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ESTS guidelines for preoperative lymph node staging for non-small cell lung cancer

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Summary

Accurate preoperative staging and restaging of mediastinal lymph nodes in patients with non-small cell lung cancer (NSCLC) is of paramount importance. It will guide choices of treatment and determine prognosis and outcome. Over the last years, different techniques have become available. They vary in accuracy and procedure-related morbidity. The Council of the ESTS initiated a workshop on preoperative mediastinal lymph node staging. This resulted in guidelines for primary staging and restaging. For primary staging, mediastinoscopy remains the gold standard for the superior mediastinal lymph nodes. Invasive procedures can be omitted in patients with peripheral tumors and negative mediastinal positron emission tomography (PET) images. However, in case of central tumors, PET hilar N1 disease, low fluorodeoxyglucose uptake of the primary tumor and LNs $\geq$ 16 mm on CT scan, invasive staging remains indicated. PET positive mediastinal findings should always be cyto-histologically confirmed. Transbronchial needle aspiration (TBNA), ultrasound-guided bronchoscopy with fine needle aspiration (EBUS-FNA) and endoscopic esophageal ultrasound-guided fine needle aspiration (EUS-FNA) are new techniques that provide cyto-histological diagnosis and are minimally invasive. Their specificity is high but the negative predictive value is low. Because of this, if they yield negative results, an invasive surgical technique is indicated. However, if fine needle aspiration is positive, this result may be valid as proof for N2 or N3 disease. For restaging, invasive techniques providing cyto-histological information are advisable despite the encouraging results supported with the use of PET/CT imaging. Both endoscopic techniques and surgical procedures are available. If they yield a positive result, non-surgical treatment is indicated in most patients.

Keywords: Lung cancer; Preoperative staging; Intra-operative staging; Mediastinoscopy

1. Introduction

Correct staging of patients with non-small cell lung cancer (NSCLC) provides accurate information on the extent of disease and guides the choice of treatment. It is also fundamental for estimating prognosis and for comparison of studies. When there are no distant metastases, mediastinal lymph node (LN) involvement is the most important prognostic factor in patients with NSCLC and influences therapeutic strategies. Patients with tumors in clinical stage III are a heterogeneous group in whom the extent of LN involvement before and after induction therapy determines outcome.

Patients with preoperatively diagnosed involved mediastinal LNs have a dismal outcome when treated with surgery or radiotherapy alone. In order to improve the outcome in these patients, the concept of multimodality treatment has been introduced. In the subgroup of patients with IIIA-N2 disease induction chemotherapy, combined with either surgery and/or radiotherapy has proved to be effective (Table 1).

Even in the setting of surgical combined modality, complete resection is an essential element in the potential of cure. Therefore, an important aim of staging procedures in these patients will be to guide the multidisciplinary decision on whether the patient is a candidate for resection, based on baseline and postinduction assessment. If complete resection is considered unlikely, a non-surgical multimodality approach

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Table 1
Influence of downstaging of mediastinal lymph nodes after induction treatment and surgical resection for mediastinoscopy proven N2 disease

Author	Year	No. of patients	Surgery (%)	Complete resection (%)	Results in surgery group			
					Downstaging (%)[a]	Survival overall (%)	Survival downstaging (%)	Survival pN2 (%)
Bueno et al. [39]	2000	NR[b]	NR (103)	NR	28	18	36	9
Betticher et al. [40]	2003	90	87	55	63	NR	61 (3 years)	11 (3 years)
Lorent et al. [41]	2004	131	57	53	45	35	44	14
Intergroup trial 0139 [24]	2005	202	81	71	41	27	41	24
EORTC 08941 Trial [25]	2005	167	92	50[c]	42	16	29	7

% Complete resection: number of complete resection on total number of included patients.
NR: not reported.
Study by Betticher et al. [40] and Lorent et al. [41] give results of induction chemotherapy for N2 disease.
Intergroup trial compares CT/RT versus CT/RT + surgery for patients with N2 disease.
EORTC trial compares RT versus Surgery in responding patients after induction chemotherapy for N2 disease.
[a] Downstaging: disappearance of tumor from mediastinal nodes.
[b] Denominator is not in manuscript. Only data on complete resections after induction chemotherapy.
[c] Strict criteria were used for complete resection (highest mediastinal lymph node had to be negative).

is preferred. Therefore, a precise and accurate preoperative and postinduction LN evaluation is mandatory.

