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Evidence-Based Series 17-6 Version 2 REQUIRES UPDATING

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario

Invasive Mediastinal Staging of Non-small Cell Lung Cancer

The Expert Panel on Invasive Mediastinal Staging of Non-small Cell Lung Cancer

An assessment conducted in November 2024 indicated that Guideline 17-6 Version 2 REQUIRES UPDATING. It is still appropriate for this document to be available while this process unfolds. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment and Review Protocol)

EBS 17-6 Version 2 is comprised of 4 sections. You can access the summary and full report here: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/2221

Section 1: Guideline Recommendations (ENDORSED)
Section 2: Evidentiary Base
Section 3: EBS Development Methods and External Review Process
Section 4: Document Assessment and Review

May 3, 2018

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Guideline Report History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES and KEY CHANGES
	Search Dates	Data		
Original October 2010	2006 to August 2010	Full Report	Peer review publication Web publication	NA
Current Version 2 May 2018	2010 to Feb 2018	New data found in Section 4: Document Assessment and Review	Updated web publication	2010 recommendations are **ENDORSED**

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Evidence-Based Series 17-6 Version 2: Section 1

Invasive Mediastinal Staging of Non-small Cell Lung Cancer: Guideline Recommendations

G. Darling, J. Dickie, R. Malthaner, E. Kennedy, and the Invasive Mediastinal Staging Expert Panel

A Collaboration of Cancer Care Ontario's (CCO)
Program in Evidence-Based Care (PEBC) and Surgical Oncology Program (SOP)

Original Report Date: October 18, 2010

The 2010 guideline recommendations are

ENDORSED
This means that the recommendations are still current and relevant for decision making

Please see Section 4: Document Assessment and Review for a summary of updated evidence published between 2010 and 2018 and for details on how this Clinical Practice Guideline was ENDORSED

QUESTIONS

Primary Questions

Is invasive mediastinal staging in stage cT1-4, N0-3, M0 non-small cell lung cancer (NSCLC) patients indicated under the following circumstances?

a) Normal-sized mediastinal lymph nodes on computed tomography scan (CT), and
   i. negative positron emission tomography (PET)-CT scan in the mediastinum
   ii. positive PET-CT in the mediastinum
b) Enlarged discrete mediastinal nodes on CT (clinical N2 or N3 nodes), and
   i. negative PET-CT in the mediastinum
   ii. positive PET-CT in the mediastinum

Secondary Questions

What constitutes invasive mediastinal staging? What is the proper technique in performing invasive mediastinal staging?

a) Which node stations should be biopsied?
b) How many lymph nodes should be biopsied?

TARGET POPULATION

NSCLC patients in Ontario who have been clinically staged T1-4, N0-3, with no distant metastases.

INTENDED USERS

Thoracic surgeons, respirologists, and medical as well as radiation oncologists who treat lung cancer.

BACKGROUND

Methods

To answer the primary questions, a systematic review of existing guidelines and primary studies, and a consensus of interpretation of evidence by the members of the Invasive Mediastinal Staging Working Group (the Working Group) and the corresponding Expert Panel were used to formulate the recommendation. To answer the secondary questions, a non-systematic search of the evidence and consensus of expert opinion was used to formulate the recommendations. Please see Section 2 for details of the review methodology.

Clinical Perspective

The Working Group constructed the questions around CT and PET-CT scans, which were assumed to be standards of care for non-invasive staging. Recognizing that there are many available options and standards involved, the Working Group has chosen the following criteria for clinical consideration. Enlargement is defined as a short-axis lymph node diameter of ≥1 cm on a transverse CT scan. Quantitative assessments of PET-CT scans have been undertaken, with a comparison based on the uptake in the lesion in question compared with background activity of the lung and liver. Standardized uptake value (SUV) is calculated as the ratio of the activity in the tissue to the decay-corrected activity injected into the patient, normalized for patient body weight (2). SUV of ^{18}F Fluorodeoxyglucose (FDG) of less than or equal to 2.5 as a cut-off for normalcy is used in some studies (1). The Working Group felt that this guideline presents the best available evidence and does not expect higher level evidence to emerge in the near future. Thus, recommendations are provided for the following groups:

Group A: Normal sized mediastinal lymph nodes (MLN) on CT, and

- A1. negative PET-CT scan in the mediastinum. The recommendations for this pathway depend on the location of the primary tumour and tumour stage. Patients with central tumours can be grouped with those who have N1 disease because it is usually difficult to assess the N1 nodes separately in such cases.
- A2. positive PET-CT in the mediastinum

Group B: Enlarged (≥1 cm) discrete ipsilateral (N2) or contralateral (N3) MLNs on CT, and

- B1. negative PET-CT in the mediastinum
- B2. positive PET-CT in the mediastinum

In developing these recommendations, the Panel considered that, although PET has a higher sensitivity and specificity for evaluation of mediastinal lymph nodes compared to CT, the accuracy of PET depends on the size of mediastinal lymph nodes. Up to 25% of lymph nodes identified by PET as malignant are falsely positive. Hence pathologic confirmation of

malignancy is required so that the patient is not denied potentially curative therapy. In contrast, for normal-sized lymph nodes, PET has lower sensitivity (82%-93%). The estimated false-negative (FN) rate for a PET scan in the setting of normal-sized nodes is 20%. In a clinical setting where the probability of mediastinal lymph node metastases is increased, pathologic confirmation that the mediastinal lymph nodes are negative is required to avoid subjecting the patient to a futile (noncurative) lung resection (5).

RECOMMENDATIONS

Based on evidence from the American Association of Chest Physicians (ACCP) guideline (3) and primary literature from the systematic search:

- Invasive mediastinal staging is not needed in the case of normal-sized MLN on CT, a negative PET-CT scan, a peripheral clinical stage 1A tumour, and a negative clinical evaluation.
  - clinical stage 1A tumour defined as T1N0M0
    - T1: primary tumour diameter of 3 cm or smaller and surrounded by lung or visceral pleura or endobronchial tumour distal to the lobar bronchus
    - N0: no lymph nodes involved
    - M0: no metastases
- Invasive staging is recommended in the following cases:
  - Normal-sized MLN on CT with negative mediastinal PET-CT, and
    - the presence of a central tumour (tumour in the central third of the hemithorax), or
    - suspected N1 disease (enlarged N1 nodes and/or positive N1 nodes on PET-CT), or
    - T2 or greater tumours
  - Enlarged discrete MLN on CT (N2, N3), and negative or positive PET-CT
  - CT negative and PET positive in the mediastinum
- Invasive staging is important to confirm PET findings
- Appendix 1, Figure 1 illustrates the corresponding algorithm for these recommendations.

Based on a consensus of expert opinion:

- Five nodal stations (2R/L, 4R/L, and 7) should routinely be examined when performing invasive mediastinal staging, with at least one node sampled from each station unless none are present after actual dissection in the region of a particular nodal station
- Any enlarged or suspicious node should be biopsied
- Mediastinoscopy is the gold standard for invasive staging of the mediastinum. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) may be useful, but more data are required before it may be considered as an equivalent procedure.

Qualifying Statement - Added to the 2018 Endorsement:

- *There is important new guidance in the use of EBUS-TBNA, as highlighted in the 2013 ACCP guideline [10]:*

  "In patients with high suspicion of N2,3 involvement, either by discrete mediastinal lymph node enlargement or PET uptake (and no distant metastases), a needle technique (endobronchial ultrasound [EBUS]-needle aspiration [NA], EUS-NA or combined EBUS/EUS-NA) is recommended over surgical staging as a best first test (Grade 1B).

  In patients with an intermediate suspicion of N2,3 involvement, i.e., a radiographically normal mediastinum (by CT and PET) and a central tumor or N1 lymph node enlargement (and no distant metastases), a

needle technique (EBUS-NA, EUS-NA or combined EBUS/EUS-NA) is suggested over surgical staging as a best first test (Grade 2B). This recommendation is based on the availability of these technologies (EBUS-NA, EUS-NA or combined EBUS/EUS-NA) and the appropriate experience and skill of the operator."

- *The 2013 ACCP evidence base covers evidence up to the end of 2012. More recently, a meta-analysis (covering comparative studies published up to March 2016) estimated the pooled risk-difference of the sensitivity of EBUS/EUS versus mediastinoscopy in cohort studies and RCTs at 0.11 (95% CI -0.07 to 0.29) and 0.11 (95% CI -0.03 to 0.25), respectively, suggesting equivalence of the two procedures. The complication rate was significantly lower with endosonographic procedures [11]. There are no studies past March 2016 directly comparing EBUS/EUS to mediastinal staging.*

KEY EVIDENCE

Invasive Staging Not Required

Normal CT, negative PET-CT, and a peripheral clinical stage 1A tumour:

- The ACCP systematic review found that the FN rate of CT in the group of patients with T1 tumours (i.e., clinical stage 1A) is approximately 9% (3).
- The Scottish Intercollegiate Guidelines Network (SIGN) recommends that patients with *small* peripheral tumours and a negative CT scan of the mediastinum require no further investigation, because the rate of false negatives in all categories of patients with lung cancer is 13% (7). SIGN does not provide a definition of small, but it may be equivalent to a clinical stage 1A tumour. The European Society of Thoracic Surgeons (ESTS) does not recommend mediastinoscopy in the case of a "T1 squamous cell tumour with N0 disease on CT scan" (8), based on the results of the SIGN systematic review.
- A negative PET-CT scan in the mediastinum carries an FN rate of approximately 5% (range 3% to 6%).

Invasive Staging Recommended

Normal CT, negative PET-CT and a central tumour, N1 disease or a T2 tumour or higher:

- The ACCP systematic review found the FN rate of CT scan in the mediastinum for patients with a central tumour is 20% to 25% (3). The same review found more limited data showing that the FN rate for PET-CT scanning in the mediastinum is similarly high (24% to 83%).
- Another systematic review found an FN rate of 22% with central tumours for a CT scan in the assessment of mediastinal nodes (4).

Additional evidence published since the ACCP guidelines:

- Cerfolio et al. (6) found that patients with clinical N1 disease suggested by integrated PET-CT/CT had a relatively high incidence (17.6% after mediastinoscopy and 23.5% after endoscopic ultrasound-guided fine needle aspiration [EUS-FNA]) of unsuspected N2 disease.

Enlarged lymph nodes on CT and PET-CT positive or negative:

- The PET-CT FN rate is estimated to be 13% to 25% in patients with nodal enlargement detected by CT scan, according to two meta-analyses. These estimates were based on indirect data and patient groups that were not clearly defined. Direct data from studies in patients with mediastinal or hilar node enlargement have found a PET-CT FN rate of 20% to 28% for N2,3 involvement.

- PET-CT scanning has been shown to falsely identify malignancy in approximately one fourth of patients with nodes that are enlarged for other reasons, usually due to inflammation or infection.(5)

Qualifying Statements

- Although there is no direct evidence, based on the International Association for the Study of Lung Cancer (IASLC) staging project showing adverse prognosis of larger tumours, the working group believes that T2 tumours should undergo invasive staging.
- In addition to tumour location (i.e., central versus [vs.] peripheral), several other factors have been noted in the literature as potentially affecting the likelihood of N2 disease, including maximum SUV (maxSUV) of the primary tumour (non-FDG avid primary tumours), tumour histology, degree of differentiation, and size, and bronchoalveolar cell carcinoma. These factors should be taken into account when deciding whether to perform invasive staging.
- Mediastinoscopy continues to be the gold standard for invasive mediastinal staging, but newer techniques such as EBUS-TBNA and EUS-FNA have shown promise. Monitoring of the literature in this field is recommended as information on the performance of newer staging techniques continues to accumulate. Please see the discussion in Section 2 for more details.

FUTURE RESEARCH

Yasufuku et al. (2007) (9) have a study in progress that compares mediastinoscopy and EBUS-TBNA in the same patients. We anticipate that the results of this study will add to the body of literature on the performance characteristics of EBUS-TBNA. Further details can be found at: http://clinicaltrials.gov/ct2/show/NCT00372203.

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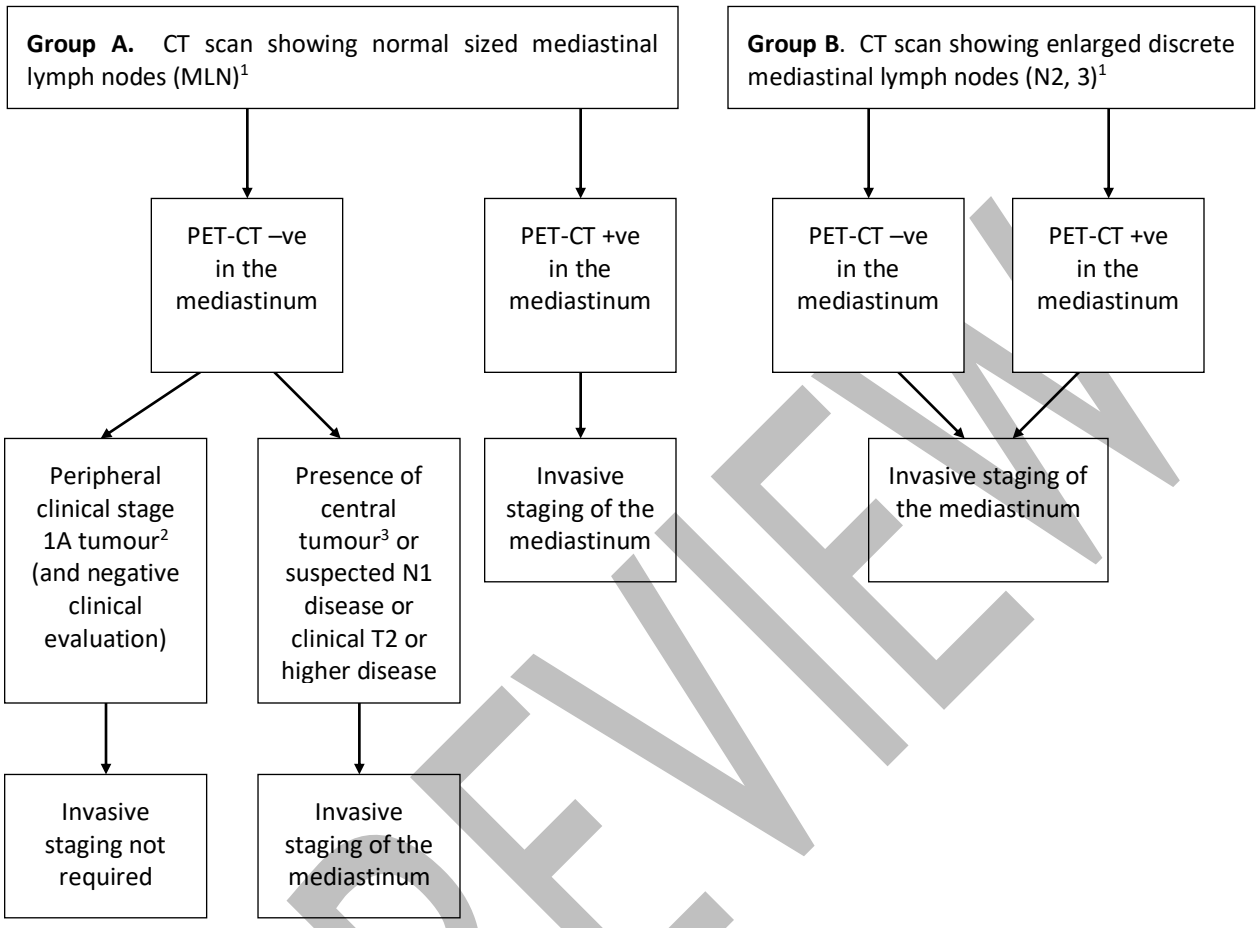
Appendix 1. Figure 1. Invasive mediastinal staging recommendations.



[1] This algorithm applies to the target population of NSCLC patients in Ontario who have been clinically staged T1-4, N0-3, with no distant metastases.

[2] Stage 1A: T1N0M0 (T1: primary tumour diameter of 3 cm or smaller and surrounded by lung or visceral pleura or endobronchial tumour distal to the lobar bronchus; N0: no lymph nodes involved; M0: no metastases).

[3] For the purposes of this guideline, a tumour in the central third of the hemithorax is considered central. A tumour in the distal two-thirds of the hemithorax is considered peripheral.

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Evidence-Based Series #17-6 Version 2: Section 2

Invasive Mediastinal Staging of Non-small Cell Lung Cancer: Evidentiary Base

G. Darling, E. Kennedy, J. Dickie, R. Malthaner, and the Invasive Mediastinal Staging Expert Panel

A Collaboration of Cancer Care Ontario's (CCO)
Program in Evidence-Based Care (PEBC) and Surgical Oncology Program (SOP)

Original Report Date: October 18, 2010

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QUESTIONS

Primary questions

Is invasive mediastinal staging in stage cT1-4, N0-3, M0 non small cell lung cancer (NSCLC) patients indicated under the following circumstances?

a) Normal sized mediastinal lymph nodes on computed tomography scan (CT), and
   i. negative positron emission tomography (PET)-CT scan in the mediastinum
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b) Enlarged discrete mediastinal nodes on CT (clinical N2 or N3 nodes), and
   i. negative PET-CT in the mediastinum
   ii. positive PET-CT in the mediastinum

Secondary Questions

What constitutes invasive mediastinal staging? What is the proper technique in performing invasive mediastinal staging?

a) Which node stations should be biopsied?
b) How many lymph nodes should be biopsied?

INTRODUCTION

Lung cancer remains the leading cause of cancer death for both men and women in Ontario, and almost 8,000 new cases are expected each year in the province (1). Most cases of lung cancer are the non-small cell type. The main factor in cancer treatment decision making is the nature and extent of the disease, represented by the stage. For NSCLC, staging is conducted according to the TNM classification system, which takes into account the size, location, and local invasion of the primary tumour; the extent of regional lymph node involvement; and the presence or absence of distant metastases. An assessment of the mediastinal lymph nodes is made to determine the N stage, which is most often used to determine whether surgical resection is appropriate. Patients without mediastinal lymph node involvement are likely to benefit from resection, while chemotherapy and/or radiotherapy may be appropriate when mediastinal lymph nodes are involved (2). The major goal of accurate staging is to avoid patients with false-negative (FN) nodes undergoing inappropriate surgery (e.g., futile lung resection), or patients with false-positive (FP) nodes being denied potentially curative surgery based on the incorrect conclusion that the cancer has become metastatic.

CT scans have historically been used to identify malignant involvement of mediastinal lymph nodes. In the past several years, PET scans have increasingly become available for use in staging the mediastinum. Integrated PET-CT is a newer option that allows the precise anatomical correlation of PET results, which can improve diagnostic accuracy. Invasive staging techniques have also evolved; mediastinoscopy has traditionally been the practice standard for invasive mediastinal staging, despite a sensitivity of only approximately 78% (3). Recently, there has been more interest in alternative methods that are less invasive, such as needle aspirations combined with endobronchial ultrasound or endoscopic ultrasound. Furthermore, the Ontario Thoracic Surgeons Community of Practice met in October 2006 and determined that a guideline for appropriate mediastinal staging was a quality of care priority.

In light of these developments, a guideline on this topic was determined to be a priority by the CCO Clinical Leadership Operations Group in September 2008, because the opinion was that quality of care could be improved through the application of consistent staging techniques throughout the province. The Invasive Mediastinal Staging Working Group (the Working Group) was subsequently formed in early 2009 to develop this guideline on the topic of invasive mediastinal staging.

The Working Group has approached the question of when invasive mediastinal staging is needed according to the results of noninvasive staging techniques (i.e., CT and PET-CT scans). Although the indications are that some locations in Ontario do not have adequate access to PET-CT scans, these recommendations are written on the assumption that PET, and integrated PET-CT in particular, are considered standard practice in the province of Ontario at this time. The guidelines do not include recommendations for mediastinal restaging or for cases of extensive mediastinal infiltration. The secondary questions of which lymph node stations to sample and how many are addressed in the discussion.

METHODS

The evidence-based series (EBS) guidelines developed by the CCO PEBC use the methods of the Practice Guidelines Development Cycle (4). For this project, the core methodology used to develop the evidentiary base was a systematic review to update the evidence base from a previously published guideline on this topic (3). Evidence was selected and reviewed by a PEBC methodologist and reviewed by the members of the Invasive Mediastinal Staging Working Group.

The systematic review is a convenient and up-to-date source of the best available evidence on invasive mediastinal staging. The body of evidence in this review is primarily

comprised of non-randomized studies. Randomized controlled trials on this topic are rare because patients are usually chosen for a particular invasive test based on the size and location of nodes detected during noninvasive staging. In addition, thoracotomy, which is considered the gold standard for determining nodal involvement, is generally only performed on patients that have negative results on invasive staging tests. Therefore, positive staging results are rarely confirmed.

The recommendations contained in this guideline are intended to promote evidence-based practice in Ontario, Canada. The PEBC is supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

Environmental Scan

In order to avoid a duplication of effort, an initial scan of the external guidelines environment was undertaken to look for existing clinical practice guidelines. This search included the National Guidelines Clearinghouse, the Canadian Medical Association Infobase, the Physicians' Query Database of the National Cancer Institute, and the Cochrane Database of Systematic Reviews.

Literature Search Strategy

MEDLINE (2006 to 11 August 2010), EMBASE (2006 to 11 August 2010), and the Cochrane Library Database of Systematic Reviews (to 11 August 2010) were searched. The literature search for this guideline started in 2006 because it is an update of the June 2006 American College of Chest Physicians (ACCP) guideline that was adopted for this guideline. The MEDLINE and EMBASE search strategies included the terms *carcinoma non-small-cell lung, lymphatic metastasis, neoplasm metastasis, neoplasm staging, biopsy, biopsy fine-needle, biopsy needle, endobronchial, endobronchial ultrasound, endoscopic, endoscopic ultrasound, endosonography, mediastinoscopy, positron-emission tomography, tomography scanners x-ray computed, ultrasound*. The reference lists from relevant articles were searched for additional relevant articles.

The systematic review was conducted to answer the primary research questions. Due to time and resource constraints, a separate systematic search for evidence regarding the secondary research questions was not conducted. Articles located through the original search were also used to answer the secondary research questions.

Study Selection Criteria

Articles were eligible for inclusion in this systematic review if they met the following criteria:

- Were the following study types: Practice guidelines, systematic reviews with or without meta-analyses, randomized phase II or III trials, other diagnostic comparative studies, or prospective case-series with diagnostic utility outcomes; non-comparative studies had to include ≥ 50 patients
- Involved an invasive staging technique, including mediastinoscopy and/or endobronchial ultrasound with needle aspiration and/or endoscopic ultrasound with needle aspiration, compared with lymph node sampling at thoracotomy;
- Reported outcomes included sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), FP rate, FN rate, and overall diagnostic accuracy. Treatment-related outcomes such as overall survival and locoregional control were also of interest but not necessary for a study to be included in the evidence base;

- Involved patient populations that underwent prior noninvasive staging using integrated CT, PET, or PET-CT;
- Published between January 2006 and 11 August 2010;
- Involved at least 20 patients.

