



Up-to date role of interventional pulmonology in the diagnosis and staging of non-small-cell lung cancer

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Contributions: (I) Conception and design: All Authors; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Lung cancer treatment plans depend entirely on accurate diagnosis and staging. Recent advances in bronchoscopic technology have provided the interventional pulmonologist with elegant and effective sampling methods that have improved the chances to get both tissue diagnosis and thorough mediastinal staging. Among these techniques, particular attentions deserve navigational bronchoscopy and radial endobronchial ultrasound (r-EBUS) for the diagnosis of peripheral lung nodules, as well as endosonography (EBUS-TBNA, EUS/EUS-b-NA) for both the mediastinal lymph node staging and the approach to peribronchial/esophageal central lesions. The main role of the Interventional Pulmonologist in this setting is to apply these procedures based on a correct interpretation of clinical and radiographic findings, in order to maximize the chances to achieving the diagnostic and staging information needed by the multidisciplinary lung cancer team for the optimal management of each specific case.

Keywords: Bronchoscopy; endobronchial ultrasound (EBUS); non-small cell lung cancer (NSCLC); surgery

Received: 14 October 2017; Accepted: 29 October 2017; Published: 31 October 2017.

doi: 10.21037/shc.2017.10.06

View this article at: <http://dx.doi.org/10.21037/shc.2017.10.06>

Introduction

Lung cancer is still the leading cause of cancer deaths in both men and women worldwide, but the last decade has seen many advances in diagnosis and management options. Low-dose CT screening will probably transform the approach to lung cancer detection in the near future. Improvements in surgical techniques, introduction of new targeted therapies for individual gene mutations in non-squamous non-small cell lung cancer (NSCLC), and refinement of stereotactic radiotherapy for early stage cancers are all contributing to improve the quality of life and the outcomes of patients. In this scenario, it is vital that the interventional pulmonologist integrates the armamentarium of minimally invasive techniques described in this review to provide all the specialists of the

lung cancer multidisciplinary team with the information needed for optimal management of each specific case. The present review is meant to provide a systematic, yet concise evaluation of the role of interventional pulmonology procedures in each of the descriptors of the TNM (Tumor, Node, Metastasis) staging system of lung cancer.

“T” descriptor

In the assessment of the “T” descriptor for diagnostic purposes, the first key moment for the interventional pulmonologist is the review and the correct interpretation of the imaging data aimed at selecting the sampling procedure with the best possible balance between diagnostic success and complication rate.

Although a lung primary tumor may basically have either

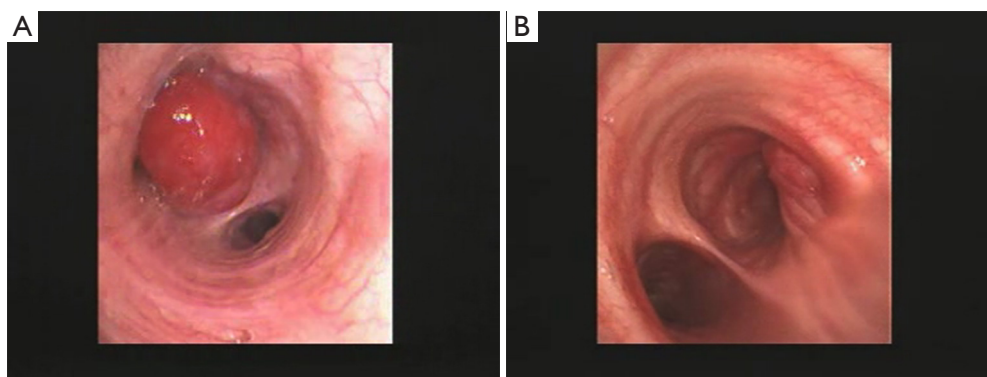


Figure 1 Bronchoscopic images. (A) Exophytic lesion occluding the anterior and apical-posterior segments of the left upper lobe bronchus; (B) exophytic and infiltrating lesions at the right tracheobronchial angle.

