Staging procedures

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Introduction

Staging of non-small cell lung cancer (NSCLC) evaluates the extent of the primary tumour and the spread to locoregional lymph nodes (LNs) or more distant structures, according to the tumour-node-metastasis (TNM) classification [1]. Correct staging provides prognostic information and guides the choice of treatment. The current standard approach for patients with early stage (I and II) NSCLC is upfront surgical resection, with increasing evidence in favour of postoperative chemotherapy [2]. Patients with advanced NSCLC (stage IV) are, in general, no longer amenable to radical therapy. As stage III NSCLC patients are the focus of this overview, the role of clinical evaluation and organ scanning to assess extrathoracic metastatic disease is not discussed.

Stage III NSCLC is a relatively heterogeneous group with different prognostic and therapeutic subsets. Therefore, this reviews concentrates on the intrathoracic staging procedures and their role in the precise evaluation of the T- and especially N-factor, which define these subsets. Most patients with stage III have mediastinal LN involvement, which is present in 30–45% of patients with newly diagnosed lung cancer. The only exceptions are patients with stage IIIA-T3N1, who can still be considered for primary resection. Patients with stage IIIA-N2 have metastases to ipsilateral mediastinal LNs, and a dismal outcome when treated with surgery or radiotherapy alone. Induction chemotherapy, combined with either surgery and/or radiotherapy, will be the best strategy [3,4]. Even in the setting of surgical combined modality treatment, however, complete resection is an essential element for cure [5,6]. An important aim of staging procedures in these patients will therefore be to guide the multidisciplinary decision as to who is a candidate for resection, based either on baseline assessment or post-induction assessment. If complete resection is considered unlikely, a non-surgical multimodality approach is to be preferred [7].

This will also be the case in patients with contralateral LN metastases (stage IIIB-N3), where the combination of cisplatin-based chemotherapy and high-dose radiotherapy is the standard. Surgery may play a role in some patients with stage IIIB (T4N0-1), usually after induction chemoradiotherapy [8].

As accurate locoregional staging is of critical importance in non-metastatic NSCLC, the different locoregional staging techniques (imaging, non-surgical and surgical invasive procedures) are reviewed first. Next, the place and optimal interplay of these often complimentary techniques is discussed, as well as the specific issue of optimal restaging after induction in patients with locally advanced lung cancer in (surgical) multimodality treatment. Finally, practical suggestions for rational locoregional staging are given.

Imaging

In general, computed tomography (CT) has gained a more central role than magnetic resonance imaging (MRI) in lung cancer staging. In the past, MRI had the advantage of allowing imaging in different planes, but indications for this are now mitigated by rapid 3D reformations and virtual bronchoscopy available on modern multi-slice spiral CT scanners.

With its excellent anatomical detail, modern CT is the best choice to assess the T-factor, e.g. the relationship of the tumour to the fissures (which may determine the type of resection), to mediastinal structures, or to the pleura and chest wall. For these purposes, different criteria to assess invasion have been described. CT criteria for probable resectability in masses contiguous with the mediastinum are a contact of <3 cm with the mediastinum, less than 90° contact with the aorta, and preserved mediastinal fat layer between the mass and mediastinal structures. The reverse findings, i.e. >3 cm contact with mediastinum,

>90° contact with aorta, obliteration of the fat plane between mass and mediastinal structures are not reliable signs of either invasion or irresectability [9–11]. Consequently, CT often does not obviate surgical exploration, as it provides reliable signs of resectability and less reliable signs of irresectability. The same is true for chest wall invasion, with the exception of the 100% positive predictive value (PPV) of bony rib destruction with or without soft tissue mass extending into the chest wall [12–14].

As for the N-factor, modern contrast-enhanced CT is highly accurate in detecting LN enlargement, but the clinical applicability of LN enlargement for staging the mediastinum is poor, because small nodes may contain metastasis and large nodes may be benign (e.g. in the case of post-obstructive pneumonia). Most studies used >10 mm short-axis diameter as the criterion for nodal metastasis. In a recent review, pooled data yielded a sensitivity of 57%, a specificity of 82%, a PPV of 56% and a negative predictive value (NPV) of 83%, with marked heterogeneity across individual studies [15]. This performance is insufficient for clinical decisions, and in many instances it is inappropriate to rely on CT alone for N-staging, but CT will be of help in selecting the most appropriate procedure for tissue sampling of the suspect LNs.

MRI is an alternative in case of intolerance to intravenous ionic contrast media, and can be of additional value in some special circumstances, such as assessment of the relationship of the tumour with large blood vessels, soft tissues, or vertebral body, especially in sulcus superior tumours (see [16] for more details). As MRI also relies on measurement of diameters, it offers no extra information for LN staging compared with CT [17,18].

Non-invasive lung cancer staging was substantially improved by the use of positron emission tomography with 18F-fluoro-2-deoxy-D-glucose (FDG-PET). For the assessment of primary tumour extension, CT with its better spatial resolution remains the standard. PET may add information in case of pleural involvement. One study in 35 patients compared the efficacy of PET versus CT in differentiating benign from malignant pleural disease [19]. PET correctly detected the presence of malignant pleural involvement in 16 of 18 patients and excluded malignant pleural involvement in 16 of 17 patients (sensitivity 89%, specificity 94%, accuracy 91%). Small or flat pleural deposits can be missed on PET, probably due to partial volume effects. The series on pleural staging often have a small number of patients with benign pleural effusions, which limits interpretation of the specificity.

