UPDATE IN RADIOLOGY

Role of imaging techniques in the TNM classification of non-small cell bronchogenic carcinoma

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Abstract The Seventh Edition of the TNM classification for non-small cell bronchogenic carcinomas includes a series of changes in the T and M descriptor, in particular a re-classification of malignant pleural and pericardial effusions and of separated tumor nodes, new tumour size cut-off values and sub-divisions of the T1–T2 and M1 categories. We review these corrections that led to the changes in the staging system that affects stages II–III. Furthermore, we describe and illustrate the role of the different imaging techniques in tumour staging (CT, PET, PET-CT and MRI), highlighting their respective indications, advantages and disadvantages, as well their complementary function.

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Papel de las técnicas de imagen en la nueva clasificación TNM del carcinoma broncogénico no microcítico

Resumen La séptima edición de la clasificación TNM para los carcinomas broncopénicos no microcíticos incluye una serie de cambios en los descriptores T y M, particularmente una re-clasificación de los derrames malignos pleurales y pericárdicos y de los nódulos tumorales separados, nuevos valores de corte de tamaño tumoral y subdivisiones de las categorías T1-T2 y M1. Revisamos estas correcciones, que generan cambios en el sistema de estadificación que afectan a los estadios II-III. Además, describimos e ilustramos el papel de las diferentes técnicas de imagen en la estadificación tumoral (TC, PET, PET-TC y RM), resaltando sus respectivas indicaciones, ventajas y desventajas, así como su función complementaria.

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Introduction

The TNM classification for non-small cell bronchogenic carcinoma (NSCBC) is an internationally accepted and validated system for the management of patients, treatment planning, and prognosis assessment. This system classifies a tumor according to its primary characteristics (T), involvement of regional lymph nodes (N), and distant metastasis (M).\textsuperscript{1-7}

The combination of these parameters determines the tumor stage at the clinical-diagnostic stage (based on the clinical history, imaging tests, and pretreatment histologic samples) or at the surgical-pathologic stage (histologic type of the resected tumor).\textsuperscript{1,3,5,6}

The Seventh Edition of the TNM (TNM-7) classification\textsuperscript{8} was developed by the International Association for the Study of Lung Cancer (IASLC) as part of the Lung Cancer Study Project. The IASLC conducted a retrospective statistical analysis of the prognostic value (expressed as survival rate) of the TNM descriptors using an international database including 100,869 NSCBC patients treated between 1990 and 2000. The TNM-7 classification was later approved by the American Joint Committee on Cancer (AJCC) and the International Union against Cancer (IUAC) for use from January 1, 2010, replacing the Sixth Edition (TNM-6) classification.\textsuperscript{3,4,6-15}

This paper describes the changes introduced in the TNM-7, mainly a re-classification of the pleuroperticardial involvement and the separate tumor nodules (formerly known as satellites), the use of new tumor size cut-off values, and sub-divisions of the T1–T2 and M1 categories.\textsuperscript{1,3-6,9-11,14,15} Although no changes were made in the N descriptor, more accurate anatomic boundaries are described between nodal stations and their distribution in nodal zones.\textsuperscript{5,4,7,11,14,16} The use of this new classification is also recommended for small-cell carcinomas and carcinoid tumors.

The TNM-7 system analyses survival rates retrospectively, specifying the methods for clinical assessment (particularly imaging techniques) and treatments applied.\textsuperscript{9,12,13} Since imaging techniques and treatments are continually being improved, which has an impact on survival a periodical follow-up is necessary. The present study also summarizes the role of imaging techniques in the NSCBC staging (computed tomography [CT], positron emission tomography computed tomography [PET CT], and magnetic resonance [MR]), highlighting their indications, advantages, disadvantages, and complementary role.

TNM-7: Changes

T descriptors define anatomic parameters of a tumor, such as size, endobronchial location, distance to the carina, invasion of neighbouring structures, atelectasis, separate nodules, etc.\textsuperscript{17} The changes introduced, which were validated for all histologic subtypes, include\textsuperscript{9,13}:

- Introduction of cut-off values for tumors 2, 3, 5 and 7 cm in size, subdividing the T1–T2 categories according to the long axis of the lesion. Although the cut-off between both categories remains 3 cm, T1 is subdivided into T1a (≤ 2 cm) and T1b (> 2 cm and ≤ 3 cm). T2 is subdivided into T2a (> 3 cm and ≤ 5 cm) and T2b (> 5 cm and ≤ 7 cm).
- Any tumor > 7 cm is reclassified as T3.
- The separate nodules localized in the same lobe as the primary nodule are moved from T4 to T3. The separate nodules localized in a different lobe from the ipsilateral lung are moved from M1 to T4.
- Pleural implants and pleuroperticardial effusions are moved from T4 to M1.

