staging and could not be validated in the clinical setting by geographic regions or by T

categories. If these findings could be confirmed and validated in the prospective phase of the IASLC Lung Cancer Staging Project [28], they could be used to modify the present N descriptors of future editions of the TNM classification of lung cancer. The innovation of this potential modification of the N descriptors would be that nodal involvement would be both qualified by location and quantified by number of involved nodal zones. For the time being, the findings regarding involvement of the different nodal zones can be used clinically to better assess the prognosis of those patients who underwent resection and whose tumours were found to have nodal disease.

There is a growing body of evidence that shows that the amount of tumour burden in the regional lymph nodes has prognostic impact and, therefore, clinical relevance, because it can be used to intensify follow up, adjust treatment or stratify patients in clinical trials. Nodal involvement can be quantified by the number of involved nodes [29], the number of involved lymph node stations [30–32], the number of involved lymph node zones [4, 33], and by the lymph node ratio [34], *i.e.*, the ratio between the number of involved lymph nodes and the number of removed lymph nodes at operation. The consistent finding is that the greater the amount of involvement, the worse the prognosis. However, all these findings, although clinically relevant, derive from small single-centre studies of pathologically staged tumours, with no clinical validation, and, therefore, more evidence and validation is needed before they can be incorporated into the TNM classification. Sooner or later, they will be incorporated, as is the case of gastrointestinal and breast cancers, among others [11, 12]. In these tumours, the number of involved lymph nodes is an essential descriptor of the N component.



**Figure 1**  
International Association for the Study of Lung Cancer lymph node map. Reproduced with permission from [27].

**Table 5. Guide to uniform classification of situations beyond the standard descriptors**

Situation	Classification
Direct invasion of an adjacent lobe, across the fissure or directly if the fissure is incomplete	T2a <sup>#</sup>
Invasion of phrenic nerve	T3
Paralysis of the recurrent laryngeal nerve, superior vena caval obstruction, compression of the trachea or oesophagus related to direct extension of the primary tumour	T4
Paralysis of the recurrent laryngeal nerve, superior vena caval obstruction, compression of the trachea or oesophagus related to lymph node involvement	N2
Involvement of great vessels: aorta, superior vena cava, inferior vena cava, main pulmonary artery (pulmonary trunk), intrapericardial portions of the right and left pulmonary artery, intrapericardial portions of the superior and inferior right and left pulmonary veins	T4
Pancoast tumours with evidence of invasion of the vertebral body or spinal canal, encasement of the subclavian vessels, or unequivocal involvement of the superior branches of the brachial plexus (C8 or above)	T4
Pancoast tumours without the above criteria for T4 classification	T3
Direct extension to parietal pericardium	T3
Direct extension to visceral pericardium	T4
Tumour extending to rib	T3
Invasion into hilar fat	T2a <sup>#</sup>
Invasion into mediastinal fat	T4
Discontinuous tumour nodules in the ipsilateral parietal or visceral pleura	M1a
Discontinuous tumour nodules outside the parietal pleura in the chest wall or in the diaphragm	M1b

<sup>#</sup>: Unless other criteria assign a higher T.

## Classification of situations beyond the standard descriptors

There are multiple situations where the TNM rules do not fit. Over the years these have been discussed [35] and listed in the UICC supplements in order to provide guidelines for uniform use [1, 13]. Most of these situations are described in table 5. In case of doubt, the lowest category, *i.e.*, less advanced, should be chosen.

The classification of lymphangitis carcinoma has never been properly addressed in the TNM classification. Its radiographic evidence usually precludes surgical treatment, but its extent is thought to have prognostic relevance. A classification based on its radiographic extent has been proposed for prospective use and validation. It is coded as cLy and is different from the lymphatic invasion (L) descriptor, which describes invasion in the specimen (table 6). It has the following five categories [1]. cLy0: there is no radiological evidence of lymphangitis; cLy1: lymphangitis is present and confined to the area around the primary tumour; cLy2: there is evidence of lymphangitis at a distance from the primary tumour but confined to the lobe of the primary tumour; cLy3: there is evidence of lymphangitis in other ipsilateral lobes; and cLy4: lymphangitis affects the contralateral lung.

