The role of endosonography-guided fine needle aspiration in preoperative restaging in the era of novel neoadjuvant therapies—a literature review

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Background and Objective: The objective of this literature review is to assess the role and diagnostic performance of endosonography (endobronchial, endoesophageal, and combined endobronchial and endoesophageal ultrasound)-guided fine-needle aspiration in restaging the mediastinum after neoadjuvant therapy in lung cancer. Currently, mediastinal restaging in lung cancer after neoadjuvant therapy is a challenging and controversial issue, and optimal approach remains unclear.

Methods: A search was performed in PubMed and Google for relevant studies, reviews and meta-analyses on diagnostic performances of endosonography-guided fine needle aspiration and other methods in restaging stage III lung cancer after neoadjuvant therapy. The articles published in English language between 1998–2021 were assessed.

Key Content and Findings: The pooled sensitivities of endobronchial ultrasound-, endoesophageal ultrasound-, combined endobronchial and endoesophageal ultrasound-, and overall endosonography-guided fine needle aspirations were 65%, 66–73%, 67%, and 67–70% while their specificities were 98–99%, 96–99%, 94–96%, and 99–100%, respectively. Significant heterogeneity was observed for sensitivity of endosonography-guided fine needle aspiration owing to several factors such as study design, prevalence of N2 disease and pathologic changes in lymph nodes due to neoadjuvant therapy and initial staging procedure. Negative results were confirmed by subsequent surgical approaches whenever feasible. There were no severe complications reported during any endosonography approaches reviewed.

Conclusions: Endosonography-guided fine needle aspiration is a safe technique with reasonable sensitivity and high specificity for mediastinal restaging of lung cancer. As an initial rule-in test, a positive result obtained by endosonography-guided fine needle aspiration reliably obviates further evaluation, particularly surgical procedures in approximately 67% of the patients. Combining endobronchial and endoesophageal ultrasonography-guided fine needle aspiration provides higher yields in mediastinal restaging as they are complementary to each other. A negative result by endosonographic restaging requires confirmation by a surgical procedure.

Keywords: Bronchoscopy; endoscopic ultrasound-guided fine needle aspiration; endosonography; restaging; lung cancer

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Introduction

Currently, chemoradiotherapy is the treatment of choice for stage III (IIIA-N2/IIIB-N3) non-small cell lung cancer (NSCLC). However, selected patients with N2/N3 disease, particularly those with a disease responding considerably to induction chemotherapy, radiotherapy, chemoradiotherapy, targeted therapy, and/or immunotherapy may be candidates for surgical resection and mediastinal lymph node dissection (1,2). Persistence of mediastinal metastases after induction therapy generally denotes poor surgical outcomes (3-5). In this regard, the importance of identifying successfully down-staged patients who can subsequently benefit from surgical resection is increasing. Restaging mediastinum accurately in lung cancer is critical as the disease stage is the main determinant of prognosis and guides for management options. However, how to restage mediastinum effectively in NSCLC patients has been a controversial issue.

The diagnostic performance of computed tomography (CT), positron emission tomography (PET) or PET/CT in restaging varies largely among different studies (6-8). Owing to their unsatisfactory sensitivities and specificities in mediastinal restaging, tissue sampling is required for determining the mediastinal lymph node status accurately.

Mediastinoscopy, an invasive surgical procedure, confirms or excludes N2 or N3 disease histologically in most patients with potentially operable NSCLC (9,10). However, remediastinoscopy is considered to be technically difficult owing to adhesions and fibrotic changes subsequent to the initial staging procedure and induction treatment (11,12). Consequently, it has lower accuracy (12,13) than primary mediastinoscopy (14). Furthermore, thoracoscopy and other surgical approaches are invasive, costly and may be challenging. Restaging by video-assisted thoracoscopic surgery (VATS), although feasible, is limited to one hemithorax because it requires single-lung ventilation. The sensitivity, specificity and negative predictive value of VATS for restaging after induction therapy were reported to be 67%, 100% and 73%, respectively by only one prospective multi-institutional trial. VATS restaged the mediastinum in 69% of patients but failed in 31% owing to the unmet pre-study feasibility endpoints in 38%, false-negative stations in 15%, necessity to abort the procedure due to pleural adhesions, tumor bulk, airway injury and inability to achieve atelectasis in 16% (15).

