



Endosonography in mediastinal staging of lung cancer: a concise literature review

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Abstract: The endoscopic assessment of the mediastinal status has become extremely widespread in the last two decades due to its safety and efficacy. While in patients with known/suspected advanced lung cancer sampling of the mediastinal lymph nodes is often carried out as the diagnostic success of endosonography is higher than that of guided bronchoscopy aimed at sampling a peripheral primary tumor, in patients with potentially operable disease a thorough mediastinal staging is key for therapeutic decision-making. While imaging studies such as computed tomography (CT) and ¹⁸F-fluoro-deoxy-glucose positron emission tomography (FDG-PET) are commonly used as first step approach in patients with suspected lung cancer, their diagnostic accuracy is insufficient and a tissue diagnosis is usually required to confirm or rule out reliably the metastatic involvement of hilar or mediastinal lymph nodes. The aim of the present review is to describe the role of endosonography [endobronchial ultrasound (EBUS); esophageal ultrasound (EUS)] in the mediastinal staging of lung cancer. Besides the rationale, equipment, and indications for endosonography in this setting, more controversial issues such as the staging strategy (“hit and run” versus systematic staging”), the role of the endosonographic staging in certain categories of patients with cN0 lung cancer, the importance of a surgical staging after a negative endosonographic evaluation, and the current means of risk stratification will be briefly discussed.

Keywords: Lung cancer; endosonography; endobronchial ultrasound (EBUS); endoscopic ultrasound (EUS); lymphadenopathy

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Background and rationale

Lung cancer staging is of key importance for therapeutic decision-making and for its prognostic implications. In particular, the assessment of the status of intrathoracic lymph nodes is a crucial step in patients potentially eligible for surgery. In the absence of distant metastases, surgery represents the first line treatment of non-small cell lung cancer (NSCLC) provided that the mediastinal lymph nodes

are normal or reactive (1,2). On the contrary, malignant involvement of the mediastinal lymph nodes (N2 or N3 disease) defines a “locally advanced” tumor (stage III), often excludes surgery as a first line therapeutic approach, and requires a complex, multimodality treatment strategy. In particular, stage IIIA disease is usually differentiated in resectable or unresectable at the time of diagnosis. In resectable stage IIIA NSCLC (T3–4/N1, T4/N0 or T1–3 non bulky single-station N2), the standard of care

should include consideration of surgical resection after multidisciplinary approach involving neoadjuvant or adjuvant chemotherapy, radiation, or both (3,4). Stage IIIB (T1–2/N3, or T3T1–2/N34/N2) and IIIC (T3T1–2/N34 N3) involve lymph node metastasis in the contralateral hemithorax or supraclavicular fossa and/or an unresectable primary tumor, making patients with this disease not ideal candidates for surgical resection. The standard treatment option for unresectable or inoperable stage IIIA, stage IIIB and IIIC disease is concurrent chemoradiation (5–7). In 2018, the standard of care for unresectable locally advanced NSCLC changed significantly after the publication of the PACIFIC trial, which demonstrated a significant survival benefit with the addition of 1 year of durvalumab after concurrent chemoradiation, regardless of the PD-L1 status (8,9).

Given the implications discussed above for the therapeutic decision-making, the mediastinal staging of lung cancer represents a key moment in the journey of a patient lacking distant metastasis at onset. While computed tomography (CT) and positron emission tomography (PET) are the first line tests in the imaging assessment of patients with suspected NSCLC, their ability to correctly define the mediastinal status is unsatisfactory owing to their relatively high rate of false negatives and false positives, which may lead to suboptimal treatment or to unnecessary surgery, respectively (1,2,10,11). In the last two decades, endosonography (endobronchial ultrasound-guided transbronchial needle aspiration, EBUS-TBNA; endoscopic ultrasound with fine needle aspiration, EUS/EUS-B-FNA), has become the first line test for mediastinal staging based on the mounting evidence about its effectiveness and safety (1,2,10–12).

