



# Controversies in Mediastinal Staging for Nonsmall Cell Lung Cancer

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## Abstract

Mediastinal lymph nodal involvement in nonsmall cell lung cancer plays a crucial role in deciding treatment strategy. Survival falls markedly with increasing involvement of mediastinal nodal stations. Hence, accurate staging of the mediastinum with lowest morbidity is of utmost importance. A wide array of invasive and noninvasive modalities that complement each other in assessing the nodes are available at our disposal. Guidelines recommend noninvasive imaging as the initial step in the staging algorithm for all tumors, followed by invasive staging. No single modality has proven to be the ideal method to stage the mediastinum when used alone. In the present decade, minimally invasive endobronchial ultrasound (EBUS) has challenged the position of surgical mediastinoscopy, which has been the gold standard, historically. However, a negative EBUS needs to be confirmed by surgical mediastinoscopy. Video-assisted mediastinoscopic lymphadenectomy has also come to the forefront in last two decades and has shown exceptional results, when performed in experienced centers. This review details the various modalities of mediastinal staging and the controversies surrounding the optimal method of staging, restaging after neoadjuvant therapy, and the most cost-effective strategy.

## Keywords

- ▶ mediastinal staging
- ▶ endobronchial ultrasound
- ▶ mediastinoscopy
- ▶ VAMLA
- ▶ nonsmall cell lung cancer

## Introduction

Lung cancer has emerged to be the most common cancer worldwide and also the leading cause of cancer death.<sup>1</sup> In India, it accounts for 6% of all cancers and is the fourth common cancer. Nonsmall cell lung carcinoma (NSCLC), being the commoner variety, carries a modest prognosis. Though most patients present in an advanced stage, 25% can be treated

radically.<sup>2</sup> In patients with nonmetastatic NSCLC, mediastinal lymph nodal involvement plays a crucial role in deciding treatment strategy (– **Table 1**). In patients with a resectable primary, ipsilateral hilar nodal disease (N1) is managed with surgical resection followed by adjuvant therapy. However, ipsilateral (N2) and contralateral mediastinal (N3) lymph nodal metastases are usually managed with a multimodal approach. Survival drops progressively with increasing

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**Table 1** Mediastinal nodal stations for lung cancer staging

Nodal stations	Location of the nodes
1	Highest mediastinal
2 R	Right upper paratracheal (above the level of brachiocephalic vein)
2L	Left upper paratracheal (above the level of arch of aorta)
3a	Prevascular
3p	Retrotracheal
4 R	Right lower paratracheal (up to left lateral border of trachea)
4L	Left lower paratracheal
5	Subaortic (aortopulmonary window)
6	Para-aortic
7	Subcarinal
8	Paraoesophageal
9	Inferior pulmonary ligament
<b>N 1 nodes</b>	
10	Hilar
11	Interlobar
12	Lobar
13	Segmental
14	Subsegmental

involvement of nodal stations (75% in N0 vs. 51% in N1 vs. 38% in N2 disease).<sup>3,4</sup> Hence, it becomes essential to accurately stage the mediastinum as the treatment strategy and survival differs markedly. The aim of mediastinal staging should be to exclude with the highest reliability and the lowest morbidity in the presence of malignant mediastinal nodes. An array of modalities, both invasive and noninvasive, have been used to assess the mediastinal nodes.<sup>5</sup> Although endoscopic techniques were established more than a decade ago, there is general consensus that these modalities should complement other invasive modalities. Noninvasive imaging forms the first step in the diagnostic algorithm followed by invasive staging. There is still no consensus on few issues that remain unsolved:

- Whether invasive (endoscopic/ mediastinoscopic) staging can be completely avoided in certain clinical situations
- The most cost-effective staging strategy
- Staging of the left mediastinum and
- Whether restaging is essential after neoadjuvant therapy.

This review focuses on the various modalities of mediastinal staging and the controversies surrounding the choice of the optimal method.