Conventional transbronchial needle aspiration (cTBNA) is a minimally invasive, safe, economical but a "blind" bronchoscopic technique that can histologically or cytologically determine the diagnosis and involvement of hilar and mediastinal lymph nodes in lung cancer. Initially introduced to medicine in 1949 but more widely used in clinical practice since 1978, cTBNA can be adequate in staging when the lymph nodes are larger than 1.5–2 cm and close to carina (paratracheal and subcarinal) in selected patients with a high pretest clinical probability of malignancy (16-19). Its accuracy in staging varies widely among pertinent studies and is shown to be significantly dependent on the prevalence of mediastinal involvement and operator skills. It has a high false-negative rate and thus, cannot be considered as a definitive mediastinal staging technique in routine practice (18,20,21). Although there is very limited data on the diagnostic performance of cTBNA in restaging (17,22), it is most likely that this technique cannot be definitive also in restaging lung cancer (17,23).

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and endoesophageal ultrasound-guided fine-needle aspiration (EUS-FNA) are minimally invasive endoscopic procedures used to detect metastases to mediastinal nodes. In the initial staging of lung cancer, both procedures are confirmed to provide accurate results (24-26). Although widely varying accuracies of EBUS-TBNA and EUS-FNA in the restaging of the mediastinum were reported by many studies with relatively small number of subjects (8,18,27), several pooled analyses of large pertinent data recently have shown reasonable diagnostic operating characteristics of both methods in mediastinal restaging after induction treatment for lung cancer (28,29).

This literature review will focus mainly on the role of endosonography (EBUS-TBNA, EUS-FNA, and combined EBUS/EUS-FNA) in preoperative restaging. For this purpose, a search was performed in PubMed for relevant studies, reviews and meta-analyses written in English in the last 2 decades on diagnostic performances of endosonography-guided fine needle aspiration and other methods in restaging stage III lung cancer after neoadjuvant therapy. I present the following article in accordance with the Narrative Review reporting checklist (available at https://asj.amegroups.com/article/view/10.21037/asj-21-104/rc).

Methods

For this literature review, an ethics committee approval was not required as it was performed to analyze already published studies, reviews and meta-analyses.

Between July 4, 2021 and November 14, 2021, a search was performed in Pubmed and Google for English

Table 1 Summary of the strategy employed for literature search

Items	Specification
Date of search	04.07.2021–14.11.2021
Databases and other sources searched	PubMed, Google
Search terms used	Bronchoscopy, endoscopic ultrasound-guided fine needle aspiration, endosonography, EBUS, EUS, mediastinal restaging, lung cancer
Timeframe	1998–2021
Inclusion and exclusion criteria	Inclusion criteria: 1. Only published studies, reviews and meta-analyses in English language 2. Only articles on diagnostic performances of endosonography- guided fine needle aspiration and other methods in restaging stage III lung cancer after neoadjuvant therapy Exclusion criteria: 1. Any unpublished relevant data 2. Relevant publications in languages other than English 3. Articles other than studies, reviews and meta-analyses 4. Articles with insufficient data on the assessed diagnostic performance measures
Selection process	The literature selection, data extraction and verification, disagreement resolution, and article quality assessment processes were conducted by one investigator (Semra Bilaceroglu) through the utilization of some of the methods reported previously (28,29)

articles published between 1998 and 2021 on diagnostic performances of endosonography-guided fine needle aspiration and other methods in mediastinal restaging of stage III lung cancer after neoadjuvant therapy. The following free text terms were used in the literature search: bronchoscopy, endoscopic ultrasound-guided fine needle aspiration, endosonography, EBUS, EUS, mediastinal restaging, and/or lung cancer.

A set of inclusion and exclusion criteria were used to select the most appropriate and reliable articles for this literature review.

