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Evidence-based Series 7-20 Version 2

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

18-Fluorodeoxyglucose Positron Emission Tomography in the Diagnosis and Staging of Lung Cancer

Members of the Lung Cancer Disease Site Group

An assessment conducted in November 2014 deferred the review of Evidence-based Series (EBS) 7-20 Version 2, which means that the document remains current until it is assessed again next year. The PEBC has a formal and standardize process to ensure the currency of each document (PEBC Assessment & Review Protocol)

The reviewed EBS report, which is available on the CCO web site consists of the following four sections:

Section 1:	**Clinical Practice Guideline (ENDORSED)**
Section 2:	**Systematic Review**
Section 3:	**Guideline Development and External Review**
Section 4:	**Guideline Summary Review**

Release Date: October 5, 2012

For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca

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Guideline Report History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES AND KEY CHANGES
	Search Dates	Data		
Original version April 2007	1996-2006	Full Report	Web publication	NA
Current Version 2 Oct 2012	2006-2012	New data found in Section 3: Document Summary and Review Tool	Updated Web publication	2007 recommendations is **ENDORSED**

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Evidence-based Series 7-20 Version 2: Section 1

A Quality Initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO) Developed by the Lung Cancer Disease Site Group

18-Fluorodeoxyglucose Positron Emission Tomography in the Diagnosis and Staging of Lung Cancer: Guideline Recommendations

Y.C. Ung, D.E. Maziak, J.A. Vanderveen, C.A. Smith, K. Gulenchyn, W.K. Evans, and the Lung Cancer Disease Site Group

These guideline recommendations have been ENDORSED, which means that the recommendations are still current and relevant for decision making. Please see Section 4: Document Summary and Review Tool for a summary of updated evidence published between 2006 and 2012, and for details on how this Clinical Practice Guideline was ENDORSED.

Report Date: October 5, 2012

Questions

What is the role of 18-Fluorodeoxyglucose (^{18}FDG) Positron Emission Tomography (PET) in:

1. The diagnosis of solitary pulmonary nodules (SPN)?
2. The staging of primary non-small cell lung cancer (NSCLC) at initial diagnosis?
3. The staging of primary small cell lung cancer (SCLC)?

Outcomes of interest include accuracy measures of imaging and the impact of PET on patient management and patient outcomes.

Target Population

This practice guideline applies to adult patients with lung cancer.

Technology

The recommendations in this practice guideline refer to PET scanning with a dedicated PET scanner.

Recommendations

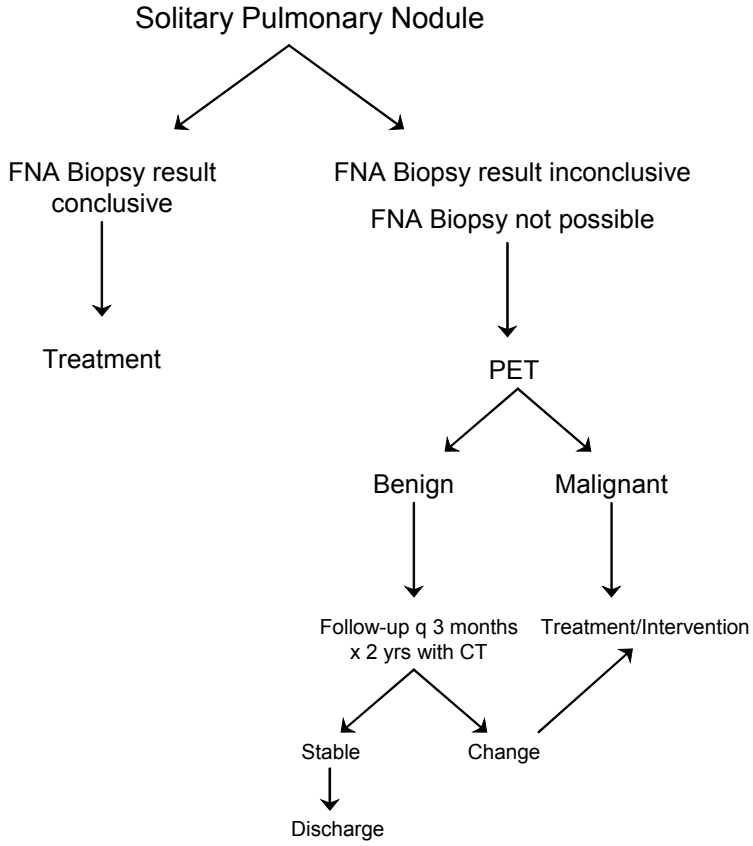
There is limited randomized controlled trial evidence related to the impact of PET on the clinical management of the lung cancer patient. In addition, PET technology has evolved significantly over time making it difficult to make recommendations based on studies using out-of-date imaging technologies. However, based on the interpretation of available evidence and expert consensus opinion, the Lung Cancer Disease Site Group recommends the following:

- **Diagnosis of Solitary Pulmonary Nodules (SPN)**
  - Fine needle aspiration (FNA) biopsy is recommended as the first-line diagnostic approach in the workup of SPN. PET should be reserved for those situations in which a biopsy is inconclusive or contraindicated
    - PET appears to have a high sensitivity and specificity to differentiate benign from malignant lesions as small as 1 cm in size. Lesions less than 1 cm are difficult to categorize as they lack a sufficient mass of metabolically active cells. False-negative results can occur with low-grade malignant tumours due to their lower metabolic activity or with ground-glass opacities as may be seen in bronchoalveolar carcinomas.