Because of a lack of translation resources, excluded articles included those published in a language other than English, and, as well, articles with a focus on diagnostics rather than staging were excluded.

RESULTS

Environmental Scan

Five guidelines were found during the environmental scan. Further information about these guidelines can be found in Appendix 2:

1. ACCP evidence-based clinical practice guideline *Invasive mediastinal staging of lung cancer (2nd edition)* (3) (September 2007).
2. European Society of Thoracic Surgeons (ESTS) *ESTS guidelines for preoperative lymph node staging for non-small cell lung cancer* (5) (July 2007).
3. Scottish Intercollegiate Guidelines Network (SIGN) national clinical guideline *Management of patients with lung cancer* (6) (February 2005).
4. United Kingdom (UK) National Institute for Health and Clinical Excellence (NICE) guidance document *Diagnosis and treatment of lung cancer* (7) (February 2005).
5. The ACCP evidence-based clinical practice guideline *Noninvasive staging of non-small cell lung cancer* (2) (September 2007).

The Working Group reviewed these guidelines and determined that the ACCP and ESTS guidelines were highly relevant and overlapped significantly with the objectives of this guideline; however, the ACCP guideline was based on a systematic review, whereas the ESTS was consensus based. An "Assessment of Multiple SysTemAtic Reviews" (AMSTAR) review of the ACCP guideline determined that the development methods were systematic and rigorous (8). Therefore, for this guideline the Working Group chose to adopt the ACCP evidence base, which was current as of June 2006. The ESTS and SIGN documents were also used for reference. The NICE guidance document was developed in collaboration with SIGN and did not provide any information that was not already available in the other guidance documents. The ACCP guideline for noninvasive staging was a helpful reference for understanding the link between noninvasive and invasive staging.

Summary of ACCP Guideline (Detterbeck et al. [3])

In 2007, the ACCP released the second edition of their clinical practice guideline for the staging of lung cancer (3) to update the initial 2003 guidelines (9). The methods included a systematic review that focused on recommendations for invasive staging in four distinct radiographic groups, assuming no distant metastases:

- Group A: patients with extensive mediastinal infiltration;
- Group B: patients with enlargement of discrete mediastinal nodes that can be measured (>1 cm in short-axis diameter on transverse CT image);
- Group C: patients with normal mediastinal nodes determined by CT scan, but with a central tumour or suspected N1 disease (enlarged N1 nodes);
- Group D: patients with normal mediastinal and hilar nodes and a peripheral clinical stage 1 tumour.

According to this guideline, invasive staging is not indicated in the case of Group A or for patients with a peripheral clinical stage I tumour if the findings of a PET-CT scan of the mediastinum are negative. The ACCP systematic review found that the FN rate of CT in the group of patients with T1 tumours (i.e., clinical stage 1A) is approximately 9% and a negative PET-CT scan in the mediastinum carries an FN rate of approximately 5% (range, 3% to 6%).

Invasive confirmation is recommended for patients with enlarged discrete mediastinal nodes (Group B), patients with a radiographically normal mediastinum on CT scan and central tumour or N1 lymph node enlargement (Group C), and patients with a peripheral clinical stage 1 tumour where the PET-CT results are positive (Group D). According to two meta-analyses, the ACCP review reported that the PET-CT FN rate is estimated to be 13% to 25% in patients with nodal enlargement detected by CT scan. These estimates were based on indirect data and patient groups that were not clearly defined. Direct data from studies in patients with mediastinal or hilar node enlargement found a PET-CT FN rate of 20% to 28% for N2 or N3 involvement. For patients with a central tumour, the ACCP review found the FN rate for CT scanning in the mediastinum to be 20% to 25%, and more limited data showed that the FN rate for PET-CT scanning in the mediastinum was similarly high (24% to 83%).

Patients with left upper lobe tumours are considered separately. In these patients, assessment should include the aortopulmonary window (APW) nodes if other mediastinal node stations are found to be uninvolved.

Invasive mediastinal staging is not recommended in the face of extensive mediastinal infiltration; however mediastinoscopy or EBUS-TBNA may be indicated for the purpose of obtaining a histologic or cytologic diagnosis.

The recommendations generally indicate that mediastinoscopy is the preferred choice for invasive mediastinal staging, but other techniques such as EBUS-TBNA are also recommended, depending on the circumstances. The search strategy for this guideline has been published elsewhere (9).

Literature Search Results

A search for relevant articles published between January 2006 and 11 August 2010 was conducted in MEDLINE and EMBASE and located 671 unique references. The abstracts for each of these papers were examined, and the full texts of 83 were reviewed. 20 of these were found to contain the comparisons of interest. An additional five relevant references were found through reference checking and hand searching (Appendix 4).

Study/Trial Design and Quality

As mentioned above, it is difficult to conduct a randomized controlled trial to evaluate different invasive mediastinal staging techniques, because tests are generally selected for patients based on anatomical characteristics such as node size and location. Furthermore, newer staging techniques such as EBUS have not been studied extensively. Therefore, the evidence in this area is not well developed. Changes to noninvasive staging techniques, which precede invasive staging techniques, have also recently occurred. The introduction of PET-CT has also not yet been fully reflected in the literature.

Of the 25 studies included in the evidence base, 20% of studies prospectively recruited patients and looked retrospectively at patient records, 32% of studies were retrospective, and 36% of studies were prospective. Two randomized controlled trials and one study in progress complete the evidence base since 2006.

Further detail on these studies is presented in Appendix 3, Table 1, parts 1-3. A summary of the results is presented in Table 1.

Table 1. Systematic literature search results.

Study	Technique	Summary of findings
Tournoy et al. 2007 (10)	PET-CT	• sensitivity of PET-CT to detect malignant LN was 84% and specificity was 85%
Al-Sarraf et al. 2008 (11)	PET-CT	• specificity of PET-CT is lower for enlarged LN than non-enlarged LN, and its ability to detect true negative nodes is reduced • incidence of N2 involvement in patients staged N0 by CT and PET-CT is <3%
Lee et al. 2007 (12)	PET-CT	• high FP rate with PET-CT • while the sensitivity of integrated PET-CT was higher than PET, the specificity was reduced from 94% to 81%
Carnochan et al. 2009 (13)	PET-CT	• PET-CT correctly staged 50% of patients • Combined error rates were >5% for stations 2, 4, 5, 7, 10, and 11 • Sensitivity, specificity, PPV, NPV, FP, and FN for N2 or greater disease were 51%, 83%, 41%, 12%, 17%, and 49%, respectively
Lee et al. 2009 (14)	PET-CT CT	• PET-CT and CT did not differ for prediction of N1 or N2 node involvement • High FP and FN for detection of N2 nodes by PET-CT
Sanli et al. 2009 (15)	PET-CT CT Mediastinoscopy	• PET-CT correctly staged 88% of patients • Mediastinoscopy was 97% accurate • PET-CT and CT did not differ for detection of MLN metastases • Sensitivity, specificity, PPV, and NPV of PET-CT for hilar LN involvement were 35%, 89%, 64%, and 70%, respectively
Ventura et al. 2010 (16)	PET-CT PET CT	• PET-CT had higher specificity but similar sensitivity compared with PET • PET-CT and PET had higher sensitivity than CT • FP with PET was associated with inflammation in LN
Fischer et al. 2009 (17)	PET-CT Conventional staging	• Sensitivity for PET-CT was 64% • Sensitivity for conventional staging was 32% • Number of justified thoracotomies and survival were similar between groups
Hwangbo et al. 2009 (18)	EBUS-TBNA PET-CT	• EBUS-TBNA and PET-CT did not differ for sensitivity but EBUS-TBNA had higher specificity, PPV, and NPV for detection of mediastinal metastases
Yasufuku et al. 2006 (19)	EBUS-TBNA PET CT	• compared to CT and PET, EBUS-TBNA has a high sensitivity and specificity for MLN and hilar LN staging • High FP with PET may be due to inflammation from other sources • Stations 5, 8, and 9 were not within reach of EBUS • EBUS correctly diagnosed all the small nodes • NPV of 97%
Rintoul et al. 2009 (20)	EBUS-TBNA PET	• relatively low NPV (60%) for EBUS-TBNA for clarification of FDG-PET positive hilar LN and MLN (28% of these

Study	Technique	Summary of findings
		patients had target LN <10 mm in short axis diameter) • FN due to sampling error or detection error
Yasufuku et al. 2007 (21)	EBUS-TBNA Mediastinoscopy	• Sensitivity and specificity of EBUS-TBNA for correct LN staging were 77% and 100%, respectively • Sensitivity and specificity of mediastinoscopy were 85% and 100%, respectively
Ernst et al. 2008 (22)	EBUS-TBNA Mediastinoscopy	• crossover study directly comparing the diagnostic yield of EBUS-TBNA to mediastinoscopy for LN stations accessible by both modalities (stations 2, 4, and 7) and enlarged on CT (≥1cm) No significant differences were found between the two in determining true pathologic N stage, although the EBUS yield was higher (93% vs. 82%) • improved yield of EBUS-TBNA may be attributed to its ability to sample the posterior subcarinal nodes (station 7), an area that is inaccessible with mediastinoscopy • An editorial in the same journal issue notes that the mediastinoscopy results of this study were low compared to studies that used large retrospective series which more accurately reflect typical results in large volume thoracic surgery centres
Herth et al. 2008 (23)	EBUS-TBNA	• in patients without MLN enlargement on CT and negative PET, sensitivity of EBUS-TBNA for detecting mediastinal malignancy was 89%, and NPV was 98.9%
Ernst et al. 2009 (24)	EBUS-TBNA	• EBUS-TBNA correctly staged 93% of patients • EBUS-TBNA identified malignant hilar LN with the same accuracy as it detects malignant central MLN
Wallace et al. 2008 (25)	EBUS-TBNA TBNA EUS-FNA	• suggests that EBUS-FNA has higher sensitivity than TBNA • EUS-FNA has a blind spot in the region immediately anterior to the trachea but can sample LN in the posterior mediastinum (stations 5, 6, 7) • anterior MLN can be visualized by EBUS (stations 2, 4, 7) • Only 42/99 patients who were staged negative for malignancy by minimally invasive staging methods underwent surgical biopsy; also, only 54% of patients had lung cancer
Gilbert et al. 2009 (26)	EBUS	• Diagnostic sensitivity, specificity, PPV, and NPV to detect cancer in LN were 88%, 100%, 100%, and 81%, respectively • Most commonly sampled stations were 4R/L, 7, and 10R
Block 2010 (27)	EBUS	• Sensitivity for detecting mediastinal disease was 80% • Sampling of four stations was required to detect mediastinal disease in all patients who had a positive biopsy

Study	Technique	Summary of findings
Tournoy et al. 2008 (28)	EUS-FNA	• looked at the accuracy of EUS-FNA in patients with small but suspicious MLN • All suspicious LN in this study were found in areas within reach of EUS • EUS-FNA sensitivity is high in patients with both enlarged and small MLN • NPV of EUS-FNA is low, due to a number of factors, e.g. anatomical misses • It is particularly low (67%) for enlarged LN in this study
Craanen et al. 2007 (29)	EUS-FNA PET	• looked at the performance of EUS-FNA with PET negative and positive LN and found a NPV of 90% • EUS-FNA confirmed absence of malignancy in all patients with a negative PET scan • In PET-positive patients, EUS-FNA confirmed malignancy in 78% of sites
Cerfolio et al. 2006 (30)	EUS-FNA Mediastinoscopy PET-CT CT	• two groups of N2 negative patients who were clinically staged by PET-CT and CT as N0 or N1 were staged using mediastinoscopy (stations 2R/L, 4R/L, 7) and EUS-FNA (stations 7, 8, 9) • 2.9% of patients clinically staged as N0 after PET-CT and CT had positive mediastinoscopy results, and 3.7% had positive EUS-FNA results
Tournoy et al. 2008 (31)	EUS-FNA Mediastinoscopy	• RCT with 21 patients assigned to surgical staging and 19 patients assigned to EUS-FNA. • 32% of EUS-FNA patients still required mediastinoscopy after EUS-FNA • 10% of patients in this study had small cell lung carcinoma
Talebian et al. 2010 (32)	EUS-FNA Mediastinoscopy	• Sensitivity and NPV of EUS-FNA for N2/N3 diseases were 74% and 73%, respectively • Sensitivity and NPV for combined staging with EUS-FNA and mediastinoscopy were 92% and 85%, respectively • FN for EUS-FNA was 27% and mostly due to sampling or detection error • Additional surgical staging in N0 patients reduced FN EUS-findings by 55% • EUS-FNA prevented surgical staging in 39% of patients
Cerfolio et al. 2007 (33)	EUS-FNA, VATS, Chamberlain procedure	• EUS was found to be less accurate than left VATS for patients with suspected nodal metastases in only stations 5 or 6
Pinto Filho et al. 2009 (34)	Mediastinoscopy VATS	• Sensitivity, specificity, PPV, and NPV of combined mediastinoscopy and VATS were 73%, 99%, 89%, and 94%, respectively

Abbreviations: CT, computed tomography; EBUS, endobronchial ultrasound-guided; EUS, endoscopic ultrasound-guided; FDG, fluoro-deoxy-glucose; FN, false negative; FNA, fine needle aspiration; FP, false positive; LN, lymph node; MLN, mediastinal lymph node; NA, needle aspiration; NPV, negative predictive value; PET, positron emission tomography; PPV, positive predictive value; RCT, randomized controlled trial; TBNA, transbronchial needle aspiration; VATS, video-assisted thoracic surgery; vs., versus.

Summary of Results

In summary, the review of literature since the publication of Detterbeck et al (3), indicates that:

- There is a FP rate with PET-CT. Some sensitivity may be gained at the expense of specificity. FP may be the result of inflammation from other sources
- A benefit of EBUS-TBNA over mediastinoscopy is its ability to sample the posterior subcarinal node station (station 7).
- Sensitivity is high with the newer endoscopic techniques. Small lymph nodes are more difficult to identify with any imaging modality (including EBUS) and probably contain a small number of malignant cells, making cytologic diagnosis difficult. EBUS-TBNA and EUS-FNA have low NPV due to a number of factors, including anatomical misses.

ONGOING TRIALS

Yasufuku et al. (21) have a study in progress that compares mediastinoscopy and EBUS-TBNA in the same patients. Preliminary results in 45 patients, which were presented at the Western Thoracic Surgery Association annual meeting in 2007, show that the EBUS-TBNA had a high level of sensitivity, specificity, and diagnostic accuracy and may reduce the number of mediastinoscopies needed for staging the mediastinum in NSCLC, but, due to the possibility of micrometastases, mediastinoscopy may still be necessary. Further details can be found at: http://clinicaltrials.gov/ct2/show/NCT00372203.

DISCUSSION

This guideline outlines when it is advisable to perform invasive mediastinal staging to determine N stage in NSCLC. The development of this guideline relied on the evidence base from the ACCP 2007 clinical practice guideline, with an additional systematic review to search for new evidence. In comparing the ACCP recommendation to that of this guideline, the ACCP guideline does not recommend invasive staging in the case of a normal CT, negative PET-CT, and peripheral clinical stage 1 tumour, while the recommendation in this guideline specifies that invasive staging is not required only in the case of normal CT, negative PET-CT, and peripheral clinical stage 1A tumour. The Working Group and Expert Panel chose to make this distinction because, in the opinion of the Working Group, the probability of nodal metastasis is greater with larger tumours. In other respects, the results of the updated systematic review were largely in accordance with the findings of the ACCP.

The recommendations for non-invasive staging are, in large measure, based on data on the use of CT and PET-CT scan. The Working Group is aware that, in some parts of Ontario, PET-CT is not always available or the waiting time for the procedure is unacceptably long. However, in the opinion of the Working Group, staging should not be considered complete without PET-CT. Therefore, the recommendations were developed on the assumption that PET-CT should be the standard of care.

Mediastinoscopy continues to be the gold standard for invasive mediastinal staging, but newer techniques such as EBUS-TBNA and EUS-FNA have shown promise. Currently, experience with EBUS-TBNA and EUS-FNA is limited and has been reported only from specialized centers and in general relates only to the sampling of enlarged lymph nodes. Whether the results obtained in specialized centers with enlarged lymph nodes is generalizable to other practitioners and to all sizes of lymph nodes is an unanswered question. Furthermore, the technique for EBUS-TBNA has yet to be standardized: for example, the number of needle punctures required and the necessity of on-site cytopathology has not yet been established. Invasive surgical staging can be avoided where the results of EBUS or EUS are positive, because FP rates are low. However, based on this systematic review, the FN rates are relatively high and accuracy in normal sized nodes has not been adequately established for these techniques. Thus mediastinoscopy remains the gold standard. In future guideline documents on this topic, it may be possible to recommend specific types of invasive mediastinal staging in addition to providing advice on when to perform the techniques. Monitoring of the literature in this field is recommended, because information on the performance of newer staging techniques continues to accumulate.

Staging Techniques

According to the ACCP, five nodal stations (2R/L, 4R/L, 7) should routinely be examined when performing mediastinoscopy, with at least one node sampled from each station unless none are present after actual dissection in the region of a particular nodal station (3). The Council of the ESTS Working Group notes that there are no internationally accepted recommendations on how many lymph node stations should be examined at cervical

mediastinoscopy (5). They recommend systematically exploring and always performing a biopsy of the right and left lower paratracheal nodes (station 4) and the subcarinal nodes (station 7). Additionally, if present, the upper paratracheal lymph nodes (stations 2R/L) should be sampled and biopsied. This may not be possible, as a survey of surgeons reported that the upper paratracheal node stations are often not identified. The Working Group supports this assessment.

There are no randomized trials that look at whether it is preferable to stage the lymph nodes of the APW (stations 5 & 6) before resection (33). These stations cannot easily be accessed via mediastinoscopy. In one study, left video-assisted thoracic surgery (VATS) proved to be the preferred sampling method if metastatic disease is suspected in lymph node stations 5 and 6, over the Chamberlain anterior mediastinotomy procedure and EUS-FNA. N2 disease isolated to these lymph nodes is reported to have better prognosis than other lymph node stations, and so the role of neoadjuvant therapy in these patients is controversial. Further research is needed in this area.

Experience with EBUS and EUS is evolving. The number of aspirations attempted is controversial, with some authors recommending three aspirations for EBUS and EUS-FNA (20, 35), whereas, others have indicated that three passes are insufficient because a plateau in yield has only been demonstrated after seven aspirates (36). Yasufuku et al. (19) terminated the procedure if adequate tissue was not identified by on-site cytology after five passes, and the Working Group agrees that this number of passes seems reasonable.

As described by Higashi et al. (37), a 22-gauge cytology needle is fed through the working channel, and multiple passes are made until diagnostic tissue is obtained. A rapid on-site cytopathology examination (ROSE) is commonly used to increase diagnostic yield. With ROSE, sampling can continue until the cytopathologist is able to make a formal conclusion. When performing EBUS-TBNA, it is important to use prior imaging studies as a reference for the lymph node examination, starting with the nodal level that would give the highest stage disease first (e.g., N3 node stations). This would avoid serial contamination from a positive node and up-staging. Needles should be rinsed between samples, but ideally different needles should be used, although this would be more costly. All accessible lymph node stations were examined with ultrasound by Vincent et al. (38) and all visible lymph nodes were sampled. EUS-FNA may be better suited to nodes on the left side because of the anatomic location of the esophagus.

Knowing the lobar location of the primary tumour may indicate what nodal station(s) to sample. Cerfolio et al. (33) reports that tumours in the right upper lobe were most likely to metastasize to the 4R and 2R stations, tumours in the right middle lobe to station 7, tumours in the right lower lobe to the 4R and 7 stations, tumours in the left upper lobe to the 5 and 6 stations, and, finally, tumours in the left lower lobe most commonly to the 5 and 7 stations (30).

Other Factors Affecting the Likelihood of N2 Disease

These recommendations reflect the fact that the primary tumour location is a factor in the prevalence of N2 disease. Several other factors have also been noted in the literature as potential indicators of N2 disease. In these situations, either PET-CT is less reliable or N2 disease may be considered more likely, and the decision to perform invasive staging should take the following factors into account:

- tumour histology, degree of differentiation and size
- non–FDG-avid primary lung tumours (maxSUV of primary tumours)
- adenocarcinoma
- certain well-differentiated low-grade malignancies, particularly bronchioalveolar cell carcinoma and typical carcinoid tumours known to have higher FN rates on PET-CT

CONCLUSIONS

Mediastinoscopy is generally the preferred choice for invasive mediastinal staging, but other techniques such as EBUS-TBNA can also be considered, depending on the clinical circumstances.

1. Invasive staging is not indicated where the CT scan is normal, the PET-CT scan of the mediastinum is negative, and the patient has a peripheral clinical stage IA tumour.

2. Invasive mediastinal staging is recommended for patients with:
   - Normal-sized mediastinal lymph nodes on CT with negative PET-CT and the presence of a central tumour, suspected N1 disease, or clinical T2 or higher.
   - Enlarged discrete mediastinal lymph nodes on CT (N2, N3) and negative or positive PET-CT in the mediastinum.

3. Patients with left upper lobe tumours are to be considered separately, and if invasive staging is indicated for these patients, assessment should include the APW nodes if other mediastinal node stations are found to be uninvolved.

CONFLICT OF INTEREST

All authors declared no conflicts of interest.

JOURNAL REFERENCE

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Appendix 1.