Inclusion criteria

(I) Only published prospective or retrospective studies, reviews and meta-analyses in English.
(II) Only articles on EBUS-TBNA, EUS-FNA, combined EBUS/EUS-FNA, and other methods used for mediastinal restaging following neo-adjuvant therapy in stage III lung cancer.

Exclusion criteria

(I) Any unpublished online or printed data, study, review, etc.
(II) Articles published in a language other than English.
(III) Articles not providing sufficient information regarding diagnostic performance measures of EBUS-TBNA, EUS-FNA, combined EBUS/EUS-FNA and other mediastinal restaging methods (sensitivity, specificity, negative predictive, positive predictive value and/or accuracy, or true-positive, true-negative, false-positive and false negative values).
(IV) Case reports, case series, conference abstracts, letters, editorials, and expert opinions.

The literature selection, data extraction and verification, disagreement resolution, and article quality assessment processes were conducted by one investigator (Semra Bilaceroglu) through the utilization of some of the methods reported previously (28,29). The strategy employed for the literature search is summarized in *Table 1*.

Endosonography-guided needle aspiration in staging and restaging

Diagnostic performance

Mediastinal lymph node staging of lung cancer can be performed using invasive or noninvasive methods. The most commonly used noninvasive methods, chest CT and PET or PET/CT, are safe but limited regarding diagnostic performance with low sensitivity and specificity. In restaging mediastinum, CT has an accuracy of only 58–60% (6,12). PET/CT has a higher sensitivity (73–92%) but a low specificity (62–89%) due to false-positive results (6,8). Furthermore, the pooled specificity of PET/CT is lower (61%) for malignancy in regions with high prevalence of endemic pulmonary infections compared with those that are nonendemic (30). Owing to false-positive results due to these infections, confirming metastasis by only imaging methods is not reliable; histological confirmation is required.

Although mediastinoscopy has been considered to be the gold standard with a sensitivity of 80–91% in staging mediastinum, the repeated procedure has several drawbacks compared with the initial one: a 2% major morbidity risk, a 0.08% mortality risk, substantial cost (6,13,31,32), technical difficulty, lower accuracy due to a high false-negative rate (22%), and a low and variable sensitivity (29–73%) (6,13,33). Transcervical extended mediastinal lymphadenectomy has a high sensitivity (97%) in mediastinal restaging but its mortality and morbidity rates are relatively high (0.3% and 6.4%, respectively), and this procedure is not widely practiced (34).

In clinical N2/N3 disease with a high disease prevalence of 75–81%, cTBNA has a sensitivity of 76–78% and a false-negative rate of 28–29% (21,35,36) in diagnosis and staging. The utility of cTBNA in routine mediastinal staging is compromised by this high false-negative rate. The sensitivity of cTBNA depends on the prevalence of mediastinal lymph node metastases and lymph node size. Its sensitivity tends to decrease with lower prevalence of mediastinal metastases (35) and smaller node size (<15–20 mm short axis on CT scan) (17,18,21). In only one study on diagnostic performance of cTBNA in restaging, correct restaging could be done by this method in 71% of 14 patients and 81% of 17 lymph nodes (22). In some of the studies on staging by cTBNA, only small number of patients were restaged using this procedure (17). Thus, owing to the inadequate evidence on its restaging performance and inferences drawn from its variable and low staging performance that has been studied widely, cTBNA cannot be used as a definitive approach in restaging lung cancer.

As minimally invasive procedures, EBUS-TBNA and EUS-FNA have become standard methods for staging mediastinal nodes in lung cancer. The Executive Summary of the American College of Chest Physicians (ACCP) Evidence-based Clinical Practice Guidelines on Diagnosis and Management of Lung Cancer (3rd edition) (26) and a more recently issued guidelines by the European Society of Gastrointestinal Endoscopy in collaboration with the European Respiratory and Thoracic Surgeons Societies (37) have recommended endosonography (EBUS-TBNA, EUS-FNA, or combined EBUS/EUS-FNA) over surgery as a best first test in staging NSCLC. The latter guidelines have further recommended combined EBUS/EUS-FNA over either procedure alone in staging. The use of EBUS-TBNA, EUS-FNA, or combined EBUS/EUS-FNA in restaging mediastinum after neoadjuvant therapy have also been suggested with a grade C recommendation (37).