Equipment and reach

The linear EBUS scope is a flexible bronchoscope with a convex ultrasound probe at its tip that enables visualization and sampling of lymph nodes (and in general of any lesion) adjacent to the airway under real-time ultrasound guidance. As for the intrathoracic lymph nodes, most mediastinal, hilar and interlobar nodes are accessible with a linear EBUS scope through the airways. The EBUS scope can be also introduced in the esophagus and the stomach, just like a regular echogastroscope, and allow for the assessment and sampling (EUS-B-FNA) of lymph node stations which can be reached only from the esophagus (i.e., stations 8, 9) or are easier to reach from the esophagus (i.e., station 4L). Furthermore, lymph nodes located in stations #5 and #6 can

be occasionally sampled using an echogastroscope.

Indications

International guidelines recommend endosonography over surgical staging as the initial procedure for mediastinal staging in patients with known or suspected lung cancer associated with possible mediastinal involvement as suggested by imaging studies (lymph nodes enlarged by CT criteria and/or PET positive). A flow chart for mediastinal staging of NSCLC is shown in *Figure 1*.

Several studies and metanalysis confirmed the high accuracy (>90%) of endosonography for assessing the mediastinal status in patients with suspect lymph node metastases (12–14), and the ASTER trial demonstrated that EBUS is as accurate as surgery, yet less invasive, in this specific setting (15).

An invasive mediastinal assessment with endosonography is also recommended by the ACCP guidelines in patients with normal mediastinum at imaging (negative CT and PET studies) but with a central tumor and/or evidence of N1 involvement. The rationale for this approach is that radiologically-occult N2 disease can be found at surgery in up to 23.5% of these patients (1,12). The guidelines issued by the ESGE/ERS/ESTS propose that an endoscopy-based staging should be considered, even in absence of lymph node abnormalities at CT and/or PET, also in patients whose primary tumor is either ≥ 3 cm in long-axis size or PET negative (*Figure 2*) (12). However, the strength of the evidence in favour of a systematic endosonographic mediastinal staging in patients with a negative mediastinum at imaging studies is debated. First, most of the studies on which this recommendation is based enrolled a very low percentage of patients with negative mediastinum. Second, the accuracy of endosonography in this setting is widely variable. While a handful of studies demonstrated good performance characteristics of EBUS even in patients with a low prevalence of mediastinal lymph node metastases (<35%), many others achieved a low accuracy in this specific setting (16–23). In particular, a well-designed, prospective, multicenter study specifically designed to assess the prevalence of occult mediastinal metastases and the EBUS performance characteristics in patients with cN1 disease and negative mediastinum at imaging studies, confirmed the high prevalence of mediastinal involvement (24%), but showed disappointing sensitivity values (38%) for the endosonographic staging (16). Mediastinoscopy performed better (73% sensitivity) than EBUS in the same subgroup