## Noninvasive Mediastinal Staging

### Imaging

The initial step in the diagnostic evaluation of lung cancer comprises contrast enhanced computed tomography (CT) of

the chest. It is essential to obtain information about the primary lesion, morphology, and location of mediastinal nodes and intrathoracic metastases. A short axis nodal diameter of  $\geq 1$  cm on a transverse CT scan is the commonly used criteria for detecting suspicious/malignant mediastinal nodes. Central necrosis, capsular disruption, round shape, loss of fatty hilum, and heterogenous density are the other morphological criteria that indicate malignancy in the nodes.<sup>5</sup> The median sensitivity and specificity of CT scans to detect metastatic mediastinal nodes are in the range of 55 and 80%, respectively.<sup>5,6</sup> CT scanning is not conclusive in excluding mediastinal metastases and this makes it insufficient as a single modality to stage the mediastinum in NSCLC.

Positron emission tomography (PET) is based on the principle of cancer cells having increased rate of glucose metabolism compared with normal cells, and it assesses the functional and metabolic status of the tissue rather than the anatomy. There are no standardized criteria for abnormal fluorodeoxyglucose (FDG) uptake in the mediastinum; however,  $>2.5$  maximum standardized uptake value ( $SUV_{max}$ ) is considered as a threshold for suspecting malignancy.<sup>7</sup> Studies have shown PET to be more accurate than CT in staging the mediastinum with higher sensitivity (80%) and specificity (88%) to detect mediastinal nodal metastases.<sup>5,7</sup> In clinical stage IA NSCLC, some argue that PET is not essential as there is a low chance (4%) of metastatic disease,<sup>8</sup> while others reckon PET reduces futile surgeries.<sup>9</sup> But, a major drawback of PET alone is its poor anatomical resolution that is overcome by integrating PET and CT scanning. This dual modality PET-CT is shown to have better specificity (90%) and high negative predictive value (NPV)<sup>7</sup> making it the investigation of choice in noninvasive lung cancer staging.

PET-CT alone is still suboptimal for mediastinal staging as it has a false-positive rate of 15 to 20% and false-negative rate of 20%, necessitating further investigation with an invasive biopsy. Inflammatory nodes, granulomas, and tuberculosis account for the false-positive cases, particularly in endemic countries like India, where the false-positive rate can go up to 65%.<sup>10</sup> Low-grade tumors like adenocarcinoma in situ are responsible for the false-negative results on PET-CT.<sup>11,12</sup> Thus, after the initial staging PET-CT, findings need to be confirmed with cytological or histological proof of the mediastinal nodes. Some authors believe PET-CT is sufficient and can obviate the need for biopsy. A meta-analysis concluded that further invasive mediastinal staging can be omitted only for peripheral tumors  $\leq 3$  cm, without suspicious hilar or mediastinal nodes on PET.<sup>13</sup> This is supported by various studies, which have shown that the NPV of PET-CT is significantly better for tumors  $\leq 3$  cm (94 vs. 89%)<sup>13,14</sup>; and adenocarcinoma with high FDG uptake has a higher propensity for nodal metastases.<sup>15</sup> Another study reported that in patients with negative nodes on PET, central tumors had higher prevalence (21.6%) of mediastinal nodal involvement when compared with peripherally located tumors (2.9%).<sup>16</sup> A Japanese study showed higher involvement (53%) of N2/N3 mediastinal nodes when there were clinically suspicious hilar nodes (N1).<sup>17</sup> With this evidence, the European Society

of Thoracic Surgeons<sup>18</sup> recommends invasive mediastinal staging for all tumors except in:

1. Peripherally located tumors
2. Tumor size < 3 cm
3. No enlarged/suspicious N1 nodes on PET-CT.

Magnetic resonance imaging (MRI) may be superior to CT scan<sup>19</sup> in delineating the tumor invasion of the surrounding structures like mediastinum, diaphragm, and bones, but its role in staging the mediastinum is not proven. Diffusion-weighted MRI improves the accuracy, with a meta-analysis showing a pooled sensitivity of 95% when compared with PET-CT (89%) in assessing mediastinal nodes.<sup>20</sup> However, as the data are still limited, MRI is not routinely used in staging the mediastinum in NSCLC.