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LHIN = Local Health Integration Network; PEBC = Program in Evidence-based Care; SOP = Surgical Oncology Program

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LHIN = Local Health Integration Network

Appendix 2. Clinical Practice Guidelines located from the initial environmental scan

Document (Reference)	Group	Release Date	Scope and Findings	Methods	Dates of search
Detterbeck et al. 2007. Invasive Mediastinal Staging of Lung Cancer. (3)	American College of Chest Physicians (ACCP)	September 2007	• This guideline is described in detail in the results section	Systematic Review	January 1980-June 2006
Silvestri et al. 2007. Noninvasive staging of non-small cell lung cancer (2)	ACCP	September 2007	• Patients were divided into the same radiographic groups as Detterbeck et al. • Pooled sensitivity of CT was 51% and specificity was 86% • Pooled sensitivity of PET was 74% and specificity was 85%	Systematic Review	January 1991 to May 2006
De Leyn et al. 2007. European trends in preoperative and intraoperative nodal staging (5)	European Society of Thoracic Surgeons (ESTS)	July 2007	• To provide guidance on accurate preoperative staging of mediastinal lymph nodes in NSCLC, including restaging • Recommendations, but no summary statistics provided	Consensus process – workshop with ESTS Council	Not stated
Management of Patients with Lung Cancer, a national clinical guideline (6)	Scottish Intercollegiate Guidelines Network (SIGN)	February 2005	• This document provides guidance on the management of patients with lung cancer, from presentation and referral to supportive and palliative care, including the staging of lung cancer • The portion of the guideline devoted to N stage in NSCLC states that "the reliability of CT in the assessment of mediastinal nodes is poor, with average FP and FN rates of 45% and 13%, respectively • FN rate is higher with central tumours and adenocarcinomas (22% and 19%, respectively) • PET was more accurate than CT, but still has a high FP rate (16%)	Systematic Review	1998 – April 2004
Diagnosis and Treatment of Lung Cancer (7)	National Institute for Health and Clinical Excellence. Developed by the National Collaborating Centre for Acute Care	February 2005	• Conducted in collaboration with SIGN	Systematic Review	Up to December 31, 2003

Abbreviations: CT, computerized tomography; FN, false negative; NSCLC, non-small cell lung cancer; PET, positron emission tomography

Appendix 3. Table 1 (part 1). Literature search results (2006-2010).

Study/Year (Reference)	Staging Procedure	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Diagnostic accuracy (%)
Tournoy et al. 2007 (10)	CT	84	61	NR	NR	69
	PET-CT	84	85	NR	NR	85
Al-Sarraf et al. 2008 (11)	PET-CT with enlarged LN	74	81	71	83	78
	PET-CT non-enlarged LN	40	98	74	91	90
Lee et al. 2007 (12)	PET	61	94	69	92	89
	PET-CT	86	81	56	95	82
Carnochan et al. 2009 (13)	PET-CT (for ≥N2)	51	83	41	12	50
Lee et al. 2009 (14)	PET-CT (for N2)	42	97	83	81	81
	PET-CT (for N1)	50	96	83	84	84
	CT (for N2)	33	81	40	76	67
	CT (for N1)	20	86	33	75	68
Sanli et al. 2009 (15)	PET-CT (for mediastinal LN)	82	90	56	97	88
	PET-CT (for hilar LN)	35	89	64	70	69
	CT (for N2)	45	80	28	90	76
Ventura et al. 2010 (16)	PET-CT	94	73	66	96	NR
	PET	90	31	64	71	NR
	CT	81	50	69	66	NR
Fischer et al. 2009 (17)	PET-CT	64	NR	NR	NR	79
	Conventional staging	32	NR	NR	NR	60
Hwangbo et al. 2009 (18)	PET-CT	70	60	38	85	62
	EBUS-TBNA	90	100	100	97	97
Yasufuku et al. 2006 (19)	EBUS-TBNA	92	100	100	97	98
	PET	80	70	47	92	73
	CT	77	55	37	88	61
Rintoul et al. 2009 (20)	EBUS-TBNA	91	100	100	60	92
Yasufuku 2007 (21)	EBUS-TBNA	77	100	NR	NR	91
	Mediastinoscopy	85	100	NR	NR	94
Ernst et al. 2008 (22)	EBUS-TBNA	87	100	NR	78	89
	Mediastinoscopy	68	100	NR	59	79
Herth et al. 2008 (23)	EBUS-TBNA	89	100	100	99	99
Ernst et al. 2009 (24)	EBUS-TBNA (for hilar LN)	91	100	92	NR	93
Wallace et al. 2008 (25)	TBNA	36	100	100	78	80
	EUS-FNA	69	100	100	88	91
	EBUS-FNA	69	100	100	88	91
	EBUS and EUS	93	100	100	97	98
Gilbert et al. 2009 (26)	EBUS	88	100	100	81	92
Block 2010 (27)	EBUS	80	NR	NR	NR	NR
Tournoy et al. 2008 (28)	EUS (Group A, <10mm)	93	100	100	92	96
	EUS (Group B, ≥10mm)	96	100	100	67	96
Craanen et al. 2007 (29)	EUS-FNA	86	100	100	90	NR
	PET	100	89	88	100	NR
Cerfolio et al. 2006 (30)	Mediastinoscopy + EUS-FNA, PET-CT negative	60	100	100	95	96
	Mediastinoscopy + EUS-FNA,	100	100	100	100	100

Study/Year (Reference)	Staging Procedure	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Diagnostic accuracy (%)
	PET-CT positive (N1)					
Tournoy et al. 2008 (31)	Surgical staging	73	100	100	73	NR
	EUS-FNA	93	100	100	83	NR
Talebian et al. 2010 (32)	EUS-FNA alone (for N2/N3)	74	NR	NR	73	85
	EUS-FNA + Mediastinoscopy	92	NR	NR	85	95
Cerfolio et al. 2007 (33)	EUS-FNA	63	70	69	64	66
	left VATS	100	100	100	100	100
	Chamberlain	83	no negatives	100	no negatives	83
Pinto Filho et al. 2009 (34)	Mediastinoscopy + VATS	73	99	89	94	NR

Abbreviations: CT, computed tomography; EBUS, endobronchial ultrasound-guided; EUS, endoscopic ultrasound-guided; FN, false negative; FNA, fine needle aspiration; LN, lymph node; NA, needle aspiration; NPV, negative predictive value; NR, not reported; PET, positron emission tomography; PPV, positive predictive value; TBNA, transbronchial needle aspiration; VATS, video-assisted thoracic surgery.

Table 1 continued (part 2).

Study/Year (Reference)	Number of patients	Patient type	Nodes
Tournoy et al. 2007 (10)	52	NSCLC	2-11
Al-Sarraf et al. 2008 (11)	206	NSCLC	gold standard – 2R/L,4R/L,7-10 for right-sided tumours, and 5-10 for left-sided tumours
Lee et al. 2007 (12)	336	NSCLC	2R/L, 4R/L, 5, 6, 7, 9
Carnochan et al. 2009 (13)	200	NSCLC patients referred for surgery	2, 4, 5-11
Lee et al. 2009 (14)	43	Newly diagnosed NSCLC	Mediastinoscopy – 2R/L, 4R/L, 7 PET-CT/CT – 2R/L, 3, 4R/L, 5-9, 10R/L, 11R/L
Sanli et al. 2009 (15)	78	NSCLC candidates for surgery	Mediastinoscopy – 4R/L, 7 most commonly sampled
Ventura et al. 2010 (16)	PET-CT = 19, PET and CT separately = 12	NSCLC	1, 2R/L, 4R/L, 5-9, APW, paraaortic, and subcarinal, paraesophageal, and pulmonary ligament nodes
Fischer et al. 2009 (17)	98	Newly diagnosed or highly suspected NSCLC	NR
Hwangbo et al. 2009 (18)	117	NSCLC	PET-CT – 2R, 4R/L, 5-9 EBUS-TBNA – 2R, 4R/L, 7, 8
Yasufuku et al. 2006 (19)	102	NSCLC	1, 2, 4, 7, 10, 11
Rintoul et al. 2009 (20)	96	NSCLC, PET positive	2R/L, 4R/L, 7, 10R/L, 11R/L
Yasufuku et al. 2007 (21)	45	NSCLC	2R/L, 3, 4R/L, 7, 10-12
Ernst et al. 2008 (22)	66	NSCLC, Mediastinal adenopathy at stations 2, 4, 7	2, 4, 7
Herth et al. 2008 (23)	97	NSCLC, CT and PET without enlarged MLN or mediastinal PET activity	2R/L, 4R/L, 7, 10R/L, 11R/L
Ernst et al. 2009 (24)	213	NSCLC	10R/L, 11R/L
Wallace et al. 2008 (25)	138	NSCLC, any size of LN	EUS-FNA – 5, 7 EBUS-FNA – 2-4, 7
Gilbert et al. 2009 (26)	172	NSCLC with abnormal MLN	4R/L, 7, 10 most commonly sampled
Block 2010 (27)	93	NSCLC	N1, N2, N3
Tournoy et al. 2008 (28)	Group A = 25, Group B = 75	NSCLC high prevalence of MLN invasion	Mediastinoscopy - 2R/L, 4R/L, 7
Craanen et al. 2007 (29)	20	NSCLC, possible N2 or N3 involvement at stations 5 and/or 7	5 and 7
Cerfolio et al. 2006 (30)	153	NSCLC, clinically N2 negative after PET-CT and CT	Mediastinoscopy - 2R/L, 4R/L, 7 EUS-FNA - posterior 7-9
Tournoy et al. 2008 (31)	EUS-FNA = 19, surgical staging = 21	NSCLC with no extrathoracic metastases and suspected mediastinal invasion based on CT and/or FDG-PET	Mediastinoscopy – 2R/L, 4R/L, 7
Talebian et al. 2010 (32)	152	NSCLC	Mediastinoscopy – 4R/L, 7 EUS-FNA – 2L, 4L, 5, 7-9
Cerfolio et al. 2007 (33)	EUS-FNA = 62, VATS = 39, Chamberlain	NSCLC clinically staged with N2 disease at stations 5 or 6 only by PET-CT	focus on N2 disease in APW nodes 5, 6

Study/Year (Reference)	Number of patients	Patient type	Nodes
	= 6		
Pinto Filho et al. 2009 (34)	62	NSCLC	Med – 2, 4, 7 VATS – 7, 8, 9

Abbreviations: APW, aortopulmonary window; CT, computerized tomography; EBUS, endobronchial ultrasound-guided; EUS, endoscopic ultrasound-guided; FDG, fluoro-deoxy-glucose; FN, false negative; FNA, fine needle aspiration; LN, lymph node; MLN, mediastinal lymph node; NSCLC, non-small cell lung cancer; PET, positron emission tomography; VATS, video-assisted thoracic surgery

Table 1 continued (part 3).

Study/Year (Reference)	Type of study	Funding or support	Details of reference or gold standard	Preoperative staging	Study question
Tournoy et al. 2007 (10)	Retrospective	No conflict of interest or funding reported	Mediastinoscopy in positive cases or resection by thoracotomy	Not applicable	Is PET-CT uniformly accurate among enlarged and non-enlarged LN?
Al-Sarraf et al. 2008 (11)	Retrospective	No conflict of interest	Mediastinoscopy and/or resection	Not applicable	Is PET-CT is uniformly accurate among enlarged and non-enlarged LN?
Lee et al. 2007 (12)	Retrospective	No details provided	Mediastinoscopy or thoracotomy	Not applicable	Have improvements in PET increased sensitivity or specificity of PET in the staging of NSCLC such that surgical staging is no longer required?
Carnochan et al. 2009 (13)	Retrospective	No details provided	Histopathology by mediastinoscopy, resection by thoracotomy	All had CT, some had PET-CT	Accuracy and utility of PET-CT for assessing extent of intra thoracic disease for surgical evaluation
Lee et al. 2009 (14)	Prospective	Supported by Korea Science & Engineering Foundation through Tumor Immunity Medical Research Center; grant from Seoul National University	Surgical pathology by pulmonary resection, mediastinoscopy, or thoracotomy	All had CT and PET-CT	Role of PET-CT in LN staging of NSCLC compared with gold standard
Sanli et al. 2009 (15)	Prospective	No details provided	Pathology by mediastinoscopy or MLN dissection at thoracotomy	CT and PET-CT	Does PET-CT decrease need for mediastinoscopy ?
Ventura et al. 2010 (16)	Retrospective	No details provided	LN sampling by mediastinoscopy and/or thoracotomy	PET-CT, or PET, or CT	Accuracy of PET and CT compared with PET-CT for detecting metastatic nodal disease
Fischer et al. 2009 (17)	RCT	Supported by grants from Danish Cancer Society and Danish Center for Health Technology Assessment; PET-CT	Mediastinoscopy and EUS or EBUS	PET-CT or CT	Clinical effect of PET-CT on preoperative staging of NSCLC

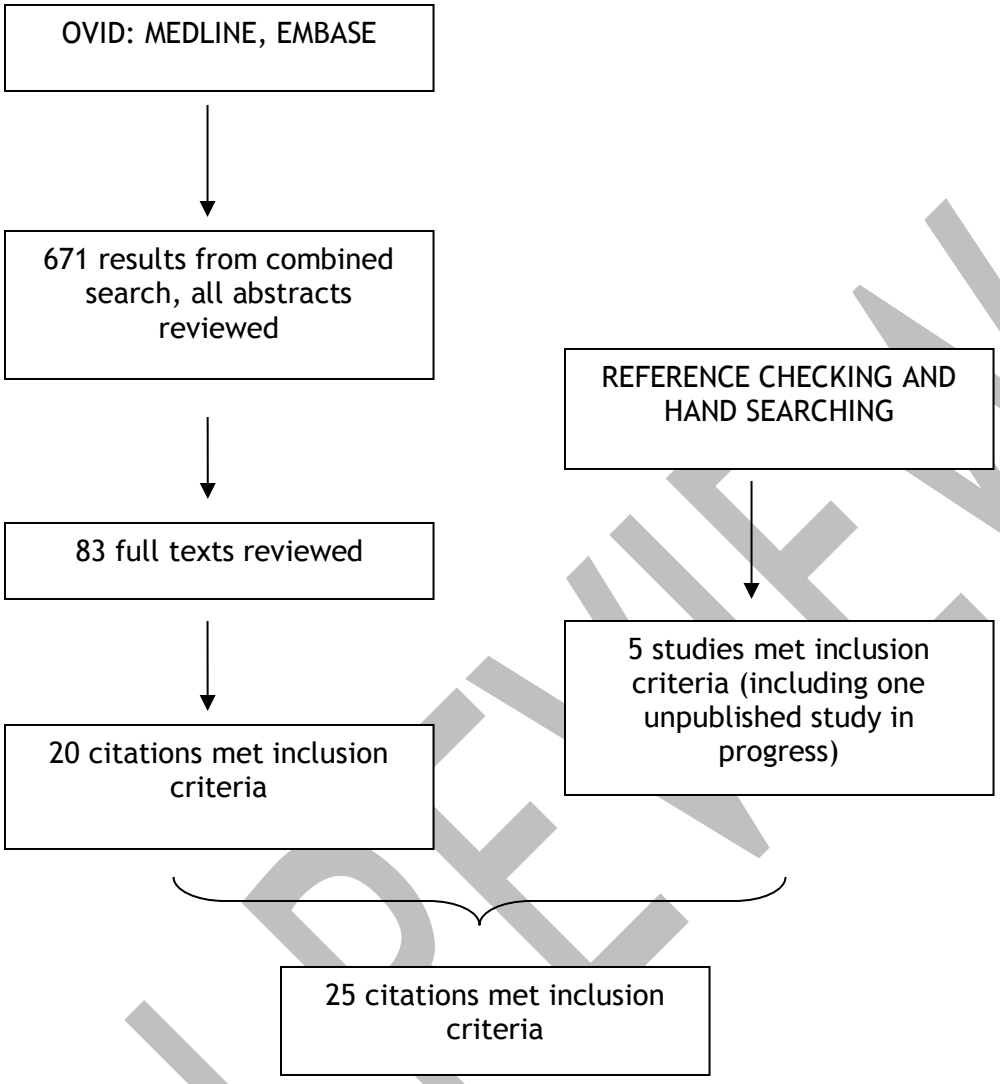
Study/Year (Reference)	Type of study	Funding or support	Details of reference or gold standard	Preoperative staging	Study question
		scanner donated by John and Birthe Meyer Foundation; lecture fees from AstraZeneca			
Hwangbo et al. 2009 (18)	Prospective	Supported by a grant from National Cancer Center; no significant conflicts of interests	Surgical LN dissection	PET-CT or CT	Comparison of EBUS-TBNA and PET-CT for MLN staging of operable NSCLC
Yasufuku et al. 2006 (19)	Prospective patient enrolment	Supported by a grant from The Japanese Foundation for Research and Promotion of Endoscopy to Dr. Yasufuku	Thoracotomy with complete MLN dissection. If positive, results were compared to clinical course consistent with malignant disease	CT and FDG-PET	Comparison of EBUS-TBNA, PET and CT
Rintoul et al. 2009 (20)	Prospective analysis, retrospective data collection	Dr. Rintoul is an advisor for Olympus Corp. His institution has received loan equipment from Olympus KeyMed and he's received unrestricted educational grants to run EBUS courses.	Mediastinoscopy, VATS, or thoracotomy	PET positive	To determine sensitivity and accuracy of EBUS-TBNA for PET positive MLN and hilar LN
Yasufuku et al. 2007 (21)	Prospective	No details provided	Mediastinoscopy, lung resection by thoracotomy if N2/N3 disease absent	Not reported	Comparison of EBUS-TBNA with mediastinoscopy for MLN staging of NSCLC
Ernst et al. 2008 (22)	Prospective crossover trial	Olympus provided grants for CME activities at authors' institutions. Authors have no direct financial involvement with any commercial entity interested in the data for this manuscript	Surgical LN dissection	risk factors and CT (no PET)	compare diagnostic yield of two modalities in radiologically enlarged LN
Herth et al. 2008 (23)	Prospective	Olympus provided grants to authors' institutions or affiliated medical schools for CME activities and loaned EBUS imaging components. Authors did not receive direct financial support.	Thoracotomy or mediastinoscopy	CT, PET negative	To determine the accuracy of EBUS-TBNA for staging MLN in lung cancer patients
Ernst et al. 2009 (24)	Prospective	Olympus loaned EBUS equipment,	Biopsy of primary parenchymal tumour and	All had CT, some had	Efficacy of EBUS-TBNA for

Study/Year (Reference)	Type of study	Funding or support	Details of reference or gold standard	Preoperative staging	Study question
		provided grants to authors' institutions and for CME events, and paid for meeting related travel expenses	pathologic staging by thoracotomy, thoracoscopy, or 6 month clinical follow-up	PET	staging hilar LN
Wallace et al. 2008 (25)	Prospective	Dr. Wallace received research grants from Olympus, Fujinon and Cook, makers of equipment relevant to EUS. Equipment provided by Olympus.	For positive result - pathologic confirmation by FNA, open surgical biopsy, mediastinoscopy, or thoracoscopy. For negative result - mediastinoscopy, thoracoscopy, open surgical exploration showing no disease, or 6-12 months follow-up with non-enlarged MLN	CT and PET performed separately and correlated	Comparison of the accuracy of TBNA, EBUS-FNA, EUS-FNA, especially EBUS-FNA and TBNA
Gilbert et al. 2009 (26)	Retrospective	No details provided	Mediastinoscopy, MLN dissection, and immunohistochemistry	CT and/or PET	Diagnostic performance of EBUS in patients with abnormal mediastinal LN by CT or PET-CT
Block 2010 (27)	Retrospective	No details provided	LN biopsy	All had CT, most had PET or PET-CT	EBUS for NSCLC staging and how many LN stations should be sampled
Tournoy et al. 2008 (28)	Retrospective study of a prospectively gathered cohort	No conflict of interest declared	Pathological staging, mediastinoscopy for patients in whom EUS-FNA did not confirm malignant MLN invasion, thoracotomy with MLN dissection if operable	CT and heterogenous PET data	Comparison of the performance of EUS in large and small LN
Craanen et al. 2007 (29)	Prospective	No details provided	Postoperative histology after systematic MLN dissection	CT and/or FDG-PET	Role of EUS-FNA in the diagnosis of patients with NSCLC in whom CT and/or FDG-PET suggest N2 or N3 involvement
Cerfolio et al. 2006 (30)	Prospective	No financial conflicts of interest	Thoracotomy, pulmonary resection, and complete lymphadenectomy (negative cases)	All had PET-CT and CT	Incidence of unsuspected N2 disease by mediastinoscopy and EUS-FNA in N2 negative NSCLC
Tournoy et al. 2008 (31)	RCT	No conflict of interest declared	Thoracotomy if mediastinoscopy or mediastinoscopy + EUS were negative	CT and/or FDG-PET	Comparison of EUS with surgical staging, with a focus on reducing number of futile surgeries

Study/Year (Reference)	Type of study	Funding or support	Details of reference or gold standard	Preoperative staging	Study question
Talebian et al. 2010 (32)	Retrospective	No conflicts of interest and funding source not applicable	Mediastinoscopy, thoracotomy	CT	Diagnostic performance of EUS-FNA alone and in combination with mediastinoscopy for staging NSCLC and does EUS-FNA reduce need for surgical staging
Cerfolio et al. 2007 (33)	Retrospective cohort using an electronic prospective database	No details provided	Thoracotomy with complete thoracic lymphadenectomy	PET or CT or both	Efficacy of different techniques of LN biopsies in NSCLC in stations 5 and 6
Pinto Filho et al. 2009 (34)	Prospective	None	Pulmonary resection and systematic mediastinal lymphadenectomy	CT	Efficacy of mediastinoscopy combined with VATS for preoperative sampling of MLN in NSCLC

Abbreviations: CT, computerized tomography; CME, clinical medical education; EBUS, endobronchial ultrasound-guided; EUS, endoscopic ultrasound-guided; FDG, fluoro-deoxy-glucose; FNA, fine needle aspiration; LN, lymph node; MLN, mediastinal lymph node; NSCLC, non-small cell lung cancer; PET, positron emission tomography; RCT, randomized controlled trial; TBNA, transbronchial needle aspiration; VATS, video-assisted thoracic surgery

Appendix 4. Literature search results.



cancer care ontario | action cancer ontario
program in evidence-based care | programme de soins fondé sur des preuves

Evidence-Based Series 17-6 Version 2: Section 3

Invasive Mediastinal Staging of Non-small Cell Lung Cancer: EBS Development Methods and External Review Process

G. Darling, J. Dickie, R. Malthaner, E. Kennedy, R. Tey, and the Invasive Mediastinal Staging Expert Panel

A Collaboration of Cancer Care Ontario's (CCO)
Program in Evidence-Based Care (PEBC) and Surgical Oncology Program (SOP)

Original Report Date: October 18, 2010

The 2010 guideline recommendations are

ENDORSED

This means that the recommendations are still current and relevant for decision making

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-based Care (PEBC) and the Surgical Oncology Program (SOP) are initiatives of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care. The mandate of the SOP is to improve the delivery of cancer surgery in Ontario through initiatives designed to increase access to care, improve the quality of care, support the recruitment and retention of cancer surgeons, support knowledge transfer and evidence-based practice, and foster research and innovation. The SOP and PEBC have worked collaboratively on a number of occasions to develop evidence-based materials relevant to the surgical community in Ontario.

The PEBC is well known for producing evidence-based guidelines, known as Evidence-based Series (EBS) reports, using the methods of the Practice Guidelines Development Cycle (1,2). The EBS report consists of an evidentiary base (typically a systematic review), an interpretation of and consensus agreement on that evidence by our Groups or Panels, the resulting recommendations, and an external review by Ontario clinicians and other stakeholders in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each document, through the periodic review

and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original guideline information.

