Early stage non-small-cell lung cancer: challenges in staging and adjuvant treatment: evidence-based staging

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Staging of non-small-cell lung cancer is a multidisciplinary process involving imaging, endoscopic and surgical techniques. Accuracy is vital in order to avoid false-positive interpretations leading to a false stage III or IV diagnosis in early stage patients, or false-negative findings leading to a false early stage diagnosis in patients with mediastinal lymph node disease. CT scan offers great anatomical detail of tumour spread, but radiological imaging lacks information on the biological nature of the lesions. The latter is brought in by 2-[fluorine-18] fluoro-2-deoxy-D-glucose-positron emission tomography (FDG-PET) scan as a metabolic imaging tool, which, however, has clearly lower spatial resolution. Therefore, contemporary staging relies on the combination of both, preferably in a fusion PET–CT scan. Absence of suspected lymph node metastasis on both CT and PET has a high negative predictive value, and these patients may in general proceed to surgery. In most others, tissue confirmation of the locoregional lymph node status is needed. The historical standard of mediastinoscopy is nowadays complemented by endoscopic techniques by the bronchial or esophageal approach. Each of these techniques remains important in modern staging algorithms. A practical scheme for rational staging in clinical practice is discussed.

Key words: non-small-cell lung cancer, staging, adjuvant.

introduction

The most important prognostic factor in non-small-cell lung cancer (NSCLC) is the stage, which comprises accurate assessment of the extent of the primary tumour (T), of the spread to locoregional lymph nodes (N) and of the presence of distant metastases (M). The stage of the tumour will also determine the choice of treatment.

Patients with distant metastasis (advanced stage IV) will be treated with cytotoxic and/or biological agents. Patients with metastatic mediastinal lymph nodes (LN) (stage III) will usually have a combined modality therapy including systemic (chemotherapy) and locoregional (surgery and/or radiotherapy) components [1].

Patients without metastatic LN or with hilar metastatic LN only (early stages I and II) will be treated with pulmonary and general medical condition—candidates for upfront surgical resection often followed by postoperative chemotherapy [2].

Staging nowadays is a truly multidisciplinary process—involving imaging, medical and surgical techniques—to determine whether the patient has an early stage tumour and may proceed to direct resection. We will review the role of these different techniques and propose a recommendation for contemporary clinical practice.

the most recent TNM staging system

The previous TNM (TNM6), published in 1997 [3], was based on a rather small (n = 5319) data set of predominantly surgical patients treated in the era before the advent of combined modality therapy. Many of these deficiencies were addressed in version 7 (TNM7), which was based on a major effort by the Lung Cancer Staging Project of the International Association for the Study of Lung Cancer (IASLC) [4]. Adequate data were sampled on 67,725 cases of NSCLC treated by all modalities between 1990 and 2000 [5]. These recommendations were the basis for the now universally adopted TNM7.

In relation to early stage NSCLC, the changes are a reclassification of the T-factor according to size of the primary tumour [6]: T1 (<3 cm) is split into T1a (<2 cm) and T1b (2–3 cm), T2 is split into T2a (3–5 cm) and T2b (5–7 cm) and tumours >7 cm are now T3. Moreover, additional pulmonary nodules are reclassified as T3 (same lobe), T4 (other lobe same side) or M1a (other lung). N-factors do not change [7], although a new LN map—solving the former discrepancies between the Western and Japanese maps—is proposed [8]. There is a change in the labelling of early stages (Table 1): T2bN0 cases move from stage IB to stage IIA, T2aN1 cases from stage IIB to stage IIA. Patients with tumours >7 cm move from IB to IIB if there are no LN metastases, and from IIB to IIIA if they have N1. Non-N3 patients with an additional nodule in the same lobe move from stage IIB to stage IIIA. It is at present difficult to estimate how this reshuffling of early stage NSCLC
Table 1. Changes from TNM6 to TNM7 classification [5]