EBUS-TBNA has been corroborated to have a high yield (89–98%) in diagnosing and staging lung cancer (38-41). The sensitivity of EUS-FNA for initial staging of lung cancer ranges between 45% and 80% (42-44). In a recent systematic review including 558 patients from 10 studies, the pooled sensitivity of EBUS-TBNA in lung cancer restaging was found to be 65%, and that of EUS-FNA to be 73% while pooled sensitivities of combined EBUS/EUS-FNA and overall endosonography-guided FNA were 67% and 70%, respectively. In this review, the pooled specificity was 100% for overall endosonography-guided FNA, 99% for each of EBUS-TBNA and EUS-FNA, and 96% for combined EBUS/EUS-FNA. The sensitivity (66%) and specificity (100%) of endosonography-guided FNA after chemotherapy alone were similar to those after chemoradiotherapy (77% and 99%, respectively) (28). Another recent systematic review and meta-analysis including 574 patients from 10 studies demonstrated that the pooled sensitivity, specificity, diagnostic odds ratio, and positive and negative likelihood ratios of endosonography (EBUS, EUS and combined EBUS/EUS)-guided FNA were 67% (40–89%), 99% (91–99%), 157, 52.0, and 0.33, respectively, with an area under the receiver-operating characteristic curve of 0.93 (29). Thus, the diagnostic performance of EBUS-TBNA, EUS-FNA, or their combination is confirmed to be lower in restaging than that in the initial staging. The diagnostic performances of endosonography-guided procedures versus those of imaging, cTBNA, and surgical methods in mediastinal restaging of lung cancer are given in *Table 2*.

Table 2 Diagnostic performances of endosonography-guided procedures, imaging, cTBNA and surgical methods in mediastinal restaging of lung cancer (8,15,18,22,28,29,34)

	Sensitivity	Specificity	NPV	PPV	Accuracy
CT	41–59% (20–91%)	62–75% (50–97%)	47–56% (38–97%)	43–70% (39–92%)	58–67% (37– 92%)
PET/CT	77–89% (54–92%)	61–80% (48–93%)	71–87% (71–100%)	36–75% (33–93%)	72–87% (67–94%)
cTBNA	71%	–	–	–	–
EBUS-TBNA	64–70% (33–82%)	85–99% (78–100%)	55–76% (20–82%)	91–96% (80–100%)	74–81% (64–92%)
EUS-FNA	61–75% (44–92%)	96–99% (90–100%)	71–82% (58–91%)	97–100% (83–100%)	72–81% (60–92%)
EBUS/EUS-FNA	67–70% (53–79%)	94–98% (86–99%)	73–76% (61–83%)	95% (83–99%)	81–83% (73–87%)
Overall endosonography-FNA	67–70% (40–89%)	99–100% (87–100%)	76–81% (20–93%)	96–100% (87–100%)	91–93% (88–95%)
Re-mediastinoscopy	61–74% (29–90%)	100%	73–79% (52–86%)	100%	84–88% (60–94%)
TEMLA	95–100%	100%	97–100%	100%	98–99%
VATS	62–67% (47–83%)	100%	73% (56–86%)	100%	63–72% (40–82%)

cTBNA, conventional transbronchial needle aspiration; NPV, negative predictive value; PPV, positive predictive value; CT, computerized tomography; PET/CT, positron emission tomography/computerized tomography; EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; EUS-FNA, endoesophageal ultrasound-guided fine needle aspiration; EBUS/EUS-FNA, combined endobronchial and endoesophageal ultrasound-guided fine needle aspiration; overall endosonography-FNA, overall endosonography-guided fine needle aspiration; TEMLA, transcervical extended mediastinal lymphadenectomy; VATS, video-assisted thoracoscopic surgery.