As part of its quality improvement mandate, the SOP convenes expert panels for the selection of quality indicators and the development of clinical guidelines and organizational standards. The panels are comprised of surgeons, other clinicians, health care administrators, other health care professionals, and methodologists and are established on an as-needed basis for specific quality initiatives.

The Evidence-Based Series

Each EBS is comprised of three sections:

- *Section 1: Guideline Recommendations*. Contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the Group or Panel involved and a formalized external review in Ontario by review participants.
- *Section 2: Evidentiary Base*. Presents the comprehensive evidentiary/systematic review of the clinical and scientific research on the topic and the conclusions reached by the Group or Panel.
- *Section 3: EBS Development Methods and External Review Process*. Summarizes the evidence-based series development process and the results of the formal external review of the draft version of Section 1: Guideline Recommendations and Section 2: Evidentiary Base.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES

Development and Internal Review

This EBS was developed by the Invasive Mediastinal Staging Expert Panel of the CCO PEBC. The series is a convenient and up-to-date source of the best available evidence on invasive staging of mediastinal lymph nodes, developed through a review of the evidentiary base, evidence synthesis, and input from external review participants in Ontario.

This report was reviewed by members of the Invasive Mediastinal Staging Expert Panel and the Lung Cancer DSG. Responses were received from 10 members. In general, most members agreed with the guideline. A few members raised some issues, which included:

- In the Recommendations in Section 1, since the answers to the primary questions are summarized, maybe the secondary recommendations should be as well.
  - **Response**: A few points were added to the recommendations in Section 1 to address the secondary questions; however, it was also emphasized that these were based on consensus of expert opinion.

- The group in Kelowna have studied and evaluated over 300 patients with EBUS and med (same patients). I am not sure where they are with their analysis and paper but it would be worth mentioning and contacting them about it.
  - **Response**: The Working Group decided not to include this study in the guideline because it was not a trial but a retrospective study that has not been published, and the data is not available for review.

- In Section 2, I would mention in the literature search strategy section why 2006 is the start date. As well the guideline needs to state why the same systematic review was used for both the primary and secondary questions. As a purest, one should do the 2 searches separately.

- **Response**: A sentence was added to the literature search strategy to explain the 2006 start date, and another sentence was added to explain why two separate searches were not done.

- In Section 2, under Staging Techniques, I would mention R10 and L10 as they are often biopsied. (even if N1)
  - **Response**: We did not include recommendations regarding stations R10 and L10 because they are considered N1 nodes, based on the 1997 staging revisions. They are considered to be intrapleural and as such are accessible only at thoracotomy. The previous staging considered station 10 as nodes that were below the azygos vein on the right and on the left main bronchus just past its origin. In the 1997 revision of the staging system, these lymph nodes are now considered station 4.

- In the Discussion in Section 2, there is a great deal of detail about EBUS sampling and therefore maybe equal time should be made about mediastinoscopy.
  - **Response:** A clearer explanation of why mediastinoscopy, and not EBUS, is the gold standard was added to the Discussion in Section 2.

- Is it worth talking/mentioning about the pathology and how they analyse specimens? frozen vs. permanent?
  - **Response:** We have not discussed the role of intraoperative frozen section versus permanent section analysis of lymph nodes because it is beyond the scope of this guideline.

- I do have some issues with the algorithm. The way it looks, at first glance, the PET doesn't seem to change anything. Is it possible to further clarify it as stated below? I realize this makes the algorithm much more complicated, and perhaps not as useful. To me, it is much more clear that we are expecting invasive staging in all but the best and worst scenarios.

Description of mediastinal lymph nodes	Requirement for staging
A) Normal sized mediastinal lymph nodes (MLN) on CT AND negative PET Peripheral clinical stage 1A tumour (and negative clinical evaluation)	Invasive staging not required
B) Normal sized mediastinal lymph nodes (MLN) on CT AND negative PET (or PET unavailable) AND none of "central tumour, or tumour > 3cm or suspected hilar disease"	Invasive staging not required
C) Normal sized mediastinal lymph nodes (MLN) on CT AND negative PET (or PET unavailable) BUT any of "central tumour, or tumour > 3cm or suspected hilar disease"	Invasive staging necessary
C) Enlarged discrete mediastinal nodes on CT (N2,3) AND negative PET	Invasive staging of the mediastinum
D) any size discrete MLN on CT AND Positive PET in the mediastinum	Invasive staging of the mediastinum
E) Confluent MLN on CT AND Positive PET in the mediastinum	Invasive staging not necessary

  - **Response:** The Working Group decided not to change the existing algorithm in Section 1 as suggested by the reviewer because, as it was, it emphasized that PET-CT

was insufficient for mediastinal staging in patients with enlarged lymph nodes. To further clarify the algorithm, it was explicitly stated that 'PET-CT +ve' and '–ve' referred to the mediastinum only.

Report Approval Panel

Prior to the submission of this EBS draft report for external review, the report was reviewed and approved by the PEBC Report Approval Panel, which consists of two members, including an oncologist, with expertise in clinical and methodology issues. Key issues raised by the Report Approval Panel included:

- The document would be strengthened by a more clear statement of outcomes that are driving recommendations – it is not clinical outcome, it is not changes to treatment decisions, it is its test construction processes. Why is this important? Should the evidence mature before moving forward with this? How do we justify this given thresholds set for PET scan standards, as an example?
  - **Response**: The Working Group felt that the FN and FP rates are a sufficient and important outcome influencing treatment approaches and is appropriate in lung cancer and for other intended users of this guideline. A brief explanation of the FN rate in the context of this guideline topic was added to the Clinical Perspective in Section 1. The Working Group felt that this guideline presents the best available evidence and does not expect higher level evidence to emerge in the near future. For example, it would be unethical to conduct a randomized controlled trial comparing mediastinoscopy to PET alone.

- There is some ambiguity about how the authors used existing guidelines vs. their own review. The document starts off suggesting that this will be a systematic review of primary literature in order to reach recommendations, and later does report about these findings. However, it is not clear that this evidence informed the recommendations. Instead, it appears that the recommendations were driven by adapting/adopting existing guidelines. The authors could make their process clearer: for instance, was the systematic review more so of a validation process of assessing evidence already included in the other guidelines? If this was predominately driven by an adoption process, would the use of formal adoption tools be beneficial?
  - **Response**: In the Recommendations in Section 1 of this guideline, a statement was added to clarify that the recommendations addressing the primary questions were based on evidence from the ACCP guideline and primary literature from the systematic search. Similarly, another statement was added to indicate that the recommendations addressing the secondary questions were based on a consensus of expert opinion.

- Using the authors' algorithm, the role of PET when mediastinal nodes are enlarged on CT is uncertain, as biopsy is recommended regardless of PET results. Describing the additional roles of PET that justify its use should be considered.
  - **Response**: The algorithm was purposely presented as such to emphasize that PET-CT was insufficient for mediastinal staging in patients with enlarged lymph nodes. In the algorithm, more information was provided about PET-CT by stating that PET-CT +ve and –ve referred to the mediastinum only.

- In the description of the literature search for primary studies, it was an update of the literature reported in the ACCP guideline. Note of this should be made to provide the rationale.
  - **Response**: A sentence about the literature search in this guideline being an update of the systematic search from the ACCP guideline was added to the literature search strategy in Section 2 of this guideline.

- The study design and sample size requirements are not listed in the criteria list.
  - **Response**: Information about the study design and sample size was added to the list of study selection criteria in Section 2 of this guideline.

- In the guideline, the authors state they used the systematic review of the existing guideline (ACCP) but they then report on the recommendations rather than provide a summary of the evidence. I think both would be valuable – currently we have no indications that underscore the source guideline.
  - **Response**: Key evidence reported by the ACCP guideline included in Section 1 of this guideline was added to Section 2 of this guideline under the Results subheading of "Summary of ACCP Guideline."

- I would move the description of the technical components out the discussion section to another section of the results section – maybe call it opinion based technical considerations or some much thing.
  - **Response**: The Working Group disagreed and felt that the description fit better in the Discussion section because it addressed the secondary questions that were based on a consensus of expert opinion. Therefore no changes were made.

- The key portion of the document that addresses the systematic review is Table 1. The authors should consider whether it is possible to report these data in a uniform manner, using either the metrics that are reported or that can be calculated. The data points/metrics would include the patient population characteristics, prevalence of positivity using the gold standard test, sensitivity, specificity, PPV and NPV. Reporting of these data across all trials might facilitate demonstrating a clearer consistency of the data.
  - **Response**: A summary of the systematic review search results is presented in Table 1 of Section 2 of this guideline because further details, including the sensitivities, specificities, PPV, NPV, patient characteristics, and the gold standard, can be found in several tables in Appendix 3 of this document.

- The document might be strengthened by addressing the clinical utility of these decisions. While accurate staging is a core principle of cancer management, it remains possible that as therapies evolve, management for various stages of disease become uniform. In these circumstances, staging may remain relevant for determining prognosis, quality assurances processes and for population/outcome research and setting of standards. If or when this occurs, it would be helpful to have this as an explicit statement so that the broader contexts of risk/benefit and cost utility are evaluated using the correct perspective. Understanding where the management of lung cancer fits within this construct would be helpful.

- **Response**: Accurate staging of NSCLC is the key to determining prognosis and treatment. As treatments evolve, it is essential to have accurate staging to compare the outcomes of new treatments versus older therapies for both individual patients and overall populations.

External Review by Ontario Clinicians and Other Experts

The PEBC external review process is two-pronged and includes a targeted peer review that is intended to obtain direct feedback on the draft report from a small number of specified content experts and a professional consultation that is intended to facilitate dissemination of the final guidance report to Ontario practitioners.

Following the review and discussion of Section 1: Recommendations and Section 2: Evidentiary Base of this EBS and the review and approval of the report by the PEBC Report Approval Panel, the *Invasive Mediastinal Staging Expert Panel* circulated Sections 1 and 2 to external review participants for review and feedback. Box 1 summarizes the draft recommendations and supporting evidence developed by the *Invasive Mediastinal Staging Expert Panel*.

BOX 1: DRAFT RECOMMENDATIONS (approved for external review on 22 March 2010)

Please note that the version of the draft recommendations below does not exactly match the current recommendations in Section 1 because some changes were made on the draft recommendations based on the feedback received from the external review.

QUESTIONS

Primary Questions

Is invasive mediastinal staging in stage cT1-4, N0-3, M0 non-small cell lung cancer (NSCLC) patients indicated under the following circumstances?

a) Normal-sized mediastinal lymph nodes on computed tomography scan (CT), and
   i. negative positron emission tomography (PET)-CT scan in the mediastinum
   ii. positive PET-CT in the mediastinum
b) Enlarged discrete mediastinal nodes on CT (clinical N2 or N3 nodes), and
   i. negative PET-CT in the mediastinum
   ii. positive PET-CT in the mediastinum

Secondary Questions

What constitutes invasive mediastinal staging? What is the proper technique in performing invasive mediastinal staging?

a) Which node stations should be biopsied?
b) How many lymph nodes should be biopsied?

TARGET POPULATION

NSCLC patients in Ontario who have been clinically staged T1-4, N0-3, with no distant metastases.

RECOMMENDATIONS

Based on evidence from the American Association of Chest Physicians (ACCP) guideline (3) and primary literature from the systematic search:

- Invasive mediastinal staging is not needed in the case of normal-sized mediastinal lymph

nodes (MLN) on CT, a negative PET-CT scan, a peripheral clinical stage 1A tumour, and a negative clinical evaluation.
  - clinical stage 1A tumour defined as T1N0M0
    - T1: primary tumour diameter of 3 cm or smaller and surrounded by lung or visceral pleura or endobronchial tumour distal to the lobar bronchus
    - N0: no lymph nodes involved
    - M0: no metastases
- Invasive staging is recommended in the following cases:
  - Normal-sized MLN on CT with negative PET-CT, and
    - the presence of a central tumour (tumour in the central third of the hemithorax), or
    - suspected N1 disease (enlarged N1 nodes on CT), or
    - clinical stage 1B disease defined as T2N0M0
      - T2: primary tumour diameter of greater than 3 cm; extension to the visceral pleura, atelectasis, or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung; lobar endobronchial tumour; or tumour of a main bronchus more than 2 cm from the carina
      - N0: no lymph nodes involved
      - M0: no metastases
  - Enlarged discrete MLN on CT (N2, 3), and negative or positive PET-CT;
- Appendix 1, Figure 1 illustrates the corresponding algorithm for these recommendations.

Based on a consensus of expert opinion:
- Five nodal stations (2R/L, 4R/L, 7) should routinely be examined when performing invasive mediastinal staging, with at least one node sampled from each station unless none are present after actual dissection in the region of a particular nodal station
- Mediastinoscopy is the gold standard for invasive staging of the mediastinum. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) may be useful, but more data are required before it may be considered as an equivalent procedure.

KEY EVIDENCE

Invasive Staging Not Required

Normal CT, negative PET-CT, and a peripheral clinical stage 1A tumour:
- The ACCP systematic review found that the FN rate of CT in the group of patients with T1 tumours (i.e., clinical stage 1A) is approximately 9% (3).
- The Scottish Intercollegiate Guidelines Network (SIGN) recommends that patients with *small* peripheral tumours and a negative CT scan of the mediastinum require no further investigation, because the rate of false negatives in all categories of patients with lung cancer is 13% (7). SIGN does not provide a definition of small, but it may be equivalent to a clinical stage 1A tumour. The European Society of Thoracic Surgeons does not recommend mediastinoscopy in the case of a "T1 squamous cell tumour with N0 disease on CT scan" (8), based on the results of the SIGN systematic review.
- A negative PET-CT scan in the mediastinum carries an FN rate of approximately 5% (range, 3% to 6%).

Invasive Staging Recommended

Normal CT, negative PET-CT and a central tumour, N1 disease or a stage IB tumour:

- The ACCP systematic review found the FN rate of CT scan in the mediastinum for patients with a central tumour is 20% to 25% (3). The same review found more limited data showing that the FN rate for PET-CT scanning in the mediastinum is similarly high (24% to 83%).
- Another systematic review found an FN rate of 22% with central tumours for a CT scan in the assessment of mediastinal nodes (4).

Additional evidence published since the ACCP guidelines:

- Cerfolio et al. (6) found that patients with clinical N1 disease suggested by integrated PET-CT/CT had a relatively high incidence (17.6% after mediastinoscopy and 23.5% after endoscopic ultrasound-guided fine needle aspiration [EUS-FNA]) of unsuspected N2 disease.

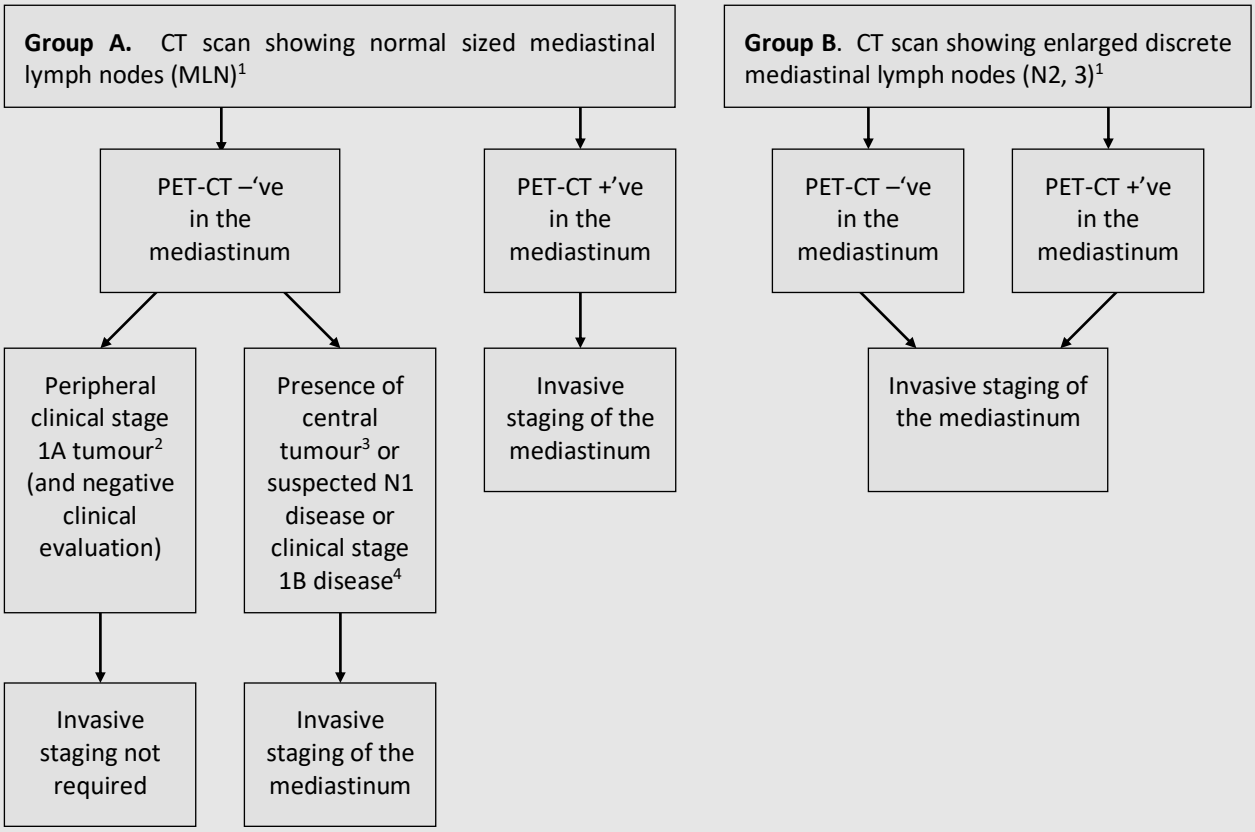
Enlarged lymph nodes on CT and PET-CT positive or negative:

- The PET-CT FN rate is estimated to be 13% to 25% in patients with nodal enlargement detected by CT scan, according to two meta-analyses. These estimates were based on indirect data and patient groups that were not clearly defined. Direct data from studies in patients with mediastinal or hilar node enlargement have found a PET-CT FN rate of 20% to 28% for N2,3 involvement.
- PET-CT scanning is very accurate in identifying malignant nodal involvement when nodes are enlarged by tumour. However, PET-CT scanning has been shown to falsely identify malignancy in approximately one fourth of patients with nodes that are enlarged for other reasons, usually due to inflammation or infection.(5)

Qualifying Statements

- In addition to tumour location (i.e., central vs. peripheral), several other factors have been noted in the literature as potentially affecting the likelihood of N2 disease, including maximum SUV (maxSUV) of the primary tumour (non-FDG avid primary tumours), tumour histology, degree of differentiation, and size, and bronchoalveolar cell carcinoma. These factors should be taken into account when deciding whether to perform invasive staging.
- Mediastinoscopy continues to be the gold standard for invasive mediastinal staging, but newer techniques such as EBUS-TBNA and EUS-FNA have shown promise. Monitoring of the literature in this field is recommended as information on the performance of newer staging techniques continues to accumulate. Please see the discussion in Section 2 for more details.

Appendix 1. Figure 1. Invasive mediastinal staging recommendations.



[1] This algorithm applies to the target population of NSCLC patients in Ontario who have been clinically staged T1-4, N0-3, with no distant metastases.

[2] Stage 1A: T1N0M0 (T1: primary tumour diameter of 3 cm or smaller and surrounded by lung or visceral pleura or endobronchial tumour distal to the lobar bronchus; N0: no lymph nodes involved; M0: no metastases).

[3] For the purposes of this guideline, a tumour in the central third of the hemithorax is considered central. A tumour in the distal two-thirds of the hemithorax is considered peripheral.

[4] Stage 1B: T2N0M0 (T2: primary tumour diameter of greater than 3 cm; extension to the visceral pleura, atelectasis, or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung; lobar endobronchial tumour; or tumour of a main bronchus more than 2 cm from the carina; N0: no lymph nodes involved; M0: no metastases).

Methods

Targeted Peer Review: During the guideline development process, eight targeted peer reviewers from Ontario, Quebec, Nova Scotia, Alberta, and British Columbia, considered to be clinical and/or methodological experts on the topic were identified by the working group. Several weeks prior to completion of the draft report, the nominees were contacted by email and asked to serve as reviewers. Five reviewers agreed to participate and the draft report

and a questionnaire were sent via email for their review. The questionnaire consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a guideline. Written comments were invited. The questionnaire and draft document were sent out on March 22, 02010. Follow-up reminders were sent at two weeks and at four weeks by e-mail. The Invasive Mediastinal Staging Expert Panel reviewed the results of the survey.

Professional Consultation: Feedback was obtained through a brief online survey of health care professionals who are the intended users of the guideline. CCO provided a list of thoracic surgeons, radiation oncologists, medical oncologists, radiologists, and respirologists from Ontario, all of whom were contacted by mail and email to inform them of the survey. Participants were asked to rate the overall quality of the guideline (Section 1) and whether they would use and/or recommend it. Written comments were invited. Participants were contacted by email and directed to the survey website where they were provided with access to the survey, the guideline recommendations (Section 1) and the evidentiary base (Section 2). The notification email was sent on March 23, 2010. The consultation period ended on April 30, 2010. The Invasive Mediastinal Staging Expert Panel reviewed the results of the survey.

Results

Targeted Peer Review: Three responses were received out of five reviewers who agreed to participate. Key results of the feedback survey are summarized in Table 1.

Table 1. Responses to items on the targeted peer reviewer questionnaire.

	Reviewer Ratings (N=3)				
Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
Rate the guideline development methods.				1	2
Rate the guideline presentation.					3
Rate the guideline recommendations.				1	2
Rate the completeness of reporting.			1		2
Does this document provide sufficient information to inform your decisions? If not, what areas are missing?			1	1	1
Rate the overall quality of the guideline report.				2	1
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
I would make use of this guideline in my professional decisions.			1	1	1
I would recommend this guideline for use in practice.				2	1

What are the barriers or enablers to the implementation of this guideline report?

Barriers include:

- availability of PET-CT
- lengthy wait times for surgical procedures or for results of frozen section reports
- expertise of surgeons to carry out mediastinoscopic examinations

Enablers include:

- ability to perform mediastinoscopy in the outpatient surgery unit
- locations where there is prompt access to PET and PET reports

Summary of Written Comments

The main points contained in the written comments were:

- Am I right to understand that invasive staging is required for all cases except for T1 lesions (<3 cm) that are peripheral?
  - **Response**: Yes.

- Discuss more about the role of EBUS over EUS and who should be doing those tests (physicians or surgeons).
  - **Response**: The discussion about EBUS and EUS is in Section 2 of this document. More studies are needed about these newer staging techniques before recommendations can be made about them.

- It should be noted that the results of PET-CT over CT alone do not really change the indication for invasive mediastinal staging.