<table>
<thead>
<tr>
<th>TNM6</th>
<th>TNM7 Stage</th>
<th>N1 Stage</th>
<th>N2 Stage</th>
<th>N3 Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 (&lt;2 cm)</td>
<td>T1a IA</td>
<td>IIA</td>
<td>IIIA</td>
<td>IIIB</td>
</tr>
<tr>
<td>T1 (2–3 cm)</td>
<td>T1b IA</td>
<td>IIA</td>
<td>IIIA</td>
<td>IIIIB</td>
</tr>
<tr>
<td>T2 (3–5 cm)</td>
<td>T2a IB</td>
<td>IIA (IIIB)</td>
<td>IIIA</td>
<td>IIIIB</td>
</tr>
<tr>
<td>T2 (5–7 cm)</td>
<td>T2b IA (IIIB)</td>
<td>IIIA</td>
<td>IIIA</td>
<td>IIIIB</td>
</tr>
<tr>
<td>T2 (&gt;7 cm)</td>
<td>T3 IA (IIIB)</td>
<td>IIIA</td>
<td>IIIA</td>
<td>IIIIB</td>
</tr>
<tr>
<td>T3 (invasion)</td>
<td>IIIA (IIIB)</td>
<td>IIIA</td>
<td>IIIA</td>
<td>IIIIB</td>
</tr>
<tr>
<td>T4 (nodules same lobe)</td>
<td>IIIB (IIIB)</td>
<td>IIIA (IIIB)</td>
<td>IIIA (IIIB)</td>
<td>IIIIB</td>
</tr>
<tr>
<td>T4 (extension)</td>
<td>T4 IIIB (IIIB)</td>
<td>IIIA (IIIB)</td>
<td>IIIA (IIIB)</td>
<td>IIIIB</td>
</tr>
<tr>
<td>M1 (ipsilateral lung)</td>
<td>IIIB (IV)</td>
<td>IIIB (IV)</td>
<td>IIIB (IV)</td>
<td>IIIB (IV)</td>
</tr>
<tr>
<td>T4 (pleural effusion)</td>
<td>M1a IV (IIIB)</td>
<td>IV (IIIB)</td>
<td>IV (IIIB)</td>
<td>IV (IIIB)</td>
</tr>
<tr>
<td>M1 (contralateral lung)</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
</tr>
<tr>
<td>M1 (distant sites)</td>
<td>M1b IV</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
</tr>
</tbody>
</table>

Shaded areas are changes in classification of early stage NSCLC.


discussion impacts on existing treatment algorithms, which are based on phase III studies using the previous TNM6 system.

imaging computed tomography

Modern spiral contrast-enhanced multi-slice computed tomography (CT) offers great anatomic detail, and is the best choice to assess the T-factor, e.g., relationship of the tumour to the fissures (which may determine the type of resection), to mediastinal structures, or to the pleura and chest wall. Different criteria to assess invasion have been described, but one should always be careful to exclude a patient from surgery based on CT criteria alone [9, 10]. Contrast-enhanced CT also is very accurate in delineating LN enlargement, but the clinical applicability of LN enlargement (usually LNs ≥10 mm short-axis diameter are considered to be suspect) is limited, because small nodes may contain metastasis and enlarged nodes may be benign (e.g., in the case of post-obstructive pneumonia).

Overall, the pooled sensitivity and specificity of CT for identifying mediastinal LN metastases is 51% [95% confidence interval (CI) 47% to 54%] and 85% [95% CI 84% to 88%], respectively [11]. Therefore, absence of enlarged LNs on CT does not reliably rule out LN metastasis. In one study in 235 patients with potentially operable NSCLC without enlarged mediastinal LNs on CT scan, cervical mediastinoscopy was positive in 47 patients (20%), more often in patients with a higher T-stage (9.5% for T1, 17.7% for T2 and 32% for T3–T4) [12]. CT will be of help, however, in selecting the most appropriate procedure for tissue sampling of the suspect LNs.