Key Evidence

- Two systematic reviews with meta-analyses and seven prospective studies examined the use of PET in the diagnosis of SPN
- Meta-analyses found sensitivity to range from 96%-97% and specificity to range from 78%-86%, and the prospective studies confirmed these results
- False-negative results occurred with low-grade malignant tumours, such as bronchoalvelolar cell carcinomas or with ground-glass opacities. False positive results occurred in inflammatory conditions
- There are no randomized trials examining the use of PET in the differentiation of benign from malignant SPN

Algorithm for SPN



- **Staging of Primary NSCLC**
  - In the opinion of the Lung DSG, the evidence on whether the addition of PET to conventional staging or the up-front use of PET in mediastinal and extrathoracic staging changes clinical management in patients with NSCLC is conflicting
  - Prospective studies have found that PET detects unexpected distant metastases in up to 15% of patients, which may lead to changes in patient management.
  - For potential surgical candidates, mediastinoscopy is recommended to verify that PET positive mediastinal lesions are due to cancer in view of the potential for false positive results. Mediastinoscopy is necessary to ensure that a patient is not denied potentially curative surgery. A solitary extrathoracic site should also be confirmed to be metastatic, if possible, in order that a patient not be denied the chance of curative therapy.

  Key Evidence
    - Eleven systematic reviews and a total of three randomized controlled trials and twenty-two prospective studies examined the use of PET in staging NSCLC.
    - Two trials randomized patients to conventional workup with or without PET. One trial reported a 51% relative reduction in futile thoracotomies (p=0.003) when PET was added to conventional workup, and the other trial found no difference in the number of futile thoracotomies avoided (p=0.2). Differences in the trial designs (patient populations, disease stage, definition of futile thoracotomies, and management of patients) may have contributed to the conflicting results.
    - One trial randomized patients to traditional staging workup or up-front PET. A statistically significant difference was not found between the two groups for the mean number of staging tests performed. As well, the mean number of function tests, non-invasive procedures, invasive procedures, and thoracotomies did not significantly differ between the two arms. However, the percentage of patients who needed more than one invasive test to determine N staging and the number of mediastinoscopies was significantly lower for the PET group, and the median time to diagnosis was significantly shorter for the PET group (14 days versus [vs.] 23 days, p<0.0001).

- **Staging of SCLC**
  - There is limited evidence on the use of PET in the staging of SCLC but three prospective trials showed good accuracy in differentiating limited from extensive stage disease.

  Key Evidence
    - Three prospective studies demonstrated an accuracy of PET in staging extensive versus limited stage disease ranging from 83% - 99%.

Future Research

The Ontario Clinical Oncology Group is currently conducting two prospective randomized controlled trials to examine the impact of PET on improving the management of patients with stage III NSCLC and potentially surgically resectable NSCLC. These trials will evaluate whether PET improves patient outcomes or changes patient management. Patients should be encouraged to participate in clinical trials evaluating PET.

Recently, integrated PET-computerized tomography (CT) scanners have been developed to provide metabolic and anatomical information simultaneously. This technique has great potential for the diagnosis and staging of lung cancer. The vast majority of

published research has been with dedicated PET; therefore, further trials using PET-CT are needed to fully access its accuracy and impact on patient outcomes and patient management.

Funding

The PEBC is supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from its funding agencies.

Contact Information

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or contact the PEBC office at:
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Evidence-based Series 7-20 Version 2: Section 2

A Quality Initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO) Developed by the Lung Cancer Disease Site Group

18-Fluorodeoxyglucose Positron Emission Tomography in the Diagnosis and Staging of Lung Cancer: A Systematic Review

Y.C. Ung, D.E. Maziak, J.A. Vanderveen, C.A. Smith, K. Gulenchyn, W.K. Evans, and the Lung Cancer Disease Site Group

These guideline recommendations have been ENDORSED, which means that the recommendations are still current and relevant for decision making. Please see Section 4: Document Review Summary and Tool for a summary of updated evidence published between 2006 and 2012, and for details on how this Clinical Practice Guideline was ENDORSED.

Section Date: April 5, 2007

QUESTIONS

What is the role of 18-Fluorodeoxyglucose (^{18}FDG) Positron Emission Tomography (PET) in:

1. The diagnosis of solitary pulmonary nodules (SPN)?
2. The staging of primary non-small cell lung cancer (NSCLC) at initial diagnosis?
3. The staging of primary small cell lung cancer (SCLC)?

INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths in both men and women in Canada. The overall survival rate for lung cancer is poor, and early diagnosis provides the best chance for survival. Diagnostic tests guide patient management decisions, and diagnostic imaging is increasingly being used in an effort to improve the clinical management of patients with lung cancer.

A number of imaging technologies are used in the diagnosis and staging of lung cancer. PET is an imaging technique that uses biologically active compounds, radiolabelled with positron emitters, to provide high-resolution images that reflect metabolic activity and tissue functioning. These radiolabelled agents are processed in vivo in a manner virtually identical to their non-radioactive counterparts, thereby producing images and quantitative indexes reflective of the underlying biological processes. The detection of a mass that is metabolically active may indicate that it is an actively growing tumour. However, metabolic activity also occurs with infectious and inflammatory processes, so caution is required in the interpretation of PET scan results.

Whereas traditional radiological imaging technologies (e.g., computed tomography [CT] scan or magnetic resonance imaging [MRI]) provide structural information and define disease states on the basis of gross anatomical changes, PET imaging provides information on the biochemical processes that may precede gross anatomic change. PET imaging is potentially useful in oncological imaging due to the uptake of the radiolabelled glucose analogue, 18-fluorodeoxyglucose (^{18}FDG), by tumour tissue as a result of more rapid glycolysis than is seen in most normal tissue (1,2). This increased glycolysis has been linked to both an increase in the number of glucose membrane transporters and an increase in the activity of the principal enzymes controlling the glycolytic pathways (3). When injected intravenously, ^{18}FDG diffuses into extracellular spaces throughout the body. It is transported across cell membranes and intracellularly phosphorylated by hexokinase (the first enzyme in glycolysis) to ^{18}FDG-6-phosphate. A second enzyme, glucose-6-phosphate isomerase, which transforms glucose-6-phosphate into fructose-6-phosphate, does not react with ^{18}FDG-6-phosphate. Since the ^{18}FDG is not catabolized further, it remains metabolically trapped within cells (4,5).

