Invasive Staging of Non-small Cell Lung Cancer

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Lung cancer is the leading cause of cancer-related death worldwide, and despite advances in therapy, the 5-year survival rate for all stages combined is approximately 16 % [1]. For these reasons, a careful initial diagnostic evaluation to determine the location and the extent of primary and metastatic disease is critical for the adequate care of patients.

The objective of non-small cell lung cancer (NSCLC) staging in the absence of distal metastases is to evaluate for mediastinal lymph node involvement. Accurate staging of NSCLC is important not only to determine the patient's prognosis but also to decide a treatment plan, as the presence of mediastinal lymph node involvement (N2 disease) is diagnostic for stage IIIA or IIIB lung cancer that suggests inoperability and the need for treatment with chemotherapy, radiation, or both.

Mediastinal lymph node staging is divided into noninvasive (imaging) and invasive staging. Noninvasive techniques include computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and PET-CT. It has been reported that the sensitivity and specificity of CT scanning for identifying mediastinal lymph node metastasis are 51 % (95 % confidence interval (CI), 47–54 %) and 86 % (95 % CI, 84–88 %), respectively, demonstrating that CT scanning has limited ability either to rule in or exclude mediastinal metastasis. Furthermore, the sensitivity and specificity of PET scanning for identifying mediastinal metastasis are 74 % (95 % CI, 69–79 %) and 85 % (95 % CI, 82–88 %), respectively [2]. The combined modality of PET-CT for preoperative staging was evaluated in a prospective randomized trial of conventional staging vs. conventional plus PET-CT with end point being avoidance of futile thoracotomy. Results showed a reduction in futile thoracotomies in the PET-CT group vs. the conventional group (21 % vs. 42 %, respectively) and that one futile thoracotomy was avoided for every 5 PET-CTs performed. Additionally, the diagnostic accuracy and sensitivity were 79 % and 64 %, respectively, compared to 60 % and 32 %, respectively, for conventional staging [3]. These data suggest that PET scanning is more accurate than CT and that the combined modality may provide additional benefit; however, all abnormal scan findings require cytological or histological confirmation of malignancy by invasive techniques, so that patients are not denied the opportunity of potentially curative treatment.

Invasive staging techniques are divided into surgical and nonsurgical procedures including endoscopic and bronchoscopic techniques. Surgical staging includes mediastinoscopy, left anterior mediastinotomy (Chamberlain procedure), and video-assisted thoracoscopic surgery (VATS).

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Nonsurgical staging includes minimally invasive needle biopsy techniques such as transbronchial needle aspiration (TBNA), transthoracic needle aspiration (TTNA), esophageal endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA), and endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA).

A wide spectrum of factors must be considered when determining the appropriate tests to assess the lymph nodes in NSCLC. These include the sensitivity and specificity of the test, the false-negative and false-positive rates, the morbidity of the procedure, the accessibility of the tumor and suspicious lymph nodes, the requirement of general anesthesia, and the surgical skills required. Knowledge of lymph node nomenclature is frequently helpful in choosing the correct staging procedure [4, 5].

Surgical Techniques of Invasive Mediastinal Staging

Cervical Mediastinoscopy

Cervical mediastinoscopy is considered the "gold standard" for mediastinal staging of NSCLC. It is performed in the operating room under general anesthesia, and in most centers, patients are discharged the same day if they are stable [6, 7]. The procedure involves a small skin incision above the suprasternal notch, insertion of a mediastinoscope alongside the trachea, and biopsy of the mediastinal nodes under direct or video-assisted view. Lymph nodes accessible with this technique include right and left high paratracheal nodes (stations 2R, 2L, 4R, and 4L), pretracheal nodes (stations 1 and 3), and anterior subcarinal nodes (station 7) (Fig. 8.1). Lymph nodes that cannot be biopsied with this approach are posterior subcarinal nodes (station 7), inferior mediastinal nodes (stations 8 and 9), aortopulmonary window (APW) nodes (station 5), and para-aortic nodes (station 6). Rates of morbidity and mortality from this procedure are very low, 0.5–1 % and 0.08 %, respectively [8]. Minor complications include left recurrent nerve injury (0.7–0.9 %), pneumothorax (0.5–0.7 %), wound infection, chylous leak, and phrenic nerve injury. Major complications including bleeding due to injury of major blood vessels (0.1–0.2 %), tracheobronchial injury, and esophageal trauma are rare [9, 10]. A meta-analysis of 19 studies [11] showed that the sensitivity of mediastinoscopy to detect mediastinal node involvement from cancer was 78 %