On PET, LN stations are considered to be abnormal if their FDG-uptake is higher than background activity of the mediastinum. In many cases, this will indicate malignant involvement, but some granulomatous or other inflammatory diseases also exhibit increased FDG-uptake. A large number of accuracy studies, already summarised in 6 meta-analyses [15,20–24], have demonstrated convincingly that PET is a superior imaging technique for mediastinal LN staging in potentially operable NSCLC. For the distinction between N0-1 and N2-3 patients, one review yielded an overall sensitivity of 89% (range 67–100%), with a specificity of 92% (range 79–100%) and an accuracy of 90% (range 78–100%). For CT, the results were a sensitivity of 65% (range 20–86%), a specificity of 80% (range 43–90%) and an accuracy of 75% (range 52–79%) [25]. Interpretation of PET images is improved by visual correlation with CT, due to better localisation of PET abnormalities with the help of the anatomical detail of CT [26,27].

Fusion PET-CT scanners, obtaining the co-registration of functional-molecular and morphological-anatomical data, have recently been introduced in small studies on staging of NSCLC. Based on previous studies, it is clear that visual correlation with CT images is the minimal standard to optimise PET interpretation [26–28]. Fusion images are a step further, with the obvious advantage of decreasing the learning curve needed to optimise the visual correlation.

For the T-stage, the possible extra information of true fusion images is more precise evaluation of chest wall and mediastinal infiltration or the correct differentiation between tumour and peritumoural inflammation or atelectasis, as suggested in a prospective study with 40 patients [29].

For the N-stage, reported results are variable, with no significant difference in accuracy of LN staging in some series [30,31], or improved results for fusion PET-CT compared with visually correlated PET and CT in others [29]. In the latter study, the conclusion was difficult to understand, because the accuracy in the comparator arm (PET) was only 49%, far below what has been consistently reported in the literature and meta-analyses [15,20–24].

One of the most challenging areas in non-invasive staging is the optimal reassessment of tumour response after induction therapy, which includes the pathological response in the primary tumour as well as the downstaging of mediastinal LNs. In stage IIIA-N2 NSCLC for instance, both factors have been proven to be important for the prognosis after multimodality therapy [6,32–35].

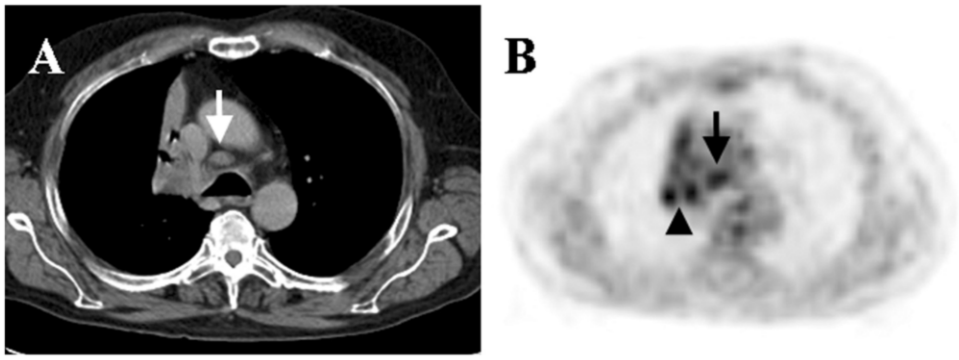

Fig. 1. (A) CT- and PET-scan after induction chemotherapy for central right upper lobe tumour, cT2N2M0. There is persistent lymph node enlargement on CT. (B) On PET, there is persistent FDG-uptake in the primary tumour (arrowhead) and right paratracheal nodes (arrow).

The accuracy of CT to assess the pathological response of the primary tumour is limited, as small residual masses may contain aggressive tumour remnants, while a major biological response may be present in patients with little change in tumour volume. PET on the other hand, usually detects the presence of residual tumour at the primary site, with sensitivities of 90% [36], 88% [37] and 97% [38]. The specificity cannot be reliably assessed in small series, because pathological complete response is uncommon in this setting, usually occurring in less than 10% of patients. According to the studies, PET correctly identified pathological complete response in 2 of 3 patients [36], 5 of 8 patients [37] and 2 of 2 patients [38]. Moreover, PET-response in the primary tumour was highly predictive for a better outcome after combined modality treatment [39,40].

In the assessment of LN downstaging, CT suffers from the same limitations as in the baseline staging (small sized LNs with metastatic deposits, large inflammatory nodes) [41]. Despite the fact that one would expect PET to complement CT imaging just as in the baseline staging, currently available evidence suggests that restaging of the mediastinal LNs after induction by PET may be better than with CT, but clearly is not as accurate as in untreated patients. In a multi-centre prospective trial, sensitivity was 50%, and specificity 71%, in the detection of residual mediastinal LN metastases after induction chemotherapy [39,40] (Fig. 1). Other studies with PET after induction chemoradiotherapy similarly reported a sensitivity of 58%, with a specificity of 93% [37], or 50% and 88% [35].

Invasive non-surgical staging

Standard bronchoscopy is considered obligatory 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 radiotherapy planning. For the N-stage, a conventional (blind) transbronchial needle aspiration (TBNA) of mediastinal LNs can be performed. A catheter with needle (available in varying gauges for either cytology or histology samples) can be passed through the working channel of the bronchoscope, advanced through the bronchial wall in a site where LN metastasis is suspected on imaging, and where the aspirate is taken. On-site cytopathological examination of the aspirate, often in place in studies, may improve the yield, as it helps to determine the number of passes to be performed until a good specimen is obtained. The technique is in essence a blind aspiration, and therefore has a very variable diagnostic yield of 15–83%, mostly related to the size and location of the nodes and the operators' learning curve [42]. In an overview, a sensitivity of 76% and a false-negative rate of 29% were reported for conventional TBNA in clinical N2-disease [43]. This high false-negative rate compromises the use of conventional TBNA for routine mediastinal LN staging. TBNA is very useful if it leads to proof of N3-disease. TBNA does not allow direct visual inspection and assessment of extracapsular LN spread.

