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

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1. Introduction
For patients with non-small cell lung cancer (NSCLC) and no systemic metastasis, mediastinal staging is very important as it provides accurate information on the extent of the disease, it guides the choice of treatment and determines the patient’s prognosis.

In 2007, the European Society of Thoracic Surgeons (ESTS) published an algorithm on preoperative mediastinal staging based on the current available literature (De Leyn 2007). These guidelines integrated imaging, endoscopic and surgical techniques. Since 2007, there is substantially more information and evidence on mediastinal staging techniques. In 2009, the International Association for the Study of Lung Cancer (IASLC) introduced a new lymph node map of the lungs and mediastinum that resulted from an international and multidisciplinary consensus (Rusch 2009). Some new changes in this map have an important impact on mediastinal staging. Moreover, new insights on the importance of restaging and techniques for mediastinal restaging have become available. Therefore, the ESTS Council took the initiative to make a revision of the ESTS guidelines on mediastinal staging.

2. Methodology
The working group had several sessions. The project was discussed in the Council at the ESTS meeting in Essen (June 2012). There were several meetings (Essen, Zürich, Brussels and Birmingham) where the participants presented their experience and discussed the relevant literature published since 2007. Initial findings were presented and discussed at the ESTS meeting in Birmingham (May 2013). The final paper was put on the website for discussion by all ESTS members. Their remarks will be discussed and included in the final manuscript.

For recommendations, a level of evidence and grading of recommendation is given. This was adapted from the Infectious Disease Society of American-United States Public Health Service Grading System (Table 1; Dykewicz 2001).

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.

3. Impact of new IASLC lymph node map
There are several modifications compared with the previous Naruke and Mountain and Dresler maps (Naruke 1978, Mountain CF, Dresler CM. Regional lymph node classification for lung cancer staging. Chest 1997; 111: 1718-23), but probably the most important modification from the clinical point of view is the shift of the anatomic mediastinal midline to the left paratracheal margin, the so-called mediastinal oncologic midline (Rush, 2009). This change is important to be understood by radiologists, bronchocopists, nuclear medicine specialists and surgeons because they have to locate...
the nodes correctly. The clinical implications of this shift, that affect exclusively nodal stations 2R, 2L, 4R and 4L (for the rest of the nodal stations, the mediastinal midline remains unchanged) is that involved pretracheal lymph nodes and lymph nodes on the left of the anatomic midline but on right side of the oncologic-midline are classified as N2 in case of right-lung tumours but as N3 in case of left-lung tumours.

Another important modification for mediastinal staging is that the anatomical borders of the LN stations are clearly defined. This is especially relevant for the lower border of station 4R and 4L. For the right lower paratracheal lymph nodes (station 4R), the lower border is the lower margin of the azygos vein. On the left side, the lower border of the left paratracheal lymph nodes (station 4L) is the upper rim of the left pulmonary artery. By cervical mediastinoscopy (and by endoscopic techniques), the lymph nodes below the azygos vein and below the upper rim of the pulmonary artery can be biopsied and they should be labeled respectively as 10R and 10L.

Definition of nodal zone and nodal station

A nodal zone is an anatomical area that includes one or several neighbouring nodal stations. The supraclavicular and the subcarinal zones include one nodal station each, station 1 and station 7, respectively. However, the limits of both nodal stations 1 and 7 are wider than they used to be in the previous maps. The other nodal zones include two, three or six nodal stations. It is important to realize that, in theory, a single N2 zone may have from 1 to multiple involved nodes in one or several nodal stations, and the nodes may be small or large. The concept of nodal zones is of especial value for those patients who will not undergo surgical treatment. For those receiving chemotherapy, radiotherapy or their combination, the precise anatomical location of the involved nodes is not so important. So, the nodal zones help locate nodal involvement without having to define the exact anatomical location of the nodes. However, nodal stations are important for those patients in whom surgical treatment is required. Precise nodal location is important preoperatively to guide surgical treatment, and also intra- and postoperatively to indicate further treatment. This is especially relevant in the upper mediastinal zone. The upper mediastinal zone includes six nodal stations that are all encompassed in the radiotherapy field; the exact involved nodal station is not important to administer chemo or radiotherapy. However, whether the right or the left paratracheal nodes are involved or not is important to confirm or rule out N2 or N3 disease and to select patients for surgical (multimodality) treatment.

4. Rationale for preoperative mediastinal nodal staging

The current guidelines for treatment of lung cancer are determined by the clinical status of the mediastinal nodes. The aim of mediastinal staging is to exclude with the highest certainty and the lowest morbidity patients with mediastinal nodal disease since these patients will not undergo upfront surgery.