After a first successful workshop on intra-operative LN staging [1], the ESTS Council initiated a second workshop on preoperative mediastinal LN staging.

The working group had three sessions in Zürich. Initial findings were presented and discussed at the postgraduate meeting of the EACTS–ESTS meeting in Barcelona (September 2005). The final paper was put on the website for discussion by all ESTS members. Their remarks were discussed and included in the final manuscript.

It is evident that both in primary staging and restaging, not every technique is available in every centre. Therefore, staging and restaging techniques can differ between different countries and centres.

2. Primary mediastinal LN staging

2.1. Imaging techniques

2.1.1. Chest CT scan

Computer tomography (CT) still plays a central role in lung cancer imaging. For the N-factor, modern contrast CT is very accurate in detecting LN enlargement, but the clinical relevance of LN enlargement for staging is poor because small nodes may contain metastases in up to 20% [2] and large nodes may be benign. A diameter larger than 1 cm in the short axis is generally considered as the standard criterion for a suspicious LN. This definition reduces the false negative interpretations, which is of importance regarding the possible inclusion in an induction protocol. In a review, pooled data yielded a sensitivity of 57%, a specificity of 82%, a positive predictive value of 56% and a negative predictive value (NPV) of 83%, with a marked heterogeneity across individual studies ([3], Table 2). In these guidelines, a LN with a diameter smaller than 1 cm in the short axis is defined as N0.

Table 2
Performance of different locoregional staging techniques (adapted from Toloza et al. [3])

	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)	Prevalence (%)
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

NPV: negative predictive value; PPV: positive predictive value; TBNA: transbronchial needle aspiration; EUS-FNA: endoscopic esophageal ultrasound-guided fine needle aspiration; prevalence: proportion of patients with metastatic mediastinal nodes in the study cohorts.

This performance is insufficient for clinical decision making, and in many instances it is inappropriate to rely solely on CT scan for N-staging, but it can be of help in selecting the most appropriate procedure for tissue sampling of suspected LNs. Cervical mediastinoscopy is recommended in patients with resectable NSCLC and N0 disease on CT scan except from those with a T1 squamous cell tumor with N0 disease on CT scan [4].

2.1.2. PET scan

Non-invasive lung cancer staging was substantially improved by the use of positron emission tomography with 18F-fluoro-2-deoxy-D- glucose (FDG-PET). A large number of accuracy studies and meta-analyses have demonstrated that PET is superior to CT for mediastinal LN staging in potentially operable NSCLC [5].

Sensitivities and negative predictive values (NPVs) were comparable for PET compared with mediastinoscopy (Table 2). However, the positive predictive value and the specificity of FDG PET scan are lower than those of mediastinoscopy due to the fact that FDG is also taken up by inflammatory processes.

Due to the high NPV of PET scan, invasive staging procedures like mediastinoscopy can generally be omitted in patients with clinical stage I NSCLC with negative mediastinal PET images. This implementation should be dealt with caution in case of patients with central tumors, central hilar N1 disease on CT scan, bronchio-alveolar cell carcinoma or in all situations with low FDG uptake in the primary tumor and mediastinal PET negative LNs 16 mm on CT scan [6–8].

In a recent meta-analysis [9], a post-test probability for N2 disease of 21% was found in patients with PET negative nodes ≥16 mm.

The implementation of PET as shown in algorithm in Fig. 5 reduced the number of mediastinoscopies by 65% [6]. Moreover, after a negative conventional staging, unknown metastasis can be found on PET in 5—29% of the patients.

We realize that some occasional patients with a false negative mediastinal PET will proceed straight to thoracotomy. When PET scan is implemented as discussed above, the rate of unforeseen N2 disease is expected to be below 10% [8,9]. In these cases however, minimal N2 is usually found and a reasonable prognosis can be expected after surgical resection.

