The multidisciplinarity of stage III non-small cell lung cancer

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Introduction

In the staging of patients with non-small cell lung cancer (NSCLC), both accurate assessment of the primary tumour extent (T), of the spread to locoregional lymph nodes (N), and the search for distant metastases (M) are important. This provides prognostic information and guides the choice of treatment. Patients without tumour growth into or lymph node (LN) spread to the mediastinum (early stages I and II) will have upfront surgical resection often followed by postoperative chemotherapy [1]. Patients with distant metastasis (advanced stage IV) are in general no longer amenable to curative therapy.

Stage III patients are the focus of this overview. Most patients with stage III have mediastinal LN involvement, which is present in 30% to 45% of patients with newly diagnosed NSCLC. They are quite a heterogeneous group of patients with different prognostic and therapeutic subsets. Patients with stage IIIA-N2 have metastases to ipsilateral mediastinal LNs, and a dismal outcome when treated with surgery or radiotherapy alone. A combination of chemotherapy with surgery and/or radiotherapy will be the best strategy [2,3]. Patients with contralateral LN metastases (stage IIIB-N3) will have non-surgical combined modality treatment. In the setting of surgical combined modality treatment, complete resection is an essential element for cure [4,5]. Therefore, the process of staging has become a true multidisciplinary effort, involving imaging, non-invasive and invasive staging techniques. The aim is both precision in intrathoracic staging and optimal estimation of complete resectability. We review the role of the different techniques in the baseline and post-induction setting, their limitations (under- or overstaging), some literature data on multidisciplinarity, and end with a recommendation for contemporary clinical practice.

The multidisciplinary process of staging

Imaging

CT-scan

Computed tomography (CT) of the thorax and upper abdomen is performed in every fit patient with NSCLC. With its excellent anatomic detail, modern spiral CT 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. For these purposes, 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 [6–8]. As for the N-factor, modern contrast-enhanced CT is very accurate in detecting LN enlargement, but the clinical applicability of LN enlargement for staging LNs is poor, because small nodes may contain metastasis and enlarged nodes may be benign (e.g. in case of post-obstructive pneumonia). Most studies have used a $\geqslant$10 mm short-axis diameter as the criterion for nodal metastasis. In a recent review, the pooled sensitivity and specificity of CT scanning for identifying mediastinal LN metastasis were 51% (95% confidence interval (CI) 47–54) and 85% (95% CI 84–88), respectively, confirming that CT scanning has limited ability either to rule in or exclude mediastinal metastasis. CT will be of help, however, in selecting the most appropriate procedure for tissue sampling of the suspect LNs [9].

PET-scan and integrated PET-CT scan

Positron emission tomography with ^{18}F-fluoro-2-deoxy-D-glucose (FDG-PET) was a major step forward in NSCLC imaging. Based on the high uptake of FDG in malignant lesions, whole-body PET was able to characterise lesions that remained equivocal on conventional imaging and to detect lesions that escaped on conventional imaging. For the T-factor, PET on its own has little to add to the anatomic detail of CT, because of its lower spatial resolution [10]. For the N-factor, PET imaging – with its metabolic information –

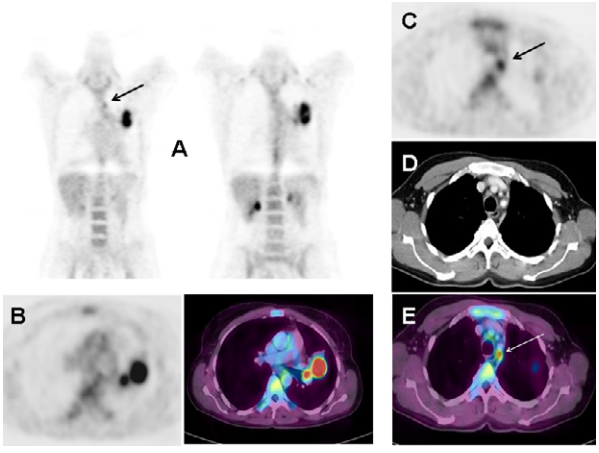

Fig. 1. PET-CT in a patient with squamous cell carcinoma of the left upper lobe. FDG uptake is present in the primary tumour and an adjacent hilar lymph node (A, B). PET also shows a focal hot spot suspected for N2 disease in level 2L (A, C arrow). PET-CT fusion images project the hot spot in brown fat tissue (D, E). Thoracotomy with lymph node dissection confirmed the absence of mediastinal involvement (pT2N1).

was proven to be superior to CT [11], a finding confirmed in different meta-analyses [12,13], with pooled estimates of sensitivity and specificity for identifying mediastinal metastasis of 74% (95% CI 69–79) and 85% (95% CI 82–88), respectively [9]. Many well designed prospective studies also demonstrated a gain in accuracy in the M-factor, mainly because PET is able to detect additional metastatic lesions in 5% to 25% of the patients, and this was especially the case in stage III NSCLC patients [14–18].