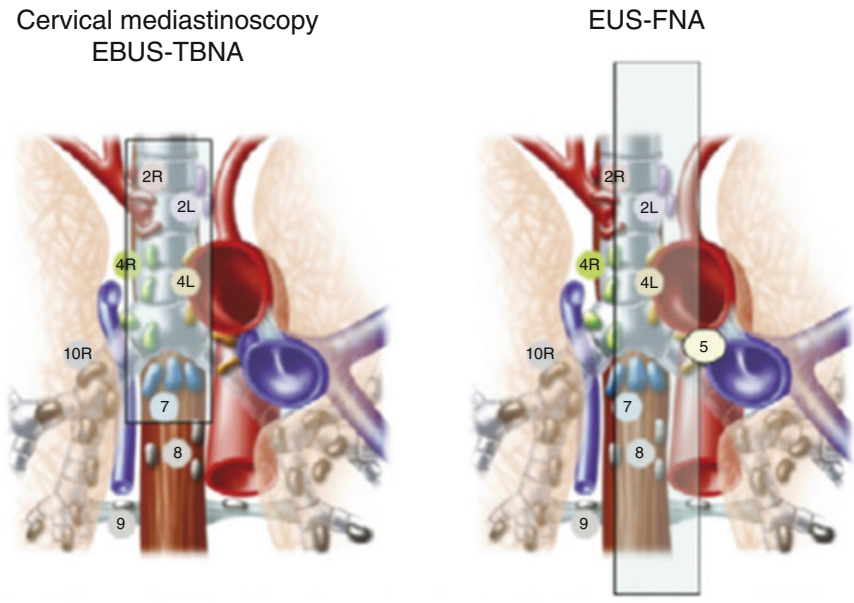

Fig. 8.1 Nodal levels accessible by cervical mediastinoscopy and EBUS-TBNA compared to EUS-FNA (From De Leyn P, et al.: ESTS guidelines for preoperative lymph node staging for non-small cell lung cancer. Eur J Cardiothorac Surg. Jul;32:1–8, 2007, with permission)

and the false-negative rate was 10 %. Some of the false-negative cases (42–57 %) can be explained by the presence of nodes that are not accessible by the mediastinoscope and by the operator skills and quality of dissection and sampling during the procedure. Videomediastinoscopy appears to improve sensitivity to 90 % and decrease false-negative rates to 7 %. The use of extended cervical mediastinoscopy, a procedure that involves directing the mediastinoscope lateral to the aortic arch, allows access to the APW and para-aortic lymph nodes (stations 5 and 6) that are not accessible by standard cervical mediastinoscopy [12], though not many surgeons perform this procedure.

Anterior Mediastinotomy

Left anterior mediastinotomy, or the Chamberlain procedure, is used for evaluation of left upper lobe tumors and lymph nodes located in the anterior mediastinum and APW. It is performed under general anesthesia in the operating room. The patient is placed in supine position and a skin incision is made over the second left intercostal space. The internal mammary artery is identified medially and preserved, and then the scope is inserted. After exploration, biopsies are taken from stations 5 and 6. The sensitivity for detecting mediastinal lymph node involvement of the anterior mediastinum ranges from 63 to 86 % [13, 14], but when it is coupled with standard cervical mediastinoscopy may increase to 87 % [11, 15]. The reported complications are very low including superficial wound infections, bleeding, and pneumothoraces.