There were no recommended changes for the N descriptor, although the IASLC suggests a new nodal map that reconciles differences between the established maps (the Narohe map, developed by Japan Lung Cancer Society, and the Mountain-Dresler map, developed by the American Thoracic Society). The new map also homogenizes the nomenclature by grouping the 14 nodal stations into 6 anatomic zones (upper, aortopulmonary, subcarinal, lower hilar, and peripheral). Furthermore, the anatomic boundaries between nodal stations are accurately described, particularly the boundary between the right and left paratracheal stations, which is now the left lateral tracheal border and not the tracheal midline. Accordingly, the paratracheal nodes belong to one or another paratracheal chain. The lower cervical nodes, supraclavicular nodules, and nodes of the sternal notch are now considered an independent station (station 1).\textsuperscript{1,4,6,7,11,14-16}

(Fig. 1).

The relationship between survival and number of stations (solitary or multiple) involved within each N category was analysed. Better survival was observed for involvement of a solitary station, although evidence was insufficient to recommend subclassification of N1–N2 into N1a–N2a (solitary) and N1b–N2b (multiple).\textsuperscript{1,4,6,9,15,16}

The relationship between the localization of the primary tumor and the associated adenopathy, and skip metastases (N2 with no evidence of N1) was also evaluated, but no significant results were obtained.\textsuperscript{1,11,15,16}

Concerning the M descriptor, the M1 category is divided into M1a (intrathoracic metastases: malignant pleuroperticardial effusion, pleural implants, contralateral lung nodules) and M1b (extrathoracic metastases).\textsuperscript{1,9,12,13,18} (Fig. 2). Although there may be a relationship between survival and number of metastasized organs, there is no evidence to justify subdivision of the M1b category.\textsuperscript{11}

The IASLC recommends the use of the TNM-7 system for small-cell lung carcinoma and carcinoid tumors since an inversely proportional relationship between survival and tumor stage has been reported.\textsuperscript{4,6,7}

Table 1 outlines T, N, and M descriptors in the TNM-7 system,\textsuperscript{8,9} highlighting the differences with respect to descriptors in the TNM-6 system.\textsuperscript{3,5,19,20} Figs. 3 and 4 illustrate such differences.

Staging

The combination of the descriptors determines tumor stage. In the TNM-7 system, staging is a more complex task since 17 stage migrations took place (10 cases were downstaged and 7 cases were upstaged), despite the fact that subdivisions of the T and M descriptors do not entail the creation of new
subgroups. Mean survival at each stage correlates with the clinical-diagnostic and surgical-pathologic stagings.\textsuperscript{1,10,11}

Table 2 outlines these migrations, and points out the main differences between TNM-6\textsuperscript{1,3,5,20} and TNM-7.\textsuperscript{9,10} The main changes are the following:

- T2aN1M0 moves from IIB to IIA.
- T2bN0M0 moves from IB to IIA.
- T3 (7 cm) N0M0 moves from IB to IIB.
- T3 (7 cm) N1M0 moves from IIB to IIA.
- T3N0M0 (nodules in the same lobe) moves from IIB to IIB.
- T3N1-N2M0 (nodules in the same lobe) move from IIB to IIA.
- T4M0 (ipsilateral pulmonary nodules) move from IV to IIIA if N0=I1 and to IIB if N2=N3.
- T4N0-1M0 (direct extent) moves from IIB to IIA.
- Malignant pleural effusion (M1a) moves from stage IIB to IV.

A correct staging has therapeutic implications. Stages I, II, and IIIA are generally candidates for surgery and stages IIIB-IV are regarded as unresectable (some T4 tumors as well as N3 and M1 tumors), although they would benefit from chemo and/or radiation therapy. The role of neoadjuvant chemotherapy followed by surgery in stage IIIA tumors is still controversial, but surgical advances have altered the approach to resectability and this procedure can nowadays be applied to a few selected patients with invasion of the mediastinum or of the vertebral body.\textsuperscript{2,7,11,17,18,21,22}

TNM-7: Limitations

Based on survival, TNM-7 revises the descriptors, and restructures tumor staging, reducing survival rate heterogeneity in stages II–III of the TNM-6 system. However, the validity of the results for prospective therapeutic cohorts is limited because this is a retrospective study.\textsuperscript{7,11}

The IASLC acknowledged that it was unable to evaluate the relevance of PET/PET CT to staging because of their limited availability during the study period.\textsuperscript{3,11} Nevertheless, these techniques are more available today, there are recommendations on their use and they are an integral part

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**Figure 1** Lung adenocarcinoma in a 47-year-old patient. Multidetector computed tomography (MDCT) images at diagnosis performed with intravenous contrast. Lung window axial image (a) shows a spiculated mass with a 33 mm long-axis diameter in the right upper lobe (arrow). Mediastinal window axial images (b–d) show adenopathy in the supravacular fossa (arrows in b), bilateral lower cervical nodes (arrowheads on c) and left paratracheal nodes (arrowhead in d). It should be noted that the supravacular adenopathy, adenopathy in the sternal notch and lower cervical adenopathy correspond to nodal station 1, and that the boundary between the right and left paratracheal stations is the left tracheal border. The findings were confirmed by PET–CT with no signs of metastatic disease at other levels (not shown). Therefore, the findings were diagnostic of a cT2aN3M0 (IIIB stage) tumor. However, one of the limitations of TNM-7 is that axillary (asterisk on d), subpectoral, internal mammary, diaphragmatic, and abdominal adenopathy are not explicitly coded.
Table 1  Definitions of descriptors T, N, and M suggested by the IASLC for the TNM-7.