There is controversy on the treatment of N2 disease because of the heterogeneity of nodal involvement. Also patient and tumor characteristics and extent of resection play a role in the selection of treatment modality for these patients. In the IASLC paper (Rush 2007), 4277 of 11619 patients clinically staged as cN2cM0 underwent resection and had information on pN category. Only a subgroup of 2876 patients underwent complete (R0) resection without any induction therapy and had information on nodal location and pN category based on pathological staging from lymphadenectomy. An exploratory analysis on the impact of lymph node zones on survival was performed in a subgroup (N=1992 patients) from this cohort, finding that pathological single N1 zone (pN1a) had better prognosis than multiple pathological N1 zones (pN1b); that the prognosis of multiple pathological N1 zones was the same as that of single pathological N2 zone (pN2a); finally, the prognosis of multiple pathological N2 zones (pN2b) was significantly worse. Five-year survival rates for pN1a, pN1b, pN2a and pN2b were 48%, 35%, 34% and 20%, respectively. These survival data should be interpreted with caution and have already been misinterpreted. It is important to have in mind that these survival analyses were performed in resected patients with pathologically staged tumours and thus based on results from lymphadenectomy: information on nodal status was available from station 2 and from stations 4 through 9 in all contributing institutions. Additionally, all centers but one provided documentation on stations 11 and 12, and most had information on stations 1, 13 and 14, while half of them provided documentation on station 3. (Rush 2007)

Therefore, the results from this highly selected population of patients used for this specific analysis cannot be extrapolated to the clinical staging setting. This is why these data cannot be invoked to propose upfront surgical treatment for patients with presumed clinical single N2 zone determined with the current clinical staging guidelines. No pretreatment test (CT, PET, EBUS, EUS, mediastinoscopy) can be compared with lymphadenectomy, except the lymphadenectomies performed through the transcervical approach (video-assisted mediastinal lymphadenectomy – VAMLA, and transcervical extended mediastinal lymphadenectomy – TEMLA). Therefore there is room for a well-designed prospective study to evaluate the possible role of primary surgery in preoperatively proven single zone or single station N2 disease.

There is a subgroup of patients with pretreatment histologically proven N2 disease who are candidate for surgical multimodality treatment. These patients are treated with induction
chemotherapy or induction chemoradiotherapy. In case of downstaging of the mediastinal lymph nodes or major response in those lymph nodes and in the tumour, resection with systematic nodal dissection can be performed with acceptable morbidity and mortality and rewarding 5-year survival. There are several prognostic indicators, some of them are related to the primary tumour and others are related to the extent of nodal disease. To include patients for surgical multimodality treatment, the disease should be initially technically resectable. Excluded for surgical multimodality are unresectable disease such as extracapsular disease (can be clearly visualized by mediastinoscopy), or bulky N2 disease based on CT. Fit patients with extracapsular disease and/or bulky N2 disease should be treated with definitive chemoradiotherapy.

Bulky N2 disease is not well defined but it correlates with the radiographic group A, as described in the American College of Chest Physicians (ACCP) Evidence-based Clinical Practice Guidelines (Silvestri GA, Gonzalez AV, Jantz MA, Margolis ML, Gould MK, Tanoue LT, Harris LJ, Detterbeck FC. Methods for staging non-small cell lung cancer. Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013; 143(5)(Suppl): e211s-e250s). This group is defined as mediastinal infiltration where the discrete lymph nodes cannot be distinguished or measured. Bulky is not strictly related to the size of the lymph nodes, but it is considered by this committee that lymph nodes larger than 25 mm short axis will also be defined as bulky disease. Bulky disease can be restricted to a single station but usually represents multistation or multiple zonal involvement. Since this paper deals with preoperative lymph node staging, techniques to obtain histology in bulky mediastinal nodal disease are beyond the scope of this article.

5. Primary mediastinal lymph node staging.
Several techniques are available and their use depends on local availability and local expertise. These techniques include:

- imaging techniques
- endoscopic techniques
- surgical techniques

Although we should aim for the test with the highest sensitivity and NPV, the working group considers a rate of unforeseen N2 disease of 10% as acceptable. After thorough mediastinal staging this unforeseen N2 is mostly single station resectable nodal disease.

5.1. Imaging techniques

Chest CT-scan
Computer tomography remains important in lung cancer imaging. However, due to its low sensitivity (55%) and specificity (81%) it is impossible to solely rely on CT-scan (Silvestri). CT-scan may help us in selecting the appropriate procedure for tissue sampling due to the anatomical images it provides.