The positive predictive value of PET scan is only 79%. In case of positive mediastinal PET, tissue confirmation is still needed to confirm LN metastasis. The main drawback of PET is the poor quality of its anatomic information. Tracing focal abnormalities to specific LNs can be difficult or even impossible with use of PET alone, specially in the exact localisation of a single focal abnormality between level 4R (N2) and level 10R (N1). Recently, integrated PET—CT scanners have been introduced [10]. The great advantage of this technique consists of the precise anatomical correlation of the radionuclide uptake, an identical positioning of the patient, no time interval for data acquisition and no additional work for collecting data. The available studies show an increased diagnostic accuracy of integrated PET—CT with respect to PET scan alone [11].

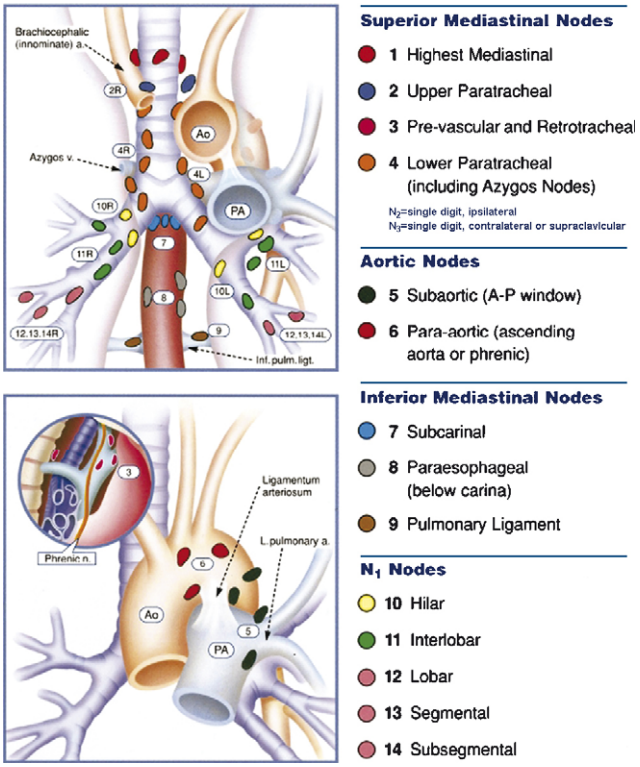


Fig. 1. Regional lymph node stations for lung cancer staging (from Mountain CF, Dresler CM. Chest 1997;11:1718—1723 [12] with permission).

2.2. Invasive techniques

2.2.1. Invasive surgical staging

2.2.1.1. Mediastinoscopy. Mediastinoscopy remains the gold standard for invasive staging of patients with potentially operable lung cancer. Different forms of mediastinoscopy have been described. Cervical mediastinoscopy is the most commonly used. It is a surgical open biopsy technique under general anesthesia.

According to the LN map proposed by Mountain and Dresler ([12]; Fig. 1), the following LN stations can be evaluated by cervical mediastinoscopy: the highest mediastinal LN station (level 1), the right and left superior paratracheal LN stations (level 2 right, level 2 left), the right and left inferior paratracheal LN stations (level 4 right, level 4 left) and the subcarinal LN station (level 7).

There is no internationally accepted recommendation on how many LN stations should be examined at cervical mediastinoscopy. There are no data indicating that more systematic sampling at mediastinoscopy makes a difference, but extrapolation from data on occasional and systematic sampling at thoracotomy suggests that this may be important [1]. The opinions vary among working groups and authors around the world:

- The American Thoracic Society stated that all reachable nodal stations should be explored. According to the ATS nodal map, these include the right and left superior paratracheal stations (levels 2R and 2L), right and left inferior paratracheal (levels 4R and 4L), right and left tracheobronchial (levels 10R and 10L) and subcarinal (level 7) stations. The ATS also recommended performing left parasternal mediastinotomy to explore the subaortic (level 5) and anterior mediastinal (level 6) stations in patients with left lung tumors.
- For Detterbeck et al. [13], the ideal exploration would include at least one node from the right and left, superior and inferior paratracheal and subcarinal stations, unless more nodes are present.
- Smulders et al. [14] assessed the quality of mediastinoscopies performed both in teaching and non-teaching hospitals. They found a large variability in the performance of mediastinoscopy for initial staging for NSCLC. In only 40% of mediastinoscopies performed for NSCLC three or more LN levels were sampled [14]. They suggest that the minimally acceptable exploration includes biopsy of nodes from the inferior paratracheal stations on both sides, and from the subcarinal station, with the addition of at least one contralateral LN. They consider that the inclusion of the superior paratracheal nodes on both sides could not be required in standard clinical practice, because they might be difficult to reach.