<table>
<thead>
<tr>
<th>T</th>
<th>TX</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>No evidence of primary tumor.</td>
</tr>
<tr>
<td>Tis</td>
<td>T in situ.</td>
</tr>
</tbody>
</table>
| T1      | T ≤ 3 cm Ø, surrounded by lung or visceral pleura, without invasion proximal to the lobar bronchus.  
           (T1a: tumor ≤ 2 cm Ø and T1b: tumor > 2 cm Ø) |
| T2      | T > 3 cm and ≤ 7 cm Ø (or with any of the following features:  
           - tumor involves the main bronchus, and is more than 2 cm distal to the carina.  
           - tumor invades the visceral pleura or fissure (understood as reflection of the visceral pleura),  
             unless it also meets criteria featuring a higher category.  
           - tumor is associated with atelectasis or obstructive pneumonitis that extends to the hilar region without involvement of the entire lung (partial atelectasis).  
           (T2a: tumor > 3 cm and ≤ 5 cm Ø and T2b: tumor > 5 cm Ø and ≤ 7 cm Ø). |
| T3      | Tumor > 7 cm across its greatest dimension or with any of the following features:  
           - direct invasion of the chest wall (including the superior sulcus), diaphragm, mediastinal pleura, parietal pericardium or phrenic nerve.  
           - involvement of the main bronchus > 2 cm distal to the carina.  
           - associated atelectasis of the entire lung.  
            Separate pulmonary nodules within the same lobe as that of the primary tumor. |
| T4      | T of any size with invasion of the mediastinum, heart, great vessels, trachea, esophagus,  
           vertebral body, carina, recurrent laryngeal nerve, or separate tumor nodules within an ipsilateral lobe different from that of the primary tumor. |

<table>
<thead>
<tr>
<th>N</th>
<th>N0</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1</td>
<td>M in ipsilateral peribronchial or ipsilateral hilar and intrapulmonary lymph nodes, including direct extension.</td>
</tr>
<tr>
<td>N2</td>
<td>M in ipsilateral mediastinal or subcarinal lymph nodes.</td>
</tr>
</tbody>
</table>
| N3      | M in the mediastinum or in the contralateral hilum.  
           Ipsilateral or contralateral M in scalene or supraclavicular lymph nodes. |

<table>
<thead>
<tr>
<th>M</th>
<th>M0</th>
</tr>
</thead>
</table>
| M1      | M1a: intrathoracic M:  
           - Malignant (non-paraneumonic) pleural or pericardial effusion.  
           - Pleural implants.  
           - Metastatic nodules in the contralateral lung.  
           M1b: extrathoracic M. |

The changes with respect to TNM-6 are in bold.  
IASLC: International Association for the Study of Lung Cancer; M: metastasis; T: tumor; Ø: longest diameter.

Table 2  Tumor staging (stages I and IV) in accordance with TNM-6 and TNM-7 descriptors.

<table>
<thead>
<tr>
<th>TNM-6</th>
<th>TNM-7</th>
<th>N0</th>
<th>N1</th>
<th>N2</th>
<th>N3</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 (≤ 2 cm)</td>
<td>T1a</td>
<td>IA</td>
<td>IIa</td>
<td>IIIa</td>
<td>IIIB</td>
</tr>
<tr>
<td>T1 (&gt; 2 and ≤ 3 cm)</td>
<td>T1b</td>
<td>IA</td>
<td>IIa</td>
<td>IIIa</td>
<td>IIIB</td>
</tr>
<tr>
<td>T2 (≤ 3 and ≤ 5 cm)</td>
<td>T2a</td>
<td>IB</td>
<td>IIb → IIa</td>
<td>IIIa</td>
<td>IIIB</td>
</tr>
<tr>
<td>T2 (&gt; 5 and ≤ 7 cm)</td>
<td>T2b</td>
<td>IB</td>
<td>IIIb</td>
<td>IIIa</td>
<td>IIIB</td>
</tr>
<tr>
<td>T2 (&gt; 7 cm)</td>
<td>T3</td>
<td>IB</td>
<td>IIIb</td>
<td>IIIa</td>
<td>IIIB</td>
</tr>
<tr>
<td>T3 (with central invasion)</td>
<td>T3</td>
<td>IIIB</td>
<td>IIIa</td>
<td>IIIB</td>
<td></td>
</tr>
<tr>
<td>T4 (with nodules in the same lobe)</td>
<td>T3</td>
<td>IIIb → IIIa</td>
<td>IIIa</td>
<td>IIIB</td>
<td></td>
</tr>
<tr>
<td>T4 (with extension)</td>
<td>T4</td>
<td>IIIb → IIIa</td>
<td>IIIa</td>
<td>IIIB</td>
<td></td>
</tr>
<tr>
<td>M1 (with nodules in the ipsilateral lung ≠ lobe)</td>
<td>T4</td>
<td>IV → IIIa</td>
<td>IV → IIIa</td>
<td>IV → IIIB</td>
<td></td>
</tr>
<tr>
<td>T4 (pleuropericardial spread)</td>
<td>M1a</td>
<td>IIIb → IV</td>
<td>IIIb → IV</td>
<td>IIIb → IV</td>
<td></td>
</tr>
<tr>
<td>M1 (with nodules in the contralateral lung)</td>
<td>M1a</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
<td></td>
</tr>
<tr>
<td>M1 (with distant metastases)</td>
<td>M1b</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
<td></td>
</tr>
</tbody>
</table>

