

# Staging lung cancer: role of endobronchial ultrasound

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**Abstract:** Accurate staging is the first step in the management of lung cancer. Nodal staging is quite important for physicians to be able to judge the primary operability of patients harboring no distant metastasis. For many years, mediastinoscopy has been considered a “gold standard” modality for nodal staging. Mediastinoscopy is known to be a highly sensitive procedure for mediastinal staging and has been performed worldwide, but is invasive. Because of this, clinicians have sought a less invasive modality for nodal staging. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a minimally invasive modality for diagnosis and staging of lung cancer. EBUS-TBNA is a needle biopsy procedure that has accessibility compatible with the reach of the convex-probe EBUS scope, so N1 nodes are also assessable. The diagnostic yield is similar to that of mediastinoscopy, and the core obtained by the dedicated needle biopsy can be used for histological assessment to determine the subtypes of lung cancer. The samples can also be used to test for various biomarkers using immunohistochemistry, polymerase chain reaction for DNA/complementary DNA, and in situ hybridization, and the technique is useful for selecting candidates for specific molecular-targeted therapeutic agents. According to the newly published American College of Chest Physicians guideline, EBUS-TBNA is now considered “the best first test” for nodal staging in patients with radiologically suspicious nodes. Appropriate training and thorough clinical experience is required to be able to perform correct nodal staging using this procedure.

**Keywords:** lung cancer, staging, endobronchial ultrasound, transbronchial biopsy

## Introduction

Nodal staging is key in the management of early-stage lung cancer. The prognosis and primary operability of a patient is influenced by the presence of mediastinal lymph node metastasis. Nodal staging is usually initiated using noninvasive radiological modalities such as chest computed tomography (CT) and integrated positron emission tomography (PET)-CT. According to the third American College of Chest Physicians guideline on nodal staging, further invasive staging can be waived in patients with a small-sized peripheral primary tumor (<3 cm) and a radiologically normal mediastinum.<sup>1</sup> In other cases, invasive staging modalities are required for tissue confirmation. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) was introduced in 2004 as a less invasive modality for the diagnosis of mediastinal and hilar lymph node metastasis.<sup>2</sup> EBUS-TBNA can be performed on an outpatient basis under local anesthesia with conscious sedation.<sup>3</sup> The accessibility is wider than with mediastinoscopy, which includes hilar lymph nodes.<sup>2</sup> If combined with endoscopic ultrasound-guided fine needle aspiration (EUS-FNA), most of the mediastinal and hilar lymph nodes

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can be assessed.<sup>4</sup> Several meta-analyses have confirmed that EBUS-TBNA is a diagnostic tool with high sensitivity and specificity in the detection of metastatic nodes adjacent to the tracheobronchial tree and it is also regarded as a safe and less invasive procedure.<sup>5-7</sup> Therefore, EBUS-TBNA is now widely accepted as a first-step procedure for confirmation of suspicious nodal disease in patients with lung cancer.

## Initial staging in lung cancer

Staging of lung cancer begins with radiology. CT is usually used for initial evaluation of the disease. For nodal staging, the sensitivity, specificity, and diagnostic accuracy of chest CT scan is 68%, 65%, and 66%, respectively, if significant lymphadenopathy is defined as a short axis of 1 cm or more in size.<sup>8</sup> PET using 18-fluorodeoxyglucose or PET-CT showed higher diagnostic accuracy than CT alone for mediastinal staging.<sup>9</sup> A meta-analysis reported that PET-CT has a median sensitivity and specificity of 100% and 78% for enlarged lymph nodes (>1 cm), and 82% and 93% for normal-sized lymph nodes in detecting metastatic lymph nodes, respectively.<sup>1</sup> There is a limitation for FDG-PET in that metastatic lesions less than 8 mm in diameter are likely to be reported as false negative.<sup>1</sup> Due to such limitations, histological confirmation is recommended when nodal disease is suspected by radiology.

## Nodal staging by mediastinoscopy

Mediastinoscopy has been a standard procedure for nodal staging in lung cancer, and is a minor surgery performed

in the operating room under general anesthesia.<sup>10</sup> Several systematic reviews and meta-analyses reported the yield of nodal staging for non-small cell lung cancer by mediastinoscopy to have a pooled sensitivity of 57%–96% and a pooled specificity of 100%<sup>11</sup> (Table 1). Complication rates are very low, but major complications, including bleeding, recurrent nerve paralysis, and mortality have been reported.<sup>12,13</sup> Mediastinoscopy can access the major areas of the mediastinum and right station 10, but there is some difficulty reaching the posterior side of the subcarinal node (station 7).