Imaging by PET is based on the detection of 511 KeV annihilation photons, which are the result of positron decay colliding with a negatively charged electron. Photons that are in coincidence (i.e., 180 degrees from each other) are detected, and these photons are considered to have originated from that point source. All the collected information is then processed into the final image in a two-dimensional or three-dimensional representation that reflects the concentration and distribution of the radioisotope. This creates the image of ^{18}FDG localization.

The two main types of PET instrumentation that have been used for imaging are dedicated PET scanners and gamma cameras modified for coincidence imaging. Dedicated PET scanners consist of multiple detectors that are arranged in a ring, which may either be a full 360-degree ring encircling the patient or a partial ring that rotates around the patient to capture the information. The detection sensitivity of a partial ring scanner is less than that of a full ring scanner. Gamma camera coincidence imaging, which uses a two-headed or three-headed gamma camera that rotates around the patient and is a less expensive alternative to PET scanning, but the technique is limited by using two to three detectors instead of the thousands of detectors used in dedicated PET scanning. In addition, the crystals used in the gamma camera have less stopping power for higher energy photos than those in the dedicated scanner. Both of these factors decrease photon detection and result in lower volume sensitivity.

The PET image does not provide accurate anatomical information, aside from areas of normal physiological uptake such as the heart, kidneys, and bladder and soft tissue (muscle) uptake that can provide an outline of the imaged body. The advanced imaging technology now available combines PET and CT to provide both functional and anatomical information simultaneously, thus improving localization accuracy (6,7).

PET data may be analysed qualitatively, semi-quantitatively, or fully quantitatively. Qualitative visual interpretation of PET data involves the assessment of differences in contrast and requires only a static emission scan. This analytical approach is particularly useful in assessing substantial changes (e.g., tumour change following therapy or the development of new lesions) but is not as valuable in assessing more subtle ones (8). Tumour to normal tissue (T/N) ratios and standardized uptake values (SUV) are examples of semi-quantitative approaches. The latter method is widely used because of its simplicity (requires only a static scan, with accurate instrument calibration) and the fact that it is about as discriminating as fully quantitative methods (9). A number of fully quantitative (or kinetic) methods are used to measure glucose metabolic rate dynamically and provide more detailed information, although the information needed and the calculations used are far more

complex. All three types of methods have advantages and weaknesses, and the optimal approach has yet to be established in prospective trials (8).

Conventional staging procedures are unable to exclude asymptomatic patients with occult metastases from an inappropriate surgical intervention, as manifested by the fact that a significant proportion of patients go on to develop metastatic disease shortly after thoracotomy. There is a clear need for better staging methods. Staging with PET has the potential to allow clinicians to accurately exclude a greater proportion of patients with metastatic disease from surgery, thereby identifying the precise subset of NSCLC patients who are suitable for curative surgery, and sparing those patients who are found to have more advanced disease from inappropriate and futile treatment interventions. Moreover, should PET scanning be shown to accurately stage lung cancer but also concurrently detect mediastinal and distant metastases, there may be the potential in the future to omit either an invasive surgical procedure (cervical mediastinoscopy) or other imaging studies presently required in the evaluation of patients with NSCLC.

The diagnosis of an SPN can be problematic. Some SPNs are not amenable to fine needle aspiration biopsy (FNAB) because of their size, location, or medical comorbidities. Similarly, open biopsy may be associated with increased risk, which would not be justified if the SPN were known to be benign. Finally, the result of an FNAB may not be diagnostic, a situation that occurs more frequently with benign nodules. PET imaging has the potential to help solve this clinical dilemma. There is very little information on PET in the staging of SCLC, and there remains much uncertainty in this area. SCLC is the most aggressive type of lung cancer; tumours are typically fast growing, and 60%–70% of patients present with extensive stage disease (10). The primary role of imaging is to distinguish between patients with extensive disease and those with limited disease, and the hope is that ^{18}FDG-PET may be well suited for this purpose.

Given the importance of diagnostic imaging, the Lung Cancer Disease Site Group (Lung DSG) felt that the development of a systematic review and practice guideline on PET scanning should be a priority.

METHODS

The Lung Cancer DSG of Cancer Care Ontario's Program in Evidence-based Care (PEBC) developed this systematic review on the use of PET in lung cancer. An initial search for evidence-based reports with systematic literature reviews on the topic yielded the Institute for Clinical and Evaluative Sciences (ICES) 2001 report entitled *Health Technology Assessment of Positron Emission Tomography in Oncology*. The report presented the results of a systematic review of the peer-reviewed, grey, and Web-based PET scanning literature up to December 2000 (with subsequent updates, the literature review was current to September 2004). The ICES systematic review was regarded as a high-quality review of the evidence and served as the basis for the development of this clinical practice guideline. A search strategy was developed for primary literature, specifically prospective studies of PET in lung cancer (a) published after the review period of the 2004 ICES report (i.e., to Sep 2004) or (b) examining the use of PET in a setting not reviewed in the ICES report (e.g., SCLC). This evidence was reviewed by three members of the group

This systematic review is a convenient and up-to-date source of the best available evidence on the use of PET in lung cancer. The body of evidence in this systematic review is primarily prospective single-arm studies. The systematic review and companion practice guideline are intended to promote evidence-based practice in Ontario, Canada. The PEBC is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

