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

Invasive Mediastinal Staging of Non-small Cell Lung Cancer


Report Date: October 18, 2010

An assessment conducted in December 2016 deferred the review of Evidence-based Series (EBS) 17-6, which means that the document remains current until it is assessed again next year. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

EBS 17-6 consists of 3 sections
and is available on the CCO Website on the PEBC Surgery page.

Section 1: Guideline Recommendations
Section 2: Evidentiary Base
Section 3: EBS Development Methods and External Review Process

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

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

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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
      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 18F 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),
    - 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, 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.

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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REFERENCES


Appendix 1. Figure 1. Invasive mediastinal staging recommendations.

**Group A.** CT scan showing normal sized mediastinal lymph nodes (MLN)\(^1\)

- **PET-CT** –ve in the mediastinum
  - Peripheral clinical stage 1A tumour\(^2\) (and negative clinical evaluation)
    - Invasive staging not required
  - Presence of central tumour\(^3\) or suspected N1 disease or clinical T2 or higher disease
    - Invasive staging of the mediastinum

**Group B.** CT scan showing enlarged discrete mediastinal lymph nodes (N2, 3)\(^1\)

- **PET-CT** +ve in the mediastinum
  - PET-CT –ve in the mediastinum
  - PET-CT +ve in the mediastinum

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\(^1\) 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.