## Tips for a proper pathological classification

### Basic requirements

Pathological classification is based on all the information gathered to determine the clinical classification complemented with the intraoperative findings and the results of the histopathologic study of the resected specimens. It usually

**Table 6. Descriptors of local tumour invasiveness**

#### L: lymphatic invasion

<b>LX</b>	Lymphatic invasion cannot be assessed
<b>LO</b>	No lymphatic invasion
<b>L1</b>	Lymphatic invasion

#### V: vascular (either venous or arteriolar)

<b>VX</b>	Vascular invasion cannot be assessed
<b>VO</b>	No vascular invasion
<b>V1</b>	Microscopic vascular invasion
<b>V2</b>	Macroscopic vascular invasion (including involvement of the vascular wall with no endovascular tumour)

#### Pn: Perineural invasion

<b>PnX</b>	Perineural invasion cannot be assessed
<b>Pn0</b>	No perineural invasion
<b>Pn1</b>	Perineural invasion



implies the resection of the tumour and an adequate regional lymph node assessment to establish the absence of nodal involvement (pNO). However, when the tumour cannot be resected, a pathological classification can be determined if biopsies taken during exploration can certify the highest pT category, for the primary tumour, or the highest pN category for the lymphatic spread.

The present requirements to define pNO include the histopathological examination of at least six lymph nodes/stations: three from the mediastinum, always including the subcarinal nodes, and three from hilar, peribronchial or intrapulmonary nodes. However, if the lymphadenectomy specimen includes fewer than six nodes, but all are negative, a pNO classification is also possible. However, the appropriate designation would be pNX if no lymph nodes are resected or examined [23]. The resected lymph nodes and those dissected from the lung specimen by the pathologist should be labelled according the IASLC lymph node map [27]. Direct invasion of lymph nodes by the primary tumour is classified as N1 or N2. There is evidence suggesting that this pattern of direct nodal involvement is associated with better prognosis compared with metastatic pattern, at least for pN1 squamous cell carcinoma [36]. However, at the moment, there is no specific descriptor to differentiate both nodal involvement patterns.

Pathological assessment of metastasis (pM) requires microscopic examination.

### Visceral pleura invasion

Visceral pleura invasion, a T2 descriptor, is defined as invasion beyond its elastic layer. If the elastic layer cannot be identified with the standard haematoxylin and eosin stains, the use of elastic stains is recommended [37]. Four pleural (PL) categories to describe its pathologic extent have been proposed for prospective use and validation: PLO: tumour within the subpleural lung parenchyma or invades superficially into the pleural connective tissue beneath the elastic layer. This situation is not a T descriptor and the T category should be assigned on other features; PL1: tumour invades beyond the elastic layer. This indicates visceral pleura invasion and is a T2a descriptor; PL2: tumour invades to the pleural surface. This also is visceral pleura invasion and, therefore, a T2a descriptor; and PL3: tumour invades into any component of the parietal pleura. This indicates invasion of the parietal pleura and is a T3 descriptor.

### Additional tumour nodules

Differing from other organ sites, the classification of additional tumour nodules includes both those grossly recognisable and those found at microscopic examination of the specimen [1].

### Features of tumour invasion

Table 6 shows optional descriptors of the TNM classification that indicate the local invasiveness of the tumour and have prognostic impact [1,11]. All are recognisable at pathologic examination and should be included in the definitive pathologic report.

### Residual tumour classification

The residual tumour (R) classification describes the presence or absence of tumour after treatment. It has four categories [1]: RX: the presence of residual tumour cannot be assessed; RO: no residual tumour; R1: microscopic residual tumour; and R2: macroscopic residual tumour

For surgical cases, the RO category is associated with complete resection. However, the mere absence of residual tumour does not indicate how the resection was performed. To further qualify the absence of residual disease, the IASLC proposed minimal requirements to classify a resection as complete: a) free resection margins confirmed microscopically, including the bronchial and vascular stumps, the peribronchial soft tissue, any peripheral margin close to the tumour and any additional resected specimen; b) a systematic nodal dissection or a lobe-specific systematic nodal dissection must be performed; c) there is no extracapsular tumour extension in nodes removed separately or in those at the margin of main lung specimen; and d) the highest mediastinal node removed must be negative [38].