The advent of endoscopic ultrasonography has allowed imaging beyond the mucosa (e.g. into the mediastinum) and improved the diagnostic yield of tissue sampling. Oesophageal ultrasonography (EUS) uses an echo-endoscope with adjustable electronic 5, 7.5 or 10 MHz curved linear array ultrasound transducer. A biopsy needle catheter is passed through the working channel of the endoscope, and is guided by the ultrasound image through the oesophageal wall towards the mediastinal LN of interest, allowing controlled fine needle aspiration (FNA). This technique particularly visualises LNs in the posterior

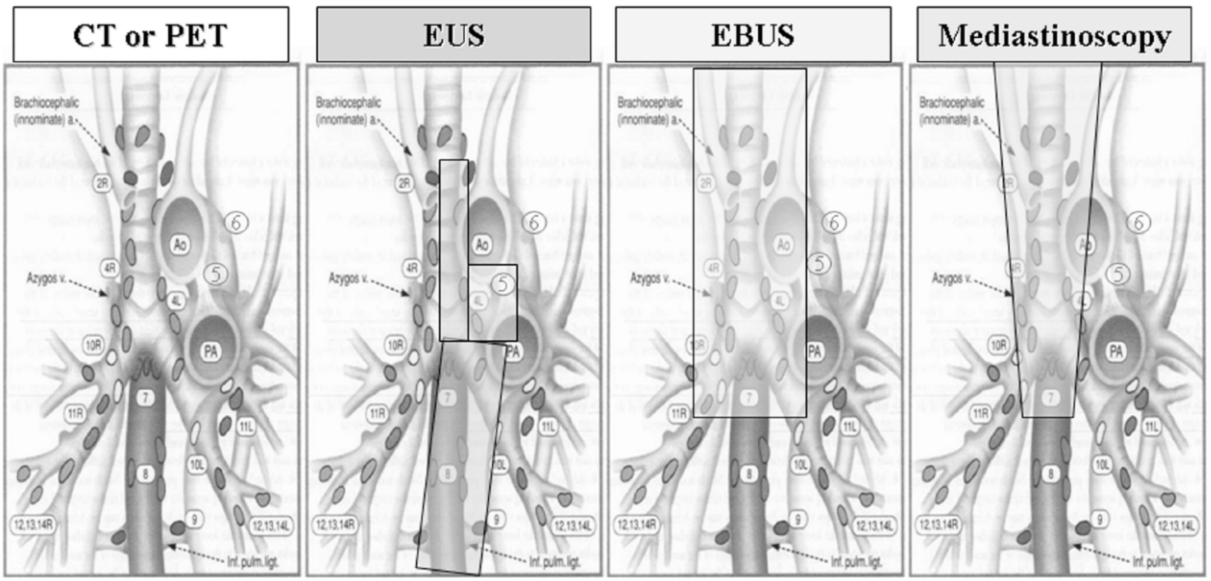

Fig. 2. Locoregional lymph node map illustrating the levels within reach of different invasive staging techniques.

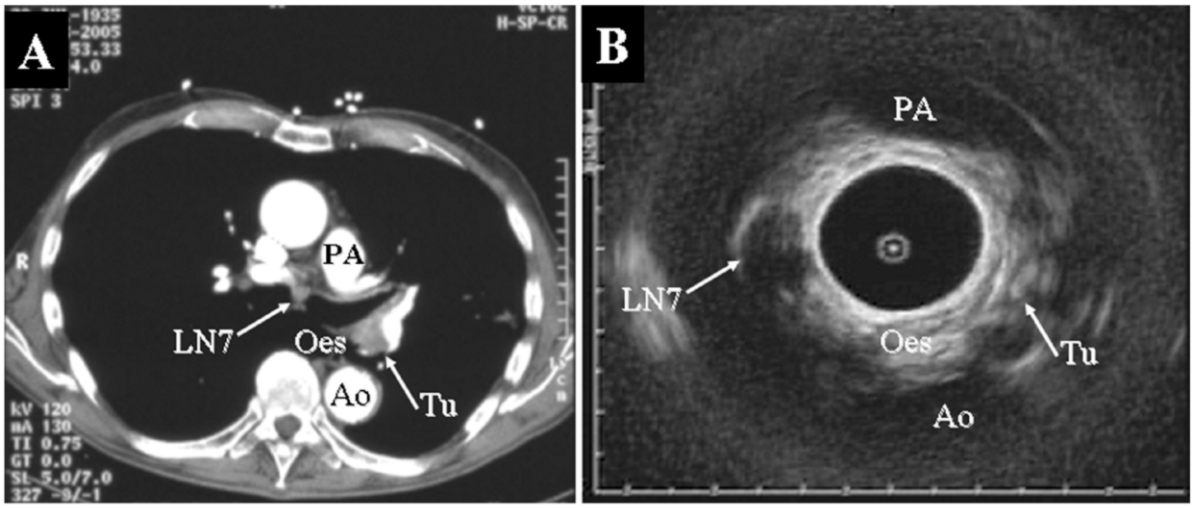

Fig. 3. (A) CT image of a patient with a centrally located left lung tumour (Tu) and non-enlarged subcarinal nodes (LN7). (B) Endobronchial ultrasound visualises the pulmonary artery (PA) interiorly, the oesophagus (Oes) and aorta (Ao) posterior, and the tumour (Tu) laterally of the bronchus. The subcarinal adenopathy (LN7) is well localised for a safe puncture.

part of levels 4L, 5 and 7, and in the inferior mediastinum at levels 8 and 9, as described on the Mountain-Dressler LN map [44] (Fig. 2). Several of these LN levels (5, 8 and 9) are not accessible by bronchoscopy or mediastinoscopy [45]. A review of the literature reported a pooled sensitivity of EUS of 88%, specificity 91%, PPV 98% and NPV 77%, respectively [46]. However, most of these studies were retrospective and report only a diagnostic yield without comment on mediastinal LN levels. Moreover, LNs more commonly involved in lung cancer are located in the anterior mediastinum (level 4L anterolateral to the trachea, level 4R or 2), which are difficult to reach by EUS-FNA, certainly if not enlarged. Recently, EUS-FNA has been compared with other techniques such as PET. EUS-FNA had a similar sensitivity to PET, but a superior specificity (100% versus 72%) [47]. The sensitivity and accuracy of EUS-FNA in analysing PET-positive mediastinal LNs was 93% and 94%, respectively, assuming that no false positive cytology occurred and that only PET-positive LNs were surgically sampled [48].