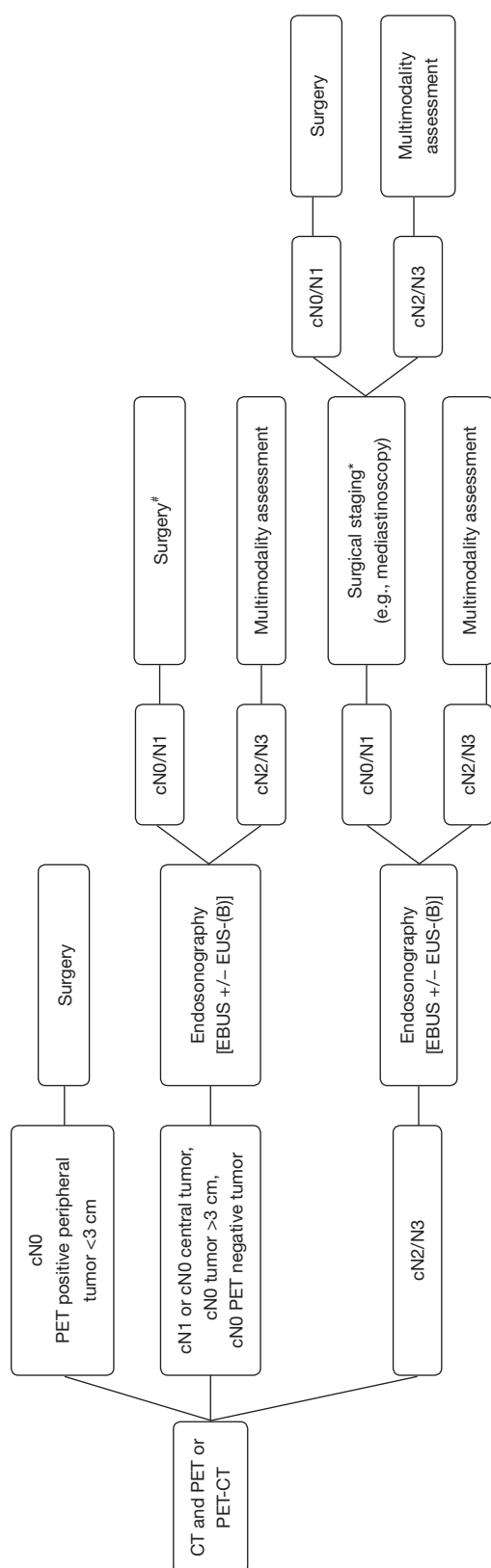


Figure 1 Flow chart for mediastinal staging of NSCLC. #, lack of studies assessing the value of surgical mediastinal staging in this specific scenario. *, large multicentric randomized trial (MEDIAS Trial NL6344/NTR6528) designed to assess the value of a confirmatory surgical mediastinal staging after a negative endosonographic staging is currently ongoing. PET-CT, positron emission tomography-computed tomography; EBUS, endobronchial ultrasound; EUS, esophageal ultrasound.

of patients, as well as in a similar group of patients enrolled by Decaluwé *et al.* in a subsequent prospective trial (24). However, endosonography in these group of patients was carried out only with EBUS, and most of the occult N2 metastases detected at surgical lymph node dissection could have been detected with a combined EBUS/EUS-B staging procedure (25).

Two systematic reviews with metanalysis were recently published with the aim to summarize the evidence regarding the value of endosonographic staging in patients with cN0/N1 lung cancer. Interestingly, the prevalence in the two studies ranged from 13% to 15%, the sensitivity of EBUS was identical and quite disappointing (49%), but the negative predictive value ranged from 91% to 93% (22,23).

Given the above unsatisfactory accuracy values and the publication of new evidence on the prevalence of unforeseen N2 disease in patients with cN0/N1 lung cancer, it is possible that the recommendations regarding the endosonographic staging in this setting will be updated in the near future. Furthermore, some studies published after the currently followed cancer guidelines were issued suggest that the prevalence of occult N2 disease in patients with negative mediastinum and central primary tumor or primary tumor >3 cm may be as high as 8%, thus considerably lower than previously thought. Such prevalence, in turn, might not warrant an invasive mediastinal staging in the absence of additional risk factors (i.e., N1 involvement) (26-28).

Endosonography versus mediastinoscopy

A limited number of individual studies compared the performance characteristics and the complications of endosonography versus mediastinoscopy in the mediastinal staging of lung cancer. Furthermore, three meta-analyses summarized these studies and found a comparable diagnostic value with a lower complication rate for endosonography as compared to mediastinoscopy (29-31).

Ge *et al.* analysed 17 studies and almost 1,000 patients and found an equivalent sensitivity for the detection of mediastinal metastases (0.84 for EBUS-TBNA versus 0.86 for mediastinoscopy). Mediastinoscopy was associated with more complication (17 *vs.* 4) and fewer false negatives as compared to EBUS-TBNA. Indirect meta-regressive method was used in this study to compare the two staging modalities, since no strong direct comparison data were available (29). On the contrary, Sehgal *et al.* provide a true head to head comparison between the two techniques. The