Video-Assisted Thoracoscopic Surgery

VATS is performed in the operating room and under general anesthesia through 5–20 mm skin incisions placed at three sites in the intercostal space. The thoracoscope is inserted through one of the lower ports, and forceps are inserted through the other ports. VATS requires double-lumen endotracheal intubation to obtain atelectasis of the ipsilateral lung. As a diagnostic tool, VATS is an alternative to transthoracic needle aspiration of the peripherally located indeterminate pulmonary nodule, with a greater diagnostic yield (100 vs. 80–95 %) [16]. In addition, VATS has been used to access lymph nodes in stations 5, 6, 8, and 9, generally considered out of the reach of standard mediastinoscopy. The sensitivity is 75 % ranging from 37 to 100 %, and the specificity is 100 % [11]. The disadvantage compared with mediastinoscopy is that VATS allows only exploration of the ipsilateral side. Besides mediastinal staging, VATS may provide additional information on tumor status and pleural carcinomatosis and evaluation of pleural effusions.

Minimally Invasive Techniques for Mediastinal Staging

Transbronchial Needle Aspiration

TBNA, also known as Wang needle aspiration, is a bronchoscopic procedure that is performed on an outpatient basis. After using the CT scan to assess the level and size of the lymph node, the needle catheter is passed through the working channel of the bronchoscope, and then it is advanced through the tracheobronchial wall into the lymph node with no direct target visualization. TBNA is most frequently used to assess subcarinal nodes (station 7). Paratracheal nodes may also be biopsied, but they are sometimes more difficult to access due to the angulation required from the bronchoscope and needle. It has been reported that adequate specimens are obtained in 80–90 % of cases. On-site cytological evaluation of the aspirates improves the yield, is cost-effective, and eliminates unnecessary passes during the procedure [17]. A meta-analysis of 17 studies that included 1,339 patients showed that the overall sensitivity for mediastinal staging with TBNA is 78 %, with values ranging from 14 to 100 % [11]. The false-negative rate is approximately 28 % (range, 0–66 %). The specificity and false-positive rates are 100 % and 0 %,

respectively [11]. This analysis, however, was not restricted to patients with NSCLC, did not assess study method quality, and did not set out to identify sources of variation in study results. A more recent meta-analysis of five studies accounting for the aforementioned data showed a much lower pooled sensitivity of 39 % (95 % CI, 17–61 %) with specificity of 99 % (95 % CI, 96–100 %) for TBNA [18]. Patients included in the first meta-analysis of TBNA studies had enlarged mediastinal lymph nodes and thus represent a different population when compared to those being considered for surgery that generally have normal-sized or single lymph node station enlargement, which is more representative of the second meta-analysis cited. The high false-negative rate makes TBNA less useful for staging patients with normal-sized nodes. Positive TBNA results demonstrate mediastinal node involvement and can obviate the need for surgical staging. However, negative TBNA results cannot sufficiently exclude mediastinal lymph node involvement and additional staging procedures should be performed.

Transthoracic Needle Aspiration

TTNA is an image-guided procedure commonly performed by a radiologist. Under local anesthesia, a needle is inserted percutaneously most often under CT guidance. Depending on size and location, guidance with conventional fluoroscopy or ultrasound can be performed. The procedure is relatively safe and well tolerated by most patients. Depending on the size of the needle used, core histological biopsies can be obtained in addition to cytological specimen. TTNA can be used for the diagnosis of suspected lung cancer of peripheral parenchymal masses as well as for the diagnosis and staging of the mediastinum. The sensitivity of TTNA for the staging and diagnosis of the mediastinum has been reported to be approximately 90 % (meta-analysis of five studies in 215 patients) [11]. Patients selected for this procedure had extensive mediastinal involvement and lymph nodes more than 1.5 cm in size. Pneumothorax is the most frequent complication (5–60 %), particularly in patients with COPD requiring chest tube insertion in approximately 10 % of patients [11]. Other complications such as hemothorax, hemoptysis, air embolism, or empyema are rare [19]. Implantation of tumor cells at the puncture site is rare and reported to be approximately 1 in 4,000 procedures [20, 21]. Relative contraindications for TTNA include COPD, poor lung function, diffuse pulmonary disease, clotting disorders, pulmonary hypertension, contralateral pneumonectomy, and arteriovenous malformation [22].