### Invasive Mediastinal Staging

Most thoracic consensus guidelines recommend minimally invasive (endoscopic) or invasive (mediastinoscopic) evaluation of mediastinal nodes either prior or at the time of definitive lung resection. The selection of the modality depends on various criteria like size and location of the nodes, available expertise, accuracy, potential risks, and patient preferences. Surgical staging by mediastinoscopy has been the gold standard for close to six decades, but it is now being either replaced or complemented by endoscopic methods and ultrasound-guided fine-needle aspiration (EBUS-FNA).

### Endosonographic Staging

Endobronchial ultrasound (EBUS) utilizes an ultrasound probe incorporated into the distal end of a specialized bronchoscope to get real-time images of the targets to sample. There are two types of EBUS probes: linear and radial. Linear EBUS is useful to approach the mediastinal nodes and central tumors, whereas radial EBUS is suitable for parenchymal lesions in subsegmental level. The advantage of ultrasound-guidance in EBUS lies in its ability to localize suspicious nodes in the mediastinum particularly in paratracheal (stations 2R/2L, 4R/4L), subcarinal (station 7), and hilar regions (stations 10, 11). However, EBUS lacks access to prevascular (station 3a), paraaortic (stations 5, 6), paraesophageal (station 8), and pulmonary ligament nodes (station 9).<sup>21</sup> A systematic nodal sampling of nodes measuring >5 mm on ultrasonography or PET positive nodes is feasible with EBUS.<sup>22</sup> The optimal number of aspirations from each station is three and the order of sampling starts from N3 followed by N2 and ends with N1 nodes (if necessary) to avoid contamination from a single needle.<sup>22,23</sup> EBUS is performed either as a day-care procedure with local anesthesia and moderate sedation or under general anesthesia. The morbidity associated is minimal in experienced centers with incidence <1%, and it rarely causes pneumothorax or mediastinitis.<sup>24</sup>

Endoscopic ultrasound (EUS), on the other hand, approaches the mediastinal nodes through the esophagus using an endoscope. This particularly helps in visualizing paraesophageal (station 8), pulmonary ligament (station 9),

subcarinal (station 7), and left paratracheal nodes (station 4L). Some centers have used EUS to sample the aortopulmonary window nodes (stations 5, 6); but, as the evidence is still limited, it is not recommended for routine sampling of these stations.<sup>25</sup> The additional benefit of EUS is in its role to evaluate direct tumor invasion of the mediastinum and suspected metastatic disease to adrenal and liver.<sup>26,27</sup> However, as a stand-alone procedure, EUS is not very helpful in staging, as there is no access to the primary tumor, hilar, and right paratracheal nodes. Thus, EUS usually complements other staging modalities of either EBUS or mediastinoscopy. An alternate technique described and practiced in some centers constitutes use of EBUS scope through the esophagus (EUS-B).<sup>28</sup> This provides an added advantage of sampling stations 8 and 9 in a single sedation and reduces the cost of additional equipment with improved sensitivity and NPV when combined with EBUS (EBUS + EUS-B).<sup>29,30</sup>

The overall sensitivity of EBUS has been reported to be 89% (ranging from 46 to 97%) and the NPV, 91%.<sup>5,31</sup> A similar sensitivity of 89% and NPV of 86% has been reported for EUS as well.<sup>5</sup> This wide variation in the sensitivity can be improved by high-volume operator expertise and multiple passes from the node with rapid onsite cytological examination.<sup>32-34</sup> Combining two modalities enhanced the sensitivity further by maximizing the access to the mediastinum. EBUS and EUS together, known as “medical mediastinoscopy” or “combined ultrasound” (CUS), was found to be more sensitive than either EUS or EBUS alone (93 vs. 69%).<sup>35</sup> The sensitivity of CUS, however, depended on the size of the nodes: higher sensitivity for enlarged nodes (93%) when compared with normal-sized nodes (68%).<sup>35,36</sup> On the contrary, a randomized trial on sequencing of the endosonographic methods<sup>37</sup> showed that adding EBUS to EUS increased the accuracy and sensitivity, while the converse i.e., adding EUS to EBUS showed no additional benefit. This study concluded that EBUS alone is a better primary procedure in endosonographic mediastinal staging.<sup>37</sup>

All the modalities are pitted against the original “gold standard” of surgical mediastinoscopy before being recommended for regular practice.