Endobronchial ultrasonography (EBUS) is able to visualise mediastinal LNs in the anterior, posterior and

inferior mediastinum at levels 2, 3, 4 and 7, as well as hilar LNs (Fig. 3). It helps to localise the puncture sites for either EBUS-guided TBNA or EBUS-controlled TBNA.

EBUS-guided TBNA (mechanical 20 MHz radial miniprobe) of mediastinal LNs in a prospective study on 242 patients reached a diagnostic sensitivity of 89%, independent of nodal size (range 0.7–4.3 cm) [49]. All cytology results with presence of only lymphocytes were confirmed to be negative for specific diseases at surgical biopsy. However, the negative predictive value (NPV) of cytology without lymphocytes was only 23%. A prospective randomised study also demonstrated that the diagnostic yield of EBUS-guided TBNA is significantly increased compared with conventional TBNA in all mediastinal LN levels except for an equal diagnostic yield in the subcarinal level [50].

The resolution of the 20 MHz EBUS miniprobe allows exclusion of T4 disease in selected cases. Imaging of the layers of the tracheobronchial wall to detect infiltration by a central tumour yields a sensitivity of 89%, specificity of 100% and accuracy of 94% [51]. EBUS or EUS have also been found to be useful in the differentiation between external tumour compression and direct tumour infiltration of large mediastinal vessels or oesophagus in some patients.

More recently, an endobronchial echo-endoscope with electronic 7.5 MHz curved linear array ultrasound transducer has been developed for TBNA under direct ultrasound visualisation (EBUS-controlled TBNA) (Fig. 4). A prospective study with this promising tool on 70 hilar or mediastinal LNs mentioned a diagnostic sensitivity of 95.7% in distinguishing benign from malignant nodes, with a false-negative rate of only 4.3% [52].

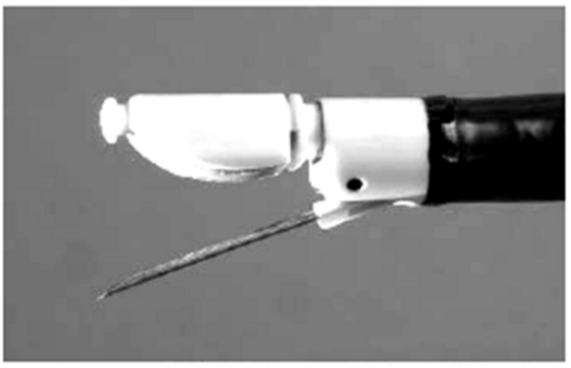

Fig. 4. Illustration of endobronchial ultrasonography with transbronchial needle aspiration (EBUS-TBNA). An electronic 7.5 MHz curved linear array ultrasound transducer is located at the tip of the bronchoscope and allows TBNA under direct visualisation.

Finally, pleuroscopy (or medical thoracoscopy) is valuable in case of pleural effusion, which may be present at diagnosis in up to 15% of all patients with lung cancer. The first diagnostic step is of course thoracocentesis. However, in cases of malignant effusion only about one-third of the cytological results of thoracocentesis, and about half of the results of blind pleural punch biopsy are positive [53]. When the results of effusion cytology are negative or equivocal in a patient with suspect pleural effusion, pleuroscopy under local anaesthesia should be carried out as the next diagnostic step. It allows examination of visceral and parietal pleura, sampling of pleural biopsies and pleural lavage, resulting in a sensitivity of more than 90% and a specificity of 100% [53].

Invasive surgical staging

Mediastinoscopy has for many years been the standard tool for staging LN involvement in patients with lung cancer. Different forms of mediastinoscopy have been described. Cervical mediastinoscopy is the most commonly used. It is a surgical open-biopsy technique performed under general anaesthesia [54]. The mediastinoscope is inserted through a small suprasternal incision. Blunt dissection then gives access to the pre-tracheal, right and left para-tracheal, and anterior subcarinal LN levels (levels 1, 2R, 4R, 2L, 4L, 7) (Figs 2 and 5). Ideally, five nodal levels (2R, 4R, 2L, 4L, 7) should be examined, with at least one node sampled from each level, unless none are present after dissection of the region concerned [43]. There is no data indicating that more systematic sampling at mediastinoscopy makes a difference, but extrapolation from data on occasional sampling and systematic sampling at thoracotomy suggests that this may be important [55].

The sensitivity of cervical mediastinoscopy is reported as between 72% and 89%, on average 81% in a recent review, with a pooled NPV of 91% [46]. 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.

In the absence of enlarged LNs on CT, some authors recommend straightforward resection [56]. In a retrospective Leuven Lung Cancer Group (LLCG) study of 235 patients, the role of cervical mediastinoscopy in patients with NSCLC without enlarged LNs on CT-scan was examined [57]. Forty-seven patients (20%) had a positive cervical mediastinoscopy, with multilevel LN-disease in 16 and extranodal spread in 21. The number of unexpected LN metastases was higher