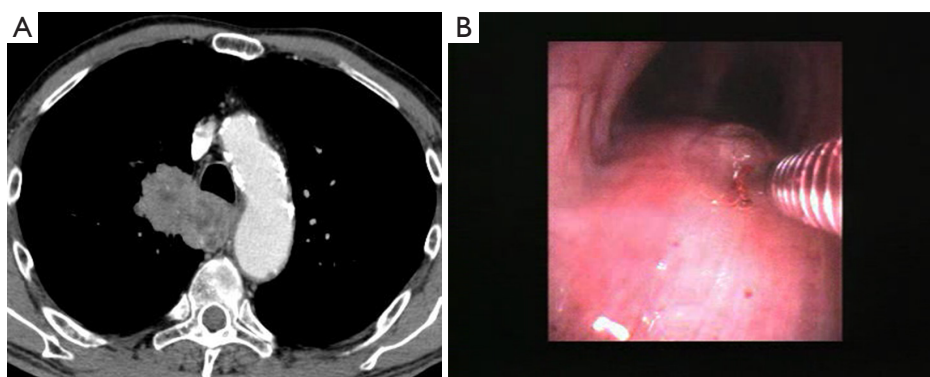


Figure 2 Peribronchial mass with airway compression. (A) CT image at the level of the aortic arch showing a lung mass of the right upper lobe that invades the mediastinum and compresses the trachea in its posterior aspect; (B) corresponding bronchoscopic image showing a stainless-steel needle piercing the posterior tracheal wall at the level of the compression, where the mucosa is uninvolved.

a central or a peripheral location, significantly different consideration may apply to individual lesions belonging to each of the above categories when it comes to choose how to biopsy them, as more specifically described below.

Central lesions

A central primary tumor is defined as a lesion that is visible at bronchoscopy and/or is located in the inner third of the lung parenchyma (1). For practical purposes, a central lesion may grow with one the following three patterns, and each of them requires a different diagnostic approach by the interventional pulmonologist: exophytic/infiltrating pattern (*Figure 1*), peribronchial pattern with airway compression (*Figure 2*), peribronchial pattern with no airway compression (*Figure 3*).

In the exophytic/infiltrating pattern, the bronchial mucosa is involved by the tumor and simple forceps biopsy, when correctly carried out, allows a definite diagnosis to be achieved in the vast majority of cases. When the surface of the lesion looks whitish due to possibly extensive necrosis, the use of a needle (transbronchial needle aspiration) that by-passes the surface and samples the lesions more in depth may reduce the risk of not getting viable tissue.

In the peribronchial pattern with airway compression, the bronchial mucosa is intact and forceps biopsy would not help you get the diagnosis. In these cases, using a needle that pierces the normal mucosa and reaches the lesion growing beyond the airway wall is indicated. Although the availability of endobronchial ultrasound (EBUS) guidance allows to elegantly visualize the lesion in almost every case and sample it safely in real time, a blind transbronchial

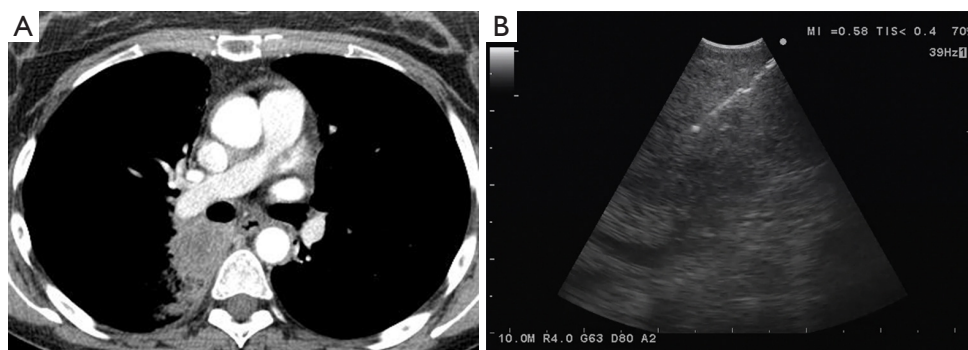


Figure 3 Peribronchial mass without airway compressions. (A) CT image taken just below the tracheal carina showing a lung mass of the right upper lobe that lies beyond the posterior wall of the right mainstem bronchus and of the bronchus intermedius without compressing them; (B) endobronchial ultrasound is used to visualize and sample (EBUS-TBNA) the lesion.

