Review Article



# Cervical mediastinoscopy and video-assisted mediastinoscopic lymphadenectomy for the staging of non-small cell lung cancer

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**Abstract:** The staging of mediastinal lymph nodes is essential for planning the most adequate treatment for patients with non-small cell lung cancer (NSCLC). For this reason, the current American and European guidelines recommend obtaining tissue confirmation of any mediastinal abnormality seen on chest computed tomography (CT) and positron emission tomography (PET). This can be done by endoscopic techniques, such as endobronchial ultrasonographic fine-needle aspiration (EBUS-FNA), esophageal ultrasonographic FNA (EUS-FNA), or a combination of the two (CUS). Traditionally, surgical methods have been reserved to validate the negative results of minimally invasive endoscopic techniques. However, based on the latest evidence, cervical mediastinoscopy and video-assisted mediastinoscopic lymphadenectomy (VAMLA) have demonstrated their superiority over minimally invasive methods in terms of performance for those tumors with normal mediastinum [clinical (c) N0-1 by CT and PET]. Therefore, cervical mediastinoscopy and VAMLA should be considered in the staging algorithms of this particular subset of NSCLC, and in the other well-established indications.

**Keywords:** Lung cancer; invasive mediastinal staging; cervical mediastinoscopy; video-assisted mediastinoscopic lymphadenectomy (VAMLA)

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## Introduction

The current international guidelines for preoperative mediastinal nodal staging of non-small cell lung cancer (NSCLC) advocate obtaining the highest certainty level before lung resection to define the prognosis and decide on the most proper treatment in each case (1,2). Consequently, performing an invasive staging of the mediastinum in all cases except in those patients with small (≤3 cm) peripheral tumors with no evidence of nodal involvement on computed tomography (CT) and positron emission tomography (PET) is recommended. Invasive staging can be performed with endoscopic or surgical techniques. When both modalities are available, starting with the less invasive endoscopic techniques, such as endobronchial ultrasonographic fine-needle aspiration (EBUS-FNA), esophageal ultrasonographic FNA (EUS-FNA), or their combination (CUS), is recommended. Cervical Mediastinoscopy or more extensive surgical procedures, such as video-assisted mediastinoscopic lymphadenectomy (VAMLA), are used to validate their negative results. However, based on the latest evidence, surgical methods seem to be more accurate for those tumors with normal mediastinum staged by CT and PET.

This review summarizes the present role and performance of cervical mediastinoscopy and its technical successor, VAMLA, in the staging of NSCLC and their integration in the current preoperative staging algorithms.

**Table 1** Accuracy of conventional mediastinoscopy, videomediastinoscopy, and transcervical lymphadenectomies for mediastinal staging in patients with lung cancer. Table adapted from Call *et al*. (11)

| Technique | N | S (median; range) | VPN (median; range) | LN range |
|---|---|---|---|---|
| CM | 9,267 (1) | 0.78 (0.38–0.92) | 0.91 (0.80–0.97) | 2R, 2L, 4R, 4L, 7, 10R, 10L |
| VAM | 995 (1) | 0.89 (0.78–0.97) | 0.92 (0.91–0.99) | |
| VAMLA | 384 (24-26) | 0.95 (0.88–0.96) | 0.98 (0.94–0.99) | 2R, 2L, 4R, 4L, 7, 10R, 10L |
| TEMLA | 928 (28) | 0.96 | 0.98 | 1, 2R, 2L, 4R, 4L, 7, 8R, 8L, 3a, 3p, 10L, 10R, 5, 6 |

CM, conventional mediastinoscopy; VAM, videomediastinoscopy; VAMLA, video-assisted mediastinoscopic lymphadenectomy; TEMLA, transcervical extended mediastinal lymphadenectomy; S, sensitivity; NPV, negative predictive value; N, number of patients.

## Cervical mediastinoscopy

Carlens' mediastinoscopy, more than half a century after it was first reported (3), remains the gold standard of the exploration of the superior mediastinum. Even in the era of endosonographies with the real-time puncture of peritracheal, peribronchial, and peri-esophageal lymph nodes and masses, cervical mediastinoscopy has preserved its role as a staging procedure of the mediastinum in patients with lung cancer, mesothelioma, and lung metastases (4-9).