Esophageal Endoscopic Ultrasound-Guided Fine-Needle Aspiration

The use of EUS-FNA to stage mediastinal lymph nodes in patients with lung cancer has been reported in the medical literature beginning in the early 1990s [23]. It is an outpatient procedure that is performed under conscious sedation. A 19- or 22-gauge aspiration needle is inserted through a working channel of the endoscope. The needle is then passed through the wall of the esophagus directly into the target using real-time ultrasonography. This is followed by aspiration of the lymph node with direct visualization of the needle. The technique has a minimal risk of infection or bleeding. It is useful for staging of APW (station 5), subcarinal (station 7), esophageal (station 8), and inferior pulmonary ligament (station 9) lymph nodes (Fig. 8.1). Nodes that are anterolateral to the trachea are more difficult to sample because of interference by air in the larger airways. Ultrasonographic properties of lymph nodes indicating possible malignancy include a hypoechoic core, sharp edges, round shape, and a long-axis diameter exceeding 10 mm, though none are reliable enough to forgo biopsy [24–26]. Signs of benign disease include a hyperechoic core (fat), central calcification (remote granulomatous disease), ill-defined edges, a long and narrow shape, and a long-axis diameter up to 10 mm [25, 27, 28]. Histoplasmosis, sarcoidosis, and anthracosilicosis may cause false-positive EUS images [28–30]. A meta-analysis of 18 studies assessed the use of EUS-FNA in the

mediastinal staging of 1,201 lung cancer patients [31]. For the detection of malignant mediastinal lymph nodes, the overall sensitivity and specificity were 83 % and 97 %, respectively. False-negative rates have been reported to be 19 % (range, 0 to 61 %) [11]. In addition, it is accepted that nodes that measure less than 1 cm can be successfully sampled using this technique [32, 33]. Among patients with normal-sized lymph nodes seen on CT scans, the sensitivity is 66 % and the false-negative rate is 14 % (specificity, 100 %; false-positive rate, 0 %) [34, 35]. Another advantage of EUS-FNA is that it allows detection of metastatic disease to subdiaphragmatic sites such as the left adrenal gland, celiac lymph nodes, and the liver. Furthermore, the cost of EUS is less than surgical staging procedures. Two studies suggested that EUS may be more cost-effective compared to mediastinoscopy [36, 37], although it was assumed that mediastinoscopy frequently required inpatient hospital admission.

Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration

EBUS-TBNA is a promising modality for mediastinal staging. Initially, EBUS was performed by introducing a catheter with an ultrasound transducer at the tip of the catheter through the working channel of the bronchoscope (radial ultrasound probe). The lymph node was localized with the probe, and the catheter was then withdrawn. The lymph node would then be sampled with TBNA without visualization. More recently, a bronchoscope with a convex ultrasound probe has been developed allowing real-time ultrasound-guided TBNA (linear ultrasound scope, Fig. 8.2) [38]. EBUS-TBNA is performed under local anesthesia and conscious sedation in an outpatient setting. A 22-gauge TBNA needle equipped with an internal sheath is inserted through the working channel of the bronchoscope. The inner diameter of the needle allows the sample of histological cores in some cases. Doppler examination may be used immediately before the biopsy in order to avoid unintended puncture of vessels between the wall of the bronchi and the lesion. Under real-time ultrasonic guidance, the needle is placed in the lesion and suction is applied by a syringe. The needle is moved back and forth inside the lesion. Finally, the needle is retrieved and the internal sheath and the catheter are removed. The aspirated material is smeared onto glass slides, air-dried, and fixed in 95 % alcohol. Dried smears can be evaluated in