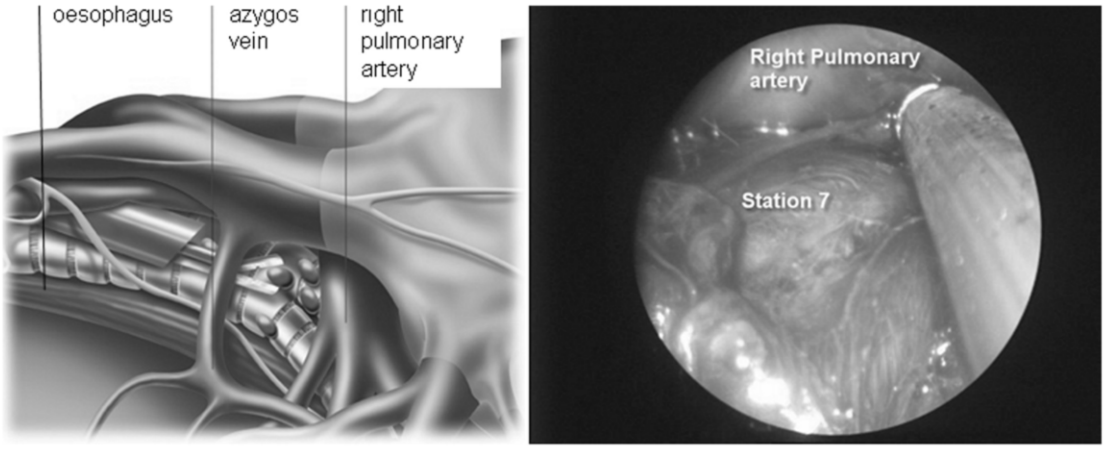

Fig. 5. Mediastinoscopy inserted in front of the trachea allows direct vision and biopsy of the anterior mediastinal LNs, and the anterior subcarinal LNs, situated just posterior to the right pulmonary artery.

in patients with a higher T-stage or with non-squamous histology. This is a relevant finding, since these patients are treated preferably by induction chemotherapy [3,4].

Cervical mediastinoscopy can be performed as an outpatient procedure and is reported to have very low mortality and morbidity in experienced hands. From 1980 to 2003, more than 4000 cervical mediastinoscopies were performed at the University Hospital Leuven, with only 11 major complications, and no mortality (9 major bleedings requiring open surgery, 1 oesophageal perforation and 1 injury of the left main bronchus) [58]. Contra-indications for mediastinoscopy are intolerance of general anaesthesia, extreme kyphosis, and cutaneous tracheostomy.

In some patients with central tumours, mediastinoscopy may also improve certainty of the T-stage, as it can prove irresectability due to invasion of mediastinal central vascular structures.

More recently, the procedure is performed by the use of a video-mediastinoscope [59]. This definitely improves visualisation and may lead to a higher accuracy in staging [60,61]. It allows recording of the findings and improves teaching. In a recent paper, the learning curve of video-assisted mediastinoscopy was low compared with conventional mediastinoscopy. After a short learning period, trainees were able to identify all LN stations, obtain adequate histological samples and perform the procedure without direct assistance in over 80% of cases [62].

Anterior mediastinotomy can be of value in patients with left upper lobe tumours. These tumours are known to metastasise predominantly to the aortopulmonary window and para-aortic nodes (levels 5 and 6), which cannot be reached by cervical mediastinoscopy (Fig. 2). The technique, as described by Chamberlain, starts with an incision in the left parasternaal second intercostal space (seldom with removal of the cartilage of the 3rd rib), which gives extrapleural access to level 5 and 6 LNs, and also allows assessment of resectability by palpating the tumour. One has to be careful not to damage the left phrenic nerve.

The technique is more demanding than the cervical approach. Based on one small retrospective series, in which the prognosis of left upper lobe tumours with negative cervical mediastinoscopy and isolated involvement of only level 5 or 6 nodes was similar to that of tumours with N1 nodes [63], it has been suggested that the technique has little indication in patients with a negative cervical mediastinoscopy. However, most teams will maintain left anterior mediastinotomy in patients with high suspicion for involvement of LN levels 5 or 6 (e.g. in case of enlargement on CT or FDG-avidity on PET).

Extended mediastinoscopy was described as a technique to allow exploration of level 5 and 6 nodes via the cervical approach [64]. After having performed classical cervical mediastinoscopy, the mediastinoscope is introduced through the cervical incision above the aortic arch, allowing biopsies of the aortopulmonary window nodes. In experienced hands, sensitivity as high as 81% has been reported [65,66]. The technique did not become widespread, because of its technical challenges and possible complications, such as embolic stroke due to the close contact of the mediastinoscope with the brachiocephalic and left carotid artery [67].

Video-assisted thoracic surgery (VATS, surgical thoracoscopy) has also become an important staging tool. With the use of spiral CT, small contralateral nodules will be detected in a substantial number

of patients. VATS can be used to biopsy these lesions in the search of unexpected contralateral lung metastasis.

LNs beyond the reach of conventional mediastinoscopy can be examined by VATS. The inferior mediastinal LNs (levels 7, 8 and 9) can be biopsied, which is indicated if they are suspect (enlarged on CT or FDG-avid on PET). LN stations 5 and 6 can be explored at left thoracoscopy, as an alternative to left anterior mediastinotomy. VATS can also be of help to rule out pleural metastasis, especially when pleural fluid is present.

Because imaging studies do not always allow one to distinguish resectable cT3 disease from irresectable cT4 disease, these patients often needed an exploratory thoracotomy, with attempted complete resection when possible. More recently, induction chemoradiotherapy has become a promising approach in patients with cT3-4 lesions. In this setting, VATS can be used selectively to evaluate T4 invasion (e.g. in the aorta), which may be of help in the decision to perform straightforward thoracotomy or induction chemoradiotherapy.

Repeat mediastinoscopy has been propagated as a tool for restaging of the mediastinum after induction therapy in patients with N2-disease. Downstaging of involved mediastinal LNs is indeed an important prognostic factor in these patients, and only a few patients with persistent N2 disease undergoing resection after induction therapy will experience long-term survival. Therefore, thoracic surgeons are more frequently faced with the need for re-mediastinoscopy. Some authors have reported that re-mediastinoscopy is feasible, with an accuracy of 85% and a sensitivity of 73% [61,68,69]. From a technical point of view, it is important to start the dissection on the left side until the left tracheobronchial angle is visualised, in order to avoid damage to the left brachiocephalic artery. In a retrograde way, the pre-tracheal space can then be reached.