In contraposition, an incomplete resection can be defined if any of the following conditions apply: a) there is tumour involvement of resection margins; b) there is extracapsular extension of tumour in nodes separately removed or in those at the margin of the main lung specimen; c) positive nodes have not been removed; or d) positive cytology of pleural or pericardial effusions [38].

There is an intermediate situation (uncertain resection) in which resection margins are negative and there is no evidence of residual disease, but the resection does not completely fulfil the requirements for a complete resection: a) the intraoperative nodal assessment has been

less rigorous than the systematic nodal dissection or the lobe-specific systematic nodal dissection requires and does not contain the number of nodes recommended for complete resection; b) the highest mediastinal node removed is positive; c) there is carcinoma *in situ* at the bronchial margin; or d) pleural lavage cytology is positive [38]. The recommended codes for these specific situations are: R1(is) for presence of carcinoma *in situ* at the bronchial margin; R1(cy+) for positive pleural lavage cytology; and R0(un) for the remaining situations qualifying for uncertain resection [1].

The R classification applies to the primary tumour, lymph node involvement and distant metastases [39].

### Special situations in the histopathologic study of lymph nodes

When the histopathologic examination is performed on the sentinel node (sn), this is indicated after the nodal descriptor: pNX(sn), pNO(sn), and pN1-3(sn).

The presence of micrometastasis, *i.e.* metastases not larger than 0.2 cm, is described by adding (mi) to the pertinent nodal descriptor: N1(mi), N2(mi), or N3(mi).

The presence of isolated tumour cells (ITC; single tumour cells or clusters not larger than 0.2 mm) in the lymph nodes does not qualify assigning a N1, N2 or N3 category because these cells do not usually show metastatic activity or penetration of vascular wall. However, their presence or absence has to be described and the appropriate classification depends on the method of their identification: immunohistochemistry stains (i+ or i-) or non-morphologic techniques, such as flow cytometry or DNA analysis (mol+ or mol-): NO(i-): no regional lymph node metastasis histologically, negative morphological findings for ITC; NO(i+): no regional lymph node metastasis histologically, positive morphological findings for ITC; NO(mol-): no regional lymph node metastasis histologically, negative non-morphological findings for ITC; NO(mol+): no regional lymph node metastasis histologically, positive non-morphological findings for ITC.

If the study is performed on a sentinel node, (sn) should be added: *e.g.* NO(i+)(sn).

### Isolated tumour cells in bone marrow

This follows the same rules for nodal staging: MO(i-), MO(i+), MO(mol-) and MO(mol+).

## Intensity and validation of the staging process

The TNM classification does not require a minimum number of tests to determine the anatomic tumour extent. There are many tests with different accuracies and, depending on the number and type of tests used in the staging process, the resulting TNM classification can be more or less accurate. In order to homogenise the staging process, the UICC recommends the use of the certainty factor (C-factor), an optional descriptor that reflects the intensity of the studies and the validity of the classification [1, 11]. It has five categories: C1: evidence from standard diagnostic means (*e.g.*, inspection, palpation, and standard radiography, intraluminal endoscopy for tumour of certain organs); C2: evidence obtained by special diagnostic means (*e.g.*, radiographic imaging in special projections, tomography, computerised tomography, ultrasonography, lymphography, angiography, scintigraphy, magnetic resonance imaging, positron emission tomography, endoscopy, biopsy, and cytology); C3: evidence from surgical exploration, including biopsy and cytology; C4: evidence of the extent of disease following definitive surgery and pathological examination of the resected specimen; C5: evidence from autopsy.

Certainty factors C1, C2 and C3 apply to clinical classification, while C4 applies to pathological classification.

Although this is a good way to assess the intensity of the staging process, certainty factor C2 is a mixture of anatomic and metabolic imaging, and endoscopies with or without biopsy or cytology. As more experience is gained in the clinical application of the certainty factor, C2 will have to be subdivided to describe more clearly the type of tests used, because their accuracy is not homogeneous; *e.g.*, computerised tomography is grouped together with bronchoscopy, that can provide cytohistological prove of the primary tumour and its nodal spread if the appropriate endoscopic procedures are used.