PET-CT scan
The addition of PET to CT results in more accurate lymph node staging than CT alone with an overall sensitivity of 80-90% and specificity of 85-95% (meta-analysis PET-CT). PET-CT has a high NPV for detecting mediastinal nodal disease in peripherally located NSCLC. Exceptions include

1. suspected N1 nodes
2. tumour >3cm
3. centrally located tumour without suspected nodes on CT or PET scan.

- In a study from Japan (Hishada 2008), 30% of 143 patients with N1 disease on CT-scan (lymph node short axis > 1cm) were found to have pathologic N2-N3.
- A recent meta-analysis (Wang 2012) has shown that the negative predictive value of PET-CT for tumours ≤ 3cm was 94% (649 patients) compared to 89% for tumours > 3cm (130 patients) staged as T2 (6th edition of TNM). This finding was confirmed in a recent prospective study from Spain (Abel Gomez Caro 2012). For peripheral tumours ≤ 3cm the negative predictive value of PET-CT was 92% while it was 85% for tumours > 3cm. Based on these studies, we now recommend that for peripheral tumours (outer third of the lung) ≤ 3cm without enlarged (hilar and/or mediastinal) lymph nodes on CT and with PET-negative nodes, further mediastinal staging can be omitted. There was a substantial difference in rate of mediastinal nodal disease between adenocarcinoma and other tumour histology (risk ratio 2.72). Also high FDG uptake in the
primary lesion was associated with greater risk of occult nodal metastasis. For tumours > 3cm (mainly adenocarcinoma with high FDG uptake) further mediastinal staging techniques providing histology should be considered (fig 1).

- Lee et al. (2007) examined the prevalence of pathologic N2 disease in patients with clinical stage I non-small cell lung cancer (6th edition of TNM version) with negative mediastinum on PET and CT. In 2.9% of peripheral tumours (outer third of lung) N2 disease was found, while the prevalence of N2 disease was 21.6% in central tumours.

**Diffusion-weighted magnetic resonance imaging**

Advances in MRI technology have allowed acquisition of diffusion-weighted MRI (DWI) which provides excellent tissue contrast because of the difference in the diffusion of water molecules among tissues. The technique yields qualitative and quantitative information that reflects changes at a cellular level and provides unique insights about tumour cellularity and the integrity of cell membranes. In a recent meta-analysis (Lian-Ming 2012) the accuracy of DWI and 18F-FDG PET/CT was evaluated. The pooled sensitivity for DWI was 0.95 (CI 0.85-0.98) and significantly better than for FDG-PET/CT 0.89 (CI0.85-0.91). However, at this moment there are no large prospective studies comparing the value of DWI and FDG-PET and it is too early to determine the true value of DWI in nodal staging in patients with NSCLC.

**5.2. Endoscopic techniques**

**Conventional TBNA.**

Although the conventional TBNA technique has been available for almost 3 decades, its use in routine clinical practice has only been adopted by a minority (10-15%) of pulmonologists for mediastinal nodal staging of patients with potentially resectable stage I-IIII lung cancer. Major reasons for its underuse are its dependency on nodal size (>15-20mm short axis on CT scan) and operator skills. Meta-analyses reported a sensitivity of 78% and a false negative rate of 28% for conventional TBNA in clinical N2 disease with high disease prevalence of 81% (Holly2005;Detterbeck2007). A conventional blind TBNA is useful if it leads to proof of N3 disease, but too often does not exclude N3 disease in cases of proven N2 disease.

**Endoscopic ultrasonography: EUS-FNA and EBUS-TBNA.**

I. Practical aspects.

EBUS and EUS procedures are generally performed under local anaesthesia using moderate sedation in an outpatient setting. EBUS is able to visualise superior and inferior mediastinal LNs at stations