- a. EBUS, though not superior, was shown to have comparable results to surgical mediastinoscopy in several studies.<sup>38-40</sup> The sensitivity (81 vs. 79%), NPV (91 vs. 90%) and accuracy (93% vs 93%) were similar for both procedures.<sup>39</sup> Most of these studies with high NPV and accuracy have been performed in high volume institutions with high volume endoscopists, in which most of them are surgeons. Also most of the earlier studies with impressive results were performed not for staging mediastinal nodes, but to confirm the histology of enlarged nodes seen on prior imaging.
- b. The Assessment of Surgical sTaging vs Endoscopic Ultrasound in Lung Cancer trial<sup>41</sup> compared EBUS+EUS followed by mediastinoscopy to mediastinoscopy alone. There was no difference in sensitivity between mediastinoscopy (79%) and EBUS+EUS alone (85%); however, there was a significant improvement to 94% when EBUS+EUS

was followed by mediastinoscopy. The rate of futile thoracotomies was also less with EBUS+EUS (7%) than with mediastinoscopy (18%). This study suggested that the baseline endosonographic staging (combined EBUS and EUS) should be subsequently followed by surgical staging, when endoscopic sampling is negative.

This controversy remains unsettled: three meta-analyses<sup>42–44</sup> have reported that the likelihood of mediastinal nodal involvement after negative EBUS±EUS sampling is 13–15%, which cannot be ignored and needs additional surgical staging. On the other hand, some studies have shown that mediastinoscopy did not increase the sensitivity after a well-performed EBUS+EUS sampling of at least three nodal stations in patients with <35% prevalence of mediastinal disease.<sup>39</sup> A recent meta-analysis<sup>45</sup> also showed that unforeseen N2 rates after negative endosonography were similar with or without confirmatory mediastinoscopy. An ongoing multicenter trial, MEDIASTinal, probably will be able to shed more light on scenarios when mediastinoscopy can be omitted in negative endosonography patients.<sup>46</sup> However, current guidelines (as well as our routine practice) still recommend preoperative surgical staging in patients with negative endosonography.<sup>5,18</sup>

### Surgical Staging

Cervical mediastinoscopy was introduced in 1959 and historically, it has been considered as the gold standard for invasive mediastinal staging in NSCLC. It is performed under general anesthesia through a pretracheal suprasternal incision. There is easy access to ipsilateral and contralateral mediastinal nodes: paratracheal (stations 2R/2L, 4R/4L), pretracheal (stations 1,3) and subcarinal (station 7) nodes. However, aortopulmonary nodes (stations 5, 6) and inferior mediastinal nodes (stations 8, 9) are not approachable using a standard mediastinoscopy. When compared with EBUS/EUS, the advantages mediastinoscopy has is direct visualization of the nodes to be sampled and acquirement of sufficient material needed for pathological and molecular analysis. Over the last two decades, a paradigm shift has taken place with the introduction of video-mediastinoscopy. It accounts for clearer visualization and simultaneous sharing of the procedure with trainees and other surgeons, thereby helping in education without compromising on safety. The associated morbidity ranges from 1 to 2% and includes recurrent laryngeal nerve injury, and rarely, vascular injury, pneumothorax, or tracheal laceration.<sup>47</sup>

A systematic review reported the overall sensitivity of cervical mediastinoscopy to be 78% and NPV of 91%.<sup>5</sup> The false-negative cases were mostly due to the inaccessibility of certain nodal stations or due to limited sampling. With the introduction of video-mediastinoscopy, there was a rise in the number of nodes sampled, but no difference was noted in sensitivity, accuracy, or NPV, on comparing with standard mediastinoscopy.<sup>44,48,49</sup> Systematic mediastinal sampling, involving at least one node from each accessible nodal station (ideally up to five stations—2R, 2L, 4R, 4L, 7), is recommended.<sup>5</sup> An alternate approach of selective sampling is

practiced in some centers, where only the suspicious mediastinal nodes are biopsied. However, the debate on systematic versus selective nodal sampling continues as the importance of thoroughness of dissection has not clearly been established.<sup>5,50</sup>