Arrows indicate stage migration from TNM-6 to TNM-7 (modified from the NCCN Guidelines™, version 3.2011, staging non-small cell lung cancer and Goldstraw et al.9).
of the NSCBC diagnostic algorithm. Considering the use of imaging techniques in future revisions is reasonable because their impact on clinical staging could be quantified and they would also be useful to reach a consensus on diagnostic algorithms.

TNM-7 offers no specific guidance for the measurement of lesions at CT.\textsuperscript{11,15} The maximum axis of the lesion must be considered, but it is not specified whether measurement is done on multiplanar reconstructions or on the axial planes. No specific guidance is provided either for the measurement of ill-defined (cavitary or infiltrative) lesions.\textsuperscript{4,11} Moreover, TNM-7 is particularly complicated to be applied to bronchioalveolar carcinomas because the newest lung adenocarcinoma classification does not include the terms bronchioalveolar carcinoma and mixed subtype adenocarcinoma, and suggests nomenclature and diagnostic criteria in order to provide uniform terminology.\textsuperscript{21}

The limitations of CT to measure endobronchial lesions or lesions with associated obstructive pneumonitis are not mentioned, nor is the role of PET/PET CT in this regard specified\textsuperscript{6,11} (Fig. 5). Furthermore, describing a T4 tumor with mediastinal infiltration and adjacent conglomerate nodal involvement may be difficult because the lesion borders can be blurred or nonexistent. However, it is important to distinguish between N0–1 and N2–3 tumors since the former are candidates for surgery\textsuperscript{11,15} (Fig. 6).

The question can be raised whether non-size-based descriptors (distance to the carina, invasion of visceral pleura or mediastinum) are independent prognostic factors or depend on tumor size. In any case, evidence is insufficient to introduce new recommendations.\textsuperscript{1,4,11,15}

Although separate nodules are classified as T3–T4 or M1a, no guidance is provided about how to differentiate metastatic nodules from synchronous-metachronous primary nodules, intrapulmonary nodes or benign lesions. Moreover, no specific descriptor has been assigned to carcinomatous lymphangitis.\textsuperscript{7,11}

Figure 2 Sample of tumor staging according to TNM-7. Epidermoid lung carcinoma in a 54-year-old patient. Multidetector computed tomography (MDCT) image in the axial plane with intravenous contrast and mediastinal window (a) shows a large right hilar mass (asterisks) that is massively infiltrating the mediastinum (it encased the trachea, carina, esophagus, right pulmonary artery and its lobar branches, and upper and lower lobar bronchi. This image shows invasion of the right lower lobar bronchus, which presents a filiform lumen). This lesion meets the criteria to be classified as T4. Contralateral hilar adenopathy was also observed (arrow), which corresponds to a N3 tumor. However, it was difficult to confirm the presence of right hilar adenopathy associated with the tumor mass. Axial MDCT with lung window (b) shows separate nodules in the middle lobe (arrow)—also indicative of T4—and in the contralateral lung (arrowhead). The tumor was classified as M1a based on the presence of these nodules and the associated right pleural effusion (arrowhead in a). The axial images with mediastinal window (c) and (d) show a right costal osteolytic lesion with a soft-tissue mass (curved arrow), hepatic metastases (curved open arrows), and right adrenal metastasis (asterisk), which classify the tumor as M1b. All these data are diagnostic of a T4N3M1b (stage IV) tumor.
Figure 3  Images illustrating the changes introduced in TNM-7; (a) T1 category including T1a tumors with a long axis \( \leq 2 \) cm and T1b tumors with a long axis \( >2 \) and \( \leq 3 \) cm; (b) T2 category, subdivided into T2a if the long axis is \( >3 \) cm and \( \leq 5 \) cm, and into T2b if the long axis is \( >5 \) and \( \leq 7 \) cm. A tumor that invades the visceral pleural or goes through a fissure is a T2 tumor; (c) T3 category includes any tumor with a long axis \( >7 \) cm; (d) T3 category includes separate tumor nodules in the same lobe as the primary tumor; (e) T4 category includes separate tumor nodules in a different lobe from the ipsilateral lung; and (f) M1a category includes intrathoracic metastases in the form of malignant pleural effusion, pleural implants, and metastatic nodules in the contralateral lung (the illustration does not show the primary tumor in the left lung).
Figure 4 Sample of tumor staging according to TNM-7. Epidermoid lung carcinoma in an 81-year-old patient. Axial images (a and c) and oblique sagittal reconstruction (b) of contrast-enhanced multidetector computed tomography of the chest, with lung parenchyma window, showed a cavitated mass with spiculated margins, $55 \times 41 \times 36$ mm in size, located in the right lower lobe (black asterisks). The lesion was infiltrating and retracting the confluence of the right minor and major fissures (arrows), invading the right middle lobe and right upper lobe. Because of its size and because it went through a fissure, this tumor was classified as T2b. Nevertheless, the mass was also infiltrating the parietal pleura, which was thickened and retracted (black arrowhead in a), the mediastinal pleura (open arrowhead in a), and separate small node $8 \text{ mm}$ in size located in the upper aspect, within the right lower lobe (arrowhead in c). This is thus a T3 tumor.