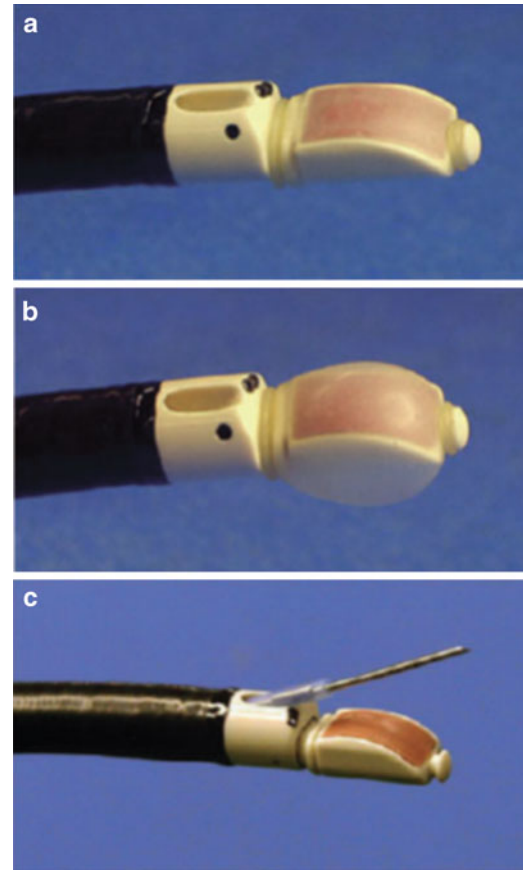

Fig. 8.2 Convex probe endobronchial ultrasound. (**a**) The tip of the convex probe endobronchial ultrasound (Olympus XBF-UC260F-OL8, Olympus, Tokyo, Japan) has a linear curved array ultrasonic transducer of 7.5 MHz. (**b**) The balloon attached to the tip of the bronchoscope is inflated with normal saline. (**c**) A dedicated transbronchial aspiration needle is inserted through the working channel (From Yasufuku K and Fujisawa T: Staging and diagnosis of non-small cell lung cancer: Invasive modalities. Respirology. 12, 173–183, 2007, with permission)

real time by an on-site cytopathologist to confirm adequate cell material, and in a substantial number of cases, a preliminary diagnosis can be made. Histological specimens obtained are fixed in formalin before being sent to the pathology department. EBUS-TBNA can be used to sample the highest mediastinal (station 1), the upper paratracheal (station 2R, 2L), the lower paratracheal (station 4R, 4L), the subcarinal (station 7), as well as the hilar (station 10), the interlobar (station 11), and the lobar (station 12) lymph nodes (Fig. 8.1). A pooled analysis of 12 studies using EBUS for mediastinal staging showed a weighted sensitivity of 93 % (range 79–99 %), false-negative rate of 9 % (range 1–37 %), and specificity of 100 % [39]. The studies using EBUS involved patients with lymph node enlargement, which is consistent with a disease prevalence of approximately 70 %. In 2006, Herth et al. evaluated the performance of EBUS-TBNA in patients with lung cancer and a radiographically normal mediastinum [40]. That study showed an unexpected detection rate of 17 % in 119 lymph nodes 5–10 mm in size. In one out of six patients, a futile thoracotomy was averted using EBUS. This was followed by a study evaluating the accuracy of EBUS-TBNA for staging mediastinal lymph nodes in patients with lung cancer without enlarged lymph nodes on CT and no detectable PET activity in the mediastinum. There was a 9 % prevalence of mediastinal lymph node metastases. The sensitivity, specificity, and negative predictive value were 89 %, 100 %, and 99 %, respectively [41].

Combining EUS-FNA and EBUS-TBNA

Current data suggest that the combination of EUS-FNA and EBUS-TBNA may allow complete access to all mediastinal lymph node stations [42]. Wallace et al. reported that the combination of EUS-FNA and EBUS-TBNA had a higher sensitivity (93 %; 95 % CI, 81–99 %) and negative predictive value (97 %; 95 % CI, 91–99 %) compared with either method alone [43].