Another area of controversy revolves around systematic complete nodal dissection versus sampling. Surgeons favoring systematic mediastinal lymph-node dissection (SMLND) believe it ensures more accurate, complete nodal staging and eliminates undetected micrometastases. Arguments against nodal dissection are increased complications, increased surgical time, and no level 1 evidence of superior survival over sampling. Hence, for mediastinal staging, either systematic nodal sampling or dissection is considered as adequate.<sup>51</sup> However, for surgical resection, most studies favor SMLND.<sup>52</sup>

Video-assisted thoracoscopic surgery (VATS) is used in mediastinal staging particularly to access aortopulmonary and paraaortic nodes (stations 5, 6) or when alternative options are nondiagnostic. The advantage of VATS is the simultaneous access to the primary tumor as well as the mediastinum and direct visualization. It requires general anesthesia with one lung ventilation making it more invasive than mediastinoscopy. The other limitation is that VATS provides access only to ipsilateral mediastinal nodes. Studies have shown a widely varied sensitivity ranging from 50 to 100% with a median at 99% and NPV of 96%.<sup>5,53,54</sup> The complication rate was low at 2% with no mortality. VATS has also been useful in the evaluation of T stage and pleural involvement. However, its role has been restricted to sampling of station 5 and 6 nodes, when enlarged or suspicious on PET-CT.

Anterior mediastinotomy (Chamberlain procedure) is an alternative option to approach the aortopulmonary nodes (stations 5, 6) in left-sided lung tumors. The procedure requires general anesthesia and involves incision over the second or third intercostal space with occasional partial resection of the costal cartilage in the left parasternal region. As the regular methods of invasive staging (EBUS/EUS, mediastinoscopy) find it difficult to access stations 5 and 6, Chamberlain procedure is one of the only few options available, though the data on its accuracy is limited. Nonetheless, a systematic review reported median sensitivity of 71% for station 5 and 6 nodes and NPV of 91%.<sup>5,55</sup>

Extended cervical mediastinoscopy or “super mediastinoscopy” is an augmentation of the standard mediastinoscopy to access the additional nodes of station 5 and 6. The mediastinoscope is inserted through a suprasternal incision and directed laterally toward the aortic arch. Integration of standard mediastinoscopy with the extended mediastinoscopy showed a median sensitivity of 71% and NPV of 91% for the assessment of aortopulmonary nodes.<sup>5</sup> Smaller case series has shown that selective use of extended mediastinoscopy only in patients with suspicious nodes has better sensitivity than routine use.<sup>56</sup> This procedure is performed only in experienced centers and has not gained popularity due to its technical difficulty and potential operative morbidity.

Video-assisted mediastinoscopic lymphadenectomy (VAMLA) has come to the forefront in the last two decades.

It involves radical dissection and removal of all accessible mediastinal nodes along with its surrounding tissue to improve the staging accuracy. It is performed using a video-mediastinoscope and the nodal stations sampled are similar to standard cervical mediastinoscopy. Studies have shown 100% sensitivity and NPV with VAMLA<sup>57,58</sup> and it was also reported to be superior to standard mediastinoscopy (94 vs. 64% sensitivity).<sup>59</sup> A recent multicenter study in clinical N1 patients also has proved the role of VAMLA to detect N2 disease with an accuracy of 93%.<sup>60</sup> However, high rates of morbidity associated with VAMLA, mainly recurrent laryngeal nerve injury (2–5%) and scarring affecting subsequent resection,<sup>53,57</sup> have reserved the procedure to be performed in high-volume experienced centers only. It is gaining popularity in mediastinal staging, but needs further validating studies.

Transcervical extended mediastinoscopic lymphadenectomy (TEMLA) is another radical invasive technique that uses a 5 to 8 cm cervical incision and sternal elevation to access prevascular (station 3), aortopulmonary (stations 5, 6), and paraesophageal nodal stations. It is an open procedure assisted by a video-mediastinoscope or thoracoscope. It differs from extended mediastinoscopy in being more invasive (as it requires sternal elevation and retraction) and having better diagnostic nodal yield (with additional access to station 3 and higher number of nodes retrieved).<sup>61</sup>

All the data regarding TEMLA has been published from a single center, which reports a sensitivity of 94% and NPV of 98%.<sup>61</sup> However, there are concerns regarding high rates of morbidity and mortality associated with TEMLA and its technical complexity.<sup>62</sup> As the available data are limited, TEMLA is not routinely recommended for use in mediastinal staging.