- Nobody samples five nodal stations during routine mediastinoscopy. Three is enough if nodes are normal.
  - **Response**: Although sampling 3 nodes may be sufficient (if nodes are normal) for invasive mediastinal staging, recommendations were made to sample 5 nodal stations during mediastinoscopy to be thorough. This is consistent with recommendations from ACCP.

- This report did not mention adjuvant or neoadjuvant therapy. This should be included because the decision regarding therapy depends on mediastinal nodal status. For example, some surgeons are now foregoing invasive mediastinal staging in patients with central tumours assuming that they will be receiving post-operative chemotherapy if positive nodes are discovered during surgery.
  - **Response**: The best evidence for survival benefit is with neoadjuvant therapy so it is better to sort this out prior to resection but more importantly, it is incumbent on the surgeon to try to identify those patients who will not benefit from resection, e.g., those with N3 disease or perhaps multistation N2.

- The guideline needs to be updated to the new 7th edition staging system. In the new system, a 5-7 cm NO tumour is stage IIA and therefore is out of step with the recommendation for invasive staging of clinical stage 1B.
  - **Response**: Clinical stage 1B was edited to T2 tumour or higher.

- I don't understand the justification for ignoring Kelowna data because the guideline includes the Yasufuku data which is observational, has been presented at meetings, and remains unpublished.
  - **Response**: Kelowna data was an invited presentation and hence there is no abstract in the public domain for review - at this point they have not published their results so all we have is memory of the presentation. The Yasufuku trial is

registered on the NIH website, preliminary results were presented at a National Meeting, and the abstract is available in the public domain

Professional Consultation: 43 responses were received. Key results of the feedback survey are summarized in Table 2.

Table 2. Responses to items on the professional consultation survey.

	Number (%)				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
Rate the overall quality of the guideline report.	0	1 (2%)	7 (16%)	20 (45%)	15 (36%)
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
I would make use of this guideline in my professional decisions.	1 (2%)	3 (7%)	5 (11%)	12 (27%)	22 (52%)
I would recommend this guideline for use in practice.	1 (2%)	2 (5%)	6 (14%)	10 (23%)	24 (57%)

What are the barriers or enablers to the implementation of this guideline report?
Barriers include:

- rapid and timely access to PET
- access to mediastinoscopy or thoracic surgery
- mediastinoscopy can add extra time in the operating room, especially if done in conjunction with thoracotomy
- mediastinoscopy can lead to complications
- determining what exactly is a central tumour
- dissemination of information in the guideline to surgeons
- resistance to changing practice

Enablers include:

- high volume thoracic centres where mediastinoscopy is routinely performed
- locations where PET is accessible

Summary of Written Comments
The main points contained in the written comments were:

- Several reviewers thought that the guideline was thorough and well written and found the Appendix algorithm helpful.

- The fundamental contribution is the recommendation that no mediastinoscopy is necessary for small peripheral tumours with CT negative, PET negative mediastinum. This keeps with evolving practice, is supported by evidence, and will be very helpful to standardize care.

- This document requires statements to emphasize that evaluation by PET is mandatory for all patients prior to surgery and that mediastinal laparoscopic staging and surgery can only be performed in level 1 surgical centres.
  - **Response**: The algorithm in Appendix 1 emphasizes that PET-CT should be done in all patients. Invasive staging and surgery can also be performed in level 2 centres.

- The recommendation to conduct mediastinoscopy in everyone other than peripheral T1 lesions waters down the absolute need to do one for a positive PET scan to ensure that it is not a false positive and potentially denying curative treatment.
  - **Response**: A bullet point was added to the Recommendations in Section 1 to emphasize that "Invasive staging is important to confirm PET findings."

- In patients at high risk for pulmonary resection, it would be important to perform invasive staging of the mediastinum irrespective of CT and PET findings to be certain that surgical decisions will be made.
  - **Response**: High risk patients still benefit from accurate staging even if they are not surgical candidates. But also the issue of surgical risk is best determined by the surgeon – many patients who are considered high risk may be fit for surgery after thorough evaluation.

- Pg. 2 last sentence should read "futile (noncurative) lung resection" instead of "futile (noncurative) thoracotomy" to reflect the fact that resection of lung malignancies is now performed thoracoscopically not only via thoracotomy.
  - This change was accepted.

- Pg. 4 first sentence regarding the recommendation for invasive staging should be "Normal CT, negative PET-CT and a central tumour, N1 disease or a stage IB tumour or higher"
  - This change was accepted.

- Two reviewers agreed that the nodal stations biopsied should be 2R/L, 4R/L, and 7, but noted that an absolute minimum of 3 stations (4R/L and 7; or 2R, 4R, and 7) should always be biopsied at mediastinoscopy. It was pointed out that routine sampling of 2L and 4L nodes may not be possible unless they are clearly visible and the left recurrent laryngeal nerve is not at risk for damage.

- One reviewer mentioned that stations 5 and 6 should be sampled for detecting cancer in the left upper lobe or left hilum.
  - **Response**: Section 2 of this document contains a discussion about stations 5 and 6. No randomized trials have examined if it is preferable to stage lymph nodes 5 and 6 before resection and these stations are not easily accessible via mediastinoscopy.

- This document did not mention biopsying station 3 lymph nodes as part of staging.
  - **Response**: Station 3 lymph nodes were not mentioned because station 3 is not routinely biopsied, i.e., pretracheal; 3A may be accessible by cervical mediastinoscopy, 3P may be accessible by EUS. However, any enlarged or suspicious node should be biopsied. A bullet point was added to the recommendations under "Based on a consensus of expert opinion" to indicate that any enlarged or suspicious node should be biopsied.

- There is no recommendation regarding when node sampling (i.e., node biopsy) for accurate staging is all that is necessary, versus recommendations when node dissection (i.e., complete removal) is indicated. Although it is clearly part of a separate issue, it would be appropriate to refer to this issue by simply stating overtly that lymph node dissection may replace lymph node biopsy in selected patients.
  - **Response**: This guideline deals with preoperative invasive mediastinal staging and therefore, recommendations regarding intraoperative LN sampling or dissection are beyond its scope.

- One reviewer noted that it would be useful to comment on the importance or not of the detection of pathologically positive versus clinically positive lymph nodes. For example, radiologically negative lymph nodes which are pathologically positive may still be amenable to resection followed by adjuvant chemotherapy.
  - **Response**: Yes, however this guideline does not address treatment. There is no strong data to support the practice of operating on CT/PET N2 negative patients with adjuvant chemotherapy compared with induction chemotherapy radiation. Please refer to the CCO guideline produced by the Lung DSG on stage IIIA disease, "7-4: Use of Preoperative Chemotherapy with or without Postoperative Radiotherapy in Technically Resectable Stage IIIA Non-Small Cell Lung Cancer"

- The evidence mainly covers false negative rates. It would be useful to have more discussion about the false positive rates of PET. It is also not clear if false negative rates are the reason for changing practice to more invasive staging.
  - **Response**: There is some discussion about the false positive rates under the Clinical Perspective subheading of Section 1 and in the Results of Section 2, the evidentiary base of this document. The authors believe this discussion is sufficient.

- One reviewer noted that many studies with high false negative rates (7% to 20%) use a size cutoff of 15 mm and that the standard for negative nodes in some centres is 10 mm. The guideline demands mediastinoscopy or histologic confirmation too liberally.
  - **Response**: When CT first came into use, the cutoff was 15 mm. 10mm has better performance characteristics but more importantly it minimizes false negatives. The goal is to avoid futile resections – using a 10 mm cutoff, more patients will get invasive staging but that does not mean they will not get a resection – only if the mediastinal staging is positive.

- The final draft should reflect the new International Association for the Study of Lung Cancer (IASLC) staging where T is T1a + T1b and not only T1.
  - **Response**: Some edits were made to reflect the T category instead of stage of tumour. For example, clinical stage 1B tumour was edited to T2 tumour or higher.

- Are there differences in the recommendations between tumours smaller or larger than 2 cm within the T1 tumour?
  - **Response**: The evidence and recommendations in this guideline are based on T1 tumours <3 cm and does not distinguish between tumours smaller or larger than 2 cm.

- One reviewer agreed that preoperative diagnosis of N2,3 status is important but indicated that other readers may require convincing arguments. Another reviewer was not sure how knowing about the microscopic involvement beforehand would ultimately

change management. It was noted that microscopic N2 disease can be cured with surgical intervention alone.
  - **Response**: Although some N2 tumours can be cured with surgery alone, survival is improved with trimodality therapy for resectable stage IIIa disease. For more information, please see CCO guideline "7-4: Use of Preoperative Chemotherapy with or without Postoperative Radiotherapy in Technically Resectable Stage IIIA Non-Small Cell Lung Cancer."

- The authors of this document quoted the ACCP systematic review to support their recommendations. However, the ACCP guideline did not differentiate between T1 and T2 tumours. This guideline recommends invasive staging for T2 tumours despite normal CT and negative PET-CT but there are no references to support this.
  - **Response**: The evidence is inferred from the adverse prognosis of larger tumours as shown by the IASLC staging project which advised the revision of the TNM staging system which upstaged larger tumours. A qualifying statement was added to Section 1 to state this.

- The question of CT negative, PET positive in the mediastinum is not specifically addressed in the recommendations – this combination would require invasive mediastinal staging
  - **Response**: This combination of CT negative and PET positive in the mediastinum was added as a bullet point to the Recommendations under "Invasive staging is recommended in the following cases:"

- One reviewer did not agree with the requirement for invasive mediastinal staging for all 1B tumours – for example, a 1B peripheral tumour which is 1B by virtue of touching the visceral pleura, but <3 cm in size should not require invasive mediastinal staging if CT and PET are negative in the mediastinum.
  - **Response**: Although this probably does not require invasive staging, these tumours do have a worse prognosis. Furthermore, stage T2 by virtue of visceral pleural invasion is a pathologic (i.e., postoperative) diagnosis, and therefore generally does not influence preoperative decision making regarding invasive mediastinal staging.

- The guideline should state that invasive mediastinal staging is only required if there is no evidence of distant metastases.
  - **Response**: The guideline's primary question defines the target population for the recommendations as patients with stage cT1-4, N0-3, M0 non-small cell lung cancer, where M0 indicates no metastases. Further, in the recommendations section, the tumour definitions are provided where M0 is explicitly defined as no metastases.

- Would patients who are not receiving surgery also need invasive staging?
  - **Response**: Yes, any patient who is planning to receive curative intent therapy should have invasive staging. Radiation oncologists are currently trying to reduce field size, so if contralateral or even ipsilateral nodes have been sampled and shown not to be involved, they will limit their field to the primary tumour only. Conversely, if the nodes have not been sampled, they will have to include the mediastinum in the radiation plan, which may result in a reduced dose and reduce chance of cure or control.

- One reviewer commented that there are enough guidelines and literature available on this topic and this document will not add to a thoracic surgeon's decision making process regarding mediastinal staging.

- Large studies are needed of postoperative pathologic correlation between preoperative PET-CT reports and postoperative findings.

- The authors of this document might want to consider discussing video-assisted versus conventional mediastinoscopy.
  - **Response**: The literature search identified some studies about video-assisted surgery (see Tables in the Results and Appendix of Section 2) and it is briefly mentioned in the Discussion of Section 2.

- Two reviewers noted that this document did not mention the use of bronchoscopy (including Wang needle biopsies) and EBUS biopsies to avoid invasive mediastinoscopy.
  - **Response**: The Discussion in Section 2 of this document mentions needle cytology and more details about EBUS.

- Would you recommend N1 staging with EBUS if we have it or will it not affect treatment?
  - **Response**: Mediastinoscopy is currently the gold standard for invasive staging of the mediastinum. More data are required about EBUS before any recommendations can be made. There is some discussion about EBUS in Section 2 of this document. N1 disease is treated surgically, with no clear evidence supporting induction treatment, so preoperative diagnosis of N1 involvement would generally not change management

- With newer development around EBUS-TBNA and EUS-FNA, the document on mediastinoscopy may need review in 2 to 3 years.
  - **Response**: As new evidence emerges about this topic, updates of this document will be conducted in future.

Conclusion

This EBS report reflects the integration of feedback obtained through the external review process with final approval given by the Invasive Mediastinal Staging Expert Panel and the Report Approval Panel of the PEBC. Updates of the report will be conducted as new evidence informing the question of interest emerges.

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Disclaimer

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2. Browman GP, Newman TE, Mohide EA, Graham ID, Levine MN, Pritchard KI, et al. Progress of clinical oncology guidelines development using the practice guidelines development cycle: the role of practitioner feedback. J Clin Oncol. 1998;16(3):1226-31.

Evidence-Based Series 17-6 Version 2: Section 4

Invasive Mediastinal Staging of Non-small Cell Lung Cancer

Document Assessment and Review

K. Yasufuku, J. Brown, and the Expert Panel on Invasive Mediastinal Staging of Non-small Cell Lung Cancer

A Quality Initiative of the
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)
and Surgical Oncology Program (SOP)

May 3, 2018

The 2010 guideline recommendations are

ENDORSED

This means that the recommendations are still current and relevant for decision making

OVERVIEW

The original version of this guidance document was released by Cancer Care Ontario's Program in Evidence-based Care in 2010.

In 2017, this document was assessed in accordance with the PEBC Document Assessment and Review Protocol and was determined to require a review. As part of the review, a PEBC methodologist (JB) conducted an updated search of the literature. A clinical expert (KY) reviewed and interpreted the new eligible evidence and proposed the existing recommendations could be ENDORSED. A panel of experts on mediastinal staging of non-small cell lung cancer (Appendix 1) endorsed the recommendations found in Section 1 (Clinical Practice Guideline) on May 3, 2018.

DOCUMENT ASSESSMENT AND REVIEW RESULTS

Question Considered

Primary Questions

Is invasive mediastinal staging in stage cT1-4, N0-3, M0 non-small cell lung cancer (NSCLC) patients indicated under the following circumstances?

a) Normal sized mediastinal lymph nodes on computed tomography scan (CT), and
   i. negative positron emission tomography (PET)-CT scan in the mediastinum
   ii. positive PET-CT in the mediastinum
b) Enlarged discrete mediastinal nodes on CT (clinical N2 or N3 nodes), and
   i. negative PET-CT in the mediastinum

ii. positive PET-CT in the mediastinum

Secondary Questions

What constitutes invasive mediastinal staging? What is the proper technique in performing invasive mediastinal staging?

a) Which node stations should be biopsied?

b) How many lymph nodes should be biopsied?

Literature Search and new Evidence

A search for relevant articles published between August 2010 and February 2018 was conducted in MEDLINE and EMBASE and located 541 unique references (Appendix 2). The abstracts for each of these papers were examined, and the full texts of 102 were reviewed. Sixty-three of these were found to contain the comparisons of interest (Table 1). Four of the studies were randomized controlled trials (RCTs); the remainder were observational studies. There were also seven guideline recommendations (Table 2) and eight systematic reviews/meta analyses (Table 3) dealing with aspects of the topic. However, since many of the guidelines and systematic reviews/meta analyses did not include studies published within the last few years, decisions were based on the individual studies (Table 1).

Impact on Guidelines and Its Recommendations

The new evidence supports the existing recommendations. However, since the last evidence summary in this series (2010), numerous studies have been published supporting the high diagnostic accuracy of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), over other methods of invasive staging such as mediastinoscopy. Several guidelines including the National Institute for Health and Care Excellence (NICE) [1], European Society of Thoracic Surgeons (ESTS) [2] and American College of Chest Physicians (ACCP) [3] currently recommend EBUS-TBNA as first line modality for invasive mediastinal staging in lung cancer with high suspicion of mediastinal lymph node involvement (Table 1).

The 2007 ACCP guideline was adapted in the 2010 PEBC evidence summary; the 2013 ACCP evidence base is current up to the end of 2012. The important new evidence in the use of EBUS-TBNA, as highlighted in the 2013 ACCP guideline [3] (Table 1), is as follows:

> "In patients with high suspicion of N2,3 involvement, either by discrete mediastinal lymph node enlargement or PET uptake (and no distant metastases), a needle technique (endobronchial ultrasound [EBUS]-needle aspiration [NA], EUS-NA or combined EBUS/EUS-NA) is recommended over surgical staging as a best first test (Grade 1B).
>
> In patients with an intermediate suspicion of N2,3 involvement, ie, a radiographically normal mediastinum (by CT and PET) and a central tumor or N1 lymph node enlargement (and no distant metastases), a needle technique (EBUS-NA, EUS-NA or combined EBUS/EUS-NA) is suggested over surgical staging as a best first test (Grade 2B)."

More recently, a meta-analysis (covering comparative studies to March 31, 2016) estimated the pooled risk-difference of the sensitivity of EBUS/EUS versus mediastinoscopy in cohort studies and RCTs at 0.11 (95% confidence interval, –0.07 to 0.29) and 0.11 (95% confidence interval,–0.03 to 0.25), respectively, suggesting equivalence of the two procedures. The complication rate was significantly lower with endosonographic procedures. [4]. There are no studies published after March 2016 directly comparing EBUS/EUS with mediastinal staging.

It was determined that the recommendations were still valid, but a qualifying statement highlighting the more recent ACCP guideline and the meta-analysis should be added.

Document Review Tool

Number and Title of Document under Review	17-6 Invasive Mediastinal Staging of Non-small Cell Lung Cancer
Original Report Date	October 18, 2010
Date Assessed (by DSG or Clinical Program Chairs)	December 8, 2017
Health Research Methodologist	Judy Brown
Clinical Expert	Kazuhiro Yasufuku
Approval Date and Review Outcome (once completed)	May 3, 2018

Original Questions:

Primary Questions

Is invasive mediastinal staging in stage cT1-4, N0-3, M0 non-small cell lung cancer (NSCLC) patients indicated under the following circumstances?

a) Normal sized mediastinal lymph nodes on computed tomography scan (CT), and
   i. negative positron emission tomography (PET)-CT scan in the mediastinum
   ii. positive PET-CT in the mediastinum
b) Enlarged discrete mediastinal nodes on CT (clinical N2 or N3 nodes), and
   i. negative PET-CT in the mediastinum
   ii. positive PET-CT in the mediastinum

Secondary Questions

What constitutes invasive mediastinal staging? What is the proper technique in performing invasive mediastinal staging?

a) Which node stations should be biopsied?
b) How many lymph nodes should be biopsied?

Target Population:

NSCLC patients in Ontario who have been clinically staged T1-4, N0-3, with no distant metastases.

Study Selection Criteria:

Articles were eligible for inclusion in this systematic review if they met the following criteria:

- Were the following study types: Practice guidelines, systematic reviews with or without meta-analyses, randomized phase II or III trials, other diagnostic comparative studies, or prospective case-series with diagnostic utility outcomes; non-comparative studies had to include ≥ 50 patients
- Involved an invasive staging technique, including mediastinoscopy and/or endobronchial ultrasound with needle aspiration and/or endoscopic ultrasound with needle aspiration, compared with lymph node sampling at thoracotomy;
- Reported outcomes included sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), FP rate, FN rate, and overall diagnostic accuracy.

Treatment-related outcomes such as overall survival and locoregional control were also of interest but not necessary for a study to be included in the evidence base;
- Involved patient populations that underwent prior noninvasive staging using integrated CT, PET, or PET-CT;
- Published between January 2006 and 11 August 2010;
- Involved at least 20 patients.

Because of a lack of translation resources, excluded articles included those published in a language other than English, and, as well, articles with a focus on diagnostics rather than staging were excluded.

Search Details:
- January 2010 to January 2018 (Medline January wk 3 and Embase wk 4)
- January 2016 to March 2018 (ASCO Annual Meeting)
- October 2001 to March 2018 (clinicaltrials.gov)

Summary of new evidence:

The search for relevant articles published between August 2010 and February 2018 was conducted in MEDLINE and EMBASE and located 541 unique references. The abstracts for each of these papers were examined, and the full texts of 154 were reviewed. There were seven guideline recommendations, with the 2013 ACCP guideline being the most relevant for this review [3] (Table 1). Sixty-four individual studies were found to contain the comparisons of interest (Table 2). Four of the studies were RCTs; the remainder were observational studies (Table 2). There were eight systematic reviews/meta analyses (Table 3) dealing with aspects of the topic. See Appendix 3 for a list of ongoing trials.

Clinical Expert and Health Research Methodologist Interest Declaration:
The clinical expert has consulted for Olympus America Incorporated for educational activities and has been in research collaborations with Olympus Corporation.
The health research methodologist had no conflict of interest declaration.

1. Does any of the newly identified evidence contradict the current recommendations? (i.e., the current recommendations may cause harm or lead to unnecessary or improper treatment if followed)	No
2. Does the newly identified evidence support the existing recommendations?	No
3. Do the current recommendations cover all relevant subjects addressed by the evidence? (i.e., no new recommendations are necessary)	Yes

Review Outcome as recommended by the Clinical Expert	**ENDORSE (with additional qualifying statement)**
If outcome is UPDATE, are you aware of trials now underway (not yet published) that could affect the recommendations?	**ACCP is working on updating the lung cancer guideline, but the mediastinal staging is not scheduled for update for another year which would put is to 2.5 years from now for publication.**
DSG/Expert Panel Commentary	Add statement emphasizing that EBUS-NA and EUS-NA should only be done in centres with appropriate skills and resources available.