Literature Search Strategy

The initial search for evidence-based reports involved the following databases and time periods: Cochrane Database of Systematic Reviews (2006, Issue 1), EMBASE (1996 through 2006, week 19), and MEDLINE (1996 through May 2006). The search terms are described in Table 1. These terms were combined with the search terms for the following publication types: practice guideline, systematic review, biomedical technology assessment, and meta-analysis. In addition, the following Web sites were searched on May 13, 2005: the Canadian Medical Association Infobase (http://mdm.ca/cpgsnew/cpgs/search/english/results.asp?Pg=3), the National Guidelines Clearing House (http://www.guideline.gov/), the National Institute for Clinical Excellence (NICE) (http://www.nice.org.uk/); the Web site of the Canadian Coordinating Office for Health Technology Assessment (CCOHTA) (https://www.ccohta.ca/entry_e.html) was searched on December 23, 2004, and the Centre for Reviews and Dissemination, (http://www.york.ac.uk/inst/crd/hfaq16.htm) was searched on February 1, 2005

In addition to the databases described above, the conference proceedings of the American Society of Clinical Oncology (ASCO) (2004-2005) were searched for abstracts of relevant trials by searching for key words or scanning the index. The Physician Data Query (PDQ) clinical trials database on the Internet (http://cancernet.nci.nih.gov/trialsrch.shtml) was searched for additional trials. Relevant articles and abstracts were selected and reviewed, and the reference lists from these sources were also searched for additional trials.

Table 1: Search terms used for electronic databases.[a]

Search Categories		MEDLINE 1966-2006	EMBASE 1980-2006	Cochrane Library 2006, Issue 2
Disease	Index terms	Lung carcinoma, Lung carcinogenesis, Lung metastasis, Carcinoma, non-small-cell lung, Carcinoma, small cell, Lung neoplasms, Lung Cancer		
	Text words	Non-small cell lung		
Imaging	Index terms	Positron emission tomography, Tomography, emission computed, fluorodeoxyglucose F18		
	Text words	PET, Positron emission tomography		
Limits		English language		

[a] Some search terms were specific to an individual database.

Study Selection Criteria

Inclusion Criteria

Evidence-based reports were selected for inclusion in this practice guideline if they reported outcomes of interest and were the following:

- Health technology assessments or practice guidelines based on a systematic review of evidence, systematic reviews, or meta-analyses that evaluated the use of PET in the staging and diagnosis of lung cancer
- Reports fully published in English after 1999.

Articles published as full reports or as abstracts after the completion of the ICES review or examining the use of PET in staging SCLC were selected if they were the following:

- Randomized or single-arm prospective studies that focused on ^{18}FDG-PET scanning in the staging and diagnosis of lung cancer compared to an appropriate reference standard.
- Reports including at least one of the following measures of effectiveness/benefit: PET specificity and sensitivity, accuracy measures of staging, changes in patient management, or improvements in patient outcomes (survival).

Exclusion Criteria

1. Studies with ≤ 35 subjects. All sample sizes were included for SCLC trials.
2. Letters and editorials reporting clinical trials were not eligible.
3. Articles published in a language other than English.

Synthesizing the Evidence

The Lung DSG decided not to statistically pool data from accuracy studies because of the availability of several meta-analyses that provided overall summaries of the diagnostic accuracy of PET for the staging and diagnosis of primary lung cancer.

RESULTS

Literature Search Results

In addition to the ICES report, 12 evidence-based reports (health technology assessments, practice guidelines, systematic reviews, and meta-analyses) were retrieved. The ICES report was the most comprehensive, and only those reports that were meta-analyses or addressed a question not covered by the ICES report are included in our results. Summaries of these other reports are provided in Appendices C and D. The ICES report included all prospective studies or randomized controlled trials (RCTs) on the diagnosis of SPN or the staging of primary NSCLC that were included in other evidence-based reports. An additional fifteen prospective studies (including RCTs) examining PET in the staging and diagnosis of lung cancer published after the completion of the ICES report (Oct 2004+) are included in this review (Table 2). Multiple publications of the same study were included in this systematic review if each report provided additional relevant data. Data from slide presentations associated with reports available in abstract form were also included if the presentations were publicly available on meeting Web sites and provided additional data.

Table 2. Summary of included literature by evidence type and by question.

Question	Topic	Prospective studies	
		ICES	Update
1	SPN: Diagnosis	(11-14)	(15-17)
2a	Primary NSCLC: Staging	(18,19), [a] (20-33)	(34), [a] (35-42)
2b	Primary NSCLC: Mediastinal Staging	(20,22,23,25-29,31,43)	(37), (36,40-42)
2c	Primary NSCLC: Extrathoracic Staging	n/a*	(36)
3	SCLC: Diagnosis & Staging	n/a	(43-45)

[a] Citations (18),(19), and (34) are RCTs of utility.

Description of Evidence-Based Reports

Institute of Clinical and Evaluative Sciences (ICES)

Key Question Areas

- Diagnosis of the solitary pulmonary nodule
- Staging of primary carcinoma of the lung and/or evaluation of mediastinal lymph nodes
- Detection of residual or recurrent carcinoma of the lung
- Detection of bone metastases from primary carcinoma of the lung
- Detection of malignant pleural effusion
- Prediction of survival
- Potential impact of PET on processes of care

Methods

The ICES report presented the results of a systematic review of the peer-reviewed, gray, and Web-based PET scanning literature up to September 2004 and focused on the use of dedicated PET scanners, which provide better quality images but are more expensive than coincidence imaging gamma cameras. Full details of the methodologies used to develop the original 2001 ICES systematic review are available online (46). The literature search for the original publication included the databases of MEDLINE, HealthStar, and CANCERLIT (all 1975 to 2000). The Cochrane Library (issue 4, 2000) was also searched. These databases were routinely searched after the original publication, with the most recent search being conducted in September 2004. Gray literature, which is generally not peer-reviewed, was identified through Web searches as detailed in the original 2001 ICES report (46).