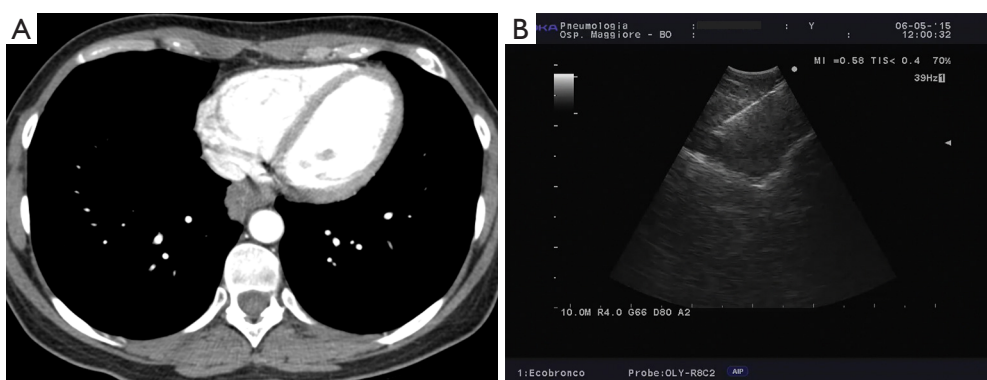


Figure 4 Periesophageal pulmonary lesion. (A) CT image taken at the lower lobes level showing a right lower lobe lung nodule lying between the heart, the descending aorta and the esophagus; (B) a regular echobronchoscope (EUS-b) is used to visualize and sample the lesion.

needle aspiration procedure can also be carried out successfully by using the landmark represented by the area of airway compression, especially when this area is quite large and evident (*Figure 2*).

In the peribronchial pattern with no airway compression, the lesion is totally invisible at bronchoscopy, regardless of its size, as it grows beyond the airway and does not compress it. In this specific case, optimization of diagnostic yield and reduction of possible complications can only be achieved by using the ultrasound guidance (*Figure 3*). Literature suggests that linear EBUS has a very high diagnostic yield (>90%) and a negligible complication rate when used to sample central parenchymal lesions not visible at standard bronchoscopy (2-4). Less frequently, the primary tumor can be difficult or impossible to access from the airways, but adjacent to the esophagus; in these cases, transesophageal needle aspiration with ultrasound guidance

using an echobronchoscope (EUS-b-FNA) or a regular echogastroscope (EUS-NA) may allow to successfully sample the tumor (*Figure 4*) (5).

Peripheral lesions

Peripheral tumors are located in the outer third of the lung and are not visible at standard bronchoscopy. The diagnostic yield of bronchoscopy for diagnosis of peripheral nodules is influenced by a variety of factors (*Table 1*).

In the past decade, the technological progress has led to the introduction in the market of several useful guidance systems, such as radial EBUS, electromagnetic navigation, and virtual bronchoscopy navigation that may help successfully steer the bronchoscopic sampling devices (forceps, needles, brushes) towards peripheral pulmonary nodules for accurate biopsy. Individual studies

Table 1 Main factors influencing the yield of bronchoscopy for the diagnosis of peripheral lung lesions

Lesion size
Bronchus sign
Sampling procedure (forceps biopsy, TBNA, brushing, washing)
Operator skills/experience
Nature of lesion (malignant vs. benign)
Number of specimens taken
Imaging guide:
Virtual bronchoscopy
Electromagnetic navigation bronchoscopy
Radial endobronchial ultrasound
Fluoroscopy
CT-fluoroscopy
Ultrathin bronchoscopy

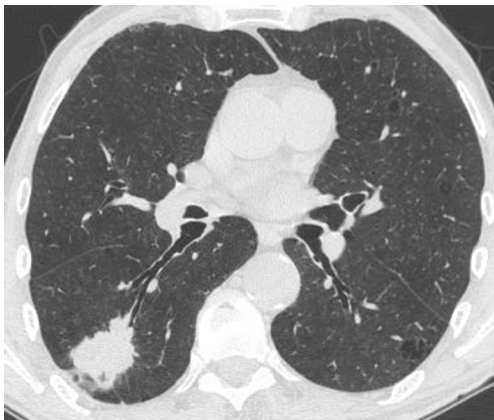


Figure 5 CT image taken at the lower lobes level showing a right lower lobe lung mass and an airway leading straight to the lesion (“bronchus sign”).

and systematic reviews regarding guided bronchoscopy with newly introduced systems suggest that a diagnostic yield of approximately 70% can be steadily reached with a very low complication rate (6-12). The drawbacks of these new methods are their quite high initial and running costs, as well as their time-consume, making them more easily doable under moderate or deep sedation.