Safety

Endosonographic procedures rarely cause complications. A systematic review on adverse events related to endosonography for mediastinal, hilar, or primary lung tumor analysis reported a 0.14% rate of serious adverse events in 16,181 patients: 0.05% with EBUS, 0.3% with EUS (45). Another systematic review including 13 studies (1,536 patients) also showed the safety of EBUS-TBNA in lung cancer (46): no complications in 11 studies, no major complication in 1 study, and rare side effects (e.g., cough) in 1 study. A third systematic review confirmed that severe complications (pneumothorax and lymph node abscess) occurred in 0.3% of the patients undergoing combined EUS-FNA and EBUS-TBNA for mediastinal staging in lung cancer (47). Furthermore, a nationwide survey on complications associated with EBUS-TBNA conducted by the Japan Society for Respiratory Endoscopy demonstrated a complication rate of 1.23% (95% CI: 0.97–1.48%) and a mortality rate of 0.01% within 7,345 procedures in 210 facilities. The death, reported in a single patient, was due to cerebral infarction after withdrawal of antiplatelet drugs that were replaced by heparin. Hemorrhage (55%) and infection (16%) were the most frequent of all complications (48).

In restaging lung cancer too, endosonographic procedures have been confirmed to be safe with comparable types and rates of complications that were not severe (27-29,34).

Limitations and challenges

The main limitation of endosonography by EBUS or EUS is that some of the mediastinal lymph node stations such as 5 (subaortic) and 6 (para-aortic) cannot be accessed by EBUS or EUS. Nevertheless, minimally invasive mediastinal staging can be accomplished to a near-complete level by combining EBUS-TBNA and EUS-FNA (49,50).

EBUS-TBNA has been demonstrated to have a higher diagnostic yield than cervical mediastinoscopy by multiple studies (51,52) as it can access lymph node stations that cervical mediastinoscopy cannot. In a meta-analysis aiming to assess the diagnostic yield of combined EBUS-TBNA and EUS-FNA in NSCLC staging (47), the sensitivity, specificity and negative likelihood ratio were 86%, 100% and 0.15, respectively. The combined approach had a significantly higher sensitivity than that of each strategy alone (47). EUS-FNA and mediastinoscopy can be combined in the diagnosis and staging of lung cancer if EBUS-TBNA is not available (18).

Of the two studies in which combined endosonography was performed for restaging NSCLC (34,53), only one has reported the sensitivity (67%), specificity (96%) and accuracy (81%) of the combined procedure in restaging (53).

However, the perfect specificity but defective sensitivity of EBUS-TBNA, EUS-FNA or the combination of both in restaging has been proved convincingly by the two recent systematic reviews mentioned above (28,29).

Formation of areas of necrosis, inflammation and fibrosis in the metastatic lymph nodes due to induction treatment (chemotherapy, radiotherapy, chemoradiotherapy, targeted therapy and/or immunotherapy) (2,53,54) and fibrotic changes secondary to the initial staging procedure (11,12) can most likely be the causes of defective sensitivity. Less cellular material even in the properly obtained samples from these lymph nodes may be challenging in histologic analysis. Focally located malignant cells within the treated metastatic lymph nodes or in dense extracellular matrix may partially explain why false-negative samples with no malignant cells occur although successful aspiration of adequate lymph node tissue is accomplished. Furthermore, necrosis within the aspirated sample challenges pathologic interpretation (27,28). Other possible reasons for the decreased sensitivity can be shrunken nodes with smaller size as well as difficulties in accessing some nodes and in differentiating metastasis from adhesions/degenerative changes consequent to induction therapy (29).

EUS-FNA using the EBUS scope

Endoesophageal ultrasound guided fine-needle aspiration using the EBUS scope (EUS-B-FNA) can be performed by a pulmonologist in the same session with EBUS-TBNA. With EUS-B-FNA, the procedural cost is not increased considerably. After EBUS-TBNA procedure, the EBUS scope is pulled from the airways and inserted into the esophagus for EUS-FNA (37,55).

EUS-B-FNA has also been used to sample left adrenal nodules as part of lung cancer staging. The EBUS scope advanced to the stomach is used to identify and sample the left adrenal nodule under real-time EUS-B-FNA. This procedure is suggested to lower the cost in selected patients (56) although no data on cost-effectiveness have been available yet.