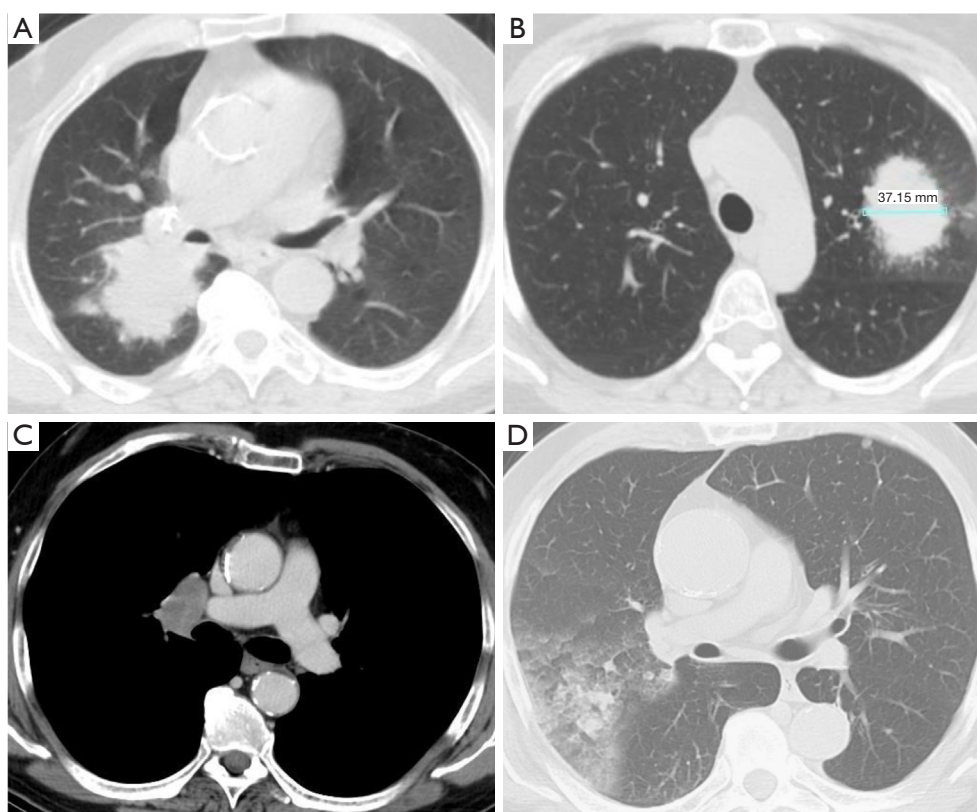


Figure 2 Current indication for a systematic endosonographic mediastinal staging in cN0/N1 NSCLC patients. (A) Primary tumor “centrally-located”; (B) primary tumor >3 cm, (C) cN1 status; (D) primary tumor lacking PET uptake. NSCLC, non-small cell lung cancer; PET, positron emission tomography.

pooled risk-difference of the sensitivity of endosonography versus mediastinoscopy was 0.11 and 0.11 respectively, suggesting equivalent performance characteristics of the two procedures. A higher major complications rate was related to mediastinoscopy (35 of 445 versus 5 of 459) including bleeding, esophageal perforation, tracheal injury, prolonged need for ventilation. However, the Authors reported a significant heterogeneity in patient population and procedures (30). In the third metanalysis, by Rossi Figueiredo *et al.*, only 5 studies with a certain degree of heterogeneity were included. The strength of this systematic review is the broad search for prospective studies of satisfactory quality with a low risk of bias. Also in this case EBUS-TBNA and mediastinoscopy showed a similar performance for mediastinal staging of NSCLC (31).

It is important to underline that most of the studies included in the above mentioned metanalyses used either EUS-FNA or EBUS-TBNA to sample the mediastinal lymph nodes. It is likely that combining the two

procedures might maximize the diagnostic accuracy of the endosonographic staging. In a randomized controlled multicenter trial comparing either surgical staging or endosonography (combined EBUS-TBNA and EUS-FNA) followed by surgical staging for mediastinal nodal staging, the surgical staging showed a sensitivity of 79% versus 85% for endosonography alone; the complication rate was respectively 6% and 1% (15). Similar results were obtained by several prospective controlled trials that directly compared the two modalities (15,32-36). Most of these studies underline that endosonography might improve the accuracy of the mediastinal staging by allowing the biopsy of lymph node stations which are not reachable by mediastinoscopy, especially if a combined EBUS/EUS approach is used (32-34).