Besides guidance systems, other factors may significantly influence the success rate of bronchoscopy in the setting of peripheral lesions (*Table 1*). While larger nodule size (>2 cm)

and greater operator skills/experience intuitively increase the success rate (12), the influence of the presence/absence of the bronchus sign as well as the sampling method that is used for biopsy are often undervalued.

The presence of the so called “bronchus sign”, a radiologic sign visible at CT and characterized by the presence of a bronchus leading to the lesion (*Figure 5*), is a key factor predicting a successful biopsy regardless of the guidance system that is used (13-15).

As for the device used for sampling, evidence from the literature suggests that transbronchial needle aspiration is the single method associated with the best diagnostic success, and should always be used, along with transbronchial lung biopsy, to optimize the diagnostic yield of bronchoscopy. It is thought that most of the added value of TBNA in patients with peripheral nodules or masses is related to the ability to diagnose peribronchial lesions. Unlike other bronchoscopic sampling tools, such as forceps for TBLB, which follow the airway lumen and are particularly valuable in the presence of lesions that grow, at least partially, within the lumen (intraluminal lesions), TBNA can be used to pierce the bronchus and also reach peribronchial lesions. Interestingly, the superiority of TBNA versus TBLB in the approach to peripheral lesions is independent of the guidance system used to reach the lesion (12,16,17).

“N” descriptor

The possibility to sample hilar and mediastinal lesions located besides the airway wall has been certainly the greatest advance associated with the use of flexible bronchoscopy. Reports on the attempt to sample mediastinal lymph nodes endoscopically date back to the 40s when E. Schieppati described the first transbronchial needle aspiration, performed during rigid bronchoscopy on a subcarinal node (18,19), but the procedure did not actually gain large popularity and widespread use probably due to technical difficulties associated with the use of rigid bronchoscopy (discomfort to the patient or need for general anesthesia, and lack of training in rigid bronchoscopy for respiratory physicians), and the contemporary development of more definitive surgical procedures such as mediastinoscopy.

The father of modern TBNA is KP Wang who, without knowledge of the abovementioned experiences, performed in 1978, five right paratracheal lymph node aspirations during rigid bronchoscopy with an esophageal varices needle (20). Encouraged by the results of the procedure



Figure 6 CT image taken at the upper lobes level showing a small (<1 cm) nodule of the right upper lobe and a 1.5 cm #4R lymph node with focal hypodense area.

and by the absence of remarkable bleeding, Wang predicted the potential application of TBNA with the flexible bronchoscope and focused on the development of flexible, disposable needles. The first dedicated transbronchial aspiration needle for use with flexible bronchoscope became available in 1983 (10), and was subsequently modified to provide better protection of the scope (21) and better suction capacity (22). The first histology needle for use with flexible bronchoscopy was developed in 1985 (23) and was subsequently improved to overcome the same problems experienced with the needle for cytology specimens (24). Almost 40 years after its introduction, strengths and limits of conventional TBNA are well known and have been listed in a recent systematic review (25). Major predictors of success in an unselected population, as well as in patients with suspected/known lung cancer, include lymph node size (short axis length ≥ 2 cm), presence of abnormal endoscopic findings, subcarinal and right paratracheal location, and the use of histological needle by an experienced bronchoscopist (25). A very interesting meta-analysis on the results of TBNA in the mediastinal staging of lung cancer selected, based on rigorous criteria, 13 studies out of 525 initially taken into account (26). Such analysis basically confirmed the very high specificity of the method, but also clearly showed that its sensitivity largely depends on the prevalence of lymph node metastasis in the population being studied. In particular, the sensitivity of TBNA proved high in studies with high prevalence of N2–N3 involvement, and the general implication was that the mediastinal nodes were markedly enlarged in these study populations. On the contrary, TBNA yield was much lower than previously thought in populations with low prevalence of lymph node metastasis.

These data suggest that the primary role for TBNA in the mediastinal staging of NSCLC should be that of confirming a neoplastic lymph node involvement which looks likely based on the results of imaging techniques, by virtue of its high specificity and sensitivity in this specific setting (26). The main reason for the above findings is that conventional TBNA is essentially a “blind” procedure, as target lymph nodes cannot be visualized directly by the operator and the site for aspiration/biopsy is chosen based on the knowledge of a few endobronchial landmarks and prior contrast enhancement CT evaluation. In the last 15 years, the advent of endobronchial ultrasounds guided transbronchial needle aspiration (EBUS-TBNA), a technique that couples ultrasounds and TBNA has led to a significant improvement of the success rate of bronchoscopic mediastinal sampling and has markedly reduced the need for diagnostic and staging surgical procedures, such as mediastinoscopy and video-assisted thoracoscopy (VATS). EBUS-TBNA is performed using a dedicated bronchoscope with a curvilinear ultrasound transducer located at its tip, and has a dedicated working channel that allows the introduction of dedicated needles. EBUS-TBNA is, by now, state of art in mediastinal diagnosis, mediastinal staging and mediastinal restaging of lung cancer owing to its simplicity, safety and effectiveness.