The limitation of stand alone PET was its limited spatial resolution, allowing far less anatomical detail than CT. Papers in the late 1990s already pointed out that interpretation of PET-images in visual correlation with CT-images improved results [19,20]. The contemporary answer to this was the combination of morphologic and metabolic information in integrated PET-CT scanners. For the T-factor, three studies reported better results with PET-CT in comparison to PET alone [21–23]. This superiority is due to the CT component of the examination, resulting in more precise evaluation of chest wall and mediastinal infiltration in some patients, and better differentiation between tumour and accompanying inflammation or atelectasis in others on the integrated images. In the Zürich group report, there was a benefit for integrated PET-CT in comparison to side-by-side reading of PET and CT-images, which was not in place in the Leuven experience [24]. Results for the N-factor give a similar picture, with PET-CT superior to PET alone [21,22]. Accurate anatomic correlation allows exact location of involved nodes, and thus better distinction between N1, N2 and N3. Furthermore, the role of PET-CT in identifying supraclavicular N3 nodes and in the distinction between FDG-avid brown fat and a metastatic lymph node is indisputable [21–23] (Fig. 1). Finally, for the M-factor, only a few results are available. In a large retrospective study, there was a significant superiority of PET/CT versus PET alone or CT alone, but not versus side-by-side correlation [10].

Post-induction imaging

Factors associated with good prognosis after induction treatment for stage IIIA-N2 are downstaging of mediastinal LNs, and the degree of pathologic response in the primary tumour. These factors are classically only available after resection. They are poorly predicted by CT, but more than a decade ago, a prospective pilot study reported that the combination of LN downstaging on PET and a SUV_{max} decrease of >50% in the primary tumour predicted a better outcome [25]. Since then, many studies have addressed the value of PET and PET-CT in assessment of LN downstaging, estimation of pathologic response, and the relationship of these findings with survival outcome [26–35].

Results for mediastinal LN restaging are listed in Table 1. These studies differ in methodological aspects, such as type of induction (chemotherapy or chemoradiotherapy), timing of imaging (interval 3–4 weeks, straight after, or at a variable interval 4–10 weeks after neo-adjuvant therapy, respectively), and interpretation of imaging (visual correlation with CT or integrated PET-CT). Nonetheless, it is clear that the sensitivity and specificity are lower than for baseline lymph node staging, but better if studies with PET-CT are considered. In terms of prediction of response in the primary tumour, the earliest studies

Table 1
Studies on the use of PET or PET-CT after induction treatment

Study	Year	*N*	Stage	CTRT	Imaging	Sensitivity	Specificity
Vansteenkiste et al. [26]	2001	31	IIIA-N2	0%	PET + CT (visual corr.)	71%	88%
Ryu et al. [28]	2002	26	III	100%	PET + CT (visual corr.)	58%	93%
Akhurst et al. [27]	2002	56	I-III	29%	PET + CT (visual corr.)	67%	61%
Cerfolio et al. [29]	2003	34	IB-IIIA	21%	PET + CT (visual corr.)	50%	99%
Port et al. [31]	2004	25	I-IIIA	0%	PET + CT (visual corr.)	20%	71%
Hellwig et al. [30]	2004	37	III	70%	PET + CT (visual corr.)	50%	88%
Hoekstra et al. [32]	2005	25	IIIA-N2	0%	PET + CT (visual corr.)	50%	71%
De Leyn et al. [35]	2006	30	IIIA-N2	0%	Integrated PET-CT	77%	92%
Pottgen et al. [34]	2006	37	IIIA/B	100%	Integrated PET-CT	73%	89%
Cerfolio et al. [33]	2006	93	IIIA-N2	100%	Integrated PET-CT	62%	88%

N: number of patients; CTRT: % of patients with chemoradiation induction treatment; PET: positron emission tomography; CT: computed tomography.

reported a sensitivity of 81–97% and a specificity of 64–67% to predict a pathological complete response on PET after neo-adjuvant therapy [27–30]. Other studies used the percentage change in the SUV_{max} on PET before and after neo-adjuvant therapy, and described a strong but imperfect correlation between this decrease and the residual amount of viable tumour in the resection specimen [30,33,34].

Several recent studies also confirmed the relevance of changes on PET for survival outcome. In one study, a cut-off value of 60% decrease in SUV_{max} after induction chemotherapy was a significant predictor of 5-year survival (60% versus 15%, $P = 0.0007$) [36].

Endoscopy

Standard bronchoscopy

Standard bronchoscopy 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.

Blind transbronchial needle aspiration (TBNA)

Data of endoscopic or surgical staging studies are often reported with the use of the LN map as described by Mountain and Dressler [37] (Fig. 2). Blind TBNA can be performed during the initial standard bronchoscopy if enlarged mediastinal LNs are present on CT. A blind TBNA is most often applied to selected LN levels, i.e. those with clear anatomic landmarks (such as lower right 4R and left paratracheal 4L nodes, as well as the subcarinal lymph nodes in position 7). When they are clearly enlarged (at least 15 mm), they can be safely aspirated using a needle through the working channel of a standard bronchoscope [38]. 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' experience. A recent meta-analysis reported a sensitivity of 78% and a false negative rate of 28% for blind TBNA in clinical N2 disease [39]. A blind TBNA is very useful if it leads to proof of N3 disease, but it should not lead to a conclusion of absence of N3 when only N2 disease is found (lack of negative predictive value).