PET and integrated PET–CT

The most important step forward in NSCLC imaging of the last decade is the use of positron emission tomography with 2-[fluorine-18]fluoro-2-deoxy-D-glucose-positron emission tomography (FDG-PET). Based on the high FDG uptake in malignant lesions, whole-body PET is able to characterize lesions that remain equivocal on conventional imaging and to detect metastatic lesions not revealed by conventional imaging. For the T-factor, PET on its own has little additive value, because its spatial resolution is lower than that of CT [13]. For the N-factor, the metabolic information on PET imaging is superior to CT alone [14, 15]. The pooled sensitivity and specificity values for identifying mediastinal LNs are 74% (95% CI 69% to 79%) and 85% (95% CI 82% to 88%), respectively [11]. Several prospective studies also demonstrated a gain in accuracy in the M-factor, mainly because PET is able to detect additional metastatic lesions in 5%–25% of patients [16, 17].

Stand-alone PET has limited spatial resolution, allowing far less anatomic detail than CT. In the late 1990s, we already pointed out that interpretation of PET images in visual correlation with CT images improved results [18]. The contemporary answer to this is the combination of morphological and metabolic information in integrated PET–CT scanners.

For the T-factor, some studies report better results with PET–CT in comparison with PET alone [19]. This superiority is due to the CT component of the examination resulting in a more precise evaluation of chest wall and mediastinal infiltration in some patients, and a better differentiation between tumour and accompanying inflammation or atelectasis in others on the integrated images. In the Zürich group report, there is a benefit of integrated PET–CT in comparison with side-by-side reading of PET and CT images, which was not in place in the Leuven experience [20].

Results for the N-factor give a similar picture, with PET–CT superior to PET alone [19]. Accurate anatomical correlation allows exact location of invaded nodes, and thus better distinction between N1, N2 and N3. Furthermore, the role of PET–CT in identifying and localizing supraclavicular N3 nodes and in the distinction between FDG-avid brown fat and a metastatic lymph node is indisputable [19] (Figure 1). One should be careful with false-negative PET findings in some particular situations: little FDG avidity of the primary tumour, presence of a central tumour or of centrally located N1 nodes, both of which may obscure nearby existing mediastinal LN metastasis. False-positive findings are due to the fact that FDG uptake is not tumour specific, and can be found in all active tissues with high glucose metabolism, in particular inflammation. Therefore, clinically relevant FDG-avid mediastinal LNs should always be examined with the most appropriate tissue sampling technique.

Finally, for the M-factor, only a few results are available. In a large retrospective study, there was a significant superiority of PET–CT compared with PET alone or CT alone, but not compared with side-by-side correlation [13].

endoscopy

standard white-light bronchoscopy and autofluorescence bronchoscopy. Standard white-light bronchoscopy (WLB) is considered mandatory in patients with suspected lung cancer. In addition to pathological confirmation in many patients, it also permits an evaluation of the endobronchial extension of the tumour (endobronchial T stage), which can be decisive for the extent of resection or for radiotherapy planning.

Autofluorescence bronchoscopy (AFB) added to WLB has a role in the routine work-up of patients suspected of having operable lung cancer based on chest imaging or in patients with newly diagnosed lung cancer planned for resection [21].
node dissection confirmed the absence of mediastinal involvement (pT2N1). PET–CT images project the hot spot in brown fat tissue (D). Thoracotomy and lymph node dissection confirmed the absence of mediastinal involvement. Therefore, the ACCP guidelines state that invasive preoperative mediastinal staging should be performed in these patients [25]. Non-randomized trials indicated the potential of EUS–FNA and/or EBUS–TBNA for mediastinal staging. However, the majority of these non-randomized trials studied the potential of echo-endoscopic techniques for the mediastinal staging of clinical N2/3 lung cancer (so-called ‘group B’ patients by Detterbeck et al. [25]). Recently published meta-analyses on EUS–FNA and EBUS–TBNA reported a pooled sensitivity of 90% and 94%, respectively, for CT-enlarged or PET-positive mediastinal LNs with a prevalence of malignant N2/3 disease of 68% [26, 27]. Clinical data focusing on the value of endoscopic ultrasonography for the mediastinal staging in so-called ‘group C’ patients (Detterbeck et al. [25]) are scarce. A non-randomized study reported a high accuracy of EBUS–TBNA in patients with lung cancer and a normal mediastinum on CT and PET [28].