Figure 5 Poorly differentiated epidermoid lung carcinoma in a 54-year-old patient; (a) axial contrast-enhanced multidetector computed tomography image of the chest showing a parahilar lesion in the left upper lobe pruning the left upper lobar bronchus (not shown) with lobe atelectasis (asterisk). The course of the left pulmonary artery was tapered by the lesion (solid arrow), which eliminated the fat plane of separation with the descending thoracic aorta (open arrow). Due to the atelectasis, it was difficult to determine the actual extent of the tumor. (b) Fused PET–CT image clearly showing an abnormal focus of hypermetabolism (asterisk) with high SUV values, of up to 18. This finding enabled to determine tumor boundaries and size and to differentiate the tumor from obstructive atelectasis. An area with lower metabolic activity located anterolaterally to the mass was observed (arrowhead), which suggested a focus of pneumonitis within the area of atelectasis.
Role of imaging techniques in the TNM classification of non-small cell bronchogenic carcinoma

Figure 6  Difficulty to stage invasive adenopathy. Epidermoid lung carcinoma in a 60-year-old patient who presented with dysphonia. Larynx examination revealed paralysis of the left vocal chord. Axial multidetector computed tomography of the chest with mediastinal window and intravenous contrast showed a 53 cm × 47 cm mass in the left upper lobe with irregular hypodense areas in the interior (white asterisk in a). An 87 mm × 68 mm large nodal conglomerate predominantly affecting the aortopulmonary window (which justified the paralysis of the recurrent laryngeal nerve) and the left pulmonary hilum (black asterisks in b and c). The oblique coronal reconstruction (d) showed how the left upper lobar mass came into contact with the nodal conglomerate through an irregular septum (open arrow). Note how the nodal conglomerate exerted a mass effect on the left pulmonary artery and its lobar branches (arrowhead in b) and that neither the left main bronchus (solid arrows on b–d) nor its lobar branches (not shown) were obstructed. No other distant lesions were observed. Accordingly, it is a T2bN2M0 tumor. It is not uncommon to mistake adenopathy for the primary tumor at diagnosis of central bronchogenic carcinoma. A central tumor as large as the one in the images would obstruct the bronchi, but adenopathy would not do so. However, a case of adenopathy with extracapsular invasion could lead to invasion of adjacent tissues, which would cause stenosis in arteries (as is our case) or bronchi.
Moreover, it is not uncommon to detect axillary, subpectoral, internal mammary, phrenic, and even abdominal adenopathy, which is not explicitly coded, and cannot be considered metastasis in the sense of non-lymphatic spread (Fig. 1). The significance of bulky N2 disease, which is indicative of a poor prognosis, is not addressed either.  

The IASLC acknowledges that those aspects that could not be determined should be assessed in prospective studies. Thanks to constant advances in medicine, data dealing with tumor biology and genetics will also play a role in future classifications.1,4,11

Imaging techniques

All patients with suspected NSCBC require imaging techniques for tumor staging and treatment planning.

Contrast enhanced CT is essential for primary tumor characterization, although further tests are required for planning of histologic sample collection, diagnosis confirmation, and disease staging. As a general procedure, samples will be collected from presumably metastatic lesions that will be classified at the most advanced stage, and will provide further information for the staging.24 An exception is patients with a peripheral, well-defined, small primary lesion without evidence through non-invasive techniques for node or distant disease who can undergo early surgery without undergone histologic analysis. Therefore, diagnosis and staging are confirmed after surgery, precluding any false negatives at the clinical-pathologic staging.1,7,22