EUS-controlled FNA

The advent of endoscopic ultrasonography has allowed imaging beyond the mucosa into the mediastinum, e.g. visualisation of LNs in the vicinity of the oesophagus, and therefore improved the diagnostic yield of endoscopic mediastinal LN sampling techniques. Oesophageal 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 ultrasonography control. This technique particularly visualises superior mediastinal lymph nodes in level 4L, and inferior mediastinal nodes in levels 7, 8 and 9, as described on the Mountain-Dressler LN map [37]. This complements other techniques, as several of these LNs (levels 8 and 9) are not accessible by bronchoscopy 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 is able to sample hilar LN stations 10R or 10L (N1, Fig. 3), in which case one has to be extremely careful not to consider these LN stations

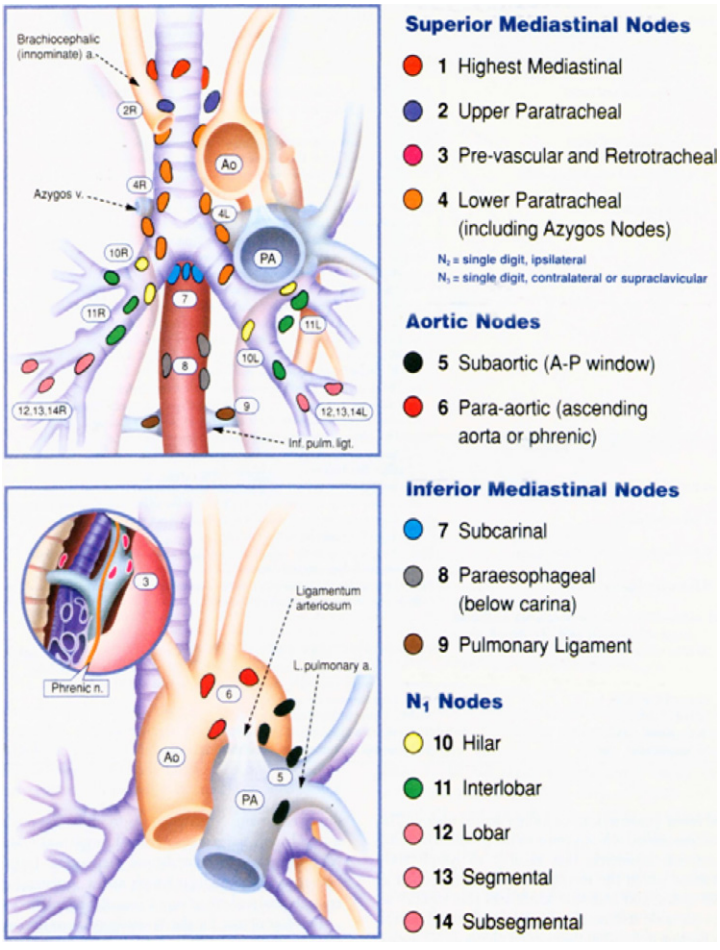

Fig. 2. Locoregional lymph node map for lung cancer staging (by Mountain and Dresler [37]).

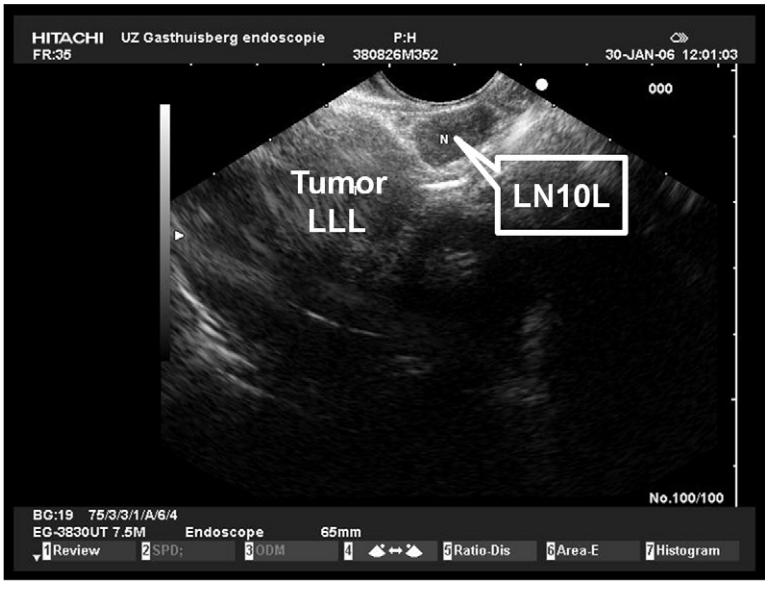

Fig. 3. EUS showing the primary lung tumour in the left lower lobe (LLL) with adjacent hilar lymph node in level 10L.