## Nodal staging by EBUS-TBNA

EBUS-TBNA is a minimally invasive modality for nodal staging in patients with lung cancer. This needle biopsy procedure shows high sensitivity and specificity. Several systematic reviews and meta-analyses have reported the yield of nodal staging for non-small cell lung cancer by EBUS-TBNA to have a pooled sensitivity of 88%–93% and a pooled specificity of 100%.<sup>5-7</sup> In comparison with PET or PET-CT, the sensitivity, specificity, and accuracy of EBUS-TBNA were superior.<sup>14,15</sup>

The accessibility of EBUS-TBNA is the same as the reach of the convex-probe EBUS scope, which includes the hilar nodes. Its utility for differentiating between N0 and N1 disease has also been reported.<sup>16</sup> Lymph nodes that are away from the airway cannot be accessed, such as the prevascular nodes (3a), the subaortic and para-aortic nodes (5 and 6), and the paraesophageal and pulmonary ligament

**Table 1** Endobronchial ultrasound-guided transbronchial needle aspiration for nodal staging in patients with lung cancer

Reference	Year	Patients	Sensitivity	Specificity	PPV	NPV	Stage	Safety
Yasufuku et al <sup>2</sup>	2004	70	96%	100%	100%	92%	cN1-3	No complication
Yasufuku et al <sup>48</sup>	2005	108	95%	100%	100%	90%	cN1-3	No complication
Herth et al <sup>49</sup>	2006	100	92%	100%	100%	96%	cN0	No complication
Yasufuku et al <sup>14</sup>	2006	120	92%	100%	100%	97%	cN1-3	No complication
Nakajima et al <sup>27</sup>	2007	43	92%	100%	100%	90%	cN0-3	No complication
Herth et al <sup>50</sup>	2008	97	89%	100%	100%	99%	cN0	No complication
Lee et al <sup>51</sup>	2008	102	94%	100%	100%	97%	cN2-3	No complication
Wallace et al <sup>52</sup>	2008	138	69%	100%	100%	88%	cN2-3	No complication
Bauwens et al <sup>53</sup>	2008	106	95%	100%	100%	91%	cN1-3	No complication
Hwangbo et al <sup>54</sup>	2009	117	90%	100%	100%	97%	cN2-3	No complication
Szlabowski et al <sup>55</sup>	2009	226	89%	100%	100%	84%	cN0-3	No complication
Rintoul et al <sup>56</sup>	2009	109	91%	100%	100%	60%	cN1-3	No complication
Fielding et al <sup>57</sup>	2009	68	95%	100%	100%	67%	cN1-3	No complication
Nakajima et al <sup>38</sup>	2010	49	67%	100%	100%	93%	cN1-3	No complication
Herth et al <sup>58</sup>	2010	139	91%	100%	100%	92%	cN1-3	No complication
Cerfolio et al <sup>59</sup>	2010	92	57%	100%	100%	79%	cN2	No complication
Hwangbo et al <sup>60</sup>	2010	150	84%	100%	100%	93%	cN2-3	No complication
Yasufuku et al <sup>19</sup>	2011	153	81%	100%	100%	91%	cN0-3	No complication
Memoli et al <sup>61</sup>	2011	100	87%	100%	100%	89%	cN1-3	No complication
Steinfort et al <sup>62</sup>	2011	117	95%	100%	100%	83%	cN1-3	No complication

**Abbreviations:** PPV, positive predictive value; NPV, negative predictive value.

nodes (8 and 9). EUS-FNA via the esophagus can access stations 8 and 9; therefore, in combination of EBUS-TBNA and EUS-FNA, the majority of mediastinum and hilar area can be assessed by combined EBUS/EUS-NA. A higher diagnostic yield has been reported using a combination of EBUS-TBNA and EUS-FNA for nodal staging in lung cancer.<sup>8,17</sup> In the ASTER trial, the combined needle biopsy modality of EBUS-TBNA plus EUS-FNA and surgical staging showed a higher diagnostic yield and fewer unnecessary thoracotomies compared with surgical staging alone.<sup>18</sup>

Recently, the diagnostic yield of EBUS-TBNA alone was proved to be similar to that of mediastinoscopy in a well-controlled prospective study of surgical candidates;<sup>19</sup> this study suggested that mediastinoscopy could be replaced by EBUS-TBNA if performed by expert hands. A recently published guideline for invasive staging in lung cancer reported that ultrasound-guided needle biopsy (EBUS-TBNA and/or EUS-FNA) is the “best first test” prior to surgical staging;<sup>20</sup> however, if the needle biopsy shows negative results, further invasive staging such as mediastinoscopy or video-assisted surgery will be needed for confirmation of the result.