### Mediastinal Restaging after Induction Therapy

In stage IIIA–N2 NSCLC patients treated with induction therapy, mediastinal down-staging plays an important role to determine prognosis and survival. Persistent N2 disease has worse prognosis compared with induction therapy responders. The topic of mediastinal restaging is highly debated as not all surgeons believe that it is mandatory to restage the mediastinum after induction therapy; while others are of the opinion that persistent N2 disease precludes surgical resection, thus making mediastinal restaging necessary.

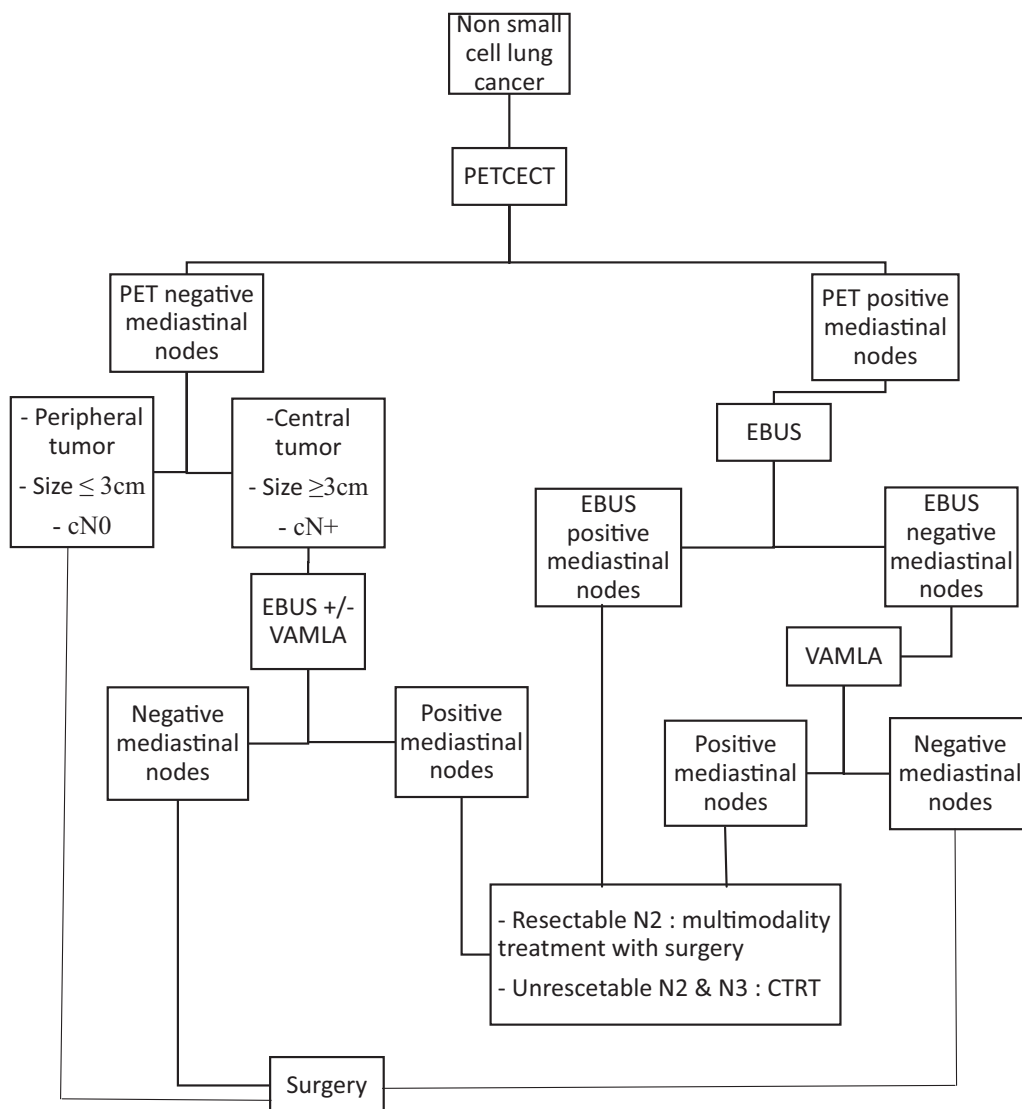
European guidelines<sup>18</sup> advise the need for mediastinal restaging and same techniques used for primary staging are employed. However, the optimal method for restaging still needs further study. Noninvasive imaging has a low accuracy and less reliability after induction therapy. PET-CT, though more accurate than CT alone for restaging, has a false-negative rate of 25% and false-positive rate of 20%.<sup>63</sup> EBUS has shown a wide variation in sensitivity (67–76%) and NPV (20–78%) for restaging.<sup>36,64</sup> Similarly, EUS also has a wide range of sensitivity (44–92%).<sup>24,65</sup> The low NPV values may be explained by high prevalence of persistent