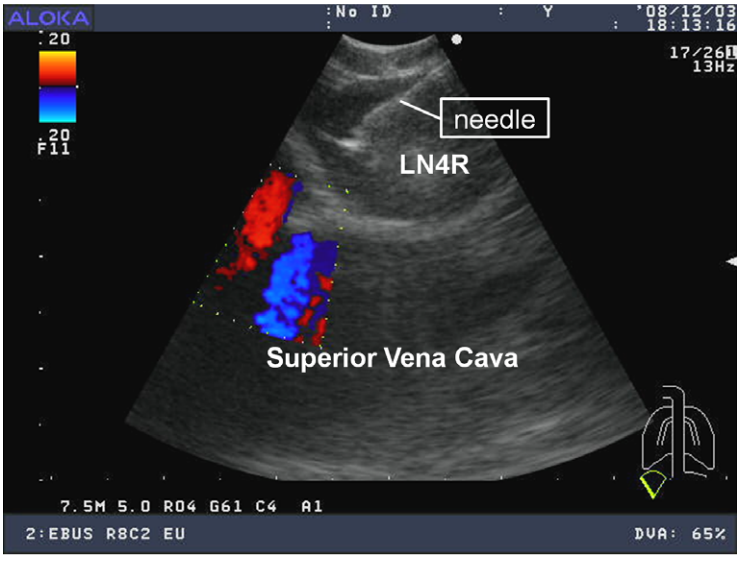

Fig. 4. EBUS showing an enlarged mediastinal paratracheal lymph node in level 4R (LN4R), while a real time transbronchial needle aspiration (needle) is being performed.

as mediastinal (N2) LNs. A meta-analysis reported a pooled sensitivity of 90% and negative predictive value (NPV) of 78% in selected patients with clinical N2 disease (i.e. having enlarged mediastinal LNs on CT) and a prevalence of malignant N2/3 disease of 73% [40]. EUS-FNA is a minimally invasive staging technique, which is advisable after a negative routine bronchoscopy in selected patients with CT-enlarged or FDG-avid mediastinal LNs. In addition, EUS is able to visualise and puncture several potential M1 sites, such as the left adrenal gland, the left liver lobe and the truncus celiacus nodes.

EBUS-controlled TBNA

Endobronchial ultrasonography (EBUS) can be performed with a linear echo-endoscope under local anaesthesia using moderate sedation. It is able to visualise 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 localise these LNs and perform a TBNA under real-time ultrasonography control (Fig. 4). The mediastinal LN stations accessible with EBUS-TBNA are the same as for a cervical mediastinoscopy. A recently published meta-analysis on EBUS-TBNA reported a pooled sensitivity of 94% for CT-enlarged or PET-positive mediastinal LNs with a prevalence of malignant N2/3 disease of 68% [41]. An important issue is that EBUS-TBNA – just as EUS-FNA – has a suboptimal NPV ranging from 60% to 80%, which requires a confirmatory surgical staging procedure in case of a non-malignant echo-endoscopic needle aspiration. It is clear that cervical mediastinoscopy remains the gold standard which is indicated after a negative needle aspiration of CT-enlarged or PET-positive mediastinal LNs. A special situation is patients with centrally located tumours with a normal mediastinum on CT and PET. As imaging techniques may miss existing mediastinal LN disease because of the vicinity of the primary tumour, histological verification of the mediastinum is warranted. Cervical mediastinoscopy remains the first choice test in that particular situation.

Post-induction endoscopy

There are a few reports suggesting that EUS-FNA can be used for mediastinal restaging after induction therapy; however, these were small studies reporting a suboptimal sensitivity and NPV [42,43]. The same comment can be made for the only study using EBUS-TBNA after induction chemotherapy reporting a NPV of 20% [44]. This NPV is far too low to advise these echo-endoscopic techniques in a post-induction setting.

Surgical techniques

Cervical mediastinoscopy

Cervical mediastinoscopy is the standard tool for staging the upper mediastinal LNs in patients with lung cancer. It is a surgical open-biopsy technique under general anaesthesia [45]. In most centres, patients are discharged from the hospital the same day. The mediastinoscope is inserted through a small suprasternal incision. Blunt dissection then gives access to the

Table 2
Studies on the use of repeat mediastinoscopy after induction treatment

Author	Year	*N*	CTRT	Sensitivity	NPV	Accuracy	Remarks
Pitz et al. [58]	2002	15	0%	50%	NA	NA	impossible in 7 pts
De Leyn et al. [35]	2006	30	0%	29%	52%	60%	
Dewaele et al.[a] [57]	2008	104	24%	71%	73%	84%	mortality 1; bleeding 1
Marra et al.[b] [56]	2008	104	100%	61%	85%	88%	