### *Range of mediastinal exploration*

Cervical mediastinoscopy explores the whole length of the trachea and the main bronchi. For lung cancer staging, and according to the International Association for the Study of Lung Cancer (IASLC) lymph node map (10), the range of exploration includes all nodal stations from the sternal notch bilaterally to the subcarinal and hilar nodes (*Table 1*).

### *Recommendations for mediastinal surgical staging*

The intensity of this procedure depends on its indications. When cervical mediastinoscopy is indicated to confirm N3 disease, it is not necessary to continue with the exploration when an intraoperative frozen section confirms malignancy. For those cases with low suspicion of mediastinal disease on CT or PET, cervical mediastinoscopy should be systematic and thorough. It is recommended to start by exploring the contralateral paratracheal nodes to rule out or confirm N3 disease, and then to proceed with the subcarinal nodes, and finally the ipsilateral paratracheal nodes (12).

At minimum, the right and left inferior paratracheal lymph nodes and the subcarinal lymph nodes should be explored and biopsied for a clinically acceptable cervical mediastinoscopy (2). Exploration of the subaortic and para-aortic nodal stations is indicated in left lung cancers. This can be done by parasternal mediastinotomy (13,14), extended cervical mediastinoscopy (15-17), or video-assisted thoracoscopic surgery (VATS) (18).

### *Results*

The precision of cervical mediastinoscopy depends on its thoroughness, which is itself based on the number of biopsies performed and the number of nodal stations explored (19). This accounts for the heterogeneous sensitivity and negative predictive values reported: 0.78 to 0.97 for sensitivity, and 0.91 to 0.99 for negative predictive value (1) (*Table 1*). The use of a video-mediastinoscope may increase sensitivity: 0.78 and 0.89 for conventional and video-assisted mediastinoscopies, respectively (20) (*Table 1*).

## Transcervical lymphadenectomies

VAMLA, a totally endoscopic procedure, and transcervical extended mediastinal lymphadenectomy (TEMLA), an open procedure assisted by the video-mediastinoscope and the video-thoracoscope at critical points of the intervention, have emerged from the natural evolution of cervical mediastinoscopy and the improvements of video technology (21-23). The aim of both procedures is to perform a bilateral mediastinal lymphadenectomy (including lymph nodes and surrounding adipose tissue). For this reason, VAMLA and TEMLA, allow the detection of minimal nodal disease that is not identifiable on CT or PET, and thus are the ideal techniques for those tumors without suspicion of N2-3 by CT and PET. Accordingly, the following indications have been described: central tumors, cN1 tumors, left-sided tumors, bilateral synchronous lung cancer, and pre-resectional lymphadenectomy in video-assisted thoracoscopic lobectomy (11).