Table 1: Clinical Practice Guidelines				
Document (Reference)	**Group**	**Scope and findings**	**Methods**	**Dates of search**
1. Baldwin et al. 2011 [1] Diagnosis and treatment of lung cancer: summary of updated NICE guidance	NICE	NICE recommendations are based on systematic reviews of best available evidence and explicit consideration of cost effectiveness. When minimal evidence is available, recommendations are based on the Guideline Development Group's experience and opinion of what constitutes good practice.	NR	NR
2. Darling et al. 2011 [5] Invasive mediastinal staging of non-small-cell lung cancer: a clinical practice guideline	American College of Chest Physicians (ACCP)	Invasive mediastinal staging in NSCLC patients who have been staged T1–4, N0–3, with no distant metastases. Invasive mediastinal staging of NSCLC is recommended in all cases except those involving patients with normal-sized lymph nodes, negative combine positron-emission tomography and computed tomography, and peripheral clinical stage 1A tumour. When performing mediastinoscopy, 5 nodal stations (2R/L, 4R/L, and 7) should routinely be examined.	Systematic Review and consensus of expert opinion	2006 to August 11, 2010
3. De Leyn et al. 2014 [2] Revised ESTS guidelines for preoperative mediastinal lymph node staging for non-small-cell lung cancer	**European Journal of Cardio-Thoracic Surgery (ESTS)**	Several meetings where the participants presented their experience and discussed the relevant literature published since 2007. Recommendations, but no summary statistics provided	Consensus process – workshop with ESTS Council	2007 to May 2013
4. Sánchez de Cos et al. 2011 [6] SEPAR Guidelines for Lung Cancer Staging	Spanish Society of Pulmonology and Thoracic Surgery(SEPAR)	Update the SEPAR limited to aspects of staging, Recommendations, but no summery statistics provided	NR	NR
5. Silvestri et al. 2013 [3] Methods for Staging Non-small Cell Lung Cancer See also: Rivera et al. 2013 [7]	ACCP	• Sensitivity and specificity of CT scanning for identifying mediastinal lymph node metastasis approximately 55% and 81%, respectively. • PET scanning, estimates of sensitivity and specificity for identifying mediastinal metastasis approximately 77% and 86%, respectively. • Needle techniques endobronchial ultrasound-needle aspiration, endoscopic ultrasound-needle aspiration, and combined endobronchial ultrasound/endoscopic ultrasound-needle aspiration have sensitivities of approximately 89%, 89%, and 91%, respectively. • In direct comparison with surgical staging, needle techniques have emerged as the best first diagnostic tools to obtain tissue. • Based on randomized controlled trials, PET or PET-CT scanning is recommended for staging and to detect unsuspected metastatic disease and avoid noncurative resections.	Systematic Review	Up to June 2012
6. Vansteenkiste et al. 2013 [8] Early and locally advanced	European Society for Medical	Overall incidence and epidemiology data are summarised	NR	NR

Table 1: Clinical Practice Guidelines				
Document (Reference)	**Group**	**Scope and findings**	**Methods**	**Dates of search**
non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†	Oncology (ESMO)			
7. Vilman et al. 2015. [9] Combined endobronchial and oesophageal endosonography for the diagnosis and staging of lung cancer	European Society of Gastrointestinal Endoscopy (ESGE) [in coop. with ERE and ESTS]	tT address the benefit and burden associated with mediastinal nodal staging of lung cancer by combined endobronchial ultrasound (EBUS) and endoscopic oesophageal ultrasound (EUS-(B).	Systematic review	1990 to Oct. 2013

Table 2: Studies assessing NSCLC staging				
Study (Reference)	**Population**	**Staging Procedure**	**Findings**	**Authors' conclusions**
1. Annema et al. 2010 [10]	RCT of patients with resectable (suspected) NSCLC in whom mediastinal staging was indicated based on computed or positron emission tomography (n=241)	endosonography (combined transesophageal and endobronchial ultrasound)	• Sensitivity (surgical staging): 79% (41/52; 95% CI, 66%-88%) vs endosonography 85% (56/66; 95% CI, 74%-92%) (P = .47) and endosonography followed by surgical 94% (62/66; 95% CI, 85%-98%) (P = .02).	Among patients with (suspected) NSCLC, a staging strategy combining endosonography and surgical staging compared with surgical staging alone resulted in greater sensitivity for mediastinal nodal metastases and fewer unnecessary thoracotomies.
2. Arslan et al. 2011 [11]	RCT of consecutive patients who were referred for TBNA (n=60).	Conventional vs. EBUS-TBNA	• Overall diagnostic yield of conventional TBNA 33.3% (10/30) vs. EBUS-TBNA yield of 66.7% (20/30; p= 0.010). • Patients with subcarinal lymph nodes, yield of conventional TBNA 33.3% (4/12) vs. 62.5% (5/8) in the EBUS-guided group (p= 0.362). • Patients with mediastinal lymph nodes yields other than subcarinal lymph nodes, EBUS-TBNA 68.2% (15/22) vs. conventional 33.3% (6/18), p= 0.028.	The diagnostic yield of EBUS-TBNA was superior to the yield of conventional TBNA at stations other than subcarinal region. We suggest that EBUS is a useful tool to guide TBNA in the evaluation of mediastinal lymph nodes.

Table 2: Studies assessing NSCLC staging				
Study (Reference)	**Population**	**Staging Procedure**	**Findings**	**Authors' conclusions**
3. Berania et al. 2015 [12]	EBUS was performed in 324 patients (99%), EUS in 295 patients (90%), and CM in 101 patients (31%); 226 patients (69%) were assumed to have undergone a virtual ideal CM and a virtual surgical mediastinal staging;	EBS, EUS, cervical mediastinoscopy (CM) vs gold standard (surgical staging)	• Distant metastatic disease was diagnosed by EBUS/EUS in 7 patients (2.1%); 22 patients (6.7%) had positive targets outside the reach of the CM or virtual CM. • If the 14 patients who had positive stations 5, 6, 10, and 11 are excluded (accessible with anterior mediastinotomy or extended cervical mediastinoscopy), there were 6 patients (1.8%) in whom endosonography upstaged the patient over ideal surgical mediastinal staging. • In 20 patients (6.1%), ultrasound-guided biopsy made the diagnoses, which changed the treatment plan over CM and ideal CM	Combined EBUS- and EUS-guided biopsies can access more targets, including lung and distant metastasis, and thus have the potential to upstage patients compared with mediastinoscopy and change the treatment plan.
4. Bolton et al, 2013 [13]	Retrospective cohort study of patients undergoing EBUS (n=190	EBUS	• Overall FN rate 2 % for all benign results, and 4 % for those benign results confirmed with lymph node dissection or mediastinoscopy. • Both false negative studies sampled levels 4L, 4R, and 7. • Sensitivity (for diagnosis) 97% • Specificity (for diagnosis) 100 %. • Sensitivity (staging) 98% • Specificity (staging) 100 %. • In staging EBUS, a mean of 2.6 nodal stations sampled, with 59 % having three lymph node stations sampled and 33 % (n = 30) had two lymph node stations sampled.	We found that EBUS is a highly accurate and minimally invasive manner in which to both diagnose mediastinal masses and stage the mediastinum.
5. Call et al. 2016 [14]	Prospective observational study of all consecutive VAMLAs (n=160)	video-assisted mediastinoscopic lymphadenectomy (VAMLA)	• rate of unsuspected N2-3 disease was 18% for the whole series: 40.7% for cN1, 22.2% for cN0 and tumor size greater than or equal to 3 cm, and 6.4% for cN0 and tumor size less than 3 cm. • Staging values were sensitivity, 0.96 (95% CI, 0.81-99.3); specificity, 1 (95% CI, 0.97-1); PPV, 1 (95% CI, 0.87-1); NPV 0.99 (95% CI, 0.95-0.99); and diagnostic accuracy, 0.99 (95% CI, 0.96-0.99). T • he complication rate was 5.9%.	VAMLA is a feasible and highly accurate technique. The high rate of unsuspected mediastinal node disease diagnosed by VAMLA in patients with cN1 or cN0 disease and tumor size larger than 3 cm suggests that preresection lymphadenectomies should be included in the current staging algorithms.

Table 2: Studies assessing NSCLC staging				
Study (Reference)	**Population**	**Staging Procedure**	**Findings**	**Authors' conclusions**
6. Cerfolio et al, 2010 [15]	Retrospective review of patients with NSCLC with suspected N2 disease (n=234)	PET, CT, Mediastinoscopy	• EBUS (n=72)16 were positive for N2 disease and 12 were FN (7 patients at station 4R/4L, 4 patients at station 7 (patient sensitivity 57%, NPV 79%, accuracy 83%). • EUS (n=79): 20 positive for N2 disease and 12 FN (4 patients at station 4R/4L, 4 patients at station 7 (patient sensitivity 63%, negative predictive value 80%, accuracy 85%). • Mediastinoscopy (n=146) which revealed N2 or N3 disease in 42 patients, and 7 were FN (patient sensitivity 88%, negative predictive value 93%, accuracy 95%).	Both EBUS and EUS are useful initial tests to biopsy suspicious N2 mediastinal lymph nodes; however, as EBUS and EUS have high false negative rates, especially at stations 4R and 7, mediastinoscopy is still required for patients with suspicious nodal disease in these stations.
7. Cetinkaya et al. 2011 [16]	Patients diagnosed NSCLC with CT scans showing enlarged lymph nodes (node >1 cm) or a positron emission tomography (PET/CT) finding of the mediastinum (n=52)	EBUS-TBNA	• BUS-TBNA in the detection of mediastinal metastasis: sensitivity 95 %,, specificity 100%, PPV 100%, NPV 83%, accuracy 96%. • EBUS-TBNA was uneventful, and there were no complications	EBUS-TBNA is an effective, safe and minimally invasive procedure following PET/CT or CT scanning in the mediastinal staging of potentially operable NSCLC.
8. Ceylon et al. 2012 [17]	Consecutive patients with suspected NCCLC (n=57)	PET-CT vs. CE-CT	• There was a significant difference between CE-CT and PET-CT for nodal staging of N0 disease ($P < 0.05$). • CE-CT: sensitivity 56%,, specificity 73%,, PPV 28%,, NPV 90%, accuracy 70% of hilar and mediastinal lymph node staging with • PET-CT: sensitivity 78%, specificity 92%, NPV 64%, PPV 96%, and accuracy 89%	Integrated PET-CT is more accurate than CE-CT for lymph node staging in NSCLC.

Table 2: Studies assessing NSCLC staging				
Study (Reference)	**Population**	**Staging Procedure**	**Findings**	**Authors' conclusions**
9. Citak et al. 2014 [18]	Retrospective sample of patients with who underwent mediastinoscopy (n=553).	Video-assisted mediastinoscopy (VAM) vs. standard cervical mediastinoscopy (SCM).	• Station 7 was the most predominant station for FN results (n = 15). • False negative (FN): SCM 5.9%, VAM 4.4%, p=0.490 • FN rate of station 7: SCM 3.8%, VAM 2.9%, p=0.623 • FN rate of station 7 found to be higher with SCM (n = 9, 3.8%) than with the VAM group (n = 6, 2.9%; p = 0.623).	FN were more common in mediastinoscopy of subcarinal LNs. VAM allows higher rates of sampling of mediastinal LN stations and station 7, although it did not improve staging of subcarinal LNs.
10. Claessen et al. 2012 [19]	Retrospective cohort study. (n=77)	EBUS - TBNA	• The sensitivity and negative-predictive values for EBUS-TBNA were 64-81% and 42-76%	In more than 50% of lung cancer patients with suspected mediastinal lymph node metastases, cervical mediastinoscopy can be avoided when EBUS-TBNA is used. This examination is the technique of first choice for the invasive staging of the mediastinum in lung cancer, but it can not replace mediastinoscopy completely.
11. Clementsen et al. 2014 [20]	95 consecutive patients with known or suspected lung cancer	EBUS - TBNA	• NPV 63/67=0.94. • If exclude station 5 and 6, NPV 66/67=0.99, sensitivity 0.76, specificity 1.0.	When EBUS-TBNA is performed under optimal conditions including general anesthesia and "bed side" microscopy performed by a pathologist resulting in representative biopsies from station 4R, 7, and 4L, the NPV is so high that mediastinoscopy seems unnecessary.
12. d'Amico et al. 2015 [21]	Prospective study of patients with radiologically-suspected lung cancer. (n=80)	PET/CT	Diagnosis of mediastinal lymph nodes, • CT able to detect 9(11.25%) true-positive, 17(21.25%) false-positive, 40(50%) true-negative and 14(17.5%) false-negative cases; sensitivity 39%, specificity 70% and accuracy 61% PPV 35%, NPN 74%. • PET/CT yielded 15(18.75%) true-positive, 12(15%) false-positive, 46(57.5%) true-negative and 7(8.75%) false-negative cases; Sensitivity	PET/CT had higher diagnostic accuracy than computed tomography in assessing mediastinal lymph nodes of patients with non-small cell lung cancer. However, a positive test requires histopathology confirmation.

Table 2: Studies assessing NSCLC staging				
Study (Reference)	**Population**	**Staging Procedure**	**Findings**	**Authors' conclusions**
			68% specificity 79%., accuracy 96%, and PPV 55%, NPV 87%y.	
13. Darling et al. 2011 [22]	Prospective study of patients with non-small cell lung cancer (NSCLC)	PET/CT vs results of mediastinal staging	• PET-CT sensitivity 70% (95% confidence interval [CI], 48-85%), specificity 94% (95% CI, 88-97%). Of 22 patients with a PET-CT interpreted as positive for mediastinal nodes, 8 did not have tumor. PPV 64% (95% CI, 43-80%), NPV 95% (95% CI, 90-98%). • Based on PET-CT alone, eight patients would have been denied potentially curative surgery if the mediastinal abnormalities detected by PET-CT had not been evaluated with an invasive mediastinal procedure.	PET-CT assessment of the mediastinum is associated with a clinically relevant false-positive rate. Our study confirms the need for pathologic confirmation of mediastinal lymph node abnormalities detected by PET-CT.
14. Dooms et al. 2015 [23]	Consecutive patients with operable and resectable cN1 non-small cell lung cancer (n=100)	endosonography and mediastinoscopy	• Invasive mediastinal nodal staging with endosonography alone: sensitivity 38%, NPV 81% • adding a mediastinoscopy: sensitivity 73%. NPV 91%, respectively. • Ten mediastinoscopies are needed to detect one additional N2 disease missed by endosonography	Endosonography alone has an unsatisfactory sensitivity to detect mediastinal nodal metastasis in cN1 lung cancer, and the addition of a confirmatory mediastinoscopy is of added value.
15. Fernandez-Bussy et al. 2015 [24]	Prospective study of patients undergoing EBUS-TBNA for diagnosis. (n=145, biopsies = 345)	EBUS-TBNA	• The mean lymph node size was 15.03 mm, and 90 lymph nodes were smaller than 10.0 mm. • EBUS-TBNA: sensitivity 91.17%, specificity 100.0%, NPV 92.9%.	EBUS-TBNA is a diagnostic tool that yields satisfactory results in the staging of neoplastic mediastinal lesions.
16. Figueiredo et al. 2015 [25]	Retrospective analysis of patients diagnosed with lung cancer and submitted to EBUS-TBNA for mediastinal lymph node staging (n=149).	EBUS-TBNA	• For staging: sensitivity 96%, specificity 100%, NPV 85%.	We found EBUS-TBNA to be a safe and accurate method for lymph node staging in lung cancer patients.

Table 2: Studies assessing NSCLC staging				
Study (Reference)	**Population**	**Staging Procedure**	**Findings**	**Authors' conclusions**
17. Fischer et al. 2011 [26]	RCT of patients with a verified diagnosis of non-small cell lung cancer, who were considered operable (n=189).	PET-CT vs. EUS-FNA vs. invasive staging without prior PET-CT (conventional work up – CWU)	• In an intention-to-treat analysis the overall accuracy of the consensus N stage was not significantly higher in the PET-CT group than in the CWU group (90% (95% confidence interval 82% to 95%) vs 85% (95% CI 77% to 91%)). • Excluding patients in whom PET-CT was not performed (n=14) the difference was significant (95% (95% CI 88% to 98%) vs 85% (95% CI 77% to 91%), p=0.034). This was mainly based on a higher sensitivity of the staging approach including PET -CT	An approach to lung cancer staging with PET-CT improves discrimination between N0-1 and N2-3. In those without enlarged lymph nodes and a PET-negative mediastinum the patient may proceed directly to surgery. However, enlarged lymph nodes on CT needs confirmation independent of PET findings and a positive finding on PET-CT needs confirmation before a decision on surgery is made.
18. Frechet et al. 2018 [27]	Retrospective analysis of 997 biopsy-proven NSCLC patients treated at a single academic medical center	CT, PET, EBUS-TBNA, EUS-FNA.	• CT sensitivity 18.9%, specificities 94.9% • PET-CT sensitivity 33.8%. specificity 93%. • EBUS-TBNA Sensitivity 72.7%, Specificity 100% • EUS-FNA sensitivity 51.9%, specificity 100%.	The majority of biopsy-proven mediastinal lymph nodes metastases are not associated with positive results on preoperative CT or PET. CT and PET have low positive predictive value for mediastinal lymph node. This study supports the routine utilization of invasive mediastinal lymph nodes staging in NSCLC, especially for patients with tumors of >4 cm diameter, regardless of CT or PET-CT results.
19. Fuso et al. 2015 [28]	Patients with suspected lung cancer who underwent bronchoscopy with conventional TBNA (n=375)	TBNA	• TBNA was positive for metastatic involvement of lymph nodes in 172 of 282 patients with cancer (sensitivity 61%) • Sensitivity achieved 65% when we considered the total of 459 TBNA specimens. • Overall diagnostic accuracy of TBNA 69%. • The nodal stations more frequently examined were 7 (subcarinal: 190 TBNAs), 4R (right lower paratracheal: 147 TBNAs), and 10R (right hilar: 76 TBNAs), with a sensitivity of 66%, 66%, and 67%, respectively.	Conventional TBNA remains a useful method for the diagnosis and staging of lung cancer, with a good diagnostic yield in several nodal stations.
20. Geraldson et al. 2012 [29]	Retrospective review of patients diagnosed with NSCLC (n=117)	CT, PET	• CT: Overall accuracy 81.2%, sensitivity was 42.1%, specificity 88.8%, PPV 42.1%, NPV 88.8%,	Our analysis confirms the use of PET scan imaging in the staging of

Table 2: Studies assessing NSCLC staging				
Study (Reference)	**Population**	**Staging Procedure**	**Findings**	**Authors' conclusions**
			FN 9.4%, FP 9.4% • PET Overall accuracy 91.5%, sensitivity 52.6%, specificity 99.0%, PPV 90.9%, NPV 91.5%, FN 7.7%, FP 0.9%	patients with NSCLC at a regional teaching institution.
21. Gómez-Caro et al. 2012 [30]	Patients with potentially operable NSCLC were assessed by thoracic CT scan and 18-fluoro-2-deoxy-d-glucose PET-CT for mediastinal staging (n=402)	PET/CT	• Composite non-invasive staging (CT scan, PET-CT): NPV 85% (CI 74–92) • There were 11 of 74 (14.8%) • Multilevel pN2 were detected in four cases	Composite results for non-invasive mediastinal staging (CT scan, PET-CT) showed 11% of FNs in cI stage (7.6% in non-central cIA and 14.8% in cIB). In tumours ≤1 cm, NPV makes surgical staging unnecessary. In women with adenocarcinoma and non-central cIB, however, the high FN rate makes invasive staging necessary, particularly in pT2b to decrease the incidence of unexpected pN2 in thoracotomy.
22. Gunluoglu et al. 2011 [31]	Cohort study of patients with histologically confirmed NSCLC diagnoses suitable for thoracotomy (n=185)	PET/CT	• Sensitivity, 84% specificity 100%, and PPV 100%, NPV 94%	The preoperative LNSGs for NSCLC proposed by the ESTS are effective.
23. Hauer et al. 2015 [32]	Group of consecutive patients with primary non-small cell lung cancer,	PET, EBUS-NA, and EUS-NA.	• Mean number of removed lymph nodes 22. • NPV EBUS-NA/EUS-NA 89.8% • NPV PET/EBUS-NA/EUS-NA-93.2%.	Patients with lung cancer with negative results of PET, EBUS-NA, and EUS-NA are at low risk of mediastinal nodal metastasis. In these patients, invasive mediastinal staging may not be necessary

Table 2: Studies assessing NSCLC staging				
Study (Reference)	**Population**	**Staging Procedure**	**Findings**	**Authors' conclusions**
24. Herth et al. 2010 [33]	Consecutive patients with a presumptive diagnosis of NSCLC who underwent endoscopic staging by EBUS-TBNA and EUS-FNA through a single linear ultrasound bronchoscope. (n=150)	EBUS-TBNA vs. EUV-FNA vs. surgical confirmation	• EUS-FNA Sensitivity 89% • EBUS-TBNA 92% • Combined approach sensitivity of 96% , NPV 95% • No complications occurred	The two procedures can easily be performed with a dedicated linear endobronchial ultrasound bronchoscope in one setting and by one operator. They are complementary and provide better diagnostic accuracy than either one alone. The combination may be able to replace more invasive methods as a primary staging method for patients with lung cancer.
25. Hu et al. 2010 [34]	Patients with tumors and enlarged mediastinal lymph nodes found by CT (N=75)	EBUS-TBNA	• For diagnosis: 0verall sensitivity 98.4%, specificity 100%, PPV 100%, NPV 91.2% ,diagnostic accuracy 98.7% • in per patient analysis and were sensitivity 95.10%, specificity 100%, PPV 100.00%, NPV 82.93%, diagnostic accuracy 96.05% • in per group analysis, higher than CT examination (P < 0.05) expect for sensitivity (P = 0.435). Staging changed in 19 (26.03%) patients after EBUS-TBNA.	EBUS-TBNA proved to be a safe procedure with a high yield for the diagnosis of lung cancer.
26. Hwangbo et al. 2010 [35]	Prospective study of patients with confirmed or strongly suspected potentially operable non-small cell lung cancer (n=150).	transbronchial and transesophageal ultrasonography using an ultrasound bronchoscope	• EBUS-TBNA in the detection of mediastinal metastasis: sensitivity 84.4%, NPV 93.3%, diagnostic accuracy 95.1% c • Combined approach of EBUS-TBNA and EUS-B-FNA; sensitivity 91.1%, NPV 96.1%, diagnostic accuracy 97.2% • Differences not statistically significant (P = .332, P = .379, and P = .360, respectively • Among 473 mediastinal nodal stations having at least one node >= 5 mm that were evaluated, the proportion of accessible mediastinal nodal stations by EBUS-TBNA was 78.6%, and the proportion increased to 84.8% by combining EUS-B-FNA with EBUS-TBNA (P = .015).	Following EBUS-TBNA in the mediastinal staging of potentially operable lung cancer, the accessibility to mediastinal nodal stations increased by adding EUS-B-FNA and an additional diagnostic gain might be obtained by EUS-B-FNA.