N2 disease in those studies. Confirmation of negative EBUS with surgical mediastinoscopy after induction therapy is still debated.

Remediastinoscopy has proven to be feasible after induction therapy, but it is technically difficult due to extensive fibrosis and adhesions from previous exploration, leading to low accuracy. Morbidity (0–4%) and mortality rates (1%) have also been reported to be high.<sup>66</sup> Hence, an alternate approach has been proposed: initial mediastinal staging by endosonography only and mediastinoscopy to be reserved for restaging after induction therapy. This approach allows first safer mediastinoscopy after induction therapy and has reported an NPV of 90%.<sup>67</sup> In experienced centers, TEMLA has also been reported to accurately restage the mediastinum.<sup>61,68</sup> A retrospective analysis has found very high sensitivity (97%) and NPV (99%) with EBUS/EUS + TEMLA performed for restaging.<sup>61</sup> However, as the data are limited, TEMLA is still not recommended. While there is no consensus yet on the need for invasive restaging and the optimal method to restage after induction therapy, very few centers in the world practice it.

### Cost-Effectiveness of Mediastinal Staging

Accuracy of a staging modality is critical for optimal diagnosis of mediastinal nodal involvement. However, for widespread implementation, cost-effectiveness of the investigation should be modest. Several studies over the past decade have analyzed the cost-effectiveness and cost-benefit. A Canadian study<sup>69</sup> reported an incremental cost-effectiveness ratio of \$26,000/QALY (quality-adjusted life-year) for EBUS and approximately \$1,400,000/QALY for EBUS followed by mediastinoscopy. They concluded that adding mediastinoscopy to EBUS negative patients becomes cost-effective (Institute for Clinical and Economic Review ~ \$79,000/QALY) only in moderate-to-high probability of mediastinal nodal involvement. In contrast, an Australian study<sup>70</sup> inferred that EBUS followed by surgical confirmation was the most cost-beneficial approach (AU\$2961) in comparison with EBUS alone (\$3344) or mediastinoscopy alone (\$8859). A recent systematic review<sup>71</sup> suggests that EBUS is cost-effective compared with mediastinoscopy. However, these studies have also noted that EBUS performed in an operation theater under general anesthesia is not cost-effective. EBUS in an endoscopy room under sedation is preferred from health economics perspective and if this is unavailable, the more cost-effective strategy is to offer mediastinoscopy. These cost-effectiveness studies are, however, context specific to the health-care system and may not be applicable across different systems. There are no formal cost-effectiveness studies in the Indian scenario; however, with few trained experts and experienced centers for both EBUS and mediastinoscopy, the cost-effective method would probably be video-mediastinoscopy followed by surgical resection on the same day under a single anesthesia. However, if the probability of mediastinal nodal disease is high and facilities to perform EBUS as a day-care procedure is available, endosonographic method should be considered.



**Fig. 1** Mediastinal staging algorithm followed at our institute. Chemotherapy + Radiotherapy; EBUS, endobronchial ultrasound; PET-CECT, positron emission tomography with contrast-enhanced computed tomography; VAMLA, video-assisted mediastinoscopic lymphadenectomy.