Limitations of current data and factors affecting endosonographic restaging performance

In the studies used for the pooled data analyses most important limitations are lack of standardization in diagnostic testing and treatment: variations in the time interval between the completion of neoadjuvant therapy and restaging by CT, PET/CT, endosonography or surgical procedures [optimally about 1 month (57) but varying from 2 to 12 weeks (8,27,57,58)], not using PET/CT routinely, methodologic heterogeneity regarding the technical aspects of endosonography and handling/processing specimens, variations in strategies for primary pathologic staging and induction treatment, use of various therapeutic agents (chemotherapy, targeted therapy and/or immunotherapy) and numbers of treatment cycles, and the use of radiation in addition to chemotherapy, targeted therapy and/or immunotherapy in some patients (28,29).

In most studies, owing to ethical issues, positive results from endosonographic restaging are not confirmed by surgery as the reference standard. Furthermore, the majority of the studies analyzed in the pooled data analyses and systematic reviews are small studies from single centers and specialized endoscopy or thoracic surgery departments. Corroboration of these results is required by larger, world-wide and multi-center studies (28).

Widely varying prevalence of N2 disease (19–94%) in the studies analyzed could have an effect on the sensitivity and accuracy since a proportional increase in sensitivity occurs with increasing N2 prevalence (27,29,58).

All neoadjuvant therapies, old or novel, also have the potential to affect the accuracy of restaging for lung cancer owing to the pathologic changes shown in resected tissues after neoadjuvant treatments: fibroelastotic changes, proliferative fibrosis, necrosis, vasculitis, vascular thickening and obliteration, neovascularization, cytologic atypia of tumor cells, lymphocytosis in tumor tissue and chronic inflammatory cell infiltrates (2,54,59,60).

More studies on the ideal restaging procedures are needed. In the studies included in the pooled data analyses for restaging, description of the lymph node histopathologic structure is not available. This description may be helpful in sampling. Further investigations on how the malignant cells are distributed in the treated lymph nodes can provide significant information. Demonstration of central, peripheral or focally scattered distribution of malignant cells in the lymph node may help the endoscopists in choosing the location for needle insertion during EBUS-TBNA or EUS-FNA. Consequently, this may have an impact on the size of the sampling needle, how many locations to sample in the lymph node, number of needle passes, and use of rapid onsite evaluation (ROSE) to increase the yield (28,29,61).

As the sensitivity of endosonography-guided needle aspiration varies widely (44–72%) for restaging in the studies reporting an average of three needle passes