Mediastinal diagnosis

EBUS-TBNA is often the easiest way to retrieve diagnostic tissue in patients with suspected lung cancer, and it represents the first step diagnostic technique in many patients with advanced lung cancer, especially if the lung primary tumor is peripheral (*Figure 6*). When used in this specific setting, the aim of the procedure is not only histologic diagnosis and accurate phenotyping, but also genotyping.

A number of individual studies suggest that the diagnostic success of EBUS-TBNA in the mediastinal diagnosis of lung cancer exceeds 85–95%, and that the procedure is extremely safe (27–34).

Interestingly, EBUS-derived samples have proven amenable for extensive cancer genotyping, a condition which is key to its continued success in the era of personalized treatment of lung cancer. While testing for a limited number of genes (EGFR, KRAS, and ALK) on EBUS-samples has been proven successful in the vast majority (>90%) of patients (35–39), new molecular markers with important therapeutic implications (i.e., ROS1, PDL1)

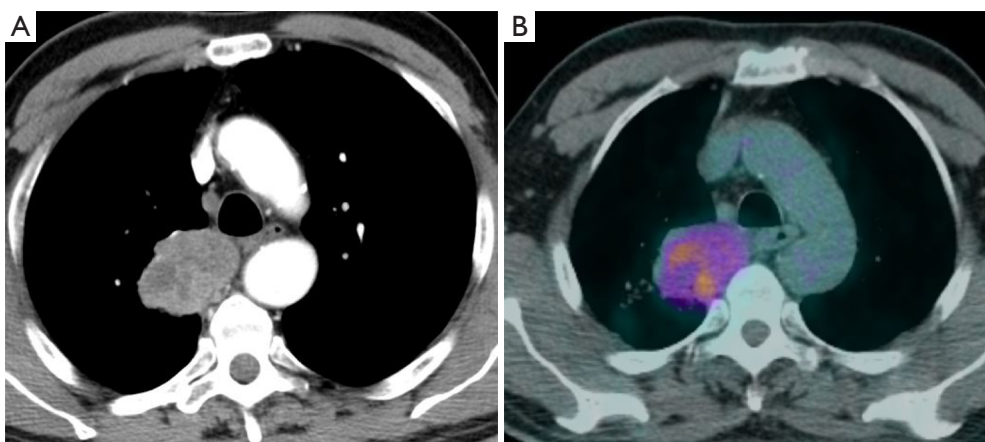


Figure 7 Central tumor with negative mediastinum at CT and PET. (A) CT image showing a right upper lobe central mass and a small (<1 cm) lymph node in the #4R station; (B) corresponding PET image showing uptake only by the lung mass.

require testing for first-line oncological treatment, and many more will probably come in the near future (40).

In the attempt to keep the pace of this evolution, several steps are being implemented. First, international associations such as the American College of Chest Physicians and the World Association for Bronchology and Interventional Pulmonology have reviewed the pertinent literature and have issued guidelines on the acquisition and processing of EBUS-TBNA samples with the idea of optimizing and possibly standardizing it, as well as promoting research in the gray areas (41,42). Meanwhile, the industry is trying to help the clinicians get better material in terms of quality and quantity by producing new needles such as the pro-core needles or the 19-gauge needles (43-47). Finally, improvement in the sensitivity of the tools used for testing (i.e., Next Generation Sequencing) will probably provide the chance to test more genes with a limited amount of neoplastic tissue (48-51).