Endosonography: staging strategy

The endosonographic mediastinal staging of lung cancer

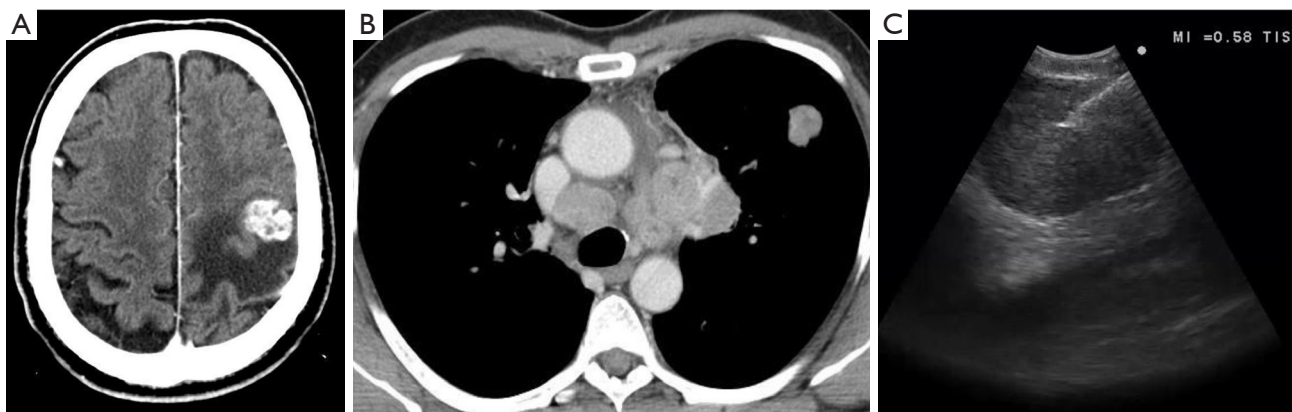


Figure 3 “Mediastinal diagnosis” through endosonography in a patient with stage IV (brain mets). (A) Left parietal brain metastasis (clinical stage IV disease); (B) enlarged mediastinal lymph nodes are evident in stations #4R, #4L, #5, #10L; (C) EBUS-TBNA from the #4R lymph node. EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration.

should keep carefully into account the clinical TNM stage and the intent of the procedure of each specific patient. Based on this information, the operator can implement a strategy that encompasses the use of EBUS alone versus a combination of EBUS and EUS-B, as well as the performance of a selective versus systematic staging.

In patients with clinical stage IV disease, endosonography is usually performed when the mediastinal lymph nodes are easier to reach than the primary tumor or the other metastatic sites, and the aim of the procedure is both to obtain a histologic diagnosis and to retrieve material of sufficient quality and quantity for thorough molecular profiling (*Figure 3*). In this setting, carrying out either an EBUS or an EUS procedure alone (depending on the location of the suspicious lymph nodes) and performing a selective sampling of one or a few lymph nodes which are likely to be metastatic based on the results of the imaging studies is justified.

In potentially operable patients lacking distant metastases at imaging studies, the thoroughness of the endosonographic staging is the key to the correct choice of the treatment. In this specific setting, evidence from the literature suggests that a systematic lymph node assessment carried out with a combined EBUS/EUS procedure is the ideal best strategy. A systematic mediastinal assessment implies that all the lymph node stations are explored and that at least the largest node with short axis size above 5 mm within each of the stations #4R, #4L and #7 are sampled even if it does not show B-mode features suggestive of malignant involvement. All the

other “abnormal” intrathoracic lymph nodes, as identified by size, FDG avidity and EBUS B-mode features can be sampled if their status is considered key to establish the treatment strategy (2,12).