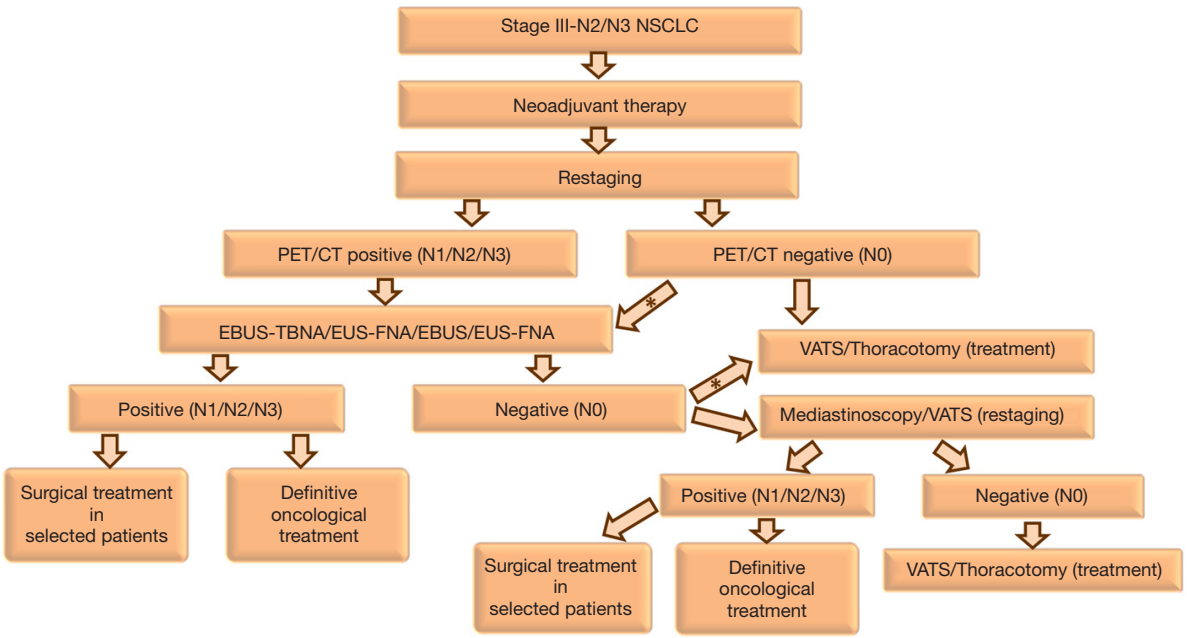

Figure 1 Clinically reasonable pathway for mediastinal restaging after neoadjuvant therapy in NSCLC (8,15,18,28,34,37,53,70). *, in selected patients. NSCLC, nonsmall cell lung cancer; PET/CT, positron emission tomography/computerized tomography; EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; EUS-TBNA, endoesophageal ultrasound-guided fine needle aspiration; EBUS/EUS-FNA, combined endobronchial and endoesophageal ultrasound-guided fine needle aspiration; VATS, video-assisted thoracoscopic surgery.

along with ROSE (27,62,63), whether the sensitivity of endosonographic needle aspiration can be improved by multiple passes together with ROSE is currently uncertain. Similar uncertainty exists for needle size. Owing to the use of a 22-G needle in most of the studies included in the pooled data analyses, the effect of needle size could not be explored. In theory, larger (19-gauge) needles are expected to obtain more diagnostic and adequate histologic and cytologic samples than smaller needles. However, in real-world practice larger needles have not provided significantly higher but rather comparable diagnostic performance in EBUS-TBNA whether it is 21-gauge versus 22-gauge (64,65), 22-gauge versus 25-gauge (66), or 19-gauge versus 21- or 22-gauge (67,68). More frequently obtained bloody cytologic specimens and inadequate specimens due to more difficulty in puncturing the tissue with a 19-gauge needle might have caused its lower than expected performance (68).

Furthermore, access to certain lymph nodes by EBUS and EUS are limited or not possible: e.g., stations 8 and 9 by EBUS and station 4R by EUS. Thus, the sensitivity and specificity of EBUS or EUS apply only to the locations accessible by either method. Indeed, these two approaches cannot be compared as each is a stand-alone staging technique but can be complementary to the other. Prospective studies are needed to answer all of the above-mentioned issues and how to increase the diagnostic yield of endosonography in restaging lung cancer (26,29,37).

Clinical implications

In clinical practice, endosonographic procedures are ideal in the initial evaluation for restaging of NSCLC owing to their high specificity and positive likelihood ratios (69). Rarely reported false-positive results (1.9–5%) are not due to the method but the misidentification of the pulmonary tumor as a lymph node and how appropriately the procedure was performed by the endoscopist (53,61). As a reliable rule-in test, a positive result obtained by endosonography-guided FNA obviates further evaluation, particularly surgical procedures in approximately 67% of the patients (28,29,70). Combining EBUS and EUS appears to provide higher yields in mediastinal restaging as they are complementary to each other (53). A negative result by endosonographic restaging requires confirmation by a surgical procedure.

However, in the pertinent literature there has been no direct comparison of endosonography and mediastinoscopy or other surgical methods in mediastinal restaging. A clinically reasonable pathway for mediastinal restaging should be implemented and tailored for each individual patient through a discussion in a multidisciplinary team consisting pulmonologists, thoracic surgeons, medical oncologists and radiation oncologists (28,29,70) (*Figure 1*). Furthermore, the observations from the pooled data analyses and meta-analyses should be evidenced by randomized controlled studies.

Conclusions

Endosonography-guided needle aspiration has a reasonable sensitivity and a high specificity in the mediastinal restaging of NSCLC. Moreover, it is safe with low complication rates. Thus, it is promising as an initial rule-in investigation in restaging the mediastinum following neoadjuvant therapy.

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Footnote

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Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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