For clinical implementation, an important issue is that EBUS–TBNA—just as EUS–FNA—has a suboptimal negative predictive value ranging from 60% to 80%, which requires a confirmatory surgical staging procedure in the case of a non-malignant echo-endoscopic needle aspiration. No false-positive mediastinal lymph node findings by EBUS–TBNA have been reported in literature, and all but one EUS–FNA series reported no false-positive needle aspirations [29]. A false-positive finding can, however, occur in the case of (i) contamination of cytological material when the needle passes dysplastic mucosa (e.g. EBUS–TBNA through mucosa of viral bronchitis) or neoplastic mucosa (e.g. EUS–FNA through malignant oesophageal mucosa), (ii) misclassification of activated/enlarged lymphocytes as suspicious epithelial cells by the cytopathologist or (iii) sampling by the endoscopist of primary tumour tissue instead of mediastinal LN material (e.g. in the case of a central hilar tumour adjacent to the mediastinal LN).

Endoscopic ultrasonography (EBUS) can be performed with a linear echo-endoscope under local anaesthesia using moderate sedation. It is able to visualize superior and inferior mediastinal LNs at levels 2R/2L, 4R/4L and 7, as well as hilar LNs at level 10, 11 and even 12. EBUS helps to localize these LNs and perform a TBNA under real-time ultrasonographic control (Figure 3). The mediastinal LN stations accessible with EBUS–TBNA are the same as for cervical mediastinoscopy.

Esophageal ultrasonography (EUS) uses an echo-endoscope with linear array ultrasound transducer at the tip, keeping the working channel of the endoscope available to pass a needle and perform a fine needle aspiration (FNA) under ultrasonographic control. This technique particularly visualizes superior mediastinal LNs in level 4L, and inferior mediastinal LNs in levels 7, 8 and 9, as described on the new LN map [8]. This complements other techniques, as several of these LNs (levels 8 and 9) are not accessible by EBUS–TBNA or mediastinoscopy. Mediastinal lymph node station 4R is often a blind spot for EUS–FNA because of the interposition of the trachea. On the other hand, EUS–FNA can sample hilar LN station 10R or 10L (N1, Figure 4), in which case one has to be extremely careful not to consider these LN stations as mediastinal (N2) LNs [24].

Patients with a centrally located primary tumour or patients with clinical N1 nodes on imaging, and normal sized FDG-negative mediastinal LNs on CT and PET can have malignant involvement in their mediastinal nodes. Therefore, the ACCP guidelines state that invasive preoperative mediastinal staging should be performed in these patients [25]. Non-randomized trials indicated the potential of EUS–FNA and/or EBUS–TBNA for mediastinal staging. However, the majority of these non-randomized trials studied the potential of echo-endoscopic techniques for the mediastinal staging of clinical N2/3 lung cancer (so-called ‘group B’ patients by Detterbeck et al. [25]).

Conventional or blind transbronchial needle aspiration. For the N stage, blind transbronchial needle aspiration (TBNA) can be performed during the initial standard bronchoscopy if enlarged LNs are present on CT. A blind TBNA is most often applied to selected LN levels, i.e. those with clear anatomical landmarks (such as lower paratracheal LNs in position 4, subcarinal LNs in position 7 and hilar LNs in position 11 right and left) (Figure 2). When they are clearly enlarged (at least 15 mm short axis diameter), they can be adequately aspirated using a needle through the working channel of a standard bronchoscope [23]. As such, a blind TBNA could be useful in clinical stage I to establish the diagnosis of lung cancer based on the TBNA of an enlarged hilar lymph node, but there is no reason to perform a blind TBNA for preoperative mediastinal LN staging in early stage I/II NSCLC.