Two reviewers reviewed abstracts of all the peer-reviewed articles, determined which articles should be reviewed in their entirety, and evaluated those articles with original data to determine whether they met the following inclusion criteria:

- Studies of PET in the diseases of interest (lung cancer, solitary pulmonary nodule, head and neck cancer, breast cancer, lymphoma or Hodgkin's disease, melanoma, colorectal cancer);
- English language studies reporting primary data, published in a peer-reviewed journal
- Studies with > 12 human subjects.

Based on a grading scheme used by the Veteran's Administration and the National Health Services Health Technology Assessment (HTA) of PET scanning, the quality of each diagnostic study was rated from A to D (see Table 3) by one reviewer (for articles dated 1975-1998) or two independent reviewers (for articles from 1999 onward). Disagreements among reviewers were resolved by consensus. It was decided a priori that grade A and B studies would be given preferential consideration in the review process. In addition, the major review articles were hand-searched and back-referenced to identify additional potentially relevant articles.

Table 3. Grading scheme for diagnostic studies.

Grade	Criteria
A	Prospective studies with broad generalizability to a variety of patients and no significant flaws in research methods.
B	Prospective studies with a narrower spectrum of generalizability and with only a few flaws that are well described (and in which the impact on conclusions can be assessed).
C	Studies with several flaws in methodology (e.g., small sample size (<35) and retrospective)
D	Studies with multiple flaws in methods (e.g., no credible reference standard for diagnosis)

Adapted from the 1999 National Health Services Health Technology Assessment and reported in the ICES reviews (46,47). *Reproduced with permission from ICES.*

Critical Appraisal

The ICES report is of high quality, and the purpose of the report, the intervention being studied, and the patient populations were adequately detailed. The inclusion and exclusion criteria for the literature search strategy, and the strategy itself, were available in the original document, allowing reproducibility of the findings. Two reviewers assessed potential abstracts and full text studies to determine if they met eligibility criteria. From 1999 onward, two reviewers extracted data from and measured the quality of the eligible studies. Prior to 1999, these tasks were completed by one reviewer. Disagreements were resolved by consensus, although the inter-rater reliability of the two reviewers was not stated

for any step in the process. Nor was it stated whether the reviewers were blind to the purpose of the systematic review. An appropriate level of detail regarding the studies' characteristics and outcomes were provided. No quantitative synthesis of the data was undertaken, and instead, a qualitative analysis was provided; the Lung DSG supports this approach. The source of funding for the project, the Ontario provincial government, can be inferred from the report.

Outcomes

The conclusions of ICES and the results of primary studies retrieved in the update search are organized into three sections, which correspond to the questions of this systematic review. Within each section, the findings the ICES report are provided, followed by a summary of the primary studies comprising the ICES report and a more detailed description of the results of primary studies retrieved in the updated literature search (e.g., published after September 2004 or concerning the staging of SCLC).

Question 1: Diagnosis of Solitary Pulmonary Nodules (SPN)

A number of primary studies have evaluated the accuracy of PET in the diagnosis of SPN, and a several systematic reviews have pooled this evidence.

Findings of ICES

The ICES report (46,47) evaluated four prospective studies (11-14) on the role of PET in the diagnosis of SPN. These studies are summarized in Tables 4 and 5. ICES concluded, "there is evidence for the efficacy of PET in distinguishing benign from malignant SPN and the use of PET in this context would reduce patient morbidity by reducing the number of unnecessary thoracotomies performed for SPN."

Results of Systematic Reviews

Two systematic reviews assessed the accuracy of PET in the diagnosis of SPN. The systematic review conducted by Fischer et al (48) estimated the mean sensitivity and specificity independently for identifying malignant pulmonary nodules and masses. The mean sensitivities and specificities calculated were 0.96 (SE 0.01) and 0.78 (SE 0.03), respectively, for dedicated PET and 0.92 (SE 0.04) and 0.86 (SE 0.04), respectively, for gamma camera PET. Sensitivity was significantly lower with gamma camera PET than with dedicated PET ($p<0.005$). There was no significant difference between the method of analysis of PET scans (SUV, visual, or both). The review concluded that PET has value to determine if a pulmonary nodule is malignant or benign but recommended that studies be conducted in populations with a low prevalence of NSCLC.

The meta-analysis by Gould et al (49) included 40 studies of pulmonary lesions and used a meta-analytic method to construct "summary" receiver operating characteristic (SROC) curves.[1] The maximum joint sensitivity and specificity of ^{18}FDG-PET from the SROC curve was 91.2% (95% CI 89.1% - 92.9%). In clinical practice, at a median specificity of 78%, the sensitivity of ^{18}FDG-PET from the SROC curve would correspond to 97%, as most studies use thresholds that favour sensitivity over specificity. There was no difference in the diagnostic accuracy of PET imaging for pulmonary nodules based on size ($p=0.43$), for semiquantitative versus qualitative methods of analysis ($p=0.52$) or for studies using dedicated PET versus gamma camera PET ($p=0.19$). Gould et al concluded that ^{18}FDG PET has

[1] An SROC curve is used to summarize ROC data from multiple studies, i.e., in the context of a meta-analysis; for further information see Walter SD. Properties of the summary receiver operating characteristic (SROC) curve for diagnostic test data. Stat Med. 2002; 21(9):1237-56.

a high sensitivity and intermediate specificity for identifying malignant pulmonary nodules and larger mass lesions but limited data exists for nodules < 1 cm in diameter.