In summary, there seem to be two standards for mediastinoscopy described according to the latest LN map of Mountain—Dresler [12]:

- Ideally, the following nodal stations should be explored and their LNs biopsied:
  - right and left superior paratracheal nodes (level 2R and level 2L),

- right and left inferior paratracheal nodes (level 4R and level 4L),
- subcarinal (level 7).

- But a lesser standard could be accepted for routine clinical practice:
  - right and left inferior paratracheal nodes (level 4R and level 4L),
  - subcarinal nodes (level 7).

The ESTS working group recommends to systematically explore and biopsy always the right and left lower paratracheal nodes and the subcarinal nodes. Additionally, if present, the upper paratracheal LNs should be sampled and biopsied.

An advantage of mediastinoscopy over fine needle aspiration is that a more complete mediastinal mapping can be performed including contralateral LN stations. This might be important in the differentiation and treatment planning of patients with single and multi-level N2 disease. In a recent review, the sensitivity of cervical mediastinoscopy varied between 72% and 89%, with an average of 81% with a NPV of 91% [15]. The prevalence of N2 disease in these series was 37% which is the expected prevalence of N2 disease in patients with potentially resectable NSCLC. The results of the suboptimal sensitivity can partly be explained by the fact that some LN stations (levels 5, 6, posterior part of level 7 and levels 8 and 9) are not accessible by cervical mediastinoscopy.

More recently, mediastinoscopy is performed by the use of a videomediastinoscope ([16] Fig. 2). This definitely improves visualisation of the operative field and may lead to a higher accuracy in staging and a better standardisation of the technique [17,18]. The learning curve of video-assisted mediastinoscopy is short compared to conventional mediastinoscopy [19].

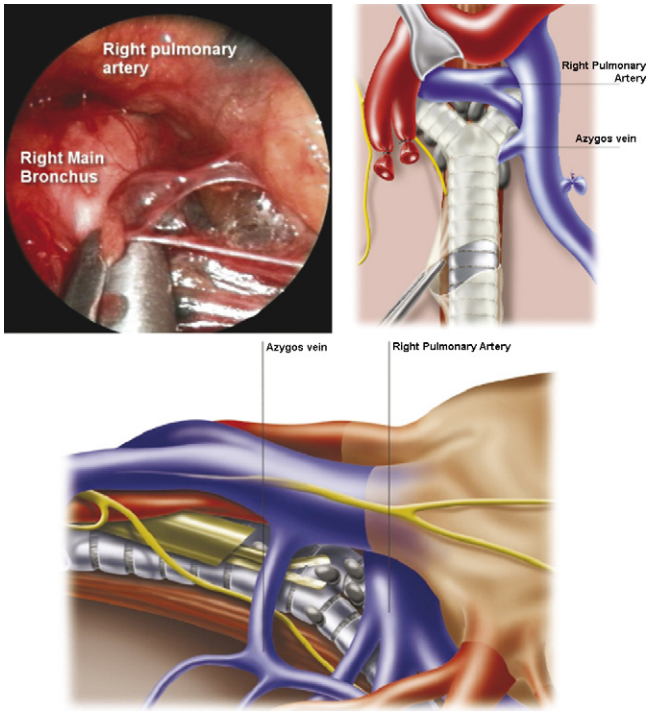


Fig. 2. Cervical videomediastinoscopy.

Some groups have developed techniques for mediastinal lymphadenectomy through a cervicotomy approach (VAMLA, video-assisted mediastinoscopic lymphadenectomy [20]—TEMLA, transcervical extended mediastinal lymphadenectomy [21]). The aim of both techniques is to perform a complete bilateral lymphadenectomy of the mediastinum including stations 2,4,7 and 8 (VAMLA) and stations 1,2,3A, 3P, 4,5,6,7 and 8 (TEMLA) for staging purposes. The potential advantage of these two lymphadenectomy techniques is that by removing the nodes, the false negative results caused by micrometastases can be reduced. The results of these two studies with a limited number of patients show a very high accuracy and NPV (between 0.95 and 1). However, the value of these techniques needs to be further explored before they can be implemented in routine practise.