Chest X-ray

Serial X-rays performed on patients with NSCBC can be the first indicators of new lesions or growth of the pre-existing ones. However, this technique has been superseded by CT in the staging and follow-up of pulmonary nodules providing a better assessment of their density, borders, size, volume, and doubling time.5,17 The doubling time of malignant lesions ranges between 30 and 480 days, but there is a wide margin for error in the measurement of small lesions. In addition, this is doubling time in volume, not in diameter (accordingly, volume doubling of nodules 1, 2 and 3 cm in size implies an increase in diameter of 2.6, 5.2, and 7.8 mm, respectively). Furthermore, the thus far known bronchioalveolar carcinoma—as previously mentioned23—and the carcinoid tumor may have slow doubling times, overextending a 2-year period. This challenges the traditional claim that a 2-year radiologic stability of a lesion suggests benignancy.25-27

Computed tomography

Numerous references and clinical guidelines recommend that patients with suspected NSCBC be examined by contrast enhanced CT of the upper abdomen and chest including the liver and the adrenal glands.1,6,17,22 It is recommended that the examination be performed a maximum of four weeks before starting treatment, and include inferior cervical region (from the vocal chords) to evaluate nodal station 1,12,29 (Fig. 1).

Thanks to a reduction in examination time, multidetector-CT scanners can detect more nodules due to a reduction in partial-volume and respiratory motion artifacts. These studies also enable to perform a densitometric and volumetric analysis and obtain multiplanar and tridimensional reconstructions with a virtually isotropic spatial resolution.25

CT scanning normally suffices to characterize T descriptors associated with tumor size. Nevertheless, it is not without limitations: (a) it can only estimate the proximal extent of an endobronchial tumor, which is confirmed by bronchoscopy; (b) it has difficulty visualizing the real borders of a tumor when associated with obstructive atelectasis (PET–CT outperforms CT in this regard; see Fig. 5)16,29,30; and (c) it has difficulty differentiating between pleuropericardial or chest wall invasion and anatomic contiguity or desmoplastic reaction. The positive predictive value of CT scanning increases in cases of severe invasion (effusion with node thickening or masses with a clear disruption of fat planes). Equivocal evidence of invasion requires complementary techniques.7,5,22 PET scan may assist in the diagnosis of pleuropericardial involvement, although determining the organ dependency of abnormal deposition of the tracer is difficult sometimes. For this reason, PET–CT outperforms PET and CT separately, although thoracentesis remains crucial for the diagnostic confirmation of malignant effusion.7,18

Although very sensitive for separate nodule assessment, CT scanning is insufficiently specific for non-metastatic pulmonary nodules in patients with NSCBC (granulomatous infections, Wegener’s granulomatosis, amyloidosis, rheumatoid nodules, etc.).31

Concerning the N descriptor, a node is considered abnormal on CT when its short axis is ≥10mm, regardless of its localization. However, this threshold has a number of limitations.6,7,17,18 Because up to 21% of metastases occur in nodes <10mm and up to 40% of nodes >10mm are benign/hyperplastic.17,21,30,31 PET–CT plays a major role here, as will be discussed below (Fig. 7).

With respect to metastases, the presence of symptoms or signs in the initial evaluation of patients with NSCBC is associated with a yield of 50% of abnormal scan findings.17 CT scanning can assess the presence of brain, hepatic, and adrenal metastases. The role of this technique will be discussed and compared with other techniques further below. CT scanning also helps in detecting lihthic or sclerotic bone lesions, although sometimes a complementary study with nuclear medicine techniques is required. The evaluation of separate nodules, pleural implants, and pleuropericardial effusion (stage M1a) has been previously discussed.

In any case, node or distant metastatic disease should be confirmed histologically for an adequate tumor staging.

Positron emission tomography

Whole body PET provides metabolic information after injection of a radiotracer associated with a-δ-glucose analog (18F-FDG, 18-fluoro-2-deoxy-δ-glucose).30 PET measures FDG uptake in a lesion, and reflects its rate of glycolysis, which correlates with tissue vascularity, cellularity,
and proliferative capacity. The outcome is provided either qualitatively—based on visual examination, which regards lesions with hypermetabolism higher than that of the mediastinum as malignant—or semiquantitatively—expressed as standardized uptake values (SUVs). 17,18 SUV is a prognostic parameter independent from clinical stage and size (more active lesions have higher SUVs with values ≥7 associated with worse prognosis). 32 Although there are no standardized quantitative criteria, SUVs > 2.5 are assumed to be indicative of malignancy in the solitary pulmonary nodule. 17,18 However, visual examination can be more sensitive with lesions <1.5 cm.

Although the IASLC failed to assess the role of PET in tumor staging, PET/PET CT is now a more available technique, as previously noted.