Results of Primary Studies

Seven prospective studies (11-17) examining the use of ^{18}FDG-PET to differentiate between benign and malignant SPN are summarized in Tables 4 and 5. Most of the seven studies enrolled patients with indeterminate pulmonary lesions after radiography and used histopathological results as the gold standard. The sensitivity of most studies using ^{18}FDG-PET for detecting malignancy ranged from 79% to 100%. Specificity was more variable and ranged from 40% to 90%. Croft et al (14) reported a specificity of 40%; however, their patient population had a high incidence of granulomas, which increased the number of false positives. Nomori et al (15) also reported a low sensitivity and specificity; however, this study selected nodules on the basis of ground-glass opacity images on CT. PET data was evaluated independently of the reference standard in six of the studies (11-15,17). In one trial the entire study group did not receive confirmation of the diagnosis by the reference standard, which can lead to biased estimates of the overall diagnostic accuracy (13). Six of the studies clearly specified explicit criteria for defining a positive PET test result (12-17). Two of the studies were conducted by the same research group and it is not clear if the same patients were included in both studies (16,17).

Nomori et al evaluated 151 non-calcified nodules that were less than 3 cm in diameter (16). Results were reported for 136 of these nodules, as 15 nodules could not be diagnosed as malignant or benign and were excluded from analyses. The study found that PET could not detect abnormal ^{18}FDG-activity in the 20 nodules that were less than 1 cm in diameter, of which eight were malignant. PET correctly detected 57 of 63 malignant nodules that were solid on CT but was positive for only 1 out of 10 malignant nodules with a faint or ground-glass aspect on CT. All of the malignant nodules with ground-glass images on CT were histologically adenocarcinoma.

Another trial by Nomori et al compared visual and semi-quantitative analyses for nodules between 1 and 3 cm in diameter (17). PET scans were performed for 213 nodules. Only 161 of these nodules were included in analyses as 34 nodules were less than 1 cm in diameter and 18 nodules could not be diagnosed as either malignant or benign. This trial found that, in nodules greater than 1 cm, PET is negative or faintly positive in patients with histologically well-differentiated or moderately differentiated adenocarcinoma. The study also found no difference in sensitivity and specificity between visual assessment and semi-quantitative methods for nodules graded as definitely positive or negative. However, in nodules that were faintly positive, using the contrast ratio (CR) to the contralateral lung and contrast ratio to the cerebellum resulted in significantly higher sensitivity than the SUV.

Nomori et al also compared ^{18}FDG-PET to ^{11}C-Acetate PET for nodules 1-3 cm in diameter with ground-glass opacity on CT imaging (15). PET scans were performed for 54 nodules. Fifteen of 37 adenocarcinoma nodules (41%) were not detected by ^{18}FDG or ^{11}C-Acetate. Fourteen of these nodules were classified as well-differentiated adenocarcinomas. ^{11}C-Acetate identified eight well-differentiated adenocarcinomas nodules that were not detected by ^{18}FDG-PET.

Table 4: Characteristics of prospective studies on diagnosis of SPN.

Trial (ref.)	N	Eligibility	Method of Analysis	Reference Standard
Trials included in ICES Report				
Bury (11)	50	Indeterminate SPNs from chest radiography and CT	Visual	Histology
Lowe (12)	89	Indeterminate SPNs from chest radiography and CT Excluded lesions less that 0.7 cm	Visual and Semi-quantitative	Histology
Imdahl (13)	87[b]	Pulmonary lesions of unknown origin verified by CT	Visual and Semi-quantitative	Histology
Croft (14)	90	Lung nodule or mass on chest x-ray	Visual and Semi-quantitative	CT[a] + Histology
Trials published after completion of the ICES review				
Nomori (16)	131	Non-calcified pulmonary nodules < 3 cm in diameter	Semi-quantitative	Histology + CT + X-ray
Nomori (17)	53	Non-calcified pulmonary nodules 1-3 cm in diameter	Visual and Semi-quantitative	Histology
Nomori (15)	50	Pulmonary nodules 1 to 3 cm in diameter with ground-glass opacity images over their whole or peripheral area on CT	Visual and Semi-quantitative	Histology

N: number of patients.
[a] No results reported for CT test.
[b] 109 patients underwent ^{18}FDG-PET but only 87 received the reference standard.

Table 5: Diagnostic accuracy of 18FDG-PET in the diagnosis of SPN.

Trial (ref.)	N	Test	Prev %	Accuracy %	Se %	Sp %	PPV %	NPV %
Trials included in ICES Report								
Bury (11)	50	^{18}FDG-PET vs.Histology	66	96	100	88	94	100
Croft (14) [a]	90	^{18}FDG-PET vs.Histology	82	84	93	40	88	55
Imdahl (13) [b]	87	^{18}FDG-PET vs.Histology	79	87	90	78	94	67
Lowe (12)	89	Visual ^{18}FDG-PET vs.Histology	67	89	98	69	87	95
		≤ 1.5 cm	-	85	100	74	75	100
		> 1.5 cm	-	91	98	60	92	86
		≤ 3.0 cm	-	88	98	69	86	95
		SUV ^{18}FDG-PET vs.Histology	67	91	92	90	95	84
		≤ 1.5 cm	-	88	80	95	92	86
		> 1.5 cm	-	93	96	80	96	80
		≤ 3.0 cm	-	91	90	92	96	83
Trials published after completion of the ICES review								
Nomori (16)	131	^{18}FDG-PET vs.Histology						
		Nodules 1-3 cm	63	74	79	65	79	65
		Nodules with CT Solid Images	62	83	90	71	84	82
		Nodules with CT GGO Images	67	13	10	20	20	10
Nomori (17)	NR	Definitely Positive or Negative by Visual Estimation						
		Visual ^{18}FDG-PET vs.Histology	65	69	70	67	80	54
		SUV vs.Histology	65	65	58	77	83	49
		CR-Lung vs.Histology	65	71	70	73	83	56
		CR-Brain vs.Histology	65	69	68	71	82	54
		Faintly Positive by Visual Estimation						
		SUV vs.Histology	77	23	0	100	NA	23

		CR-Lung vs.Histology	77	64	53	100	100	38
		CR-Brain vs.Histology	77	41	29	80	83	25
Nomori (15)	50	FDG-PET vs.Histology	-	48	38	71	74	34
		^{11}C-Acetate PET vs.Histology	-	57	51	71	79	40

CR = contrast ratio, SUV = standardized uptake value, Se = Sensitivity, Sp = Specificity, Prev = Prevalence, PPV = Positive Predictive Value, N = number of patients, NA = Not Applicable, NPV = Negative Predictive Value, vs. = versus, NR = Not Reported.