Tumors of the left upper lobe may metastasize to the subaortic (level 5) and anterior mediastinal (level 6) nodes. These nodal stations cannot be reached by cervical mediastinoscopy. Left parasternal mediastinotomy, extended cervical mediastinoscopy, and left thoracoscopy allow exploration and biopsy of these nodal stations and should be used in combination with cervical mediastinoscopy to stage these LN stations as indicated. Thoracoscopy can also be used for LN levels which are not accessible by routine mediastinoscopy (levels 8 and 9). These lymph node levels can be biopsied with esophageal ultrasound-guided fine needle aspiration (EUS/FNA).

2.2.2. *Invasive non-surgical staging*

Endoscopic techniques are minimally invasive approaches that provide histological or cytological confirmation of nodal tumor involvement. Transbronchial needle aspiration (TBNA) has been shown to be safe and useful in patients with enlarged mediastinal LNs. However, this technique has a moderate yield, is a 'blind' technique, operator dependent, and the results depend on the size of the LN. In a recent overview, a sensitivity of 76% and a false negative rate of 29% were reported for conventional TBNA in clinical N2 disease (Table 2). This high false negative rate compromises the use of conventional TBNA for routine mediastinal LN staging, however it can be used as a preliminary diagnostic test complemented in negative cases with surgical staging. The accuracy can be improved by guidance with endoscopic ultrasonography (EBUS-TBNA). Additionally, the hilar (station 10) and intrapulmonary nodal stations can be biopsied with TBNA. EBUS-TBNA and cervical mediastinoscopy can provide histology of the superior mediastinal LNs (levels 2 and 4, right and left) and the subcarinal LNs (level 7) (Fig. 3).

In a recent meta-analysis including 13 studies in which all TBNA results were confirmed by surgical biopsies, it was shown that the sensitivity of TBNA critically depends on the prevalence of mediastinal LN metastases. In populations with a lower prevalence of mediastinal metastases, the sensitivity of TBNA is much lower than reported in recent lung cancer guidelines [22].

Esophageal ultrasound-guided fine needle aspiration (EUS-FNA) is mainly suitable for the assessment of LNs in the posterior part of levels 4L, 5 and 7 and in the inferior

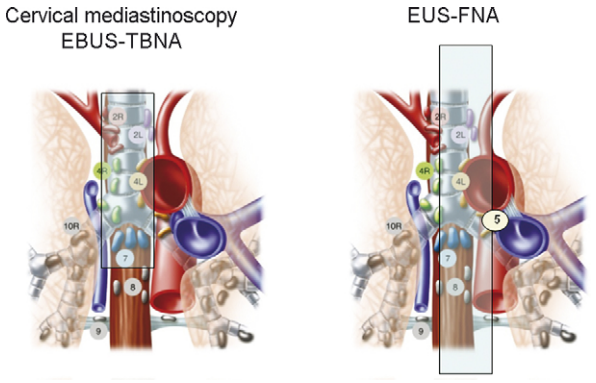


Fig. 3. Illustration of nodal levels which can be reached by cervical mediastinoscopy and EBUS-TBNA versus nodal levels which are accessible by EUS-FNA.

mediastinum at levels 8 and 9 as described on the Mountain—Dresler map (Fig. 3).

A review of the literature reported a pooled sensitivity of 88%, a specificity of 91%, a positive predictive value of 98% and a NPV of 77%. A recent study in 100 patients with potentially operable NSCLC who were scheduled for mediastinoscopy showed that the combination of mediastinoscopy and EUS-FNA significantly improved sensitivity and NPV [23].