## The future

The classification of anatomic tumour extent is a strong predictor of prognosis, but it is not the only one. Prognosis of lung cancer depends on several factors related to the tumour itself, to the patient and to the environment [1], and all these are not addressed by the TNM classification. In

the retrospective phase of the IASLC Lung Cancer Staging Project, simple parameters such as performance status, age, sex and certain laboratory tests, such as albumin, white blood tests and hypercalcaemia, were found to be significant prognostic variables [40, 41]. In the TNM7, the stage grouping of several tumours has already been complemented with non-anatomic parameters (age, mitotic rate, histopathologic grade and location, among others), and tables combining the TNM classification with other information to produce prognostic groupings have been added to help in the assessment of prognosis. In their latest staging manuals, the UICC provides separate tables to describe stage grouping and prognostic grouping, while the AJCC combines both in the same table [11, 12]. Sooner or later, as more information is gathered, including molecular and genetic features, this will be the case of lung

cancer but, at the moment, the TNM classification of lung cancer remains to be the assessment of its anatomic extent and the strongest predictor of prognosis [40–42].

## Conclusion

TNM7 better separates groups of tumours of significantly different prognosis compared with TNM6, but requires more precision in the determination of tumour size. The different T, N and M descriptors, the core of the TNM classification, are supplemented by rules and optional descriptors, that also are periodically revised, that help classify tumours in a very precise way, both in the clinical and pathological settings. Therefore, TNM7 should be incorporated into clinical practice because it better fulfils the objectives of the TNM classification.

### Educational questions

1) In the 7th edition of the TNM classification, T4 tumours with no nodal involvement and no distant metastases (T4N0M0) are grouped in stage...

- a) IIB
- b) IIIA
- c) IIIB
- d) IV
- e) IB

2) A 55-yr-old, current smoker man complaining of hoarseness is found to have a 2.5 cm peripheral lesion in the left upper lobe and a bulky nodal conglomerate in the aortopulmonary window on chest radiograph. Physical examination does not reveal any abnormality. Sputum cytology examination has been positive for malignant cells, compatible with non-small cell carcinoma. What would be the clinical classification of this tumour based on the information provided?

- a) T2a N1 M0
- b) T4 N2 M0
- c) T1b N2 M0
- d) T4 N0 M0
- e) T1b N2 MX

3) A 64-yr-old, current smoker man complains of persistent cough with blood-stained sputum. Physical examination is normal. Postero-anterior and lateral chest radiograph reveal a 3 cm mass in the right upper lobe. Computerised tomography confirms the presence of a 3.4 × 3 × 2.9 cm mass with some cavitation; enlarged 4R nodes of maximum shorter axis of 1.8 cm. Bronchoscopy revealed a mass obstructing the posterior segment of the RUL. Biopsy was positive for squamous cell carcinoma. PET scan showed abnormal uptake in the RUL mass with a SUVmax of 5.6, and of 1.6 in the right inferior paratracheal nodes. Mediastinoscopy, with removal of 7 nodes from 4R, 7 and 4L stations, was negative. What is the clinical tumour classification with the information provided?

- a) T2 N1 M0
- b) T4 N2 M0
- c) T2a N0 M0
- d) T3 N0 M0
- e) T2b N0 M0

4) The same patient as in question 3 underwent right thoracotomy. Right upper lobectomy and systematic nodal dissection were performed. At intraoperative exploration, a 1 cm nodule in the apical segment of the RLL was identified and removed by wedge resection. At pathologic examination, the RUL mass was diagnosed as well differentiated squamous cell carcinoma of 5.2 cm. One centimetre anterior to the main mass, the pathologist found a 2 mm squamous cell carcinoma. The nodule of the RLL was diagnosed as well differentiated adenocarcinoma of 7 mm in greatest dimension. All removed nodes were negative, but an intrapulmonary node close to the RUL tumour was directly invaded by the tumour. What is the pathologic tumour classification with the information provided?

- a) T2b N0 M0
- b) T3 N1 M1
- c) T3 N1 M0 and T1 N0 M0
- d) T3(2) N1 M0
- e) T4 N1 M0

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P-7  
 C-E  
 C-Z  
 Q-L

Suggested answers