Endoscopic ultrasonography: EUS–FNA and EBUS–TBNA. The advent of endoscopic ultrasonography has allowed imaging beyond the mucosa into the mediastinum, e.g. visualization of LNs in the vicinity of the oesophagus, trachea or main bronchi, and therefore improved the accuracy of endoscopic mediastinal LN sampling techniques.

Adding AFB to WLB may reveal synchronous multi-centricity of pre-invasive and radio-occult invasive lesions in 10% of the patients in whom a primary radiographically visible invasive lung cancer was detected [22]. Video-AFB systems are nowadays available, making an easy access possible to anatomic and functional information at the time of the first bronchoscopy without significantly increasing examination time.

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It is clear that cervical mediastinoscopy remains the first choice baseline invasive mediastinal staging test in patients with clinical early stage I and II lung cancer requiring preoperative invasive mediastinal staging. Additional clinical research is needed to establish the value of mediastinal staging by endoscopic ultrasonography in subsets of patients with early stage I and II lung cancer.

**surgical techniques**

**cervical mediastinoscopy**

Cervical mediastinoscopy remains a central tool for staging the upper mediastinal LNs in patients with early stage I/II lung cancer. It is a surgical biopsy technique under general anaesthesia [30]. The mediastinoscope is inserted through a small suprasternal incision. Blunt dissection then gives access to the pretracheal, right and left paratracheal, and anterior subcarinal LNs. There was no internationally accepted recommendation on how many LN stations should be examined at cervical mediastinoscopy. The guidelines of the European Society of Thoracic Surgeons (ESTS) now recommend systematic exploration and biopsy of the right and left paratracheal and the subcarinal LNs. Additionally, if present, the upper paratracheal LNs should be sampled and biopsied [31]. In experienced hands, the average sensitivity of cervical mediastinoscopy to detect mediastinal LN involvement

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**Figure 2.** Locoregional lymph node map for lung cancer staging (© IASLC 2009 [8]).
is ~80% according to a recent review, with a high NPV of 89% [25]. The results of the suboptimal sensitivity are partly explained by the fact that some LN stations (5, 6, 7 posterior, 8, 9) are not accessible by cervical mediastinoscopy. Other advantages of cervical mediastinoscopy are that it allows a complete mapping of mediastinal LNs, discrimination between extra- and intracapsular LN disease, and between nodal disease and direct invasion of the mediastinum by the tumour itself. More recently, the introduction of video-mediastinoscopes has improved visualization, allowing recording of the findings, and leading to improved teaching possibilities [32, 33].

**anterior mediastinotomy**

Left upper lobe tumours are known to metastasize predominantly to the aortopulmonary window and para-aortic LNs (levels 5 and 6). These LN stations cannot be reached by cervical mediastinoscopy, and need either left anterior mediastinotomy or left thoracoscopy (see below). The mediastinotomy procedure is more demanding and has a higher morbidity than the cervical approach. When a cervical mediastinoscopy is negative, this procedure may be indicated in cases of high suspicion of involvement of LN level 5 or 6 (e.g. in the case of enlarged or FDG-avid LNs in that area).

**video-assisted thoracic surgery**

Video-assisted thoracic surgery (VATS, surgical thoracoscopy) can be a useful add-on to cervical mediastinoscopy, as it allows one to reach subcarinal nodes or inferior mediastinal nodes on the right side, and para-aortic nodes or inferior mediastinal nodes on the left side. For VATS, the false-negative rate was 15% both in enlarged and normal sized nodes with a sensitivity varying widely from 37% to 100% [25]. The advantage over left anterior mediastinotomy is that anatomical landmarks such as the vagal and phrenic nerve are more easily recognized. There are no recent series on the use of VATS for staging of mediastinal nodes, which probably reflects the fact that less invasive staging methods such as EUS–FNA have become the preferred technique for staging of inferior mediastinal LNs.