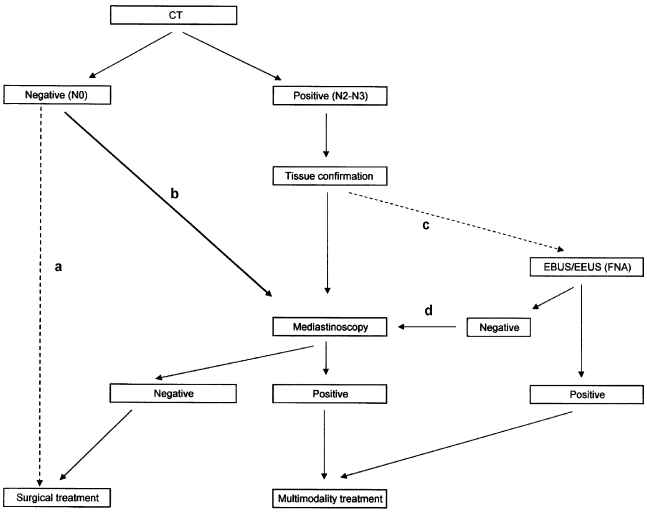
However, most of the accuracy studies on invasive non-surgical staging were performed in patients with a high suspicion of N2—N3 disease. When the prevalence of involved mediastinal LNs is high as mentioned above, an improved sensitivity is to be expected which does not reflect the accuracy in patients with normal sized LNs. It is generally accepted that endoscopic techniques (both EBUS and EUS/FNA) are suitable to provide histological proof of suspicious mediastinal LNs but cannot be used to exclude mediastinal LN disease because of the low NPV.

Transthoracic needle aspiration (TTNA) is performed with CT or, less often, with fluoroscopic guidance. Generally, TTNA is used in patients with enlarged or bulky mediastinal LNs. Almost all mediastinal nodal stations are accessible with this technique; stations 1, 2, 4, 5 and 6 are accessible using anterior parasternal approach and stations 4, 7, 8 and 9 are approached with the posterior paraspinal approach.

2.3. Guidelines for baseline mediastinal LN staging

- Chest CT is still the basic imaging modality in lung cancer. However, CT scan of the chest is not accurate enough for mediastinal LN staging. When only CT scan is available, invasive staging is advised in every patient except for a T1squamous cell tumor with LNs $<$ 1 cm on CT scan.

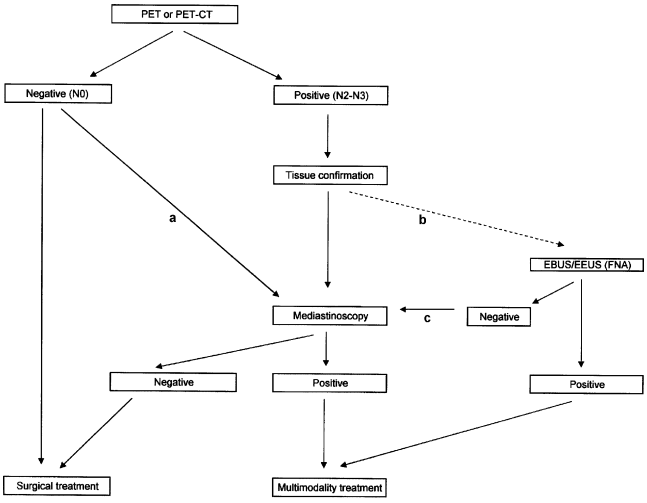
  Invasive staging can be omitted in patients with stage I NSCLC and negative mediastinal PET images. However, in case of central tumors, PET hilar N1 disease, low FDG uptake of the primary tumor and LNs $\geq$ 16 mm on CT, invasive staging remains indicated.
- PET positive mediastinal findings should be histologically or cytologically confirmed.
- Transbronchial needle aspiration, ultrasound-guided bronchoscopy (EBUS-FNA), esophagoscopy (EUS-FNA) and transthoracic needle aspiration (TTNA) are new techniques that provide cyto-histological diagnosis and are minimally invasive techniques. They can be complementary to surgical invasive staging techniques. Their specificity is high, but their NPV is low. For this reason an invasive surgical technique is indicated if they yield negative results. However, if fine needle aspiration is positive, this result may be valid as proof of N2 or N3 disease.
- Cervical mediastinoscopy provides the advantage that a more complete mapping of mediastinal LNs can be



a : only in T1N0 squamous cell tumors invasive staging is not necessary
b : in all other tumors, nodal metastasis need to be excluded by mediastinoscopy
c : Endoscopic techniques are minimally invasive and can be the first choice
d : Due to its higher NPV mediastinoscopy remains indicated