N: number of patients; CTRT: % of patients with chemoradiation induction treatment; PV: negative predictive value; NA: not available, pts: patients.
[a] Compilation of series of Van Schil [59] and Mateu-Navarro [55]. [b] Same patients as in the series of Stamatis [60].

pretracheal, right and left paratracheal, and anterior subcarinal LN levels (levels 1, 2R, 4R, 2L, 4L, 7 on the Mountain-Dressler map [37]). There is no internationally accepted recommendation on how many LN stations should be examined at cervical mediastinoscopy. One study assessed the quality of mediastinoscopy performed in teaching and non-teaching hospitals [46]. There was a large variability in the performance of the technique. An adequate number of three or more LN levels were sampled in only 40% of the procedures. There was a correlation between the number of yearly performed mediastinoscopies and the number of LN levels sampled. Therefore, guidelines of the European Society of Thoracic Surgery (ESTS) were most welcome. They 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 [47]. In experienced hands, the average sensitivity of cervical mediastinoscopy to detect mediastinal LN involvement is approximately 80% according to a recent review, with a high NPV of 89% [39]. Other advantages of cervical mediastinoscopy is that it allows a complete mapping of mediastinal LNs to be performed, and also allows 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 improved visualisation, allowed recording of the findings, and led to improved teaching possibilities [48–51].

Anterior mediastinotomy

This technique mainly has its place in patients with left upper lobe tumours, which are known to metastasise predominantly to the aortopulmonary window and para-aortic nodes (levels 5 and 6), which cannot be reached by cervical mediastinoscopy. An alternative is left thoracoscopy (see below). The 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 case of high suspicion of involvement of LN levels 5 or 6 (e.g. in case of enlarged or FDG-avid LNs in that area).

Extended mediastinoscopy, where the scope is brought over the aortic arch, was described to reach level 5 and 6 nodes via the cervical approach, with reasonable sensitivity up to 81% in some series [52, 53]. The technique never became widespread because of its technical challenge and possible complications, such as embolic stroke due to the close contact of the mediastinoscope with the brachiocephalic and left carotid artery [54].

Video-assisted thoracic surgery (VATS, surgical thoracoscopy)

This technique 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. On the latter side, the advantage over left anterior mediastinotomy is that anatomical landmarks such as the vagal and phrenic nerve are more easily recognised. 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 aortic and inferior mediastinal LNs.

Post-induction staging

Repeat mediastinoscopy has been propagated as a tool for restaging of the mediastinum after induction therapy in patients with N2-disease, as it may offer histological evidence of mediastinal LN status [55]. Retrospective studies from a few centres have reported that repeat mediastinoscopy after induction treatment has a fairly good accuracy [56,57] (Table 2). In other centres with ample experience, repeat mediastinoscopy was disappointing. In a prospective study in 30 patients who had a thorough baseline staging mediastinoscopy to establish IIIA-N2, followed by induction chemotherapy, the sensitivity of repeat

mediastinoscopy to detect residual mediastinal LN disease was only 29% with a NPV of 52% [35]. Poor results were due to fibrosis and dense adhesions caused by initial thorough mediastinoscopy. Similar findings were reported by other groups [58]. It is very unlikely that a scenario with two mediastinoscopies (one baseline and one post-induction) will be the best one in future multimodality treatment. If adequate baseline staging can be achieved based on imaging tests in combination with endoscopic LN staging, one is able to reserve the first mediastinoscopy for post-induction assessment, where it has the same accuracy as in the baseline setting in one study [49].

When is it really stage III?

Understaging

False negative imaging findings

With a pooled sensitivity of CT for identifying mediastinal LN metastasis of 51% [9], this technique will often be false negative: absence of enlarged nodes does not 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) [61].

PET (with a pooled sensitivity of 74% [9]) will obviously do better, but carries a risk of false negative 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. Fusion PET-CT, where the lack of anatomical detail on PET stand-alone images is largely corrected, has improved this situation.

False negative endoscopic findings

In patients with evidence of mediastinal LN metastases on imaging (CT-enlarged or PET-avid nodes) at the time of diagnosis, the sensitivity of both EUS-FNA and EBUS-TBNA is around 90% [40,41]. False negative results will not be very common. A first condition in interpretation is that the sample should be valid. Although there is no common definition on validity of needle aspiration cytology, the presence of lymphocytes is important. In case of adequate representative samples, false negative findings can occur in case of (1) anatomic miss if the wrong lesion has been sampled, (2) sampling error in the target lesion due to the presence of only micro-metastatic foci (deposits <2 mm), or (3) representative sample with too few suspicious cells to assure a conclusive report. In patients without signs of mediastinal LN metastasis on imaging, or in the post-induction setting, the sensitivity and NPV are much lower. The suboptimal NPV of echo-endoscopic needle aspiration technique requires a confirmatory surgical staging procedure in case of a non-malignant echo-endoscopic needle aspiration.

False negative surgical staging

The average false negative rate of cervical mediastinoscopy is approximately 10% [39]. 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.