[a] Patients from region with high histoplasmosis prevalence.

[b] Three different se/sp were reported in the paper and it was unclear how they were calculated.

Question 2: Staging of Non-Small Cell Lung Cancer (NSCLC) at Initial Diagnosis

The results of studies on the role of PET in the staging of primary NSCLC are presented in the following three subsections: overall results for staging in primary NSCLC (both utility and accuracy), results specific to mediastinal staging (accuracy only), and extrathoracic staging (accuracy only). Most available primary studies evaluate the accuracy of PET in the staging of primary NSCLC, although three randomized studies present evidence on utility (18,19,34).

(a) Primary NSCLC Staging: Utility and Accuracy of PET

Findings of ICES

The ICES reported on 14 prospective studies (20-32) examining the effectiveness of PET in staging primary NSCLC. These studies are summarized in Tables 6 and 7. The ICES report stated that the evidence on whether preoperative PET would reduce the number of unnecessary thoracotomies for patients diagnosed with lung cancer is conflicting.

Utility of PET in Primary NSCLC Staging: Results of Primary Studies

To date, there have been three fully published RCTs evaluating the value of preoperative PET assessment for NSCLC (18,19,34), two of which were included in the ICES report. Summary data for these trials are provided in Tables 8 and 9. All three trials adequately described the method of patient randomization. Two trials stratified randomization by institution (18,34), and one also stratified by performance status (34). Patient eligibility criteria were clearly stated, and the baseline characteristics were presented for both groups. The trials described the statistical basis for the estimation of trial sample size. All three trials met target accrual and stated that analyses were conducted on an intent-to-treat basis (18,19,34).

The PLUS (PET in Lung Cancer Staging) multicentre trial randomized 188 patients with suspected lung cancer to conventional workup either with or without PET imaging (18). Fifty percent of the patients had a definite diagnosis of NSCLC, and 70% had clinical stage I or II disease at baseline. The primary outcome was the number of futile thoracotomies. Thoracotomy was regarded as futile if the patient had benign disease, exploratory thoracotomy, pathological stage IIIA (mediastinal node positive) or IIIB disease, or postoperative relapse or death within 12 months of randomization. The addition of PET to the conventional workup produced a 51% relative reduction in futile thoracotomies (from 41% to 21%, p=0.003) and prevented unnecessary surgery in 20% of patients with suspected NSCLC. Twenty-seven percent of the patients in the combined PET and conventional workup were up-staged, compared to 12% of patients in the conventional workup group.

An Australian multicentre trial randomized 183 patients with histologically or cytologically proven stage I-II NSCLC to either conventional workup with or without PET imaging (19). The primary endpoint was the proportion of patients undergoing thoracotomy. Patient management (whether the patient underwent thoracotomy) was determined at the discretion of the surgeon, and 65% of patients were assessed by one surgeon. PET led to changes in the staging of 24 patients (22 patients up-staged [13 patients to stage IIIA, six

patients to stage IIIB, and three patients to stage IV] and two patients staged as benign) and confirmed the staging in 61 patients. Of the 22 PET–up-staged patients, the majority were confirmed pathologically to have been correctly up-staged. However, two stage I patients were incorrectly up-staged—one patient had metastatic thyroid cancer to the mediastinal nodes, and the other had silicosis. Across the trial arms there was no significant difference in the number of thoracotomies performed (p=0.2), and PET only resulted in changes in patient management in 12 patients (14%). PET could have altered patient management in an additional 12% of patients; however, the surgeons operated on patients with potentially completely resectable stage IIIA disease without further evaluation.

The POORT multicentre trial randomized 465 patients with suspected NSCLC upon initial presentation to either traditional staging workup or a PET scan (34). PET was followed by the histologic and/or cytologic verification of lesions or further imaging and follow up. If the PET scan was positive for distant metastases, the results were verified and CT and/or magnetic resonance imaging (MRI) of the brain was performed before patients underwent mediastinal staging. If the PET scan was positive for mediastinum involvement (>N1) but negative for distant metastases, patients were referred for mediastinoscopy. Patients who had negative findings on mediastinoscopy were referred for thoracotomy, and patients with positive findings were treated with chemotherapy and/or radiation. If the PET scan was negative for distant metastases and mediastinum involvement (<N2), patients with peripheral tumours were referred to thoracotomy, patients with central tumours were referred for mediastinoscopy and mediastinotomy, and patients with presumed benign lesions were followed for at least 12 months. The primary outcome was the number of tests and procedures to finalize staging and define operability. A statistically significant difference was not found between the two groups for the mean number of tests to finalize staging. Secondary outcomes were the length of the diagnostic process, morbidity associated with staging procedures, and cost. The median time to diagnosis was significantly shorter for the PET group (14 days vs. 23 days, p<0.0001). There was no difference for morbidity associated with the staging procedures. The mean number of functional tests, non-invasive procedures, invasive procedures, and thoracotomies did not significantly differ between the arms; however, the percentage of patients who needed greater than one invasive tests for N staging and number of mediastinoscopies was significantly lower for the PET group. It is not clear whether these outcomes were a priori or post hoc comparisons or whether statistical analyses were adjusted for multiple comparisons.