Experience at the LLCG suggests fibrosis and dense adhesions make repeat mediastinoscopy technically difficult, if the initial cervical mediastinoscopy was performed thoroughly. In an ongoing prospective study, we looked at the sensitivity of redo video-mediastinoscopy in 24 patients who were treated with induction chemotherapy for mediastinoscopy proven N2-disease. The mean number of lymph node levels biopsied at the first mediastinoscopy was 3.6 (range 3–5). In seven patients, the LN level (level 7: five patients; 4R: two patients) which was originally positive could not be reached by re-mediastinoscopy due to extensive fibrosis. Re-mediastinoscopy was positive in 4 patients. There were no intra-operative complications. However, in 10 of 20 patients with negative re-mediastinoscopy, residual mediastinal LN disease was found at thoracotomy. The sensitivity to detect residual mediastinal disease was 28.6% with a negative predictive value of only 50% [70].

Discussion

There have been major changes in the staging requirements and techniques for patients with NSCLC over the last decades. Historically, the aim of locoregional staging was to determine resectability, and this process was based on CT and mediastinoscopy. Since then, new staging tools (PET, EUS, EBUS, VATS) have been developed and validated to a variable extent. Staging also became a far more demanding process with evaluation of exact tumour spread, not only in the light of surgery, but even so in non-surgical combined modality approaches. Furthermore, not only resectability at diagnosis, but also possible resectability after induction treatment, has to be determined.

In the field of imaging, there is no doubt that PET has complemented CT in a substantial way. Historically, CT was the standard non-invasive imaging to assess locoregional LN spread: LNs >10 mm in the short axis were considered suspect for malignancy. Even with modern multi-slice spiral CT this results in only moderate accuracy, simply because size is a relative criterion: large nodes may be inflammatory or fibrotic, while small nodes may harbour metastatic deposits, resulting in overstaging as well as understaging [57]. PET has the potential to characterise the primary lesion, to evaluate locoregional LN spread, and to look for distant metastases in a single non-invasive test. It has therefore improved overall NSCLC staging [71].

In a landmark LLCG study, PET proved to be significantly more accurate than CT in LN staging, and if CT and PET images were correlated, the NPV proved to be slightly better than the one of mediastinoscopy [72]. This high NPV is the true strength of PET. It has been confirmed in several other studies and meta-analyses, and creates the possibility to leave out invasive staging if PET suggests absence of LN disease. This should be done cautiously, meaning that 3 ' side conditions' should be taken into account: (i) sufficient FDG-uptake in the primary tumour; (ii) absence of a central tumour or important hilar LN disease that may obscure co-existing N2-disease on PET; (iii) use of a dedicated PET-camera [73]. If these rules of interpretation are handled correctly,

Table 1
Performance of different locoregional staging techniques[a]

	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)	Prevalence[b](%)
CT	57	82	83	56	28
PET	84	89	93	79	32
Blind TBNA	76	96	71	100	70
EUS-FNA	88	91	77	98	69
Mediastinoscopy	81	100	91	100	37

[a] Adapted from Toloza et al. 2003 [15,46].
NPV, negative predictive value; PPV, positive predictive value; TBNA, transbronchial needle aspiration; EUS-FNA, oesophageal ultrasound guided fine needle aspiration; PET, positron emission tomography; CT, computed tomography.
[b] Proportion of patients with metastatic mediastinal nodes in the study cohorts.

relevant LN disease will rarely be missed. In some patients, minimal N2-disease may be discovered at surgical exploration, but resection in these patients is rewarding [74,75], which may even be more the case in the era of adjuvant chemotherapy [2]. The PPV value of PET is less optimal. Therefore, in case of positive LN findings on PET, tissue confirmation is still mandatory to avoid radical surgery in node-free patients with false-positive nodes on PET. In these instances, PET will often help to direct invasive staging procedures. When properly used, PET also seems to be cost-effective [76], mainly due to the reduction in futile surgical procedures, as shown in one randomised study comparing a conventional work-up alone with the same plus PET [77].

Although equivocal localisation is an issue when reading PET alone, many situations can be solved by visual correlation with CT by experienced readers. The combined PET-CT is a very attractive step forward, but we feel that forthcoming larger prospective studies, optimally also focusing on patient outcome, still need to clarify whether PET-CT should be the new standard approach for imaging NSCLC. In the long run, however, this will be an academic discussion, since most of the currently purchased scans are of the combined type.

As for invasive staging, mediastinoscopy, completed by a left anterior approach in appropriate cases, has long been the gold reference (besides intra-operative LN staging of course).

When looking at the different sensitivity and specificity results in Table 1, one could suppose that the less invasive endoscopic methods do equally well, and might be preferred. However, two types of bias should be kept in mind. First, EBUS-TBNA/EUS-FNA series usually report on patient cohorts with markedly enlarged LNs on CT (and more recently with FDG-uptake on PET [48]). This results in a decreased chance of false-negative results and thus ' optimised' sensitivity. Secondly, even with apparently similar sensitivity, the NPV of mediastinoscopy (and PET) is much better than the NPV of TBNA/FNA (Table 1). This is because the prevalence of pathological N2–N3 disease in TBNA/FNA series is about 70%, whereas this prevalence in both imaging and mediastinoscopy series is between 28% and 37%.

It is hazardous to apply the TBNA/FNA results to patients without markedly enlarged LNs, as small LNs can contain metastatic deposits of clinical importance [57]. Thus, the question as to whether TBNA/FNA is a valid substitute for mediastinoscopy in the community setting is not solved. Only sufficiently large randomised comparator trials in unbiased populations will be able to give an answer in the near future.