For VATS, the false negative rate was 15% both in enlarged and normal sized nodes with a sensitivity varying widely from 37% to 100% [39].

Overstaging

False positive imaging findings

Enlarged mediastinal nodes on CT does not necessarily mean N2 or N3 disease, because enlargement may be due to other factors such as granulomatous or inflammatory disorders (post-obstructive pneumonia with infectious LN enlargement being a typical example).

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.

False positive endoscopy findings

No false positive findings by EBUS-TBNA have been reported in the literature, and all but one EUS-FNA series reported no false positive needle aspirations [62]. A false positive finding can however occur in case of (1) contamination of cytologic material when the needle passes dysplastic or neoplastic mucosa (e.g. EUS-FNA through malignant oesophageal mucosa), (2) misclassification of activated/enlarged lymphocytes as suspicious epithelial cells by the cytopathologist, or (3) sampling by the endoscopist of primary tumour tissue instead of a mediastinal LN material (e.g. in case of a central hilar tumour adjacent to the mediastinal LN).

False positive surgical staging

The specificity and the false positive rates of mediastinoscopy are reported to be 100% and 0% respectively. Strictly speaking, these values can not really be assessed because patients with a positive

Table 3
Different categories of mediastinal lymph node according to the American College of Chest Physicians (ACCP) [39]

Class	Category	Description mediastinal LNs	Preoperative imaging tests	Peroperative tissue findings	Postoperative (resection specimen) findings
A	bulky	mediastinal infiltration	positive +++	NA (positive)	–
B	clinical	enlarged discrete nodes	positive	positive	–
C	subclinical	no enlarged nodes but central tumour	negative	positive	–
D	unforeseen	no enlarged nodes peripheral tumour	negative	NA (negative)	positive

LNs: lymph nodes; NA (positive): not applicable (considered positive based on imaging); NA (negative): not applicable (considered negative based on imaging).

biopsy finding were not subjected to any further procedure (such as thoracotomy) to confirm the results. Nevertheless, it seems reasonable to assume that the false positive rate is extremely low.

The heterogeneity of stage III

The number and volume of nodal mediastinal involvement is responsible for the heterogeneity in clinical presentation of stage IIIA-N2 NSCLC, which also has an impact on treatment and prognosis for these patients. An important distinction is subdividing these patients into those with clinical or preoperatively known N2 versus those with unforeseen N2 detected at the time of surgery, and the distinction between single level versus multilevel mediastinal LN metastasis [63]. Unfortunately, the actual staging classification and definitions do not allow clear separation of the various subsets of patients with nodal involvement. The most recent American College of Chest Physicians (ACCP) guidelines suggest a practical way to sub classify stage IIIA-N2 NSCLC patients into four subsets mainly based on the volume of LN involvement (Table 3) [39].

The importance of multidisciplinarity in treatment decisions

The effect of hospital type

In a landmark study on the effect of hospital volume, the outcome of more than 2000 surgically treated patients with stage I, II, or IIIA NSCLC was studied [64]. Patients treated at high-volume centres had a better 5-year survival (44% versus 33%; $P < 0.001$) and lower postoperative mortality risk (3% versus 6%). More recently, much larger surveys from different regions in the world confirmed these findings: both short-term (postoperative mortality) and long-term survival are better in large-volume versus small volume hospitals [65,66], and in teaching versus non-teaching hospitals [66–68].

In a very large North-American survey, the absolute differences in adjusted mortality rates between very-low-volume and very-high-volume hospitals was >5% for pneumonectomy, and >2% for lobectomy [69]. The same authors later reported statistically significant relationships between hospital volume and survival for different cancer types, including NSCLC, where the absolute difference in 5-year survival was 6% [70].

Similar but less abundant data are available for chemoradiation for stage III NSCLC [71]. In a retrospective analysis of 239 patients enrolled in clinical trials, the cohort of patients treated at centres with $\geqslant 5$ inclusions had a 3-year survival rate of 31% versus 13% for centres with <5 inclusions. Multivariate analyses confirmed the independent value of this factor.

The effect of multidisciplinary boards

While hospital size matters for different aspects of outcome, there is less evidence for multidisciplinary boards (MBs).

Most of the studies made a historical comparison of outcome measures between a period with and the past period without the MB [72–75]. It is well known that these types of analyses are prone to different sources of bias and confounding factors [76] and to stage migration effects leading to a better survival in each stage subset, without improvement in survival of the whole population [77]. In these studies, some impact on patterns of care is often demonstrated: e.g. addition of a dedicated thoracic surgeon instead of a cardio-thoracic surgeon resulted in a higher resection rate (from 12% to 23%; $P = 0.001$) and a major decrease in pneumonectomies in favour of (sleeve) lobectomies [73]; introduction of a multidisciplinary team resulted in an increase in chemotherapy from 7% to 23% ($P < 0.001$) [74]; and waiting times are decreased [75]. Better survival was reported in only two studies [74,78]. There is only one pilot randomised trial, in which survival in the MB group