In a well-known randomized trial comparing EBUS-centered versus EUS-centered staging, Kang *et al.* demonstrated that a combined, systematic EBUS/EUS mediastinal approach is associated with the best sensitivity values, but also that a systematic EBUS staging alone is superior to a systematic EUS staging alone (82.4% *vs.* 60% sensitivity, respectively) (37). More recently, the SCORE study compared the outcomes of a systematic, combined EBUS/EUS staging (investigation of FDG-PET-CT suspect lymph nodes and routine sampling of stations #4R, #4L and #7 in the presence of nodes with a short axis of ≥ 8 mm) with a targeted EBUS staging (assessment and sampling of CT-enlarged and/or FDG-PET positive nodes only). The combined, systematic approach was found to have 9% higher sensitivity for the detection of mediastinal lymph node metastases, while additional clinically relevant staging information was found in 10% of patients (38). Finally, a meta-analysis showed a significant increase in sensitivity (+12%) and detection rate of lymph node metastases using a combined EBUS and EUS compared with either procedure alone (39).

While no study has evaluated the added value of a combined EBUS/EUS procedure versus either procedure alone in patients with cN0/N1 lung cancer, it is likely that the usefulness of a combined procedure would be even more important in this specific setting. One might

in fact speculate that a thorough systematic lymph node assessment carried out with a combined EBUS/EUS-B approach might help reduce the impact of some of the factors that contribute to undermine the efficacy of the endosonography staging in patients with radiologically-occult disease. Among these, the most important are the involvement of stations which are usually out of reach (#5, #6), the presence of micrometastasis, the presence of multiple lymph nodes in the same station (which makes it difficult to sample them all), and an insufficient thoroughness of the staging (i.e., lack of systematic lymph node assessment and/or sampling).

Surgery after a negative endosonography

As a false negative result is considered the main limit of endosonography, a negative EBUS and/or EUS staging should ideally be followed by a surgical evaluation if the pre-test probability of lymph node malignant involvement is thought to be high, typically in patients with nodes which are enlarged at CT or PET positive (1,12,40). However, the scientific evidence backing such an approach is scant and debated.

A recent systematic review with metanalysis involving 3,248 patients evaluated the rate of unforeseen N2 disease in patients who were submitted to lung tumor resection after a mediastinal staging carried out with endosonography alone or with endosonography followed by mediastinoscopy in case of negative endosonography. Interestingly, the rate of unforeseen N2 disease was similar (9.9% after endosonography versus 9.6% after endosonography + mediastinoscopy), at the cost of 6.0% rate of complications by mediastinoscopy (41). A large multicenter, parallel, randomized non-inferiority trial is currently ongoing with the aim of comparing a mediastinal staging performed with EBUS/EUS with or without confirmatory mediastinoscopy in 360 patients with potentially operable NSCLC (42).

Furthermore, differences in term of survival in patients undergoing lung resection after a mediastinal staging based on endosonography alone versus endosonography followed by mediastinoscopy in case of negative endosonography results have not been demonstrated, to our knowledge. Kuijvenhoven *et al.* reported the 5-year survival of patients enrolled in the prospective, multicenter ASTER trial, which was designed to compare the value of an endosonographic versus a surgical mediastinal staging. Interestingly, the survival was 35% in both groups (43). In an attempt to

explain such an outcome, one should consider that most of the unforeseen N2 cases missed by endosonography are single station (81% in a Dutch registry), are caused by micro-metastatic lymph node involvement, and/or involve stations #5 and #6 (28). Studies demonstrate, in fact, that the worst survival rates are seen in patients with multiple station N2 disease and/or with macroscopic (>2 mm) N2 disease (28,44,45). There is also evidence suggesting that single station lymph node metastasis in the #5 or #6 locations are associated with a better 3-year survival than the involvement of other mediastinal lymph nodes in patients with a left upper lobe NSCLC (28,46).

Risk stratification

Theoretically, an accurate risk stratification of metastatic involvement of mediastinal lymph nodes would allow for a more reliable selection of patients who really need a surgical staging when endosonography does not show evidence of N2–3 disease. In particular, an optimal pre-test malignancy assessment could help identify both false positives of CT and PET and false negatives of endosonography, thus reducing the number of patients who require a confirmatory mediastinoscopy. In clinical practice, tumor histology, CT, PET, ultrasound and elastographic characteristics are the main parameters which can be taken into account to estimate a pre-test probability of malignancy for the intrathoracic lymph nodes. Several attempts have been made to use the results of these tests, alone or in various combinations, to predict the risk of malignancy of mediastinal lymph nodes, but none of them has proved reliable enough up to now.