Mediastinal staging

Accurate mediastinal staging of lung cancer is key to appropriate treatment planning in the absence of distant metastases. Endosonography (EBUS-TBNA ± EUS-NA/EUS-b-FNA) represents a valid alternative to surgical staging, as shown by studies demonstrating improved nodal tissue staging, reduction of number of futile thoracotomies, and cost-effectiveness (34,52-55). In the most robust of such trials, patients undergoing mediastinal staging were randomized towards mediastinoscopy or endosonography (EBUS +

EUS), followed by mediastinoscopy in those cases in which no metastases were found by endosonography (53). The investigators found a 79% sensitivity for endosonography, an 85% sensitivity for mediastinoscopy and a 94% sensitivity for endosonography followed by mediastinoscopy (53). Based on these results, both the ACCP and the combined ESGE/ERS/ESTS guidelines suggest that endosonography, followed by mediastinoscopy in patients with negative endosonography but high risk of mediastinal metastasis, should be the preferred staging modality (56-58).

The importance of surgical staging after a negative endosonography evaluation remains particularly important in lung cancer patients lacking evidence of lymph node metastases at imaging studies (CT and PET) if the tumor is centrally located (Figure 7) or has clinical N1 involvement (Figure 8). The prevalence of occult mediastinal metastases (i.e., as metastases detected at surgery in spite of negative CT and PET) in these patients, in fact, may be as high as 20–25%, whereas the results of mediastinal staging via endosonography may be variable and somehow unsatisfactory (Table 2).

Initial studies that evaluated the staging role of EBUS in lung cancer patients with either radiologically (lymph nodes <1 cm at CT) or PET normal mediastinum attributed at this method sensitivity and negative predictive values (NPV) as high as 92%/96% and 89%/99%, respectively (59,60). More recent trials performed in the same setting came to quite different results. Shingyoji *et al.* carried out a single center retrospective analysis of their 113 EBUS procedures performed for staging purposes in lung cancer patients with

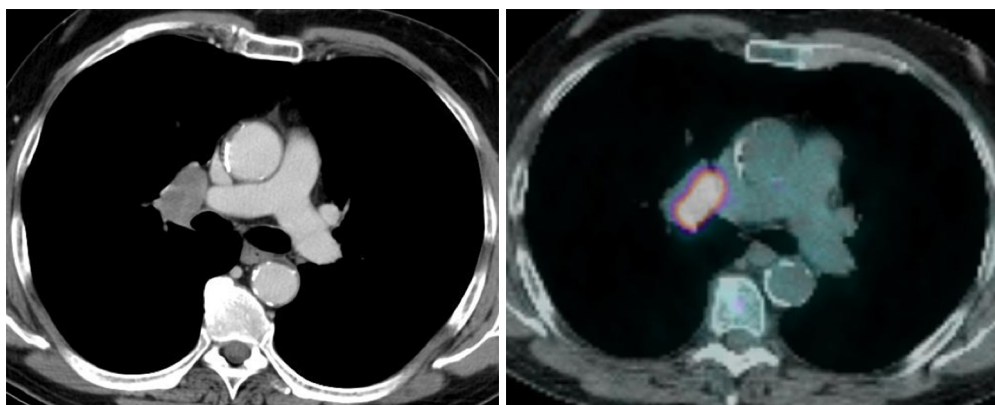


Figure 8 cN1 involvement. (A) CT image at the level of the tracheal carina showing an enlarged right hilar lymph node (station #11Rs); (B) corresponding PET image showing marked lymph node uptake.

Table 2 Recent trials designed to evaluate the role of systematic staging with endosonography in patients with cN0/1 lung cancer

Study	Design	Patients	Region	Inclusion criteria	Index test	Ref. standard	Prevalence of N2	Sensitivity/NPV
Dooms <i>et al.</i> <i>Chest</i> 2015	Prospective, multicenter	100	EU	Resectable pts with cN1 (CT-PET)	EBUS ± EUS	Surgery	N2 = 24%	38%/83%
Shingyoji <i>et al.</i> <i>ATS</i> 2014	Retrospective, single center	113	Japan	Resectable pts with cN0 (CT-PET)	EBUS	Surgery	N2 = 17.6%	35%/88%
Ong <i>et al.</i> <i>Ann ATS</i> 2015	Retrospective, multicenter	220	USA	Resectable with cN0 (CT-PET)	EBUS	Surgery or imaging follow-up	N1 + N2 = 22%; N2 + N3 = 8%	36.7%/84.7%

negative mediastinum at CT and PET. The prevalence of occult mediastinal metastases in this series was 17.6%, whereas sensitivity and NPV of EBUS were 38% and 88%, respectively (61). Ong *et al.* retrospectively review the EBUS-TBNAs performed for lung cancer staging at two major academic centers from 2009 to 2014 (62). Two hundred and twenty patients with radiographic N0 disease [lymph nodes (LN) ≤ 1 cm in the short axis and SUV max ≤ 2.5 by PET/CT] were included. Primary outcome was sensitivity and NPV of EBUS-TBNA. Overall sensitivity and NPV of EBUS were 36% and 85%, respectively. Excluding patients with occult disease “outside” the reach of EBUS the sensitivity and NPV of EBUS were 60% and 93%, respectively.