## Our Protocol

In our institute, the protocol followed is shown in ►**Fig. 1**. PET-CECT is the initial staging modality. Further invasive mediastinal staging is with EBUS-guided systematic nodal sampling in all except peripherally located < 3 cm tumors with no nodal disease on PET. If EBUS is negative, surgical video-mediastinoscopy is performed prior to lung resection. In cases of restaging the mediastinum after induction therapy, either CT or PET-CT is performed for reassessment. Invasive mediastinal restaging is not practiced at our institute as we do not change the treatment decision based on the postinduction therapy mediastinal nodal status.

## Summary

Mediastinal staging plays a crucial role in the management of NSCLC. An array of modalities, which complement each

other, are available at our disposal to stage the mediastinum (►**Table 2**).

To summarize, the main controversies in mediastinal staging are as follows:

- Is PET-CT sufficient for mediastinal staging without histological confirmation?  
PET-CT is sufficient and invasive mediastinal staging can be omitted only in peripheral tumors <3 cm in size and with no enlarged/suspicious hilar or mediastinal nodes; all other patients planned for surgical resection should have invasive mediastinal staging.
- Is cervical mediastinoscopy still considered as the “gold standard”?

EBUS is challenging the position of mediastinoscopy as the gold standard. Whenever the expertise is available, EBUS/ EUS should be considered as the first invasive modality to sample the mediastinal nodes;

**Table 2** Various modalities of mediastinal staging

Mediastinal staging modality	Accessible lymph node stations	Sensitivity (%)	Specificity (%)	NPV (%)
<b>Noninvasive</b>				
CT <sup>5,6</sup>		55	80	83
PET-CT <sup>5,7</sup>		80	90	90
<b>Minimally invasive</b>				
EBUS <sup>5,31,38</sup>	1, 2, 3p, 4, 7, 10, 11	89	100	91
EUS <sup>5</sup>	4L, 5, 6, 7, 8, 9	89	100	86
EBUS + EUS <sup>5,35</sup>	2,4, 7, 8,9, 10, 11	93	100	96
<b>Invasive</b>				
Cervical mediastinoscopy <sup>5,48,49</sup>	1,2,4,7,10	78	100	91
Extended cervical mediastinoscopy <sup>5</sup>	1,2,3,4,5,6,7	71	100	91
VAMLA <sup>57-59</sup>	1,2,3,4,7	94	100	100
TEMLA <sup>61,62</sup>	3, 5, 6	94	100	98
VATS <sup>5,53,54</sup>	Ipsilateral 2,3, 4, 5,6, 7, 8,9, 10	99	100	96
Anterior mediastinotomy <sup>5,55</sup>	5,6	71	100	91

Abbreviations: CT, computed tomography; EBUS, endobronchial ultrasound; EUS, endoscopic ultrasound; NPV, negative predictive value; PET-CT, positron emission tomography-computed tomography; TEMLA, transcervical extended mediastinoscopic lymphadenectomy; VAMLA, video-assisted mediastinoscopic lymphadenectomy; VATS, video-assisted thoracoscopic surgery.

mediastinoscopy should be done if the EBUS is negative.

- c. If EBUS/EUS is negative, further confirmation with mediastinoscopy is needed?

With the available data, guidelines propose that negative endosonography should be confirmed by surgical mediastinoscopic staging.

- d. Systematic mediastinal sampling versus selective mediastinal sampling using EBUS?

Still debatable. However, wherever feasible, systematic nodal sampling is to be considered.

- e. Systematic nodal dissection versus nodal sampling using mediastinoscopy?

Still debatable. Either systematic nodal dissection or sampling is to be considered.

- f. Should we restage the mediastinum invasively after induction therapy? If yes, how?

This controversy remains unresolved. While European guidelines advise invasive restaging of the mediastinum after induction therapy, very few centres perform restaging not only due to the complex and inaccurate nature of the procedure, but also in light of the updated OS results of PACIFIC, which has shown that a nonoperative management is feasible and can lead to equivalent outcomes.

In conclusion, no single modality has proven to be the ideal method to stage the mediastinum when used in isolation. Recommended guidelines should be followed to formulate individual institution policies based on available infrastructure and expertise and results need to be audited to optimize staging.

#### Conflict of Interest

Nil.

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