Comparing Technologies

With the relatively recent emergence of data supporting nonsurgical invasive techniques including EUS-FNA and EBUS-TBNA for mediastinal lymph node staging in lung cancer, there has been interest in comparing these modalities with their surgical and nonsurgical counterparts. Wallace and coworkers [43] compared the diagnostic accuracy of blind transbronchial needle aspiration, EBUS-TBNA, EUS-FNA, and their combinations. As mentioned previously, the combination of EBUS-TBNA and EUS-FNA was better than either alone, even in scenarios that favored one methodology over another. Additionally, both technologies far outperformed blind TBNA, with EBUS-TBNA detecting 33 % more malignant mediastinal lymph nodes. A recent randomized controlled trial by Annema and coworkers compared minimally invasive endosonography (EBUS-TBNA plus EUS-FNA) followed by surgical staging (if no nodal metastases found) to immediate surgical staging with mediastinoscopy in two hundred forty-one patients over a 2-year period [44]. Results showed that the sensitivity for surgical staging was 79 % (95 % CI, 66–88 %) and for endosonography plus surgical staging, 94 % (95 % CI, 85–98 %). The negative predictive value for surgical staging was 86 % (95 % CI, 76–92 %) and for endosonography and surgical staging, 93 % (95 % CI, 84–97 %). The number of unnecessary thoracotomies was also substantially reduced in the endosonography group as compared to the surgical group (7 % vs. 18 %, respectively). There was no difference in complication rates between the two groups; however, when studied separately the complication rate with endosonography was significantly lower than with surgery (1 % vs. 6 %, p-value 0.03). Conclusions from this study suggest that endosonography should be the first step for mediastinal nodal staging.

Table 8.1 summarizes performance characteristics of invasive techniques for mediastinal staging.

Table 8.1 Techniques for mediastinal lymph node staging

Technique	Nodal stations	Accessible sensitivity (%)	Specificity (%)	FP (%)	FN (%)
Cervical mediastinoscopy	1, 2, 3, 4, anterior 7	78 90 (*)	100	0	11 7 (*)
Anterior mediastinotomy	5, 6	75	100	0	6
VATS	5, 6, 8, 9 ipsilateral	75	100	0	7
TBNA	2, 4, 7	39	100	0	8
TTNA	Mediastinal	89	100	0	
EUS-FNA	2, 4, 5, 7, 8, 9	84	99.5	0.4	19
EBUS-NA	1, 2, 4, 7, 10, 11, 12	90	100	0	24

FP false-positive, *FN* false-negative, *VATS* video-assisted thoracoscopic surgery, *TBNA* transbronchial needle aspiration, *TTNA* transthoracic needle aspiration, *EUS-FNA* esophageal endoscopic ultrasound-guided fine-needle aspiration, *EBUS-NA* endobronchial ultrasound-guided transbronchial needle aspiration, * videomediastinoscopy
Source: Detterbeck FC, Jantz MA, Wallace M, et al. Invasive Mediastinal Staging of Lung Cancer: ACCP Evidence-Based Clinical Practice Guidelines (2nd Edition). Chest 2007; 132:202S–220S, with permission

Guidelines for Mediastinal Staging

Guidelines of the American College of Chest Physicians [11] and the European Society of Thoracic Surgery (ESTS) [45] were published in 2007. There has been recent evidence further supporting the increased use of multimodality staging for lung cancer. A cohort study using 7 years of data involving 43,912 patients concluded that multimodality staging is being increasingly used. Additionally, the use of a greater number of staging modalities was associated with a lower risk of death. Trimodality (CT, PET, and invasive staging) vs. single modality (CT only) showed a hazard ratio of 0.49 (99 % CI 0.45–0.54), and trimodality vs. bimodality (CT and PET or CT and invasive staging) showed a hazard ratio of 0.85 (99 % CI 0.77–0.93) [46].

Chest CT is considered the basic imaging modality in lung cancer, but it is not considered accurate enough for mediastinal lymph node staging. Only in patients with extensive mediastinal infiltration of tumor without distant metastases is CT scan assessment sufficient, and there is no need for further invasive confirmation.