Table 4
Overview of accessible lymph node levels for the different invasive staging procedures

LN station	EUS-FNA	EBUS-TBNA	Cervical mediastinoscopy	Anterior mediastinotomy	Left-sided VATS
2R	+/–	+	+	–	–
2L	+/–	+	+	–	–
4R	–	+	+	–	–
4L	+	+	+	–	–
5	+/–	–	–	+	+
6	–	–	–	+	+
7	+	+	+	–	–
8	+	–	–	–	+
9	+	–	–	–	+
10 R/L	+/–	+	–	–	–
11 R/L	–	+	–	–	–

Lymph node mapping according to Mountain and Dresler [37].
LN: lymph node; EUS-FNA: oesophageal Ultrasonography-fine needle aspiration; EBUS-TNBA: Endobronchial ultrasonography – transbronchial needle aspiration; VATS: Video-assisted thoracic surgery.

was actually a little inferior (33% versus 40% at 2 years), albeit not statistically significant.

Multimodality treatment offers better survival in clinical trials, but as many lung cancer patients are (ex)smokers with co-morbidities, management patterns in real practice can be difficult, and several clinical practice guidelines therefore recommend MBs – bringing together different specialists – to take treatment decisions.

In the absence of a large randomised trial with a contemporary control group, the main conclusion is that MBs often change practice patterns. The lack of convincing survival data does not mean that MBs are ineffective, but rather points at the difficulty to sample randomised evidence on a complex process like MBs.

Conclusion: practical recommendations: assessment of stage III

Catching the heterogeneity of stage III NSCLC

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

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. Moreover, the techniques are often complementary (Table 4), and not competitive, which allows suspicious LNs in all locations to be reached, and avoids more invasive tests in patients with important co-morbidity.

When it is truly stage III, a distinction has to be made between the quite heterogeneous subsets of stage III, as these different subsets have clearly different prognoses and optimal therapeutic approaches. In that respect, the recent ACCP classification offers a good framework (Table 3) [39].

The patients with bulky N2 (type A) are not – just as with stage IIIB-N3 patients – candidates for surgical multimodality treatment. In fit patients, concurrent chemoradiation is the preferred approach.

In patients with intra-operatively detected or unforeseen N2 (type D), surgical resection followed by adjuvant chemotherapy is recommended, while there is ongoing debate on the role of postoperative radiotherapy [79].

Most controversy exists for the patients with clinical (type B) or subclinical (type C) N2. In general, they will not be treated by upfront surgery or radiotherapy, but by surgical or non-surgical combined modality treatment. Here, based on the available data, an overall recommendation for each patient cannot be made, and the multidisciplinary effort to distinguish unresectable from resectable disease is of crucial importance [80].

One randomised study compared induction chemotherapy followed by either resection or radiotherapy in patients with *unresectable* IIIA-N2 disease [81]. Induction chemotherapy did not convert unresectable disease into resectable – as illustrated by the 50% incomplete resection rate in the surgery arm – but did, and not unexpectedly, result in a sobering 15% 5-year survival with both approaches. Unfortunately, the hypothesis that surgery might improve the prognosis of unresectable N2 if performed after induction