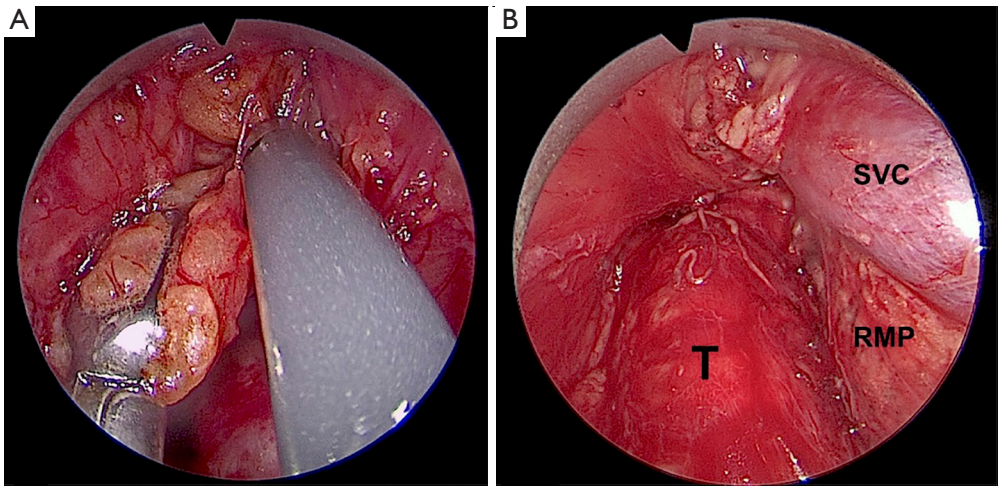


**Figure 1** Endoscopic images of video-assisted mediastinoscopic lymphadenectomy (VAMLA). (A) View of a bimanual dissection of the right paratracheal space; (B) view of the right mediastinal pleura (RMP) and superior vena cava (SVC) after removing the right inferior paratracheal lymph nodes.

### *Range of mediastinal exploration*

For VAMLA, mediastinal exploration ranges bilaterally from the superior paratracheal to the hilar nodes. For TEMLA, it ranges bilaterally from the supraclavicular to the para-esophageal nodes, including the hilar nodes (11) (*Table 1*). For left lung cancers, VAMLA and extended cervical mediastinoscopy are used to explore the subaortic and the para-aortic nodal stations (24-26). Those performing TEMLA include them in the exploration when the cancer is on the left lung (27,28).

### *Results*

Sensitivity and accuracy are high, at 0.88–0.96 and 0.94–0.99, respectively (24-28) (*Table 1*). These results represent the best staging values reported to date for patients without suspicion of N2 by CT and PET. As we have stated previously, the high and homogenous precision reported in all series of transcervical lymphadenectomies for staging NSCLC is due to both techniques allowing the complete removal of the mediastinal nodes and the surrounding adipose tissue, instead of merely taking biopsy samples from the lymph nodes (*Figure 1*).

## Cervical mediastinoscopy and VAMLA for staging NSCLC

### *Locally advanced NSCLC*

The current guidelines suggest starting with an endosonographic method (EBUS-FNA, EUS-FNA, or their combination) (29-31). When these procedures are positive, this information can be enough to start a multidisciplinary treatment protocol. However, their negative results should be validated with a cervical mediastinoscopy because endosonography procedures have a high post-test probability of nodal disease (>0.10) (30-32) (*Table 2*). Although the ideal indication for VAMLA is in tumors with normal mediastinum identified by CT and PET, VAMLA also has been reported to be useful in patients with enlarged lymph nodes in whom frozen sections during cervical mediastinoscopy do not yield a positive result. In these cases, cervical mediastinoscopy can be converted to VAMLA (26) (*Table 2*).

### *Early stage NSCLC*

European guidelines suggest avoiding invasive staging in the following situations: (I) peripheral tumors; (II) tumors ≤3 cm; (III) absence of N2 disease on CT and PET (2), a rate of unsuspected pathologic mediastinal nodal disease <10% (2,41,42). However, early stage NSCLC can have a higher risk of mediastinal involvement (33.8%) when some tumor characteristics [histological type, consolidation/tumor ratio, tumor size, maximum standardized uptake value (SUVmax value)] are combined with other clinical parameters [serum carcinoembriogenic antigen (CEA) level, patient's age] (43,44). For this reason, in these subgroups of patients, invasive mediastinal staging can be useful (33)

**Table 2** Summary of current indications of videomediastinoscopy and transcervical lymphadenectomies for staging NSCLC. Table adapted from Call *et al*. (11)

| Technique | Current ESTS/ACCP guidelines | Additional evidence and comments |
|---|---|---|
| VAM | cN2-3: if endosonography methods are negative (1,2) | cN2-3: Mediastinoscopy can be converted to VAMLA when all frozen sections of mediastinal lymph nodes performed during the procedure fail to provide a positive result |
| | cN0: invasive staging can be omitted (1,2) | Early stage NSCLC (cN0): Some subgroups of patients with an increased risk of N2 (histological type, tumor size, SUVmax, CEA level, patient's age) may benefit from invasive staging (33) |
| | cN1, central tumors & tumors >3 cm: ACCP, EBUS/EUS over surgical methods as first test (1); ESTS, The election of the invasive method depends on local expertise (2) | cN1 tumors: Based on the latest evidence, surgical methods should be the staging method of election (26,34,35) |
| VAMLA & TEMLA | ESTS: their use is limited to clinical studies (2) | Based on latest studies (26,28,36,37), these procedures have been demonstrated to be feasible and safe, and represent the best staging methods in terms of accuracy, especially for those tumors classified cN0-1 by PET-CT |
| | | Both methods are also used as a preresectional lymphadenectomy in VATS lobectomy (21,38-40) |