Table 2: Studies assessing NSCLC staging				
Study (Reference)	**Population**	**Staging Procedure**	**Findings**	**Authors' conclusions**
27. Iskender et al. 2012 [36]	Cohort study of consecutive patients diagnosed with NSCLC (n=212)	PET/CT and mediastinoscopy	• In PET/CT analysis 60 true-positive, 45 false-positive, 103 true-negative and 4 false-negative patients were found. • The rate of PET/CT positivity of mediastinal lymph nodes was 49.5%.; sensitivity 93.8%, specificity 69.6%, PPV 57.1%, NPV 96.3% accuracy 76.9% • Incidence of N2 disease in NSCLC patients with negative mediastinal lymph node uptake on PET/CT was 3.7% (4 of 107) • In univariate analysis, right upper lobe tumours were significantly ($p < 0.05$) more associated with occult N2 disease.	In patients with positive mediastinal lymph node uptake on PET/CT invasive mediastinal staging appears necessary for exact staging. Mediastinoscopy can be omitted in NSCLC patients with negative mediastinal uptake on PET/CT in regions where the rate of PET/CT positivity of mediastinal lymph nodes is high.
28. Jhun et al. 2012 [37]	Consecutive patients who underwent EBUS-TBNA of mediastinal or hilar lymph nodes for staging or diagnosis of NSCLC (n=151)	EBUS-TBNA	• overall diagnostic sensitivity 91.6%, specificity 98.6%, accuracy 93.8%, NPV 84.3% • NPV of the left side nodal group was significantly lower than those of the other groups (P = 0.047) • Sensitivity of the left side nodal group tended to decrease (P = 0.096) compared with those of the other groups. • Diagnostic sensitivity and NPV of 4L lymph node were 83.3% and 66.7%, respectively. • Diagnostic performances of EBUS-TBNA did not differ according to nodal size.	Bronchoscopists should consider the impact of nodal stations on diagnostic performances of EBUS-TBNA.
29. Joo et al. 2011 [38]	Retrospectively review of the records of patients who underwent EBUS-TBNA for mediastinal staging (n=142)	EBUS-TBNA	• Prediction of mediastinal metastasis: sensitivity 94.4% specificity 100%	We demonstrated the high diagnostic value of EBUS-TBNA for mediastinal staging.
30. Kambartel et al. 2012 [39]	Patients with confirmed lung cancer (n=111)	EBUS and mediastinoscopy	• The diagnostic accuracy of EBUS (94%) was superior to that of MS (86%) ($p < 0.05$). The negative predictive value of EBUS and MS was 83% for both, the sensitivity was 94% vs. 58%, the prevalence of N2 /N3 was 84% vs. 32% and the rate of complications was 0% vs. 3%.	Due to the at least similar accuracy the EBUS should be the first diagnostic procedure for histological staging of the mediastinum in patients with lung cancer.

Table 2: Studies assessing NSCLC staging				
Study (Reference)	**Population**	**Staging Procedure**	**Findings**	**Authors' conclusions**
31. Kang et al. 2014 [40]	RCT of histologically confirmed or strongly suspected potentially operable NSCLC (n=160)	EBUS (n=80) vs. EUS (n=80)	• Diagnostic accuracy EBUS vs. EUS: 93.2% (95% CI 87.5% to 99.0%) vs 97.3% (95% CI 93.6% to 101.0%), p=0.245; • Sensitivity EBUS vs. EUS: 85.3% (95% CI 68.9% to 95.0%) vs 92.0% (95% CI 74.0% to 99.0%), p=0.431) • In detecting mediastinal metastasis: not statistically different. • Adding EUS-FNA to EBUS-TBNA: did not significantly increase the accuracy (from 91.9% to 93.2%, p=0.754) or sensitivity (from 82.4% to 85.3%, p=0.742). • Adding EBUS-TBNA to EUS-FNA: increased the accuracy (from 86.5% to 97.3%, p=0.016) and sensitivity (from 60.0% to 92.0%, p=0.008). • No intergroup differences in procedure time, cardiorespiratory parameters during procedures, complications or patient satisfaction.	Using a combination of EBUS-TBNA and EUS-FNA in mediastinal staging, we found that diagnostic values and patient satisfaction were not different between the EBUS-centred and EUS-centred groups. However, the necessity for EBUS-TBNA following EUS suggests that EBUS-TBNA is a better primary procedure in endoscopic mediastinal staging of potentially operable lung cancer.
32. Kubota et al. 2011 [41]	Patients with operable NSCLC (n=81).	CT and FDG-PET vs. CT alone	• Accuracy improved from 69.1% (56/81) for CT alone to 75.3% (61/81) for CT + PET (p = 0.404). These findings contributed to treatment decisions in 63.0% (51/81) of the cases, mainly with regard to the selection of the operative procedure. • The results of the image interpretation committee showed that the accuracy improved from 64.2% (52/81) (95% CI 52.8-74.6) for CT to 75.3% (61/81) (95% CI 64.5-84.2) for CT + PET. • The accuracy for 106 mediastinal lymph nodes improved significantly from 62.3% (66/106) (95% CI 52.3-71.5) for CT to 79.2% (84/106) (95% CI 70.3-86.5) for CT + PET (p < 0.05).	The addition of FDG-PET to contrast-enhanced CT imaging for the staging of NSCLC improved the diagnostic accuracy for mediastinal lymph node metastasis. FDG-PET improved the precision of the staging of NSCLC and contributed to the surgical decisions.

Table 2: Studies assessing NSCLC staging				
Study (Reference)	**Population**	**Staging Procedure**	**Findings**	**Authors' conclusions**
33. Lee et al. 2012 [42]	Retrospective review of a prospective database of consecutive patients with NSCLC (n=73)	EBUS-TBNA	• Overall: sensitivity 95%, specificity of 100%, NPV 94%, accuracy 97% • Mediastinoscopy would have changed the tumor stage and treatment planning in only 2 (2.7%) of the 73 patients. • 30 had benign findings and underwent surgical resection, 1 of whom was found to have stage N2 disease.	EBUS-TBNA might be a feasible option for most patients with NSCLC for whom histologic assessment of the mediastinum is necessary. The rates of nondiagnostic and false-negative biopsy findings using EBUS-TBNA were low, small subcentimeter nodes could be routinely biopsied, and most patients with a radiographically positive mediastinum had their disease pathologically confirmed.
34. Li et al. 2012 [43]	Data from the patients with stage1 NSCLC who received preoperative (18)F-FDG PET/CT staging and radical surgery was retrospectively reviewed in five centers (n=200)	PET/CT	• For lymph node metastases: sensitivity 44%, specificity 83%, accuracy 78%, PPV 29%. NPV 91% • There were eight and 19 cases positive for lymph node metastases with central (n=62) and peripheral (n=138) NSCLC (P>0.05), respectively	(18)F-FDG PET/CT was specific in N(0) staging for T(1-2) NSCLC. The NPV was about 91% in clinical N(0) patients, suggested that (18)F-FDG PET/CT may help to accurately stage N(0) patients and thus identify patients for SBRT.
35. Liberman et al. 2014 [44]	Prospective selection of patients with confirmed or suspected NSCLC who required SMS based on current guidelines (n=166)	EBUS/EUS vs. surgical staging	• EBUS: sensitivity 72% (95% CI, 0.58-0.83), NPV 88% (0.81-0.93), diagnostic accuracy 91% (0.85-0.95) • EUS: sensitivity 62% (0.48-0.75), NPV 85% (0.78-0.91), diagnostic accuracy 88% (0.82-0.92) • Combined EBUS/EUS: sensitivity 91% (0.79-0.97), NPV 96% (0.90-0.99), diagnostic accuracy 97% (0.93-0.99) • Endosonography was diagnostic for N2/N3/M1 disease in 24 patients in whom SMS findings were negative, preventing futile thoracotomy in an additional 14% of patients.	The combined EBUS/EUS procedure can replace surgical mediastinal staging in patients with potentially resectable NSCLC. Additionally, endosonography leads to improved staging compared with SMS because it allows the biopsy of LNs and metastases unattainable with SMS techniques.
36. Lin et al. 2012 [45]	Patients with pathological early stage disease (n=83)	PET/CT	• The cut-off point of mediastinal LN SUV(max) was 1.6 calculated by receiver operating characteristic (ROC) curve (sensitivity: 40%, specificity: 88.7%, negative predictive rate: 95.1%).	Integrated PET-CT is a useful tool for predicting the negativity of mediastinal LN status pre-operatively in clinically early stage (Stages I and II) lung cancer but may

Table 2: Studies assessing NSCLC staging				
Study (Reference)	**Population**	**Staging Procedure**	**Findings**	**Authors' conclusions**
			• The false positive rates by PET-CT scan in N1 and N2 nodes were 70% and 78%, respectively, primarily due to inflammatory process (as anthracosis the leading cause).	be relatively inaccurate in predicting hilar LN status and largely confounded by false positives caused by
37. Mao et al. 2014 [46]	Patients were suspected or diagnosed with lung cancer or mediastinal lymph nodes enlargment(short diameter >/=1.0 cm) (n=308)	mediastinoscopy	• diagnostic accuracy 98.1%, sensitivity 976%, specificity 100%, PPV 100%, NPV 91.7% • 100% to mediastinal masses and mediastinal lymph node metastasis of lung cancer. • Seven cases suffered from complications of surgery-related, the complication rate was 1.93 percent (P<0.05).	The trauma of the mediastinoscopy is slight, which is safe, reliable, able to take in sufficient tissue quantities. Mediastinoscopy is highly helpful not only in diagnostic of mediastinal mass, but also in the differential diagnosis of lung cancer, and it's an important method and the gold standard of preoperative staging on lung cancer.
38. Medford et al. 2010 [47]	A prospective analysis of 79 TBNA procedures over a 2-year period	EBUS-TBNA	• TBNA avoided mediastinoscopy in 25% of the cases overall (37% in high probability vs. 13% in the 'mixed' cohort, p = 0.03). • he overall prevalence of malignancy was 84%, sensitivity 79%, NPV 58% and accuracy 85%. • Diagnostic utility varied with pre-test probability and nodal station. • TBNA down-staged 8% of lung cancer patients to receive surgery and confirmed the pre-treatment stage (inoperability) in 74%. TBNA led to theoretical cost savings of GBP 560 per patient.	TBNA can achieve a high diagnostic sensitivity for cancer in high probability patients and stage the majority appropriately, thereby avoiding unnecessary mediastinoscopies and reducing costs. It may also down-stage a minority to have surgery.
39. Nguyen et al. 2011 [48]	A retrospective review was conducted on all patients undergoing mediastinal EUS (n=148)	EUS-FNA	• Staging of known NSCLC: sensitivity 92.9%, specificity 88.9%), • Mediastinal lymphadenopathy: sensitivity 100%, specificity 100%) • Lung lesion: sensitivity 94.4%, specificity 85.7%). There were no major complications.	This large series of mediastinal EUS shows that it is an important and useful tool for the assessment of mediastinal pathology. It is safe and highly accurate, and should be incorporated into the staging algorithm for NSCLC.
40. Ohnishi et al. 2011 [49]	A consecutive series of patients with suspected resectable lung cancer on CT findings (n=120)	PET-CT and combined EUS-FNA/EBUS-TBNA	• Combined approach (EUS-FNA/EBUS-TBNA): sensitivity 71.8%, specificity 100%, PPV 100%, NPV 86.6% • PET-CT: sensitivity 47.4%, specificity 87.5%, PPV	The combined endoscopic approach using EUS-FNA and EBUS-TBNA provided excellent diagnostic performance. Therefore, this

Table 2: Studies assessing NSCLC staging				
Study (Reference)	**Population**	**Staging Procedure**	**Findings**	**Authors' conclusions**
			66.7%, NPV 75.9% • The accuracy of the combined approach using EUS-FNA and EBUS-TBNA was significantly higher than that of PET-CT (90.0 % vs. 73.6 %; P < 0.0001).	approach is strongly recommended before surgery or mediastinoscopy to avoid futile thoracotomy and surgical intervention.
41. Oki et a. [50]	Patients with potentially resectable known or suspected NSCLC (n=150)	EBUS-TBNA and EUS-FNA with a single bronchoscope	• EBUS-TBNA: sensitivity 52%, NPV 88% • EUS-FNA: sensitivity 45%, NPV 86% • Combined approach: sensitivity 73%, NPV 93%; EBUS-TBNA vs the combined approach, P=.016, McNemar's test). • Two patients (1%) developed severe cough from EBUS-TBNA.	he combined endoscopic approach with EBUS-TBNA and EUS-FNA is a safe and accurate method for preoperative hilar and mediastinal staging of NSCLC, with better results than with each technique by itself.
42. Ong et al. 2015 [51]	Retrospective review of EBUS-TBNA performed for lung cancer staging at two major academic centers (n=220)	EBUS-TBNA.	• Overall false-negative rate of EBUS was 14.1% (sensitivity, 36.7%; specificity, 100%; and NPV, 84.7%). • False-negative rate was 27 and 3.3% in surgical and nonsurgical populations, respectively. • Excluding patients with occult disease "outside" the reach of EBUS, the overall false-negative rate of EBUS-TBNA was 5.5% (sensitivity, 60%; specificity, 100%; and NPV, 93.4%).	This is the largest report of EBUS-TBNA in patients with N0 disease by "integrated" PET-CT. The majority of false-negative EBUS results were in LN stations outside its reach. In our study, both sensitivity and NPV of EBUS-TBNA were lower than early reports despite more extensive LN sampling.
43. Redondo-Cerezo et al. 2015 [52]	After the finding of a lymphadenopathy in a conventional CT, both PET-CT and EUS-FNA were performed (n=54)	PET-CT and EUS-FNA	• EUS-FNA: sensitivity 91.3%, specificity 100% PPV 100%, NPV 92.5%, overall accuracy 95.8%, PET-CT sensitivity 75%, specificity 25%, PPV 50%, NPV 50%, overall accuracy 50%.	In our series, EUS-FNA has proven to be the best diagnostic procedure to accurately establish the etiology of isolated adenopathies, showing a much better diagnostic yield than PET-CT, the role of which should be re-evaluated in this setting.
44. Sharples et al. 2012 [53]	Patients with non-small cell lung cancer (NSCLC) who are otherwise candidates for surgery with curative intent. 9n=241)	endoscopy	• Sensitivity for detecting N2/N3 metastases was 79% (41/52; 95% CI 66% to 88%)for the surgical arm compared with 94% (62/66; 95% CI 85% to 98%) for endosonography strategy (p = 0.02). • Corresponding NPVs were 86% (66/77; 95% CI 76% to 92%) and 93% (57/61; 95% CI 84% to 97%; p = 0.26).	Endosonography (followed by surgical staging if negative) had higher sensitivity and NPVs, resulted in fewer unnecessary thoracotomies and better quality of life during staging, and was slightly more effective and less expensive than surgical staging alone.

Table 2: Studies assessing NSCLC staging				
Study (Reference)	**Population**	**Staging Procedure**	**Findings**	**Authors' conclusions**
45. Shingyoji, et al. 2016 [54]	Non-small cell lung cancer patients with both CT-negative and PET/CT-negative lymph nodes (N0) in preoperative nodal staging performed by EBUS-TBNA (n=113)	EBUS-TBNA	• Overall rate of N2 disease was 17.6% (20 of 113). • For nodal staging by EBUS-TBNA: the sensitivity 35.0%, specificity 100%, NPV 87.7%, diagnostic accuracy 88.4% • No severe complications from EBUS-TBNA staging	The overall rate of unsuspected N2 was not low. EBUS-TBNA was accurate and feasible for preoperative mediastinal nodal staging of non-small cell lung cancer with both CT-negative and PET/CT-negative lymph nodes. The sensitivity of EBUS-TBNA for radiologically normal mediastina and hila was low. Further investigations are required.
46. Sivrikoz et al. 2012 [55]	Prospective, single-institution study of 68 consecutive patients with suspected or pathologically proven, localized, clinically resectable NSCLC	PET/CT vs. mediastinoscipy	• Mediastinoscopy for the detection of mediastinal lymph node metastases: sensitivity of 81.8% (95% CI: 63-82), specificity 100% (95% CI: 96-100), a PPV 100% (95% CI: 77-100), a NPV of 96.6% (95% CI: 93-96), and an accuracy of 97% • PET/CT for the detection of intrathoracic N2 and N3 nodal metastases: sensitivity of 72.7% (95% CI: 51-80), specificity 97.7% (95% CI: 92-99), PPV f 88.9% (95% CI: 62-97), NPV 93.3% (95% CI: 88-95) accuracy 92.6% (95% 83-95)	Our data shows that due to its high sensitivity and accuracy, mediastinoscopy is still the most reliable method to evaluate mediastinal lymph nodes in patients with NSCLC.
47. Soja et al. 2010 [56]	Patients with lung cancer and enlarged mediastinal lymph nodes on computed tomography scans underwent TBNA (n=84)	blind TBNA in staging of lung cancer, using systematic mediastinal lymph node dissection (SLND) at thoracotomy as a confirmatory test	• TBNA: sensitivity 81.5%, specificity- 100%, accuracy - 86.5%, NPV 66.7%. • In 8 of 28 operated patients (28.6%), N2 meta static nodes were identified.	Our results suggest that TBNA may be a useful method for initial NSCLC staging in patients suspected of N2-3 disease. Positive TBNA in 1 station only should not be considered as a true single-level N2 disease, because of a relatively low NPV for TBNA.
48. Srinivasan et al. 2012 [57]	A review of 107 consecutive patients	EUS-FNA	• Sensitivity 82.35%,, specificity 100%,, accuracy 90% for EUS-FNA of mediastinal LNs, NPV 80%, PPV 100%. • There were 20 patients with suspicious mediastinal LNs of uncertain etiology, with a definitive diagnosis being made using EGD/EUS-FNA in 95%	Our data supports the use of EUS-FNA in the work-up of enlarged mediastinal LNs on cross sectional imaging, thus avoiding more invasive mediastinal sampling procedures and potentially futile surgery.

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Study (Reference)	**Population**	**Staging Procedure**	**Findings**	**Authors' conclusions**
49. Steinhauser et al. 2016 [58]	Consecutive patients who, during the period from January 2010 to August 2012, were submitted to EBUS and later to thoracic surgery (n=287).	EBUS - TBNA	• NPV for mediastinal staging was 89 % (IC 95 % 84.9-92.7) • From a total of 21 false negative cases of mediastinal staging, 16 (76 %) did not undergo positron emission tomography-computed tomography (PET-CT) before the EBUS and in 15 (71 %) the affected lymph node chain was not punctured by EBUS-TBNA. • Ten (47 %) patients had only lymph node metastases not directly accessible by the EBUS.	Performed in hospital routine and in patients submitted to thoracic surgery, EBUS-TBNA proved to be a good tool for proper pathological diagnosis of lung cancer. The negative predictive value of 89 % for mediastinal staging of lung cancer is comparable to that reported in previous studies, but the relatively high number of 21 false negative cases points to the need for standardization of routine strategies before, during and after EBUS.
50. Szlubowski et al. 2010 [59]	Prospective study of 120 NSCLC patients	EBUS/EUS/CUS-NA	• CUS-NA for normal mediastinum: sensitivity 68% (95% CI: 48-84), specificity 98% (95% CI: 92-100),, total accuracy 91% (95% CI: 86-96), PPV 91% (95% CI: 70-99), NPV 91% (95% CI: 83-96), respectively. • The sensitivity of CUS-NA was significantly higher than with EBUS-NA alone (p=0.04) and higher, close to the level of significance than with EUS-NA alone (p=0.07). • The NPV of all techniques was high and that of CUS-NA was significantly higher than EBUS-NA alone and EUS-NA alone (p=0.01, p=0.03).	In the radiologically normal mediastinum, CUS-NA is a highly effective and safe technique in NSCLC staging and, if negative, a surgical diagnostic exploration of the mediastinum may be omitted.
51. Szlubowski et al. 2012 [60]	Consecutive LC patients, clinical stage IA-IIIB 9n=214)	Combined (i.e. transbronchial and transoesophageal) ultrasound imaging with needle biopsy of the mediastinum by use of a single ultrasound bronchoscope (CUSb) and (b) by using two scopes (CUS).	• There was 'minimal N2' in 11 of 14 false negative patients. • Diagnostic sensitivity of CUS: 91.7% , specificity 98%, accuracy 94.6%, PPV 98.2% 90.7% • Diagnostic sensitivity of CUSb 85%, specificity 93.2%, accuracy 88.5%, PPv 94.4%, NPV 82%, • No significant difference in yield of CUS vs CUSb (P = 0.255 and P = 0.192). • The mean time of CUS (25 ± 4.4 min) was significantly longer as compared to CUSb (14.9 ± 2.3 min) (P < 0.001). • No severe complications of either method were observed.	The combined ultrasound imaging of the mediastinum by use of CUSb is significantly less time-consuming and equally as effective and safe as the use of CUS for LC staging.