PET does not provide sufficient spatial resolution to assign a T category to a tumor, 6,17,30 but it provides further evidence of malignancy in tumors ≥1 cm, 32,33 with sensitivity and specificity values of 97% and 79%, respectively, and higher diagnostic accuracy than CT. 30,33,34

Nevertheless, PET’s major contributions are: (a) to assess intra- and extrathoracic extent of the disease, involving major therapeutic implications; and (b) to avoid unnecessary invasive procedures (there is evidence that PET reduces futile thoracotomies). 15,21,36–38

PET can detect lymph node metastasis even in normal-size nodes, overcoming one of the major limitations of CT (Fig. 7), and providing a sensitivity, specificity and a positive and negative predictive values higher than those provided by CT. 6,7,17,18,33,35,39,40

Furthermore, PET is more sensitive than CT to detect metastasis in the most commonly affected sites, except for the brain (given its high metabolic uptake). 6,7,30 A number of series report that whole body PET detects metastases that modify the M descriptor in up to 14–50% of patients. 2,17,30,36,41,42
As for hepatic metastases, PET reduces the number of potential false positives detected with CT, and confirms inconclusive findings, although subcentimeter lesions may be the cause of false negatives. The accuracy of PET scanning to detect adrenal metastases is high, particularly if CT and MR imaging is inconclusive. An abnormal deposition of the tracer is suggestive of malignancy with a sensitivity of 100% and a specificity of 80–90%. It has previously been highlighted that PET can assist in characterizing pleural implants. However, PET is inferior to PET–CT due to PET’s limited anatomic resolution.

PET/CT has replaced bone scintigraphy in the assessment of bone metastases. Although both imaging techniques have similar sensitivity values, PET/CT has higher specificity, and detects distant metastasis in the same procedure, even in asymptomatic patients. It is true that NSCBC induces osteolytic lesions (with or without soft tissue mass) more frequently than osteoblastic lesions, but scintigraphy is less likely to yield false negatives for osteoblastic lesions, and thus, it could have a complementary role.

Overall, PET has a high negative predictive value (excluding malignancy correctly), but it has a low positive predictive value, which entails false positives commonly occurring when assessing inflammatory/infectious processes. In these cases, uptake is generally lower than in malignant processes, but in cases of granulomatosis or acute infections, uptake can be intense. Therefore, PET findings suggestive of lymph node or distant involvement require histologic confirmation to prevent up-staging. However, PET can be obliterated when examinations are negative given its high negative predictive value. While less common, false negatives can occur in tumors with low metabolic activity (the thus far called bronchioloalveolar carcinoma, carcinoid tumors, well-differentiated adenocarcinomas, and sometimes, metastases of renal, prostrate, and testicular carcinoma) and in lesions <10 mm (a critical mass of active malignant cells is required for their detection), and uncontrolled hyperglycemia (FDG uptake is delayed because of the FDG-glucose antagonist interaction on binding to the membrane receptor).

PET–CT is useful for (a) correct assessment of T in a tumor when there is distal lung collapse or consolidation since PET–CT can distinguish tumor mass with abnormal deposition of the radiotracer from aplectasis or pneumonitis; (b) assessment of satellite nodules; (c) evaluation of possible pleural involvement (hypermetabolic foci in a nodular/thickened pleura are indicative of malignancy); and (d) selection of the most appropriate histologic sampling sites (areas of hypermetabolism). PET–CT can also be used in radiation therapy planning.

With respect to lymph node staging, PET–CT has a 98% sensitivity, which is higher than that estimated for CT and PET separately, and a high negative predictive value (98%). However, PET–CT quite frequently yields false positives (low positive predictive value) with the possibility of up-staging, as previously discussed. Although the reference standard is mediastinoscopy, PET–CT is the most appropriate non-invasive modality for lymph node staging because it enables to differentiate adenopathy or mediastinal nodes from vascular structures on isolated CT imaging, and adenopathy from granulomatous node involvement or from a node with underestimated SUV on isolated PET, and enables to easily assess physiological uptakes of brown fat.

Concerning distant spread, PET–CT detects extrathoracic metastasis with sensitivity, specificity, and positive and negative predictive values higher than those provided by PET and CT separately.

Although PET–CT provides a more accurate clinical-diagnostic staging, and spares the patients futile thoracotomy, it may up-stage a tumor (yield false positives) with respect to CT, and thus, preventing an indicated surgical intervention. For this reason, it is crucial to histologically confirm suspicious findings. False negative have already been described at the PET section. Due to low rate of false negatives, PET can be the sole modality to diagnose patients with poorly differentiated NSCBC with no evidence of node involvement or distant metastasis do not require further examination. Nevertheless, the indication for histological analysis should be individually assessed for each patient. If the presence of tumor deposits may result in a change in the therapeutic decision, an intraoperative histological analysis can be performed in selected patients, or through confirmatory thoracotomy before surgery, depending on the workflow of each institution.