VAM, videomediastinoscopy; VAMLA, video-assisted mediastinoscopic lymphadenectomy; TEMLA, transcervical extended mediastinal lymphadenectomy. NSCLC, non-small cell lung cancer; PET-CT, positron emission tomography-computed tomography.

(*Table 2*). In early stage NSCLC, endosonographic methods have low sensitivity (0.17–0.41) (45-50), while in cervical mediastinoscopy, the sensitivity and negative predictive value is investigator dependent, accounting for the reported heterogeneity of 0.32 to 0.97, and 0.8 to 0.99, respectively (1,46). Transcervical lymphadenectomies, in patients without suspicion of mediastinal nodal disease by PET-CT, provide the highest clinical staging certainty, with sensitivity and negative predictive values of 0.88–0.96 and 0.94–0.99, respectively (24-28) (*Table 2*).

A special clinical setting of this subgroup of tumors is left lung cancer. Left lung cancers tend to spread by a lymphatic route to the right paratracheal nodal stations. If these nodal stations are not explored preoperatively, they cannot be explored from the left side by thoracotomy or by VATS with the same thoroughness as they can be explored from the right side, and they will remain unexplored. If they harbor lymph node metastases, the N3 status will be unknown, postoperative prognosis will be inaccurate, and no adjuvant treatment will be indicated. In addition, the left paratracheal nodal stations cannot be thoroughly explored from the left side unless the aortic arch is mobilized, which is a procedures that is not routinely done. Dissection of the left inferior paratracheal lymph nodes has a survival benefit and, therefore, they should not be neglected (47). From the technical point of view, these lymph nodes are more easily explored or removed by cervical mediastinoscopy or VAMLA, respectively, than by dissection from the left side by thoracotomy or VATS.

### *Intermediate suspicion of N2-3 disease*

Tumors considered with an intermediate suspicion of N2-3 disease are the following: central tumors, cN1 tumors, and cN0 tumor size greater than 3 cm (1). The rate of unsuspected N2 disease for central or cN1 tumors ranges from 20% to 42% (26,34-36,51,52). Therefore, staging guidelines recommend this subgroup of patients undergo invasive staging of the mediastinum (1,2). For cN1 tumors by PET-CT explored by endosonography, sensitivity values of 0.38 (34) and 0.43 (52) to diagnose N2 disease have been reported. In one study, adding cervical mediastinoscopy increased sensitivity to 0.73 (34). In this clinical situation, cervical mediastinoscopy or VAMLA clearly have higher sensitivities and negative predictive values than those reported by endosonography: 0.73 and 0.92, respectively (35). Therefore, in this particular group of tumors, it seems reasonable to avoid endosonography and explore directly with cervical mediastinoscopy or VAMLA (*Table 2*).

For cN0 tumors more than 3 cm in greatest dimension but with high SUVmax, particularly adenocarcinomas, the

 

unsuspected N2 rate has been reported to be between 6% and 15% (41,42). However, when patients with these tumors undergo VAMLA, the rate of unsuspected mediastinal nodal disease is as high as 22% (19% N2 and 3% N3) (26) (*Table 2*). Therefore, in these clinical situations, it would be prudent to confirm negative endosonography results with a surgical invasive procedure such as cervical mediastinoscopy or, better yet, VAMLA.

## Conclusions

In the era of ultrasound-assisted endoscopies with real time puncture of peribronchial and periesophageal lymph nodes, cervical mediastinoscopy and VAMLA have evidence-based indications that offer the highest certainty for clinical staging of NSCLC. Therefore, they should be applied in current clinical practice according to the well-established indications.

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