Table 2: Studies assessing NSCLC staging				
Study (Reference)	**Population**	**Staging Procedure**	**Findings**	**Authors' conclusions**
52. Tasci et al. 2010 [61]	One hundred and twenty-seven consecutive patients were enrolled in the study where PET/CT was performed due to pathologically defined non-small cell carcinoma from a single center.	PET/CT	• PET/CT in N2 cases: sensitivity 72.0%, specificity 94.4%,, accuracy 92.7%,, NPV 97.7%, PPV 49.2%	Staging of non-small cell lung cancer (NSCLC), according to the PET/CT for which we determined 97.79% NPV, we consider that thoracotomy without preoperative mediastinal invasive staging in cases of negative mediastinal involvement in PET/CT can be certainly performed.
53. Taverner et al. 2016 [62]	Retrospective cohort of patients who underwent EBUS-TBNA before resection with mediastinal lymph node sampling for NSCLC (n=57)	EBUS-TBNA	• Per-node NPV 78/82=0.95. • All malignant nodes were located in patients with moderate-high risk disease (cN2/3), giving a disease prevalence in cN2/3 patients of 11%, and 0% in cN0/1. • In patients staged cN2, per-node NVP was 0.89.	The prevalence of mediastinal nodal disease following negative EBUS-TBNA is very low, at 4.9%. The per-node NVP of EBUS-TBNA is 0.95, decreasing to 0.89 in moderate-high risk patients. We suggest that a negative EBUS-TBNA of mediastinal nodes does not need to be confirmed by mediastinoscopy of those nodal stations, regardless of PET/CT findings.
54. Turna et al. 2017 [63]	571 patients with potentially resectable NSCLC (n=571) to assess the validity of the updated European Society of Thoracic Surgeons staging guideline in lung cancer patients	video-assisted cervical mediastinoscopy or video-assisted mediastinoscopic lymphadenectomy in all patients except those with peripheral nonadenocarcinoma tumors peripheral cT1N0 nonadenocarcinoma tumors.	• Sensitivity 95.0%, specificity 100%, PPV 100%, NPV 94.6%, accuracy 97.2%	The ESTS revised preoperative lymph node staging guidelines for patients with NSCLC seem to be effective and valid, and may provide high survival following resectional surgery.
55. Um et al. 2015 [64]	Prospective trial was conducted in a tertiary referral center in Korea. Patients with histologically proven NSCLC and suspicion for N1, N2, or N3 metastasis were enrolled (n=138).	EBUS vs. Mediastinoscopy	• Sensitivity 88.0% vs. 81.3% • Specificity 100% vs. 100%, • Accuracy 92.9% vs. 89.0%, • PPV 100% vs. 100%, • NPV 85.2% vs. 78.8% • Significant differences in the sensitivity,	BUS-TBNA was superior to mediastinoscopy in terms of its diagnostic performance for mediastinal staging of cN1-3 NSCLC. Because EBUS-TBNA is both less invasive and affords superior

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Study (Reference)	**Population**	**Staging Procedure**	**Findings**	**Authors' conclusions**
			accuracy, and NPV were evident between EBUS-TBNA and mediastinoscopy ($p < 0.005$). • N2/N3 disease was confirmed in 59.1% of the patients.	diagnostic sensitivity, it should be the first-line procedure performed in patients with NSCLC.
56. Verhagen et al. 2013 [65]	In a retrospective cohort study, the records of 147 consecutive patients with an indication for mediastinal lymph node staging and a negative result of endosonography were analysed.	mediastinoscopy	• When using cervical mediastinoscopy as the gold standard, the NPV for endosonography was 88.7%, resulting in a NNT of 8.8 patients. • For patients with fluoro-2-deoxyglucose positron emission tomography positive mediastinal lymph nodes, the NNT was 6.1. • Overall, a futile thoracotomy could be prevented in 50% of patients by an additional mediastinoscopy. • A representative lymph node aspirate, containing adequate numbers of lymphocytes, did not exclude metastases.	In patients with a high probability of mediastinal metastases, based on imaging, and negative endosonography, cervical mediastinoscopy should not be omitted, not even when the aspirate seems representative.
57. Vial et al. 2018 [66]	Patients with proven or suspected lung cancer staged as N0/N1 by PET/CT and without metastatic disease (M0), who underwent staging EBUS-TBNA. (n=75)	EBUS-TBNA.	• EBUS-TBNA for N2 disease: sensitivity 40% (95% CI: 16.3–67.7%).	A significant proportion of patients with N0/N1 disease by PET/CT had N2 disease (20%) and EBUS-TBNA identified a substantial fraction of these patients, thus improving diagnostic accuracy compared with PET/CT alone. Sensitivity of EBUS-TBNA however appears lower compared with historical data from patients with larger volume mediastinal disease. Therefore, strategies to improve EBUS-TBNA accuracy in this population should be further explored
58. Volterrani et al. 2011 [67]	Consecutive patients with histopathologically proven NSCLC (n=86)	multi-slice computed tomography (MSCT	• MSCT using a multi-criteria approach in the detection of the N2 stage: sensitivity 100%, specificity 98.5%, PPV 100%, NPV 94.4%, accuracy 98.8% • Using the size criterion alone: sensitivity 64%, specificity 61%, PPV 87%, NPV 40%, accuracy 62%	To improve MSCT accuracy for diagnosing N staging other criteria can be associated with lymph node size. The use of different dimensional cut-offs for each mediastinal lymph node station, the matching of positive nodal stations with tumour location, the structural

Table 2: Studies assessing NSCLC staging				
Study (Reference)	**Population**	**Staging Procedure**	**Findings**	**Authors' conclusions**
				characteristics and the type of enhancement allow for a high accuracy of MSCT in the staging of mediastinal nodes in NSCLC.
59. Warren et al. 2016 [68]	All cases where EBUS-TBNA and PET-CT were performed for mediastinal staging (N=333)	EBUS-TBNA, PET-CT	• EBUS-TBNA plus PET-CT: sensitivity 98.6%, specificity 100%, 94.87%, compared with mediastinoscopy for detecting metastasis.,	EBUS-TBNA is accurate in detecting mediastinal metastasis of lung cancer in the community setting. PET-CT without uptake in lymph nodes reduces the likelihood of malignancy but cannot rule out mediastinal involvement.
60. Whitson et al. 2013 [69]	We retrospectively analyzed our prospectively gathered database (January 2007 to November 2011) to include NSCLC patients who underwent EBUS-FNA for mediastinal staging (n=120).	EBUS-FNA	• The NPV with and without inclusion of nondiagnostic samples was 65.9% and 85.3%,	The inclusion of nondiagnostic specimens into the conservative, worst-case-scenario calculation of NPV for EBUS-FNA in NSCLC lowers the NPV from 85.3% to 65.9%. The true NPV is likely higher than 65.9% as few nondiagnostic specimens are false negatives. Caution is imperative for the safe application of EBUS-FNA in NSCLC staging.

61. Yasufuku et al. 2011 [70]	Prospective Cohort osaxzf patients with confirmed or suspected non–small cell lung cancer who required mediastinoscopy to determine suitability for lung cancer resection (n=190)	EBUS TBNA vs. mediastinoscopy	• EBUS-TBNA and mediastinoscopy sampled an average of 3 and 4 lymph node stations per patient, respectively.
			• The mean short axis of the lymph node biopsied by EBUS-TBNA was 6.9 +/- 2.9 mm.
			• The prevalence of N2/N3 disease was 35% (53/153).
			• Excellent agreement between EBUS-TBNA and mediastinoscopy for mediastinal staging in 136 patients (91%; Kappa, 0.8; 95% confidence interval, 0.7–0.9).
			• Specificity and positive predictive value for both techniques 100%.
			• For mediastinal lymph node staging for EBUS-TBNA and mediastinoscopy
			  • Sensitivity 81% vs. 79%
			  • Negative predictive value 91% vs. 90%
				EBUS-TBNA and mediastinoscopy achieve similar results for the mediastinal staging of lung cancer. As performed in this study, EBUS-TBNA can replace mediastinoscopy in patients with potentially resectable non-small cell lung cancer.

Table 2: Studies assessing NSCLC staging				
Study (Reference)	**Population**	**Staging Procedure**	**Findings**	**Authors' conclusions**
			• Diagnostic accuracy 93% vs. 93% • No significant differences found between EBUS-TBNA and mediastinoscopy in determining the true pathologic N stage (McNemar's test, P = .78). • There were no complications from EBUS-TBNA. • Minor complications from mediastinoscopy were observed in 4 patients (2.6%).	
62. Yasufuku et al. 2013 [71]	Retrospective review of EBUS-TBNA results in patients with potentially resectable clinical N0 or N1 non-small cell lung cancer (n=981)	EBUS-TBNA	• EBUS-TBNA to accurately differentiate between N0 and N1 disease: sensitivity 76.2%, specificity 100%, diagnostic accuracy 96.6%, NPV 96.2% • Accuracy of mediastinal staging was 95.7%.	Endobronchial ultrasound-guided transbronchial needle aspiration can accurately access the hilar and interlobar lymph nodes in patients with potentially resectable lung cancer. Accurate assessment of cN0 versus cN1 by EBUS-TBNA may be used to guide induction therapy before surgery.
63. Zhang et al. 2012 [72]	Patients with mediastinal lymphadenopathy underwent simultaneous EBUS-FNA/ TM at our institution (n=36)	EBUS-TBNA and transcervical video-assisted mediastinoscopy (TM)	• EBUS-FNA achieved significantly less conclusive, but more indeterminate pathological results in comparison to TM (78.7% vs. 98.6%, p < 0.001; 14.9% vs. 1.4%, p = 0.007). • ess paratracheal nodes were sampled by EBUS-FNA (right: 46.2% vs. 88.5%, p = 0.003; left: 23.1% vs. 65.4%, p = 0.005), while sampling rates in the subcarinal localisation were comparable (96.2% vs. 80.8%, p = NS). • Among patients with confirmed NSCLC and conclusive EBUS-FNA/ TM findings (n = 18), the prevalence of N2/N3 disease was 66.7% (n = 12) according to TM findings. • Diverging nodal stages were found in five patients (27.8%).	Compared to TM, EBUS-FNA had a lower diagnostic yield and resulted in systematic mediastinal nodal understaging. At this point we suggest corroborating negative EBUS-FNA results by transcervical mediastinoscopy.
64. Zielinski et al. 2013 [73]	Retrospective cohort study of consecutive patients undergoing primary staging and restaging after neodjuvant chemo- or chemo-	EBUS and/or Endoesophageal Ultrasound with vs. Transcervical	• Sensitivity: 87.8 vs. 96.2, p < 0.01 • Specificity: 98.7 vs. 100, p = 0.03 • NPV: 82.5 vs. 99.6, p < 0.01 • PPV: 99.1 vs. 100, p = 0.07	The results of this largest reported series comparing the endoscopic and surgical primary staging and restaging of NSCLC showed a

Table 2: Studies assessing NSCLC staging				
Study (Reference)	**Population**	**Staging Procedure**	**Findings**	**Authors' conclusions**
	radiotherapy for NSCLC with EBUS, EUS, or EBUS combined with EUS (CUS) with fine needle aspiration biopsy and cytological examination	Extended Mediastinal Lymphadenectomy (TEMLA) (primary staging PET/CT)	• Prevalence: 63.1 vs. 18.4, < 0.01 • Primary staging (PET/CT) Sensitivity of was 54%, specificity 78%, positive predictive value (PPV) 37%, and ne gative predictive value (NPV) 87%.	significantly higher diagnostic yield of TEMLA when compared with that of EBUS or EUS.

Table 3: Systematic Reviews and Meta-analyses (2012 to present)			
Document (Reference)	**Dates of search / Articles**	**Staging procedures**	**Findings**
1. Dong et al. 2013 [74] Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration in the Mediastinal Staging ofNon-Small Cell Lung Cancer: A Meta-Analysis	January 1995 to July 2012 / n=9	Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration	Pooled specificity was 0.99. All studies but one had specificity of 100% [14]. Study reported a false-positive result in 1 patient, and specificity of EBUS-TBNA in this study was 98.4%. Pooled accuracy of the included studies was 0.96. The pooled PPV was 0.99 and pooled NPV was 0.93
2. Ge, et al. 2015 [75] Comparison of Endobronchial Ultrasound-Guided Fine Needle Aspiration and Video-Assisted Mediastinoscopy for Mediastinal Staging of Lung Cancer	1960 to 2014	Endobronchial Ultrasound-Guided Fine Needle Aspiration and Video-Assisted Mediastinoscopy	Pooled sensitivities for EBUS-TBNA and VAM were 0.84 (95% CI 0.79-0.88) and 0.86 (95% CI 0.82-0.90), respectively. Subgroup analyses of quality score, study design, station number and rapid on-site cytologic evaluation showed no significant influence on the overall sensitivity of the two modalities. After adjusting quality score, study design, and station number, the pooled sensitivities of VAM and EBUS-TBNA were not significantly different. However, more procedural complications and fewer false negatives (FN) were found with VAM than EBUS-TBNA. VAM and EBUS exhibited equally high diagnostic accuracy for mediastinal staging of lung cancer. Due to lower morbidity with EBUS-TBNA and fewer FN with VAM, EBUS-TBNA should be performed first, followed by VAM in the case of a negative needle result.
3. Korevaar et al. 2016 [76]	January 2000 to Feb 2016 / n=13	Evaluated the added value and diagnostic accuracy of the combined use of EBUS and EUS.	On average, addition of EUS to EBUS increased sensitivity by 0.12 (95% CI 0.08-0.18) and addition of EBUS to EUS increased sensitivity by 0.22 (0.16-0.29). Mean sensitivity of the combined approach was 0.86 (0.81-0.90), and the mean negative predictive value was 0.92 (0.89-0.93). The mean negative predictive value was significantly higher in studies with a prevalence of 34% or less (0.93 [95% CI 0.91-0.95]) compared with studies with a prevalence of more than 34% (0.89 [0.85-0.91]; p=0.013). We found no significant differences in mean sensitivity and negative predictive value between studies that did EBUS first or EUS first, or between studies that used an EBUS-scope or a regular echoendoscope to do EUS.
4. LaBarca et al. 2016 [77] Minimally Invasive Methods for Staging in Lung Cancer: Systematic Review and Meta-Analysis	Up to April 2015/ N=12 (2 RCTs)	Endobronchial ultrasound (EBUS) + endoscopic ultrasound EUS, compared to surgical staging	pooled sensitivity for combined EBUS + EUS was 87% (CI 84–89%) and the specificity was 99% (CI 98–100%). For EBUS + EUS performed with a single bronchoscope group, the sensitivity improved to 88% (CI 83.1–91.4%) and specificity improved to 100% (CI 99-100%).

Table 3: Systematic Reviews and Meta-analyses (2012 to present)			
Document (Reference)	**Dates of search / Articles**	**Staging procedures**	**Findings**
5. Sehgel et al. 2016 [4] Endosonography Versus Mediastinoscopy in Mediastinal Staging of Lung Cancer: Systematic Review and Meta-Analysis	Up to March 31, 2016 / n=9	Endosonography vs. mediastinoscopy	The pooled risk-difference of the sensitivity of endosonography versus mediastinoscopy in observational studies and randomized controlled trials was 0.11 (95% CI,0.07 to 0.29) and 0.11 (95% con CI 0.03 to 0.25), respectively Complication rate was significantly lower with endosonographic procedures. Endoscopic ultrasound-guided fine needle aspiration/endobronchial ultrasound–guided transbronchial needle aspiration was found to have similar yield but lower complication rate compared to mediastinoscopy in the initial mediastinal staging.
6. Wang et al. 2012 [78] Negative Predictive Value of Positron Emission Tomography and Computed Tomography for Stage T1-2N0 Non–Small-Cell Lung Cancer: A Meta-Analysis	Up to Feb. 2011 /n=10	Emission Tomography and Computed Tomography	NPVs of combined PET and CT for mediastinal metastases were 0.94 in T1 disease and 0.89 in T2 disease. Including both T1 disease and T2 disease, the NPVs were 0.93 for mediastinal metastases and 0.87 for overall nodal metastases.
7. Yan-LingLv et al. 2011 [79] Diagnostic Performance of Integrated Positron Emission Tomography/Computed Tomography for Mediastinal Lymph Node Staging in Non-small Cell Lung Cancer: A Bivariate Systematic Review and Meta-Analysis	Up to Dec. 18, 2010 / N=14	Integrated Positron Emission Tomography/Computed Tomography	pooled weighted SEN and SPE were 0.73 (95% confidence interval [CI]: 0.65–0.79) and 0.92 (95% CI: 0.88–0.94), respectively. In the patient-based data analysis, the pooled weighted SEN was 0.76 (95% CI: 0.65–0.84) and the pooled weighted SPE was 0.88 (95% CI: 0.82–0.92). In the MLN-based data analysis, the pooled SEN was 0.68 (95% CI: 0.56–0.78) and the pooled SPE was 0.95 (95% CI: 0.91–0.97).
8. Zhang et al. 2013 [80] Combined endobronchial et al. and endoscopic ultrasound-guided fine needle aspiration for mediastinal lymph node staging of lung cancer: A meta-analysis	up to 15th July 2012 / n=8	endobronchial et al. and endoscopic ultrasound-guided fine needle aspiration	EBUS-TBNA plus EUS-FNA for mediastinal nodal staging: sensitivity, 0.86 (95% confidence interval [CI], 0.82–0.90); specificity, 1.00 (95% CI, 0.99–1.00); positive LR, 51.77 (95% CI, 22.53–118.94); negative likelihood ratio, 0.15 (95% CI, 0.09–0.25); diagnostic OR, 416.83 (95% CI, 140.08–1240.31); and area under the curve (AUC), 0.99.

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Appendix 1. Members of the Expert Panel

Name	Affiliation	Conflict of Interest
Dr. Gail Darling Thoracic Surgery	University Health Network, Princess Margaret Hospital Toronto, ON	Has been a principal investigator for a clinical trial involving any of the objects of study (the ELPET trial)
Dr. John Dickie Thoracic Surgery	Lakeridge Health Oshawa, ON	None
Dr. Ken Gehman Thoracic Surgery	Thunder Bay, ON	None
Ms. Amber Hunter Program Manager, Surgical Oncology Program	Cancer Care Ontario Toronto, ON	None
Ms. Michelle Lee Specialist, Surgical Oncology Program	Cancer Care Ontario Toronto, ON	None
Dr. Richard Malthaner Thoracic Surgery	London Health Sciences Centre London, ON	None
Dr. Donna Maziak Thoracic Surgery	Ottawa Hospital Ottawa, ON	None
Ms. Leigh McKnight Lead, Surgical Oncology Program	Cancer Care Ontario Toronto, ON	None
Dr. Michael Sanatani Medical Oncology	London Health Sciences Centre London, ON	None
Dr. Yee Ung Radiation Oncology	Odette Cancer Centre Toronto, ON	None
Dr. Alice Wei Surgical Lead, Quality Improvement, Surgical Oncology Program	Cancer Care Ontario Toronto, ON	Employed by Cancer Care Ontario; has received $5000 in a single year in a consulting capacity for Ethicon

Appendix 2. Search Strategy

SEARCH STRATEGY: MEDLINE	
Methods Terms	1. letter.pt.
	2. comment.pt.
	3. editorial.pt.
	4. or/1-3
Cancer Terms	5. carcinoma non-small cell lung.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
	6. lymphatic metastasis.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
	7. neoplasm metastasis.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
	8. or5-7
Medistinal staging	9. neoplasm staging.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
	10. biopsy.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
	11. biopsy fine-needle.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
	12. biopsy needle.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
	13. or/9-12
	14. endobronchial.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
	15. endobronchial ultrasound.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
	16. endoscopic.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

	17. endoscopic ultrasound.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
	18. endosonography.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
	19. mediastinoscopy.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
	20. Or/14-19
	21. positron-emission tomography.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
	22. tomography scanners.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
	23. x-ray computed.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
	24. ultrasound.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
	25. or/21-22
Limiting Terms	26. 8 and 13 and 20 and 25
	27. 26 not 4
	28. limit 27 to English language
	29. limit 28 to human
	30. limit 29 to yr="2010-Current".

SEARCH STRATEGY: EMBASE	
Methods Terms	1. letter.pt.
	2. editorial.pt.
	3. or/1-2
Cancer Terms	4. carcinoma non-small cell lung.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy]
	5. lymphatic metastasis.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy]
	6. (neoplasm metastasis.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy]
	7. or/4-6
Medistinal	8. neoplasm staging.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf,

staging	px, rx, an, ui, sy]
	9. biopsy.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy]
	10. biopsy fine-needle.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy]
	11. biopsy needle.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy]
	12. endobronchial.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy]
	13. endobronchial ultrasound.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy]
	14. endoscopic.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy]
	15. endoscopic ultrasound.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy]
	16. endosonography.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy]
	17. mediastinoscopy.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy]
	18. positron-emission tomography.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy]
	19. tomography scanners.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy]
	20. x-ray computed.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy]
	21. ultrasound.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy]
	22. Or/8-22
Limiting Terms	23. 7 and 22
	24. 23 not 3
	25. limit 24 to yr="2010 -Current"
	26. limit 25 to english language
	27. limit 26 to human

Appendix 3. Ongoing Studies

Protocol ID(s)	Title and details of study
NCT01786590	**Official title:** Endobronchial Ultrasound-guided Transbronchial Needle Aspiration for Lymph Node Staging in Patients With Non-small Cell Lung Cancer Pursuing Stereotactic Body Radiotherapy (SBRT) **Study type:** Interventional **Treatment groups:** EBUS-TBNA vs EBUS-TBNA (procedural) **Estimated enrollment:** 150 **Start date:** Feb. 2013 **Date trial summary last modified:** Feb. 23, 2018 **Estimated primary completion date:** Dec. 2019 **Status:** Recruiting **Primary results reported:** none
NCT02997449	**Official title:** Complete Endosonographic Intrathoracic Nodal Staging of Lung Cancer Patients in Whom Stereotactic Ablative Radiotherapy (SABR), is Considered **Study type:** Observational **Treatment groups:** NSCLC, SABR, nodal staging **Estimated enrollment:** 102 **Start date:** Dec. 2013 **Date trial summary last modified:** Dec. 20, 2016 **Estimated primary completion date:** June 2017 **Status:** Recruiting **Primary results reported:** none
NCT02030444	**Official title:** Randomized Study Comparing Standard Staging of Lung Cancer With Extended Staging Including EBUS-TBNA and PET-MRI **Study type:** RCT **Treatment groups:** standard vs. extensive diagnostic workup **Estimated enrollment:** 150 **Start date:** Aug. 2014 **Date trial summary last modified:** June 16, 2017 **Estimated primary completion date:** Dec. 2017 **Status:** Recruiting **Primary results reported:** none
NCT00559611	**Official title:** Prospective Comparison of Endobronchial Ultrasound Needle Biopsy Versus Mediastinoscopy for Staging of Mediastinal Nodes in Patients With Clinical Stage IIIA Non-Small Cell Lung Cancer (NSCLC) **Study type:** Interventional **Treatment groups:** EUS vs. Mediastinoscopy **Estimated enrollment:** 100 **Start date:** Oct. 2007 **Date trial summary last modified:** Sep. 13, 2017 **Estimated primary completion date:** Oct. 2019 **Status:** Active, not recruiting **Primary results reported:** none
NCT01799980	**Official title:** Evaluation of Endobronchial Ultrasound (EBUS) for Staging Lung Cancer **Study type:** Observational **Treatment groups:** Cervical medistinscopy vs. EBUS **Estimated enrollment:** 37 **Start date:** June 2012 **Date trial summary last modified:** Sep. 19, 2017 **Estimated primary completion date:** Aug. 2019 **Status:** Active, not recruiting **Primary results reported:** none
NCT03188562	**Official title:** Comparison of Diagnostic and Therapeutic Efficacy of Transbronchial and Transoesophageal Endoscopic Ultrasound Guided

	Needle Aspiration and Transcervical extended Mediastinal Lymphadenectomy (TEMLA) in Operable Non-small-cell Lung Cancer. A Randomised Controlled Trial **Study type:** RCT **Treatment groups:** PET/CT vs EBUS, EUS-NA **Estimated enrollment:** 200 **Start date:** May 2011 **Date trial summary last modified:** June 15, 2017 **Estimated primary completion date:** July 2017 **Status:** Recruiting **Primary results reported:** none
NCT02592837	**Official title:** Endobronchial Ultrasound Transbronchial Needle Aspiration (EBUS-TBNA) Versus Flexible 19G Endobronchial Ultrasound Transbronchial Needle (Flex 19G EBUS-TBNA) in the Assessment of Mediastinal and Hilar Lymphadenopathy: a Randomised Trial **Study type:** RCT **Treatment groups:** EBUS-TBNA vs Flex 19G EBUS-TBNA **Estimated enrollment:** 250 **Start date:** May 2016 **Date trial summary last modified:** Nov. 28, 2016 **Estimated primary completion date:** March 2018 **Status:** Recruiting **Primary results reported:** none

DEFINITIONS OF REVIEW OUTCOMES

1. **ARCHIVE** – ARCHIVE means that a Clinical Expert and/or Expert Panel has reviewed new evidence pertaining to the guideline topic and determined that the guideline is out of date or has become less relevant. The document will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of our website and each page is watermarked with the words "ARCHIVE."

2. **ENDORSE** – ENDORSE means that a Clinical Expert and/or Expert Panel has reviewed new evidence pertaining to the guideline topic and determined that the guideline is still useful as guidance for clinical decision making. A document may be endorsed because the Expert Panel feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. **UPDATE** – UPDATE means the Clinical Expert and/or Expert Panel recognizes that the new evidence pertaining to the guideline topic makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The Expert Panel advises that an update of the document be initiated. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making, unless the recommendations are considered harmful.