For patients with discrete mediastinal lymph node enlargement and no evidence of distant metastases, invasive confirmation is suggested despite of the presence of positive or negative mediastinal nodes on PET scan. If nonmalignant results from a needle technique (EUS-FNA, TBNA, EBUS-TBNA, or TTNA) are obtained, they should be further confirmed by mediastinoscopy, irrespective of whether the findings of a PET scan of the mediastinal nodes are positive or negative. In patients with a normal mediastinum by CT and a central tumor or N1 lymph node enlargement without distant metastases, invasive confirmation is recommended regardless of PET scan mediastinal node status. In general, mediastinoscopy is suggested, but EUS-FNA or EBUS-TBNA may be a reasonable option if nondiagnostic results are followed by mediastinoscopy [47]. This recommendation is likely to change in the next iteration of the guidelines based on the recent randomized controlled trial results showing greater sensitivity for mediastinal nodal metastases and fewer unnecessary thoracotomies with EUS-FNA and EBUS-TBNA. In patients with a peripheral clinical stage I tumor in whom a PET scan shows uptake in the mediastinal nodes (and no distant metastases), invasive staging is recommended. In patients with a left upper lobe cancer in whom invasive mediastinal staging is indicated, the assessment of the APW nodes should be included using one of the following techniques, Chamberlain procedure,

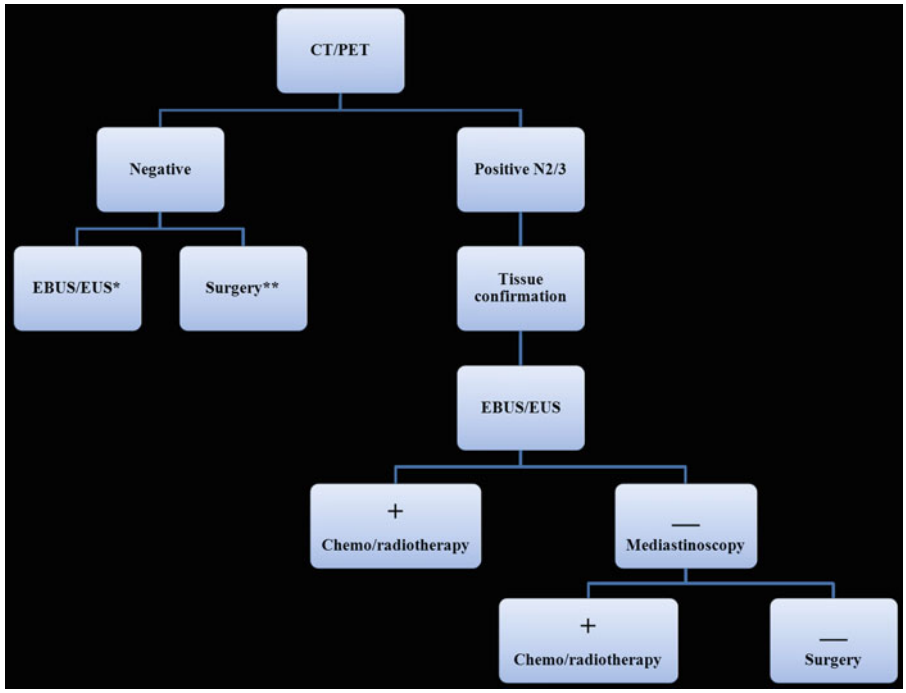

Fig. 8.3 Proposed algorithm for mediastinal staging. *Single asterisk* central tumors, large tumors, enlarged N1 nodes. *Double asterisk* T1a peripheral (Note: because of the 10 % chance of occult metastatic disease to the mediastinum, it is reasonable to invasively stage)

thoracoscopy, extended cervical mediastinoscopy, EUS-FNA, or EBUS-TBNA, if other mediastinal node stations are found to be uninvolved.

A proposed algorithm for mediastinal staging is detailed in Fig. 8.3.

Conclusion

Accurate mediastinal nodal staging is essential for the management of patients with NSCLC in the absence of distant metastases. Imaging studies are not sufficiently reliable, making invasive tests an important part of the staging procedure. Different invasive modalities exist, including surgical and needle-based minimally invasive techniques. These tests should be seen as complementary as they target particular nodal stations and patient groups. Needle techniques are most useful in patients with enlarged mediastinal nodes, while mediastinoscopy remains the "gold standard" in patients with normal-sized nodes though studies are emerging that show that combining EUS and EBUS provides a minimally invasive accurate assessment of the mediastinum in lung cancer.

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