II. Performance characteristics.

Several meta-analyses on EUS-FNA alone, EBUS-TBNA alone, and combined EUS+EBUS reported a pooled sensitivity of 83 to 94% for mediastinal staging of lung cancer (Table 2) (Micames2007; Gu2009;Adams2009;Chandra2012;Zhang2013). Only one randomized controlled trial (Aster trial, Annema 2010) has been performed, comparing the two staging strategies proposed in the ESTS 2007 guidelines (either mediastinoscopy, or alternatively endosonography followed by mediastinoscopy) (;DeLeyn2007). There was no difference in sensitivity or NPV when mediastinoscopy was compared with endoscopic staging. However, the staging strategy starting with combined endosonography and if negative combining it with surgical staging has proven to detect significantly more mediastinal nodal N2/3 disease compared to mediastinoscopy alone (Annema2010), although all cases of N2 disease detected by mediastinoscopy after negative EBUS-EUS-NA were limited to single station (ASTER trial, unpublished results). Another consequence is that the implementation of endosonography for baseline mediastinal nodal staging clearly reduces the need for mediastinoscopy (Tournoy2009;Annema2010). On the other hand, the negative likelihood ratio reported by three of the meta-analyses is 0.13 to 0.15 (Table 2) (Adams;Chandra;Zhang). This implies that the probability
of having mediastinal nodal involvement for any individual patient with a negative endosonography result is 13-15%. In our and others’ opinion this probability based on endosonography alone is not low enough to directly proceed to a surgical resection (Detterbeck 2008). Therefore in the routine practice we still recommend a preoperative surgical staging procedure (i.e. VAM) in case of a negative endosonography. However, there is evidence coming from prospective studies performed in experienced endosonography centers, that mediastinoscopy may not improve sensitivity after a well-performed negative endosonography with needle aspiration of at least three mediastinal nodal stations in patients with low (<35%) prevalence of mediastinal disease (Herth 2008; Szlubowski 2010; Yasufuku 2012). EBUS-TBNA and EUS-FNA are safe procedures with reported minor complications in <1% of cases (Micames Chest 2007; Gu ERJ 2009; Varela-Lema ERJ 2009). With the rapidly increasing number of procedures, occasional reports of moderate to severe complications have been published, such as pneumothorax requiring chest tube drainage, infection of bronchogenic cyst, empyema, lung and/or mediastinal abscess, and haemopneumomediastinum are published. So far, only one death has been reported related to an EBUS-TBNA procedure (Navani AJRCCM 2012).

5.3. Surgical staging techniques

- Cervical mediastinoscopy

Cervical mediastinoscopy through a pretracheal suprasternal incision was introduced by Carlens in 1959 and further popularized by Pearson in North-America. It allows a full mapping of the ipsilateral and contralateral superior mediastinal lymph nodes. Cervical mediastinoscopy is performed under general anaesthesia and can be safely done as an outpatient procedure. For many years it was the gold standard for invasive staging of patients with potentially operable lung cancer. Since 1995, use of video techniques has been introduced leading to video-assisted mediastinoscopy (VAM). VAM clearly improved visualization and teaching (Martin Ucar) since both the trainer and the trainee can share the magnified image on the monitor. For more details on the technique of cervical mediastinoscopy, we refer to a recent publication on this topic (Rami-Porta 2012). There are only retrospective studies comparing the safety and accuracy of conventional mediastinoscopy with VAM (table 3). Although some authors (Leschber, Anraky, Cho) found an increase in the number of LN or LN stations biopsied, no difference in sensitivity or NPV was found (table). In some of these studies a reduction in the complication rate (mainly of recurrent nerve palsy) was observed. Very recently, (Zacker 2012) a best evidence topic has been published on the safety and accuracy of VAM compared to conventional mediastinoscopy (table 4). The authors analysed 108 papers published between 1989 and 2011. There were 5156 conventional mediastinoscopies and 956 VAMs. Both procedures are safe with no mortality in that time frame and a low morbidity. Although by VAM more lymph node stations are sampled, the negative predictive value and accuracy were identical.

Although the videomediatinoscope is not strictly necessary to achieve a thorough, clinically acceptable mediastinoscopy, it has many advantages over the conventional one: larger and clearer images, the possibility to simultaneously share the procedure with trainees and all the personnel in the operative theatre, the possibility to record the operation for future educational uses and discussion, and the possibility to improve its teaching without compromising the safety or accuracy of the procedure. Moreover it allows bimanual dissection with possibilities to perform nodal dissection and removal rather than sampling or biopsy. This is especially important and technically feasible for the subcarinal LN station. After removal of station 7 LNs, the oesophagus can be clearly visualized (figure). The ESTS working group recommends to perform VAM.

- VATS

Although video-assisted thoracoscopic surgery (VATS) can reach almost every mediastinal lymph node station, it is more invasive than cervical mediastinoscopy (it needs double lumen intubation and a chest tube), it is limited by pleural adhesions, and it can only evaluate ipsilateral nodal disease. For the para-aortic lymph nodes (station 6) and the subaortic lymph nodes (station 5), left VATS is a surgical technique that allows obtaining large tissue samples. It is indicated when enlarged PET-positive lymph nodes are visualized at level 5 or 6. These lymph node stations can not be biopsied by routine mediastinoscopy, EBUS-FNA or EUS-FNA. An alternative to VATS is the left anterior mediastinotomy. In some experienced centres, extended mediastinoscopy is performed for these lymph node stations and it gives good negative predictive values: 0.89-0.97, (Rami-Porta 2012). Extended cervical mediastinoscopy is performed from the mediastinoscopy incision (Call S, Rami-Porta R, Obiols C. Extended cervical mediastinoscopy. Multimedia Manual of Cardio-Thoracic Surgery 2012 2012: mms018-mms18). DOI:10.1093/mmcts/mms18