The true strength of TBNA/FNA is that it is less invasive and nonetheless has a very high PPV. If N3-disease can be proven, this will usually be sufficient for locoregional staging, as it designates non-surgical stage IIIB. Moreover, the risk of a false-positive finding is considered to be very low, and mainly due to interpretation error rather than to sampling error [78,79]. If TBNA/FNA only proves N2-disease, the situation is more difficult. Because of the restrictions mentioned in the previous paragraph, it is not known how important the chance of missing N3-disease in normal-sized contralateral LNs may be, which leaves uncertainty about IIIA or IIIB staging. Nor is it known how certainly single- versus multiple-level N2 can be distinguished, a factor of prognostic importance [80]. An additional problem is that series on EUS-FNA often do not use the standard LN map for lung cancer and simply consider ' N2/N3-disease' as sufficient proof of unresectable disease, without considering the consequences for multimodality therapy.

Studies with EUS-FNA pretend that the finding of malignant cytology reduces the number of medi-

astinoscopies and exploratory thoracotomies by 25% in case of normal-sized mediastinal LNs on CT [81], 59% in case of enlarged LNs on CT [82], or even 62% in case of PET-positive LNs [83]. The main problem with all these studies is that they simply omit the standard control of mediastinal LN mapping with mediastinoscopy and/or thoracotomy and automatically assume that treatment decisions based on one malignant aspirate (sometimes even classified as ' N2-N3') are as adequate as decisions based on full LN mapping by mediastinoscopy, which still needs to be proven.

EBUS-TBNA is certainly the most exciting technique, because it targets the LN stations that are most commonly involved in lung cancer (levels 2, 4L anterolateral to the trachea, 4R or 7). The first results with this approach are very promising, as it was proven in a randomised study that EBUS-guided TBNA does better than blind TBNA [50], and as EBUS-controlled TBNA demonstrated a very high sensitivity in a Japanese trial [52].

A specific problem in surgical multimodality treatment is how restaging can be of help in making the decision regarding thoracotomy with attempted complete resection after induction treatment. Well-known prognostic factors in this setting are the pathological response in the primary tumour as well as the downstaging of mediastinal LNs [6,32–34].

Because pathological response and downstaging can only be assessed post-resection, the standard approach is repeat CT with assessment of radiological response, followed by surgery in patients with at least disease stabilisation, or preferably partial response. As CT is only a rough tool to measure pathological response, this strategy is not very satisfactory. Optimally, one should be able to assess the response and downstaging before thoracotomy.

PET has been shown to be superior to CT, both in the evaluation of primary tumour response [36–38] and downstaging [37,39,40], although LN assessment by PET after induction clearly has a lower sensitivity than at baseline. The reason for this poorer sensitivity is not clear. A very small mass of tumour, such as post-treatment microscopic foci surrounded by fibrosis, may be more difficult to detect. Changes in the micro-environment of the tumour, such as altered perfusion due to post-chemotherapy changes, may impair presentation of FDG to the metastatic LNs. Nonetheless, PET-response was highly predictive for a better outcome after combined modality treatment in our multi-centre experience [39,40]. Despite the important evidence that PET has the ability to complement structural imaging in this setting, we feel there is insufficient confirmatory evidence to use PET in therapeutic decisions when restaging patients after induction therapy in stage III NSCLC. The hypothesis that surgery after induction therapy is only beneficial in patients with an objective metabolic response has to be challenged in larger prospective outcome studies.

Repeat mediastinoscopy and endoscopic ultrasonography are techniques that allow pathological assessment of potential downstaging after induction, but they lack information on the pathological response of the primary tumour. Some teams have reported promising experience with repeat mediastinoscopy [61,68,69]. In our experience, repeat mediastinoscopy remains technically difficult and often incomplete, if the initial cervical mediastinoscopy was performed thoroughly [70]. On the other hand, if one can demonstrate persistent LN disease in the mediastinum after induction, this may suffice to cancel thoracotomy, as the overall 5-year survival, even after complete resection, is disappointingly low (<10%) in these patients [6,32,33,84,85].

In this setting endoscopy-controlled TBNA/FNA may become a useful complementary or alternative technique, as shown in an appealing pilot study, where LN sampling with EUS-FNA for restaging of stage IIIA-N2 NSCLC after induction chemotherapy yielded a diagnostic sensitivity of 75% [86]. Tissue proof of persistent LN disease with a minimally invasive technique is very attractive, as it is the only issue needed for clinical decision-making in this situation, in contrast with the baseline setting where the distinction between IIIA-N2 and IIIB-N3 is very important.

Conclusion and practical suggestions

It is hardly possible to give an overall recommendation for ' optimal' locoregional staging. First, all examinations are not present everywhere, and even when present, they depend on local skills, certainly for the invasive procedures. Secondly, as for each medical test, there is a balance between sensitivity and specificity, and information on both involved or uninvolved LNs can be relevant, according to the clinical setting. Thirdly, the techniques are often complementary and not competitive, which is an asset as this allows to reach suspicious LNs in all locations, and avoid more invasive tests in patients with important co-morbidity; on the other hand, this may increase the cost of the process. Finally, while there are sufficient comparator trials applicable to standard clinical practice for CT, PET and mediastinoscopy, this is not the case for the new ultrasound-controlled endoscopic procedures.