**practical recommendations: locoregional staging of NSCLC**

Staging of NSCLC has become a truly multidisciplinary process involving imaging, endoscopic and surgical techniques. The aim is to determine the stage as accurately as possible: on the one hand to avoid false-positive interpretations (leading to a false stage III/IV diagnosis in early stage patients), and on the other hand to avoid false-negative interpretations (leading to a false early stage diagnosis in patients with mediastinal LN disease). Additionally, resectability needs to be estimated as precisely as possible.

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**Table 2. Overview of accessible lymph node levels for different invasive staging procedures**

<table>
<thead>
<tr>
<th>LN station</th>
<th>EUS–FNA</th>
<th>EBUS–TBNA</th>
<th>Cervical mediastinoscopy</th>
<th>Anterior mediastinotomy</th>
<th>Left-sided VATS</th>
</tr>
</thead>
<tbody>
<tr>
<td>2R</td>
<td>++/−</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>2L</td>
<td>++/−</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
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<tr>
<td>4R</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>4L</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
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<td>−</td>
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</tbody>
</table>

Lymph node mapping according to the IASLC staging committee [8]. LN, lymph node; EUS–FNA, esophageal ultrasonography–fine needle aspiration; EBUS–TNBA, endobronchial ultrasonography–transbronchial needle aspiration; VATS, video-assisted thoracic surgery.

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**Figure 3.** Endobronchial ultrasonography showing an enlarged mediastinal paratracheal lymph node in level 4R (LN4R), while a real-time transbronchial needle aspiration (needle) is being performed.

**Figure 4.** Endobronchial ultrasonography showing an enlarged mediastinal paratracheal lymph node in level 4R (LN4R), while a real-time transbronchial needle aspiration (needle) is being performed.
We cannot give an overall recommendation for ‘optimal’ locoregional staging. First, all examinations are not available everywhere, and even when available, they depend on local skills, certainly for the invasive procedures. Moreover, the techniques are often complementary (Table 2), and not competitive, which allows suspicious LNs in all locations to be reached, and avoids more invasive tests in patients with important co-morbidity. Practical guidelines at the European level have been developed by the ESTS [31].

A first algorithm (Figure 5, upper part) depicts the situation where FDG-PET scan is not available. If there are no enlarged mediastinal LNs on CT, a cervical mediastinoscopy is recommended in most patients, except those with peripheral T1 tumours, because of the insufficient NPV of CT in this respect. If there are enlarged LNs, tissue proof of these is required, because of the low positive predictive value of CT. Lower panel: endoscopic techniques are minimally invasive and can be the first choice; (2) due to higher NPV, mediastinoscopy remains indicated. Lower panel: (1) in central tumours, tumours with low 2-[fluorine-18]fluoro-2-deoxy-D-glucose uptake, tumours with LNs >1.5 cm and/or positron emission tomography N1 disease, invasive staging remains indicated; (2) endoscopic techniques are minimally invasive and can be the first choice; (3) due to higher NPV, mediastinoscopy remains indicated (adapted from [31]).

Here, an important evolution has occurred over recent years, as staging by EUS–FNA and EBUS–TBNA has become a valid alternative to mediastinoscopy, if performed in experienced hands. In many patients with positive needle aspirates, invasive surgical staging can be avoided. However, in the case of negative findings, one should realize that the NPV remains lower than for mediastinoscopy; on average 19% false-negative results for EUS–FNA, and 28% for EBUS–TBNA [25], so confirmatory mediastinoscopy is indicated.

The lower part of Figure 5 shows the situation where CT is complemented by PET. Due to the high NPV of PET, invasive staging procedures can be omitted in a much larger proportion of patients (all with clinical stage I NSCLC and negative mediastinal PET images). Care should be taken in situations with a small FDG-avid primary tumour, presence of a central tumour or centrally located N1 nodes (see above). The implementation of PET, as in this algorithm, reduced the number of mediastinoscopies by 65% [18]. On the other hand, because false-positive findings may occur (see above), tissue confirmation remains warranted in the case of positive mediastinal PET findings.

disclosures

The authors declare no conflict of interest.

references