- VAMLA and TEMLA

During the last decade, 2 new invasive staging techniques representing more radical methods of mediastinal exploration have been introduced: video-assisted mediastinoscopic lymphadenectomy (VAMLA) (Hurtgen 2002) and transcervical extended mediastinal lymphadenectomy (TEMLA) (Kuzdzal 2005). These 2 techniques aim for a complete removal of all the mediastinal nodes with the surrounding adipose tissue to improve the accuracy of staging. VAMLA is completely performed with the use of the videomediatinoscope whilst TEMLA uses a 5-8 cm collar incision in the neck and elevates the sternum with a hook. The dissection is performed in an open way and with the use of...
the videomediastinoscope. By VAMILA, the lymph nodes which are usually accessible through mediastinoscopy are removed. By TEMLA, more lymph node stations are accessible such as the prevascular, the para-aortic, the subaortic and the para-oesophageal lymph node stations. The negative predictive value is very high and approaches 98.7% for TEMLA. The results of VAMILA and TEMLA regarding sensitivity and side effects are shown in table 4. Although there is no doubt that the accuracy of mediastinal staging increases when lymphadenectomy is performed compared to nodal biopsy, these techniques have a higher morbidity and mortality. The complications after VAMILA and TEMLA are well recorded (table 5) and are probably more studied in detail than after CM or VAM. These procedures are performed in very experienced centres. For VAMILA mainly problems with recurrent nerve palsy and important scarring with an impact on subsequent resection are reported. The published data for TEMLA are mainly from one very experienced centre and there are concerns on morbidity and mortality.

For TEMLA and VAMILA we conclude that currently available data regarding its use are limited and, therefore, we do not recommend its use except of clinical trials. We encourage other centres to publish their data with these new staging techniques.

6. Minimal requirements for mediastinal nodal staging.

The ESTS clinical practice guidelines 2013 for preoperative mediastinal nodal staging recommend that at least the following nodal stations should be explored and biopsied:

- right and left lower paratracheal lymph nodes (stations 4R and 4L)
- subcarinal lymph nodes (station 7)

If present, the right and left upper paratracheal stations 2R and 2L should also be biopsied

When required to determine subsequent treatment strategy, lymph node station 10R (below azygos vein) and 10L (below upper rim of left pulmonary artery) should be biopsied

In case of left-sided tumors, station 5 and 6 should be biopsied if it changes the treatment strategy.

The same applies to the lower mediastinal lymph nodes (station 8 and 9).

7. Algorithm for primary mediastinal staging

The algorithm for preoperative mediastinal staging is shown in fig. 1. For NSCLC, both for mediastinal as for distant staging, PET or PET-CT is indicated.

- When there are no enlarged lymph nodes on CT and when there is no uptake in lymph nodes on PET or PET-CT, direct surgical resection with systematic nodal dissection is indicated for tumours 3 cm (Stage IA) located in the outer third of the lung. (Level IIB).
- In central tumours, or N1 nodes enlarged on CT or PET-positive N1 nodes, exploration of mediastinal lymph nodes is indicated (Level IIIA). In case of tumours > 3 cm (mainly in adenocarcinoma with high FDG uptake) the NPV for mediastinal nodal disease is < 90% and invasive staging may be considered (Detterbeck 2013) (level IIIB). In all of the above-mentioned cases there is the choice between VAM with biopsy or lymph node dissection, or endoscopic staging by EBUS/EUS with fine needle aspiration. The choice depends on local expertise to adhere to minimal requirements for staging (V). If video-assisted mediastinoscopy is negative, these patients can undergo surgical treatment. They also can undergo surgical treatment after negative EBUS/EUS if the number of nodes explored and the number of needle passes in each node meet the established requirements. Otherwise, surgical exploration is recommended after negative EBUS/EUS.

- In case of enlarged mediastinal lymph nodes on CT or PET-positive mediastinal lymph nodes, tissue confirmation is indicated. In this case, endosonography (EBUS/EUS) with fine needle aspiration is the first choice (when available) since it is minimally invasive and has a high sensitivity to rule in mediastinal nodal disease (level IB). If negative, video-assisted mediastinoscopy is indicated (level IB). The combined use of endoscopic staging and surgical staging results in the highest accuracy.