EUS : endoscopic esophageal ultrasound
EBUS : endobronchial ultrasound
NPV : negative predictive value
N0 : LN < 1 cm

Fig. 4. The proposed algorithm to follow for primary mediastinal staging when PET scan is not available.



a : In central tumors, tumors with low FDG uptake, tumors with LNs ≥ 1,6 cm and/or PET N1 disease invasive staging remains indicated
b : Endoscopic techniques are minimally invasive and can be the first choice
c : Due to its higher NPV mediastinoscopy remains indicated

EUS : endoscopic esophageal ultrasound
EBUS : endobronchial ultrasound
NPV : negative predictive value
N0 : LN < 1 cm

Fig. 5. The proposed algorithm to follow for primary mediastinal staging when PET or PET/CT scan is available.

performed. Ideally, all accessible lymph node stations (2R, 4R, 2L 4L and 7) should be explored and biopsied. At least one ipsilateral, one contralateral and the subcarinal LNs should be biopsied.
- The proposed algorithm for primary mediastinal staging when no PET scan is available is detailed in Fig. 4. Fig. 5 shows the algorithm when PET or PET/CT scan is available.

3. Mediastinal lymph node restaging after induction therapy

Recent studies suggest that mainly patients with initial stage IIIA or IIIB and mediastinal downstaging will benefit from surgical resection (Table 1). However, postoperative morbidity and mortality may be higher after resection following induction therapy compared with resection without induction treatment. As a consequence, mediastinal restaging after induction therapy is required to aid proper selection of patients likely to benefit from surgical resection.

An important question remains whether a better local control and survival are obtained by induction therapy and surgery compared to standard chemoradiotherapy. Recently, the results of two large randomized trials became available. In the Intergroup, 0139 trial patients with proven stage IIIA-N2 NSCLC were randomized between a full course of chemoradiotherapy and induction chemoradiotherapy + surgery [24]. There was no significant difference in overall survival between both arms. However, there was a difference in progression-free survival favoring the surgical arm, and patients downstaged to ypN0 disease had a far better prognosis. The rate of locoregional recurrence was also significantly less in the surgical arm.

In the EORTC 08941 phase III trial, patients with unresectable clinical stage IIIA-N2 disease were randomized between surgery and radiotherapy after a response to induction chemotherapy [25]. There was no difference in overall and progression-free survival between both arms. The data of these two trials are however only available in abstract form which impairs a precise analysis and a fair interpretation of the results.

The mediastinum can be principally restaged by the same techniques as applied in primary staging.

3.1. Imaging techniques

In primary staging, CT scan has proved to have a low accuracy. It is not surprising that the accuracy of CT scan in restaging the mediastinum is also low. In two studies, the sensitivity of CT scan for mediastinal restaging was 41% and 59%, specificity 75% and 62% and accuracy 58% and 60%, respectively [11,26].

For mediastinal restaging after induction chemotherapy, PET scan is more accurate than CT but is clearly not as accurate as in untreated patients [27–31]. In most studies, the sensitivity is reported to be 50–60% with a good specificity of 85–90%. So, in a high proportion of patients, PET scan is false negative regarding mediastinal nodal involvement after induction therapy. The reason for this poor sensitivity is not clear. A very small mass of residual tumor, such as post-treatment microscopic foci surrounded by fibrosis may be more difficult to detect. Changes in the microenvironment of the tumor such as altered perfusion due to postchemotherapy changes, may also impair presentation of FDG to the metastatic LNs.

In a prospective study [11], the use of PET–CT fusion images significantly increased the accuracy through better localisation of focal FDG update in mediastinal LNs or other vascular–mediastinal structures. This study showed that PET–CT had a high positive predictive value (93%) in detecting residual mediastinal disease. Moreover, complete resectability was low (57%) in patients with persistent mediastinal findings on PET–CT. However, in another study [32] the PPV was only 75% and the authors concluded that persistent positive mediastinal findings on PET should be histopathologically proven.

It seems that the comparison of SUV max values before and after induction chemotherapy allow prediction of histopathologic response in the primary tumor and mediastinal LNs and have prognostic value [32].

3.2. Invasive techniques

3.2.1. Invasive surgical staging

Repeat mediastinoscopy, although technically more difficult than the first procedure, offers the advantage of providing histological evidence of response after induction therapy.