Dooms *et al.* performed a prospective multicentric study aimed at evaluating the role of endosonography in patients with clinical N1 tumors (63). Consecutive patients with operable and resectable cN1 NSCLC underwent a lobe specific mediastinal nodal staging by endosonography.

The primary study outcome was sensitivity to detect N2 disease. The secondary end points were the prevalence of N2 disease, the NPV of both endosonography and endosonography with confirmatory mediastinoscopy, and the number of patients needed to detect one additional N2 disease with mediastinoscopy. Of the 100 patients with cN1 on imaging, 24 patients were diagnosed with N2 disease. Invasive mediastinal nodal staging with endosonography alone had a sensitivity of 38%, which increased to 73% by adding a mediastinoscopy. NPV was 81% and 91%, respectively. Ten mediastinoscopies were needed to detect one additional N2 disease missed by endosonography.

Although the latter 3 studies have been criticized because the use of EUS along with EBUS was not used in 2 (61-63) and was left at the discretion of the each investigators in the remaining one (63), the suboptimal results of EBUS staging in lung cancer patients with normal mediastinum at imaging studies or cN1 deserve further attention and, possibly, evaluation in larger prospective well designed trials.

Table 3 Results of the studies evaluating the role of endosonography in the mediastinal restaging of lung cancer

Study	Design	Patients	Region	Inclusion criteria	Index test	Ref. standard	Prevalence of N2	Sensitivity/NPV
Herth <i>et al.</i> <i>JCO</i> 2008	Retrospective, multicenter	124	EU, USA, Japan	N2 disease after neoadjuvant CT	EBUS	Surgery	94%	76%/20%
Szlubovski <i>et al.</i> <i>EJCTS</i> 2010	Prospective, single center	61	Poland	N2 disease after neoadjuvant CT	EBUS	Surgery	44%	67%/78%
Szlubovski <i>et al.</i> <i>EJCTS</i> 2014	Prospective, single center	106	Poland	N2 disease after neoadjuvant CT	EBUS + EUS-b	Surgery	51.90%	67%/73%
Nasir <i>et al.</i> <i>ATS</i> 2014	Retrospective, single center	32	USA	N2 disease after neoadjuvant CT	EBUS or EUS	Surgery or imaging follow-up	18.80%	50%/88%
Cetinkaya <i>et al.</i> <i>Endosc Ultras</i> 2017	Retrospective, multicenter	44	Turkey	N2 disease after neoadjuvant CT and/or RT	EBUS	Surgery	63.60%	82%/88%

Mediastinal re-staging

The role of endosonography for mediastinal restaging of N2 disease after induction chemotherapy and/or radiotherapy has been evaluated in a limited number of studies with a similar study design (*Table 3*) (64–68). Albeit variable, the sensitivity of endosonography in this setting (50–82%) proved somewhat lower than that usually achieved in lung cancer patients undergoing the procedure for upfront mediastinal staging. Furthermore, data show a quite evident relationship between prevalence of residual N2 disease after induction treatment and the sensitivity of EBUS restaging (*Table 3*). Interestingly, in the only study in which restaging was carried out with combined EBUS and EUS, the overall sensitivity (67%) was significantly higher than that of either EBUS (48%, $P < 0.001$) or EUS (61%, $P < 0.02$) alone (67). Small lymph node size, presence of extensive lymph node fibrosis, very limited metastatic lymph node involvement, and metastatic involvement of lymph nodes out of reach of EBUS (i.e., station #6) are the main reasons taken into account to explain the suboptimal result of mediastinal restaging with endosonography (64–68).

Given the above results, endosonography for mediastinal restaging can be considered a useful test to confirm, but not to rule out metastatic lymph node involvement. Therefore, surgical staging remains crucial in patients with negative endosonography results (64–68).

“M” descriptor

The interventional pulmonologist may also have a role in confirming the presence of intra and extrathoracic metastases belonging to the “M” descriptor.