EBUS-TBNA can be used for nodal staging in patients with small cell lung cancer. Surgical indication for small cell lung cancer is limited to stage I disease, so diagnosis of N1 nodes is also important and EBUS-TBNA is very useful in this regard. It was reported that the sensitivity, specificity, and diagnostic accuracy rate of EBUS-TBNA for small cell lung cancer is 96.4%, 100%, and 97.2%, respectively.<sup>21</sup>

## Restaging in lung cancer

After induction treatment using chemotherapy and/or radiotherapy, we often find that we need to restage the lymph nodes. Repeat mediastinoscopy is possible;<sup>22</sup> however, the diagnostic yield is not as high as the initial mediastinoscopy due to technical difficulties caused by adhesions.<sup>23</sup> EBUS-TBNA can be repeated during and after treatment. Because of the limitations of the needle biopsy procedure, the diagnostic yield for restaging is not as high as for the initial EBUS-TBNA, which is the same as mediastinoscopy.<sup>22</sup> Although it has a lower diagnostic yield for restaging, EBUS-TBNA is minimally invasive and is still of value as a restaging procedure.

## Diagnosis of recurrent nodal disease

EBUS-TBNA is also useful for diagnosis of lymph node recurrence after treatment for lung cancer.<sup>24</sup> This is because swollen nodes due to benign entities or neoplasms other than the previous lung cancer are at times encountered. In our experience,

benign adenopathy is often recognized after surgery.<sup>25</sup> Lymph node inflammation after surgery mimics cancer recurrence by radiology, and tissue confirmation by mediastinoscopy or video-assisted thoracic surgery is difficult due to adhesions after surgery. Hence, EBUS-TBNA can be a useful procedure for diagnosis of post-surgical nodal recurrence.<sup>26</sup>

## Subtyping of lung cancer and biomarker testing

Samples obtained by EBUS-TBNA are essentially cytological materials. Using several techniques, such as the “tissue coagulation clot method” or “cell block” making, the sample can be used for histological evaluation including immunohistochemistry.<sup>27,28</sup> In combination with immunohistochemistry, the rate of non-small cell lung cancer not otherwise specified is low,<sup>29</sup> and the majority of the samples can be used to diagnose the subtypes of lung cancer.

Moreover, the EBUS-TBNA samples can be used for tests using several biomarkers if an adequate sample is obtained.<sup>30,31</sup> Detection of gene mutations, including epidermal growth factor receptor and K-Ras, and of aberrant fusion genes, such as ALK fusion gene, can be done using EBUS-TBNA samples.<sup>32–35</sup> EBUS-TBNA can be repeated during treatment, so EBUS-TBNA samples may play an important role in exploration of drug-resistance mechanisms.<sup>36</sup> We recently demonstrated that transbronchial biopsy needle rinse solution (ultra-micro sample) can be used for multiplex polymerase chain reaction with the same accuracy as conventional biopsy samples.<sup>37</sup> In the era of biomarker and molecular-targeted management in clinical oncology, multiple biomarker testing is quite important in tailoring treatment for the individual patient, EBUS-TBNA should play a pivotal role in practice.<sup>38,39</sup>

## Training in EBUS-TBNA

Training is mandatory to obtain a high diagnostic yield, and an adequate amount of sample must be obtained for multimodal testing in EBUS-TBNA. There is a learning curve for EBUS-TBNA,<sup>40</sup> and basic training is needed to be able to perform this technique, such as a training model and simulators.<sup>41</sup> The development of an EBUS-TBNA training program and training model are important for trainees, and recent data suggest that the early use of a virtual reality simulator improves the skills and satisfaction of trainees.<sup>42</sup> Another important tool for EBUS-TBNA training is evaluating EBUS skills.<sup>43</sup> The quality of EBUS-TBNA has been evaluated using a large registry in the USA, which has provided a benchmark for this procedure and may help in quality control.<sup>44,45</sup>

Given the increasing number of EBUS-TBNA procedures being performed, we need to reconsider the education and training for bronchoscopic procedures.<sup>46</sup> Recently, we introduced a preliminary training program that consists of multistep lessons in a tandem trainee and trainer setting.<sup>47</sup> Twelve successful needle punctures is the minimum for the trainee to obtain a satisfactory diagnostic yield. We need to identify the optimal education and training program for the next-generation bronchoscopist.

## Conclusion

With the introduction of EBUS-TBNA, the paradigm has shifted for nodal staging of patients with lung cancer. The gold standard modality for this purpose, ie, mediastinoscopy, is gradually being replaced with EBUS-TBNA, and this method is the best first test for patients with radiologically suspicious lymph nodes. In addition, samples obtained by EBUS-TBNA can be used for molecular testing, which is useful for selecting appropriate candidates for molecular-targeted therapy. Therefore, EBUS-TBNA plays a pivotal role in the diagnosis and treatment of lung cancer.

## Disclosure

The authors report no conflicts of interest in this work.

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