For patients with a left upper lobe tumour, surgical staging of the aorto-pulmonary window nodes (if enlarged on CT and/or PET-CT-positive) can be performed (by anterior mediastinotomy, VATS or extended cervical mediastinoscopy) if involvement changes treatment strategy (IVB).

If only CT is available, we refer to the algorithm of the 2007 edition of the ESTS guidelines.

8. Mediastinal restaging after induction therapy

Mediastinal downstaging after induction therapy for locally advanced stage III non-small cell lung cancer (NSCLC) is an important prognostic factor for long-term survival. Patients with persisting mediastinal involvement have a worse prognosis compared to patients with proven mediastinal downstaging.

The same techniques used in primary staging can be used for mediastinal restaging. Noninvasive imaging techniques are not accurate enough for mediastinal restaging. PET provides additional metabolic information, but there are conflicting data regarding its use. PET has been shown to be more accurate in predicting the T component than the N status (Port 2004). Although experience is rather limited, integrated PET-CT combining precise anatomical and functional information seems to be more accurate for restaging (De Leyn, 2006). In a prospective study of 93 patients who were restaged by chest CT and integrated PET-CT after induction chemoradiotherapy, repeat PET-CT was
found to be more accurate than CT alone for all pathological stages [Cerfolio 2006]. However, there were 20% false-negative and 25% false-positive cases. So, in case of suspicion of residual mediastinal disease, nodal biopsies are still required [Cerfolio 2006].

Different techniques providing histology can be used for restaging (table 6). Endoscopic techniques can be used but EBUS-TBNA reported a variable NPV of 20% (Herth, 2008) and 78% (Szlubowski 2010). The difference in NPV may be explained by the prevalence of ypN2 after induction therapy, which was 94% in the study of Herth and 44% in the study of Szlubowski. These results underline that a negative EBUS for restaging should be confirmed by invasive surgical mediastinal restaging.

Remediastinoscopy (reMS) was found to be technically feasible, also after induction therapy [Pauwels 1998, Stamatis 2005]. However, remediastinoscopy is only used in very selected experienced centres and is not widely adoptable due to severe fibrosis and increased morbidity. Although feasible, the accuracy is lower than of mediastinoscopy for primary staging and this questions the timing of mediastinoscopy (baseline or at restaging, timing of further radiotherapy after induction which should not be delayed).

In experienced hands transcervical extended mediastinal lymphadenectomy (TEMLA) is also an accurate restaging technique. In a series of 63 patients induction chemotherapy (n=54) or chemoradiotherapy (n=9) was administered for N2 or N3 NSCLC. Initial mediastinoscopy was performed in 7 patients. Sensitivity, specificity and accuracy of TEMLA were 95.5%, 100% and 98.3%, respectively [Zielinski M, 2010]. In a recent retrospective analysis from the same institution EBUS/EUS and TEMLA performed for restaging after neoadjuvant treatment were compared in 78 patients. Sensitivity, specificity and negative predictive value of TEMLA were 97, 100 and 99%, respectively [Zielinski M, 2013].

Only one study reported the results of VATS for restaging after induction therapy [Jaklitsch MT, 2013]. In this CALGB 39803 trial a negative result of VATS was defined as negative lymph node biopsies from at least 3 lymph node stations, whereas a positive result consisted of a pathological proof of persisting N2 disease or the demonstration of pleural carcinomatosis. Sensitivity, specificity and NPV of VATS for restaging were 67, 100 and 73%, respectively. Restaging by VATS is feasible but requires single-lung ventilation and is limited to one hemithorax only.

An alternative approach that needs prospective validation is to rely on endosonography for baseline mediastinal nodal staging and a first mediastinoscopy for restaging after induction therapy. In this ‘restaging’ setting the NPV of “a first and more easy and safe mediastinoscopy” was 90% (with a prevalence of ypN2 of 46%, Lardinois 2003).

We conclude that optimal mediastinal lymph node staging is a truly multidisciplinary process, with a variety of possible techniques, to be performed by experienced hands.
In tumours > 3 cm (mainly adenocarcinoma with high FDG uptake) invasive staging should be considered depending on local expertise to adhere to minimal requirements for staging. Endoscopic techniques are minimally invasive and are the first choice if local expertise with EBUS/EUS needle aspiration is available. Due to its higher NPV, in case of PET positive or CT enlarged mediastinal LN’s, video-assisted mediastinoscopy (VAM) with nodal dissection or biopsy remain indicated when endoscopic staging is negative. Nodal dissection has an increased accuracy over biopsy.