Magnetic resonance imaging

The role of MRI in local staging of NSCBC is limited by the signal loss secondary to respiratory motion and heterogeneity of the magnetic field caused by the tissue/air interfaces. MRI is reserved for cases of suspected irresectability and inconclusive findings on CT as well as for patients with contraindications to the use of iodine contrast medium, because of the better tolerance to paramagnetic media. MRI has been used for mediastinal node staging (predominantly subcarinal and aortopulmonary adenopathy), but it yields overall sensitivity and specificity values similar to those on CT. The use of gadolinium seems to improve the diagnostic accuracy. A number of research studies are evaluating the utility of diffusion-weighted MRI and apparent diffusion coefficient (ADC) map in lymph node staging (with...
Figure 8  Epidermoid carcinoma (not shown) in the right upper lobe in a 67-year-old patient. (a) Axial multidetector computed tomography (MDCT) image showed a nodular thickening of the right adrenal gland (solid arrow) with signal loss in the opposed-phase gradient-echo sequence (b), without hypersignal in the T2 sequence with fat suppression (c) and homogeneous enhancement after gadolinium administration. The characteristics of the lesion were consistent with an adenoma. Apart from this, the left adrenal gland was irregularly thickened (open arrow) on MDCT (e), without signal loss in opposed-phase imaging (f) but with hypersignal on T2 sequences (g), and showing peripheral and irregular enhancement. PET-CT and FNPA confirmed the diagnosis of metastasis (not shown).

Figure 9  Lung adenocarcinoma in a 64-year-old patient. Axial multidetector computed tomography image with intravenous contrast and mediastinal window (a) showed a paravertebral mass in the left lower lobe encasing the bronchus of segment VI (asterisk), the lower lobar pulmonary artery, and the left pulmonary veins (not shown), without fat plane of separation with the descending aorta and D6 vertebral body; and left subcarinal and hilar adenopathy (arrows). Fused PET-CT image confirmed hypermetabolism of these lesions, and detected no other abnormalities. A chest MRI was performed for better characterization of aortic and vertebral involvement. Axial contrast-enhanced T1 image with fat suppression showed invasion of left paravertebral fat with spiculated hyper-enhancing tracts in contact with the D6 vertebra (arrows); absence of the fat plane separating the mass and the left posterolateral wall of the descending thoracic aorta (white arrowhead) with higher spatial resolution than CT. These signs were interpreted as invasion by contiguity and the tumor was classified as cT4N2M0 (stage IIIb). The vertebral body and the spinal canal were invaded during follow-up.
a high negative predictive value\textsuperscript{54,55} to differentiate tumor from postobstructive atelectasis.\textsuperscript{36} These studies also seek to differentiate benign from malignant pulmonary nodules with no apparent differences with SUV, although SUV better correlates with the degree of tumor activity.\textsuperscript{2,22} Other studies are examining the role of perfusion MRI in pulmonary node characterization.\textsuperscript{57}

However, contrast-enhanced MRI undoubtedly has a role in characterizing hepatic metastasis\textsuperscript{4} thanks to dynamic studies and ADC maps. This imaging technique is the modality of choice for brain metastasis assessment in patients with neurological symptoms or signs\textsuperscript{1,31} because it can detect more and smaller lesions than unenhanced MRI and unenhanced or contrast enhanced CT. Contrast-enhanced CT is an acceptable alternative when MRI is not available since it does not involve differences in terms of survival.\textsuperscript{17} Asymptomatic patients do not need contrast-enhanced CT unless other clinical criteria are suggestive of abnormalities (extensive local disease, node involvement and other distant metastases, predominantly in patients candidates for radical treatment).\textsuperscript{2,17} Accordingly, a negative contrast enhanced CT should be followed by a contrast enhanced MRI study in case of a high clinical suspicion of involvement of the CNS.

MRI can also help in differentiating adrenal adenoma from metastases. Adrenal adenomas show signal suppression in the opposed-phase gradient-echo sequence and low density on CT due to intracellular fat component.\textsuperscript{31} Findings suggestive of metastatic disease are >3 cm in size, ill-delineated margins, irregular ring-enhancement, and hypersignal in T2-weighted sequences\textsuperscript{2} (Fig. 8). PET and PET–CT are useful as well since an abnormal deposition of the tracer is indicative of malignancy with a high sensitivity and specificity.

As a technique complementing CT scanning, MRI is able to identify infiltration of bone marrow in symptomatic patients or in patients with suspicious analytical findings.

In addition, MRI is very useful to characterize lesions affecting the lung apexes and bronchial plexus, diaphragm, spinal canal (paraspinal masses), mediastinal, vascular (Fig. 9), pleural, and chest wall invasion (Fig. 4).\textsuperscript{2,6,11,17} Although the gap between multidetector CT and MRI systems has been narrowed, MRI is equal or superior to CT in the aforementioned cases because MRI still provides a better contrast between normal and abnormal tissue. Nevertheless, while both techniques can detect the extensive invasion of the abovementioned structures, CT and MRI have difficulty differentiating between actual invasion and anatomic contiguity or desmoplastic reaction.\textsuperscript{2,31}

**Conclusion**

TNM-7 for lung cancer is the first classification based on really international data. This classification lays greater emphasis on tumor size, can determine better the prognosis of patients, and will have an impact on the new clinical trials to test adjuvant treatment and its indications. TNM-7 has been revised and illustrated to help radiologists to become familiar with this tool in daily clinical practice. This study has also examined the utility of each imaging modality, and highlighted their complementary role.

**Authorship**

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**Conflicts of interest**

The authors declare not having any conflicts of interest.

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