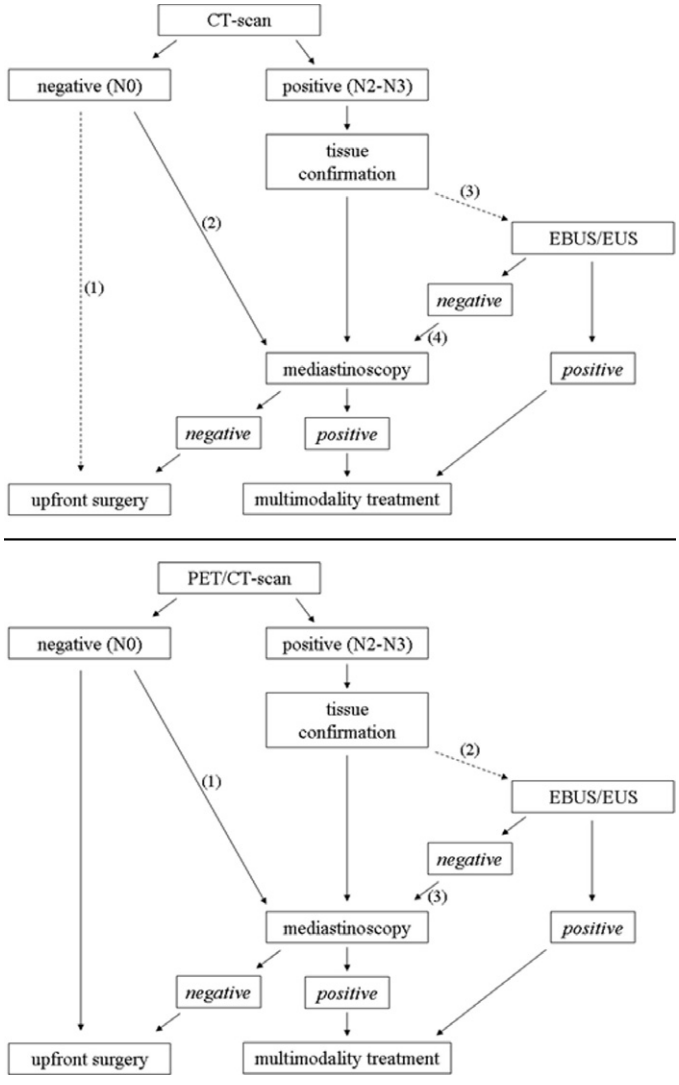

Fig. 5. ESTS guidelines for locoregional LN staging in NSCLC. Upper panel: (1) only in T1N0 squamous cell tumours; (2) in all other tumours; (3) endoscopic techniques are minimally invasive and can be the first choice; (4) due to higher NPV mediastinoscopy remains indicated. Lower panel: (1) in central tumours, tumours with low FDG-uptake, tumours with LNs >1.5 cm and/or PET 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 [47].)

chemotherapy did not become a reality, meaning chemoradiation remains the standard for this group.

In patients with *potentially resectable* IIIA-N2, as judged by dedicated multidisciplinary assessment, different European series point at remarkably similar 5-year survival rates of 36% (Swiss group) [82], 34% (Essen group) [83], and 30% (Leuven group) [5], respectively, in IIIA-N2 patients with resection after induction treatment. Even if non randomised, all were well designed prospective trials, with intent-to-treat reporting and reliable long-term follow-up. In the randomised US Intergroup data, 5-year survival again was 36%, and clearly superior to the non-surgical arm, if pneumonectomy could be avoided [84]. The rationale of these studies is to provide surgery as the best local treatment for resectable NSCLC and improve outcome by induction therapy to manage distant micro-metastasis. In this respect, it is noteworthy that in the European Organisation for Research and Treatment of Cancer (EORTC) experience, surgery provided better local control (32% locoregional failure) than radiotherapy (55%).

How to do baseline staging in practice?

In patients with truly bulky mediastinal LN disease, tissue confirmation is often not needed, but for all

others very practical guidelines on the European level were developed by the European Society of Thoracic Surgery (ESTS) [47].

A first algorithm (Fig. 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 wanted, because of the low positive predictive value of CT. 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 by experienced hands. In many patients with positive needle aspirates, invasive surgical staging can be avoided. However, in case of negative findings, one should realise that the NPV remains lower than for mediastinoscopy, on average 19% false-negative results for EUS-FBA, and 28% for EBUS-TBNA [39], so confirmatory mediastinoscopy is indicated.

The lower part of Fig. 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 little 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% [19]. On the other hand, because false positive findings may occur (see above), tissue confirmation remains warranted in case of positive mediastinal PET findings.

How to do post-induction staging in practice?

Factors associated with good prognosis after induction treatment and surgical resection for stage IIIA-N2 are complete resection, downstaging of mediastinal lymph nodes, and the degree of pathologic response in the primary tumor. These factors are poorly predicted by CT, and classically only available after resection. As for imaging, a unique feature of repeat PET after induction is that it not only assesses mediastinal nodes, but response in the primary tumor as well (see above) (Fig. 6). In this context, fusion PET-CT images are likely to be superior to side-by-side comparisons of PET and CT images.

For the invasive tests to be used after induction, the choice will be determined by the tools used at initial staging. As repeat mediastinoscopy after induction is in general disappointing and difficult to achieve (see above), the use of endoscopic techniques for baseline staging becomes very attractive. In that scenario, a first mediastinoscopy can be performed in optimal conditions after the induction treatment, thereby giving maximum information on LN status. A recent paper explored how the use of different tools for reassessment after induction might be optimised if one works in a scenario with upfront endoscopic staging. It described that the combination of pathologic response in mediastinal LNs and primary tumour response as assessed on serial PET might be a very powerful tool to predict outcome after multimodality therapy for stage IIIA-N2 NSCLC [85].

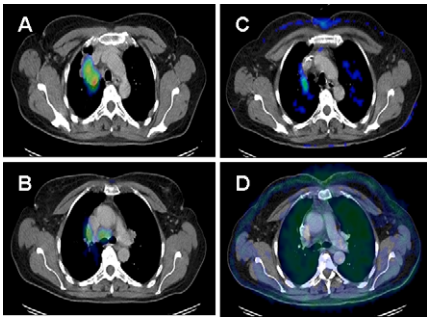

Fig. 6. Right upper lobe large cell carcinoma (A) with right hilar and paratracheal adenopathy (B), both clearly FDG-avid on PET-CT fusion images. After induction chemotherapy, a major decrease in the metabolic activity of the primary tumour and absence of FDG-uptake in the mediastinum is noted. Patient underwent complete resection, pT1N0.

Conflict of interest statement

None declared.

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