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**Table 1: Level of evidence and grading of recommendation**

- **I** Evidence from at least one large randomized control trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
- **II** Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
- **III** Prospective cohort studies
- **IV** Retrospective cohort studies or case-control studies
- **V** Studies without control group, case reports, experts opinions

- **A** Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
- **B** Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
- **C** Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantage
- **D** Strong evidence against efficacy or benefit, not recommended
- **E** Strong evidence against efficacy or benefit, never recommended

Evidence from at least one large randomized control trial of good methodological quality (low potential for bias) or meta-analysis of well-conducted randomized trials without heterogeneity.
### Table 2: Published meta-analyses on endobronchial and oesophageal endosonography with fine needle aspiration for mediastinal nodal staging of lung cancer.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Modality</th>
<th>Pts (N)</th>
<th>Pooled Sens % (95%CI)</th>
<th>Pooled Spec % (95%CI)</th>
<th>NLR</th>
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<tr>
<td>Micames, et al.</td>
<td>2007</td>
<td>EUS</td>
<td>1201</td>
<td>83 (78-87)</td>
<td>97 (96-98)</td>
<td>-</td>
</tr>
<tr>
<td>Gu, et al.</td>
<td>2009</td>
<td>EBUS</td>
<td>1298</td>
<td>93 (91-94)</td>
<td>100 (99-100)</td>
<td>-</td>
</tr>
<tr>
<td>Adams, et al.</td>
<td>2009</td>
<td>EBUS</td>
<td>817</td>
<td>88 (79-94)</td>
<td>100 (92-100)</td>
<td>0.12</td>
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<tr>
<td>Chandra, et al.</td>
<td>2012</td>
<td>EBUS</td>
<td>1658*</td>
<td>92 (90-93)</td>
<td>100 (97-100)</td>
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<tr>
<td>Zhang, et al.</td>
<td>2013</td>
<td>EUS+EBUS</td>
<td>823</td>
<td>86 (82-90)</td>
<td>100 (99-100)</td>
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</table>

N, number; EUS, esophageal endosonography; EBUS, endobronchial endosonography
Pts, patients; Sens, sensitivity; Spec, specificity; NLR, negative likelihood ratio.

* some small series also included sarcoidosis

### Table 3: Staging values of conventional mediastinoscopy and videomediastinoscopy

<table>
<thead>
<tr>
<th>Author and Reference</th>
<th>Type of mediastinoscopy</th>
<th>N</th>
<th>Sensitivity</th>
<th>NPV</th>
<th>Diagnostic Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rami-Porta &amp; Mateu-Navarro, 2002</td>
<td>CM</td>
<td>148</td>
<td>0.78</td>
<td>0.85</td>
<td>0.90</td>
</tr>
<tr>
<td>Venissac et al, 2003</td>
<td>VAM</td>
<td>137</td>
<td>0.86</td>
<td>0.90</td>
<td>0.94</td>
</tr>
<tr>
<td>Lardinois et al, 2003</td>
<td>VAM</td>
<td>240</td>
<td>0.91</td>
<td>NA</td>
<td>0.98</td>
</tr>
<tr>
<td>Leschber et al, 2008</td>
<td>VAM</td>
<td>195</td>
<td>0.87</td>
<td>NA</td>
<td>0.95</td>
</tr>
<tr>
<td>Karfis et al, 2008</td>
<td>CM</td>
<td>24</td>
<td>NA</td>
<td>0.81</td>
<td>0.84</td>
</tr>
<tr>
<td>Anraku et al, 2010</td>
<td>CM</td>
<td>119</td>
<td>NA</td>
<td>0.83</td>
<td>0.88</td>
</tr>
<tr>
<td>Cho et al, 2011</td>
<td>VAM</td>
<td>140</td>
<td>0.95</td>
<td>0.98</td>
<td>0.98</td>
</tr>
</tbody>
</table>

Abbreviations: CM: conventional mediastinoscopy, N: number of patients, NA: not available, NPV: negative predictive value, PPV: positive predictive value, VAM: videomediastinoscopy.

Adapted from Rami-Porta et al. Thorac Surgery Clinics 2012;22:177-189
### Table 4: Overall comparison VAM vs. CM

(Studies 1989-2011)

<table>
<thead>
<tr>
<th></th>
<th>VAM (n=956)</th>
<th>CM (n=5156)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Morbidity</td>
<td>0.83-2.9%</td>
<td>0-5.3%</td>
<td>NS</td>
</tr>
<tr>
<td>No of LN biopsied</td>
<td>6-8.5</td>
<td>5-7.13</td>
<td>NS</td>
</tr>
<tr>
<td>No LN stations sampled</td>
<td>1.9-3.6</td>
<td>2.6-2.98</td>
<td>NS</td>
</tr>
<tr>
<td>Accuracy</td>
<td>87.9-98.9%</td>
<td>83.8-97.2%</td>
<td>NS</td>
</tr>
<tr>
<td>NPV</td>
<td>83.0-98.6%</td>
<td>81.0-98.7%</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Abbreviations:** CM: conventional mediastinoscopy, NPV: negative predictive value, VAM: videomediastinoscopy.