Only a few centres have reported their experience with repeat mediastinoscopy (Table 3). Mateu-Navarro et al. [26] reported on 24 patients who underwent re-mediastinoscopy after induction chemotherapy for mediastinoscopy proven N2 disease. The sensitivity to detect residual mediastinal disease was 70%. Van Schil et al. [33] reported very similar results in 27 patients with no mortality and only minimal morbidity. The largest experience of repeat mediastinoscopies after induction therapy to date was recently reported by Stamatis et al. [34]. In a study from the Netherlands, re-

Table 3
Diagnostic accuracy of re-mediastinoscopy after induction treatment for mediastinoscopy proven N2 disease

Author	Year	No.	Sensitivity (%)	NPV (%)	Findings at initial mediastinoscopy	
					No. of levels biopsied	Multilevel disease (%)
Mateu-Navarro et al. [26]	2000	24	70	NR	NR	12
Van Schil et al. [33]	2002	27	73	75	NR	37
Pitz et al. [35]	2002	15	NR	NR	NR	NR
Stamatis et al. [34]	2005	165	78	86	4.2	NR
De Leyn et al. [11]	2006	30	29	52	3.8	33

NR: not reported.
NPV: negative predictive value.

mediastinoscopy was performed in 15 patients. Re-mediastinoscopy was inadequate or incomplete in 6 patients and the authors concluded that the examination was not that effective [35].

A prospective study evaluated the accuracy of re-mediastinoscopy and PET—CT in restaging the mediastinum after videomediastinoscopy proven N2 disease in 30 patients [11]. The authors concluded that, after a thoroughly performed initial videomediastinoscopy, repeat videomediastinoscopy was technically feasible but inaccurate due to severe adhesions and fibrosis. The sensitivity to detect residual positive mediastinal LNs was only 29%, with an accuracy of 60%. It seems that the degree of adhesions and mediastinal fibrosis is mainly secondary to preinduction mediastinoscopy rather than to induction treatment itself [36]. In a study comparing accuracy and safety of videomediastinoscopy in patients without pretreatment and in patients after induction therapy but without preinduction mediastinoscopy, sensitivity, specificity and accuracy were comparable without additional morbidity [18].

A study investigated the role of VATS in restaging of the mediastinum after induction therapy for N2 disease in 70 patients [37]. In 17 patients, the VATS procedure was not successful due to fibrosis. A sensitivity of 75%, a specificity of 100% and a NPV of 75.8% were reported. However, the value of this technique needs to be further explored before it can be implemented in routine practise.

3.2.2. Invasive non-surgical techniques

An alternative, less invasive test to restage the mediastinum after induction chemotherapy is transbronchial or transesophageal ultrasound-guided biopsy. A study from the Netherlands reported results in 19 patients with proven N2 disease which were restaged by EUS after induction chemotherapy [38]. Diagnostic accuracy in this study was 83%.

Restaging of the mediastinum after induction treatment for N2 disease is of paramount importance. CT is by far not accurate enough for restaging. Re-mediastinoscopy has proven to be feasible but due to adhesions and fibrosis, the intervention is technically challenging and sensitivity and accuracy are lower than after a first mediastinoscopy. The accuracy of PET in mediastinal restaging is far from optimal, mainly due to its low sensitivity. Fusion images with PET—CT are reported to improve the results. Less invasive techniques, such as EUS-FNA seem to yield similar results as VATS and re-mediastinoscopy. An alternative approach is the use of EBUS or EUS-FNA for primary staging and reserve mediastinoscopy for mediastinal restaging after induction therapy.

In order to obtain the most precise restaging, an integration of these procedures is highly recommended, especially in the context of clinical trials and to maintain the morbidity as low as possible.

3.3. Guidelines for restaging

Restaging of the mediastinum after induction therapy is necessary.

At the present time, neither CT, PET or PET—CT are accurate enough to make final further therapeutic decisions based on their results.

An invasive technique providing cyto-histological information is recommended. For restaging, endoscopic techniques or surgical invasive techniques can be used. If they yield a positive result, non-surgical treatment seems to be indicated in most of the patients. The choice may be dependent on the availability of the technique and expertise of the centre.

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