The endosonography B-mode findings, in particular, have largely been used to try to predict the risk of malignancy of a given lymph node. Fujiwara *et al.* found that some B-mode features such as round shape, distinct margins, heterogeneous echogenicity, and the presence of the so-called central necrosis are independent predictors of malignancy (47). However, several subsequent studies have failed to replicate the above results and have shown significant discrepancy and subjectivity in the use of these ultrasound features, with consequent limited diagnostic utility (48–52).

Elastography is another ultrasound-based method that estimates the elasticity of a tissue and can help predict the probability of malignancy. Several pilot studies suggest that strain elastography (SE), used along with EBUS (EBUS-SE, *Figure 4*) can be used to differentiate

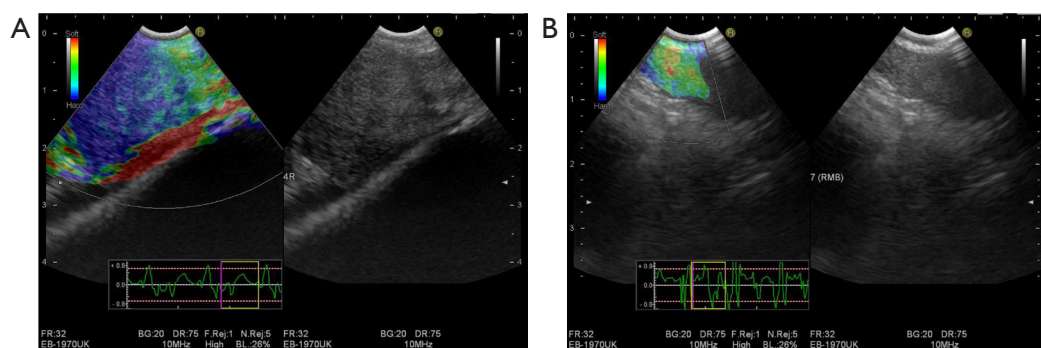


Figure 4 EBUS strain elastography. (A) Enlarged #4R lymph node characterized by a predominantly blue visual elastography pattern, indicating marked tissue stiffness. Pathology evaluation of EBUS-TBNA specimens demonstrated malignant involvement by adenocarcinoma. (B) Centimetric #7 lymph node characterized by a predominantly green visual elastography pattern, indicating low tissue stiffness. Pathology evaluation of EBUS-TBNA specimens showed a predominance of lymphocytes, as seen in a normal lymph node. EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration.

between malignant and benign mediastinal lymph nodes with high accuracy and can be useful both in guiding mediastinal lymph node sampling and in stratifying the risk of malignancy in a negative sample obtained during endosonography (53–60).

The combined assessment of EBUS-SE and EBUS B-mode findings (61), as well as the combined use of the information retrieved with CT, PET and EBUS-SE have shown promising results in their ability to correctly predict the metastatic intrathoracic lymph node involvement (60).

Finally, Ceron *et al.* have designed a mathematical model that tries to predict the probability of nodal metastasis after CT, PET and endosonography results by using the Bayes' theorem (62). The model is currently being tested in a prospective multicenter study.

Conclusions

Endosonography has revolutionized the invasive mediastinal staging of lung cancer and is certainly the best first choice in potentially operable patients with either enlarged (>1 cm on the short axis) or PET positive mediastinal lymph nodes. The sensitivity and accuracy of endosonography in the mediastinal staging of cN0/N1 patients seem significantly worse, but they have only been assessed in a handful of studies, often of poor quality. Furthermore, it is currently unclear if performing a surgical mediastinal staging in a patient with a negative endosonography assessment is associated with any advantage in terms of survival after lung resection.

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Footnote

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