Adapted from Zakkaer et al. J Cardiothorac Surg 2012;14:81-84

### Table 5: Results of VAMLA and TEMLA

<table>
<thead>
<tr>
<th>Author</th>
<th>Procedure</th>
<th>N</th>
<th>NPV</th>
<th>Sensitivity</th>
<th>Side effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hürtgen et al 2002</td>
<td>VAMLA</td>
<td>46</td>
<td>100%</td>
<td>100%</td>
<td>Recurrent laryngeal nerve palsy 2.2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Scarring with impact on subsequent resection : 25%</td>
</tr>
<tr>
<td>Leschber et al 2003</td>
<td>VAMLA</td>
<td>23</td>
<td>100%</td>
<td>100%</td>
<td>Blood loss &gt; 100 ml : 12%</td>
</tr>
<tr>
<td>Witte et al 2006</td>
<td>VAMLA</td>
<td>144</td>
<td>NA</td>
<td>100%</td>
<td>Recurrent laryngeal nerve palsy : 3.4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Vascular lesions : 2.1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mediastinitis : 0.7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Marked scarring : 19%</td>
</tr>
<tr>
<td>Zielinski et al 2013</td>
<td>TEMLA</td>
<td>256</td>
<td>97.4%</td>
<td>94%</td>
<td>Mortality : 0.3%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Recurrent laryngeal nerve palsy : 2.5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pneumothorax : 0.7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pleural effusion : 1.1%</td>
</tr>
<tr>
<td>Yoo et al 2011</td>
<td>VAMLA</td>
<td>108</td>
<td>NA</td>
<td>NA</td>
<td>Recurrent laryngeal nerve palsy : 3.4%</td>
</tr>
</tbody>
</table>

**Abbreviations:** VAMLA: video-assisted lymphadenectomy, TEMLA: transcervical extended mediastinal lymphadenectomy, NPV: negative predictive value, N: number of patients.
### Table 6A. Restaging with EUS and EBUS after induction therapy

<table>
<thead>
<tr>
<th>Technique</th>
<th>Author, year</th>
<th>n</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBUS</td>
<td>Krasnik, 2006</td>
<td>83</td>
<td>0.70</td>
<td>1.0</td>
<td>0.75</td>
</tr>
<tr>
<td>EBUS</td>
<td>Herth, 2008</td>
<td>124</td>
<td>0.76*</td>
<td>1.0</td>
<td>0.77</td>
</tr>
<tr>
<td>EUS</td>
<td>Stigt, 2009</td>
<td>25</td>
<td>0.92</td>
<td>1.0</td>
<td>0.92</td>
</tr>
<tr>
<td>EBUS</td>
<td>Szubowski, 2010</td>
<td>61</td>
<td>0.67</td>
<td>0.86</td>
<td>0.80</td>
</tr>
<tr>
<td>EUS</td>
<td>von Bartheld, 2011</td>
<td>58</td>
<td>0.44</td>
<td>NR</td>
<td>0.60</td>
</tr>
</tbody>
</table>

EUS: endoscopic (esophageal) ultrasound; EBUS: endobronchial ultrasound; n: number of patients; NR: not reported

* negative predictive value was only 20%

### Table 6B. Restaging with repeat mediastinoscopy after induction therapy

<table>
<thead>
<tr>
<th>Author, year</th>
<th>n</th>
<th>IT</th>
<th>Morbidity</th>
<th>Mortality</th>
<th>Sensitivity</th>
<th>Negative predictive value</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stamatis, 2005</td>
<td>165</td>
<td>CT-RT</td>
<td>2.5</td>
<td>0</td>
<td>0.74</td>
<td>0.86</td>
<td>0.93</td>
</tr>
<tr>
<td>De Leyn, 2006</td>
<td>30</td>
<td>CT</td>
<td>0</td>
<td>0</td>
<td>0.29</td>
<td>0.52</td>
<td>0.60</td>
</tr>
</tbody>
</table>

*combined, updated series  ** results of restaging after induction therapy

n: number of patients; IT: induction therapy; CT: chemotherapy; CT-RT: chemoradiotherapy