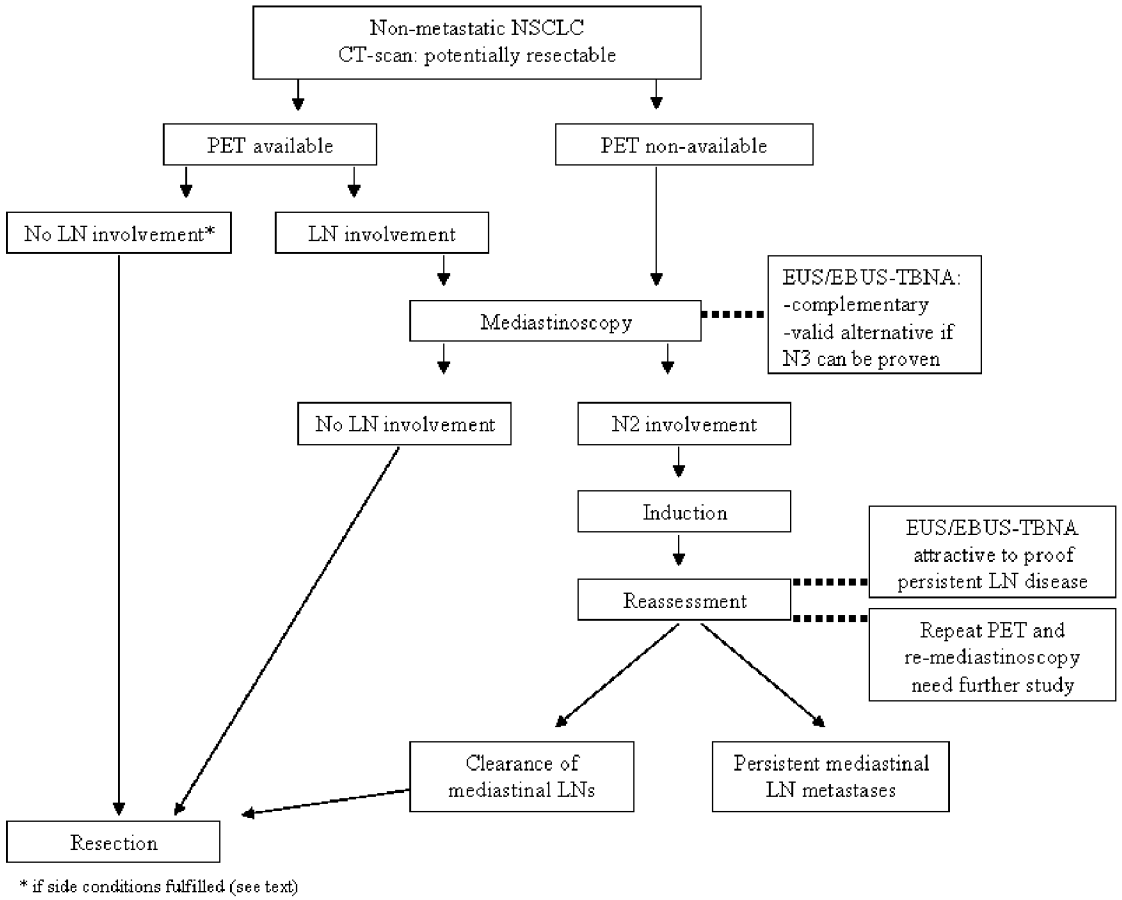

Fig. 6. Pragmatic scheme for contemporary locoregional staging of non-metastatic NSCLC. Also refer to text for correct understanding and additional details.

Interpretation of the diagnostic value of these tests is often hampered by the lack of direct comparisons, the lack of randomised studies and by the selection bias inherent in this study design. Their diagnostic yield is promising enough to launch large randomised trials with the standard approach as a control arm. Prospective studies comparing the diagnostic accuracy of EBUS-TBNA and EUS-FNA for routine (re)staging of both enlarged and normal sized LNs with both PET and mediastinoscopy are eagerly awaited. They will ultimately determine the true clinical value and then may cause a shift in algorithms for mediastinal staging and restaging of lung cancer in the near future, with a potential impact on health economics as well.

For the time being, a possible scheme for contemporary locoregional staging in NSCLC is given in Fig. 6, based on the following considerations:

Just as treatment, optimal staging is a multidisciplinary process, with a variety of possible techniques, which should be performed by experienced hands.

Imaging techniques rely on either LN size or metabolism to detect cancer spread, while invasive tests may be required further to define the exact stage.

Nowadays, a thoracic CT is available in almost every patient with non-metastatic NSCLC. It shows the exact location and extent of the primary tumour, and it will serve as a first evaluation, be it far from sufficiently accurate, of locoregional LN spread. It may also guide invasive techniques.

When available, PET has an important place, as the good NPV allows omission of invasive staging in case of absence of FDG-uptake in the mediastinum, provided that ' side conditions' are taken into account. Additional advantages are characterisation of the primary mass and screening for distant metastases. Positive findings on PET should be pathologically verified. The procedures needed to obtain tissue may be guided by PET.

Mediastinoscopy remains the standard tool for invasive staging in patients without bulky mediastinal involvement. It has a good NPV and a 100% PPV. Visual inspection at mediastinoscopy also distinguishes

intra- from extra-nodal LN disease, and resectable from irresectable disease in difficult cases. Left anterior mediastinotomy should preferably complete the cervical approach in left upper lobe tumours with suspicion of LN metastases in levels 5 and 6 based on CT and/or PET.

Blind TBNA has insufficient NPV for clinical decision making, but the high PPV allows decision on management in some patients, e.g. if N3-disease can be proven.

Endoscopic ultrasonography (EUS of EBUS) improves the diagnostic yield of mediastinal LN aspirates, and has great potential to challenge mediastinoscopy. Proof of N3 disease at baseline, or proof of persistent LN disease after induction, may suffice to guide clinical management. The technique also complements mediastinoscopy for LN levels that cannot be reached by it, e.g. posterior subcarinal nodes or lower mediastinal nodes. NPV is probably lower than for mediastinoscopy, which remains a problem for the optimal distinction between stage IIIA-N2 and stage IIIB-N3 disease in initial staging. Endoscopic ultrasonography is also accurate to exclude or confirm T4 disease in specific cases.

Redo PET and redo mediastinoscopy to assess response to therapy after induction have been described as better tools to evaluate the indication for resection, but both strategies need further validation before being implemented in clinical patient management.

Conflict of interest statement

None declared.

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