It is increasingly more common to see patients with multiple lung nodules, sometimes bilateral, that can be either expression of metastatic disease or of multiple synchronous lesions. Use of the previously described endoscopic biopsy procedures aimed at sampling parenchymal lesions, coupled with molecular biology testing aimed at studying the genetic status of the different lesions may help classify them correctly and help choose the most appropriate treatment plan (*Figure 9*) (69).

Metastatic pleural effusion can be safely and elegantly demonstrated with ultrasound-assisted thoracentesis (*Figure 10*) or medical thoracoscopy (70).

Furthermore, recent data demonstrate that the left adrenal can be seen and safely sampled transgastrically by the interventional pulmonologist with a regular EUS in the vast majority of patients (*Figure 11*). In a pilot study, Crombag *et al.* could identify the left adrenal in 85% of patients in whom an attempt was made to visualize the gland (71). More recently, a multicenter randomized trial showed that left adrenal gland could be analyzed and sampled with similar success rate with the regular echogastroscope as well as with an EUS (72).

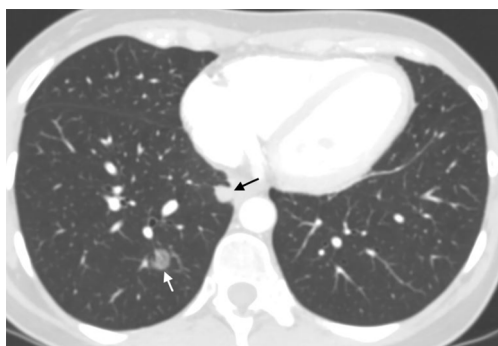


Figure 9 CT image showing a 1 cm pure ground glass nodule of the posterior segment of the right lower lobe bronchus (white arrow), as well as a 1 cm solid nodule adjacent to the esophagus, between heart and descending aorta (black arrow). Cytology from the solid nodule that was sampled through EBUS-b-FNA, yielded a diagnosis of metastasis from colonic adenocarcinoma. The ground glass lesion was sampled with a CT-guided needle approach and proved to be a lung adenocarcinoma.



Figure 10 Transthoracic ultrasound showing a free-flowing right-sided pleural effusion in a patient with cT2N0 lung adenocarcinoma. Cell-block prepared from the fluid taken during ultrasound-guided thoracentesis showed metastatic involvement.

Acknowledgments

Funding: None.

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/shc.2017.10.06>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related

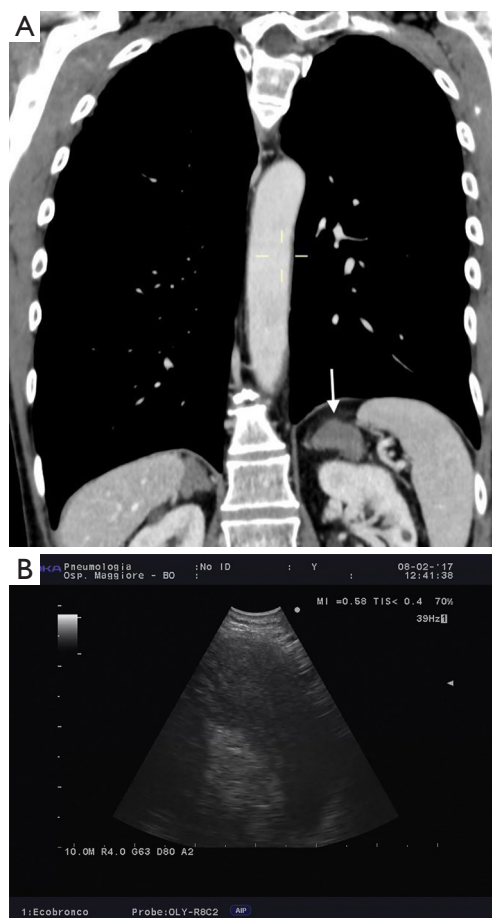


Figure 11 Left adrenal metastasis from lung adenocarcinoma. (A) CT image (coronal section) showing an enlarged left adrenal gland (arrow) in a patient with cT2aN0 lung adenocarcinoma; (B) endoscopic ultrasound, performed with a regular echobronchoscope (EUS-b), allows perfect visualization and sampling of the lesion.

to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/shc.2017.10.06

Cite this article as: Trisolini R, Natali F, Fois A. Up-to date role of interventional pulmonology in the diagnosis and staging of non-small-cell lung cancer. *Shanghai Chest* 2017;1:50.