Accuracy of PET in Primary NSCLC Staging: Results of Primary Studies

Twenty-two prospective studies examined the use of PET in staging primary NSCLC and are summarized in Tables 6 and 7 (20-33,35-42). Most studies enrolled patients with potentially resectable NSCLC and used histopathological results as the gold standard. The protocols for nodal sampling varied between the trials and were not always clearly described. The methods used for reporting PET scans as positive varied, with some studies visually interpreting the scan and others using semi-quantitative methods such as calculating the SUV. PET data were evaluated independently of the reference standard in twenty of the studies (20-33,35,38-42). PET was included in the reference standard in one study, which could have overestimated diagnostic accuracy (33). In four trials, the entire study group did not receive confirmation of the diagnosis by the reference standard, which could have led to biased estimates of the overall diagnostic accuracy (23,30-32). Eighteen of the studies clearly specified explicit criteria for defining a positive PET test result (20-28,31-33,37-42). Four studies reported results using lymph nodes as the unit of analysis (22-24,37). These observations are not statistically independent as a patient with one positive lymph node is likely to have other positive lymph nodes, which may bias the estimates of diagnostic

accuracy. Results from studies examining staging of the primary tumour were variable, as the criteria used to determine a positive result (e.g., N0 vs. N1/2/3 or N0/N1 vs. N2/3). The sensitivity of ^{18}FDG-PET for detecting distant metastases ranged from 82% to 90%, and specificity ranged from 90% to 98%. Eight studies reported the usefulness of PET for detecting unexpected distant metastases, and PET detected distant metastases in 4% to 17% of patients.

Cerfolio et al compared integrated PET-CT with dedicated PET for staging in 129 patients with NSCLC (38). Integrated PET-CT was more accurate for predicting stage I ($p=0.03$) and II ($p=0.04$) disease and was a better predictor of overall T ($p=0.001$) and N ($p=0.008$) status than was dedicated PET. Integrated PET-CT was also more accurate overall for N2 nodes ($p=0.01$) and N1 nodes ($p=0.001$), as well as predicting T2 ($p=0.04$), T3 ($p=0.03$), N0 ($p=0.03$), and N1 ($p=0.04$) disease. Lardinois et al also compared integrated PET-CT to dedicated PET, and found that integrated PET-CT improved the accuracy of tumour staging ($p=0.001$), and node staging ($p=0.013$), as well as detecting metastases (30). Halpern et al compared integrated PET-CT to dedicated PET and found integrated PET-CT was more accurate for assigning T stage ($p<0.05$) and had greater accuracy for determining the overall TNM stage ($p=0.01$) (40). Shim et al compared integrated PET-CT to stand-alone CT. Integrated PET-CT was significantly more accurate than CT for nodal staging ($p<0.001$) and overall staging ($p=0.001$) but was not significantly different for tumour staging ($p=0.25$) (41).

Oturai et al compared gamma camera PET with dedicated PET, and found no statistically significant difference for detecting primary pulmonary lesions or evaluating regional lymph nodes between the two techniques (39). Gamma camera PET did have reduced sensitivity for detecting lymph nodes compared to dedicated PET.

(b) Primary NSCLC: Mediastinal Staging: Accuracy of PET

Findings of ICES

The ICES report concluded that "there is evidence for the efficacy of PET in predicting the histological status of mediastinal lymph nodes and in detecting pleural involvement and malignant pleural effusion in patients with carcinoma of the lung, and that PET is more efficacious than CT."

Results of Systematic Reviews

A systematic review conducted by Fischer et al estimated the mean sensitivity and specificity independently for the staging metastases in the mediastinum (48). The mean sensitivities and specificities calculated were 0.83 (SE 0.02) and 0.96 (SE 0.01), respectively, for dedicated PET and 0.81 (SE 0.04) and 0.95 (SE 0.02), respectively, for gamma camera PET. The review concluded that PET is a valuable tool for staging NSCLC, but although its use for preoperative staging is strengthened by its high specificity, further examinations are still required.

A meta-analysis by Birim et al (50) included 17 studies (21,24-26,29,51-62) that compared ^{18}FDG-PET with CT in detecting mediastinal lymph node metastases. The maximum joint sensitivity and specificity of ^{18}FDG-PET from the SROC curve was 90% (95% CI 86% -95%). Birim et al concluded that ^{18}FDG PET was more accurate than CT imaging ($p<0.0001$) in detecting mediastinal lymph node metastases. The authors recommended that PET images be correlated with a CT scan as PET has limited ability to determine precise anatomic localization. A meta-analysis by Gould et al also concluded that ^{18}FDG-PET is more accurate than CT ($p<0.001$) for mediastinal staging in patients with potentially resectable NSCLC (63). For the 32 studies in which the patient was the unit of analysis (20,21,25-27,29,52-54,56,58-60,62,64-81) a maximum joint sensitivity and specificity of ^{18}FDG-PET was calculated from the SROC curve as 86% (95% CI 84% - 88%), which, at a median specificity of 90%, would correspond to a sensitivity of 81%. The authors also examined the use of PET for identifying

mediastinal metastasis in patients with and without enlarged lymph nodes on CT, on the basis of data from 14 studies (20,21,25,26,52,54,56,58,60,62,68,70,71,82). This meta-analysis found ^{18}FDG-PET was more sensitive but less specific when the CT scan showed enlarged mediastinal lymph nodes. The authors concluded that "positive ^{18}FDG-PET findings should be confirmed by biopsy before curative surgery is excluded as a treatment option", and "negative ^{18}FDG-PET findings should be interpreted in light of the patient's pretest probability of mediastinal metastases and whether CT reveals enlarged mediastinal nodes" (63).

Results of Primary Studies

Halter et al evaluated PET in staging mediastinal lymph nodes in 155 patients with pulmonary tumours (35). PET was associated with accuracies of 91%, 77%, 95%, and 100% for N0, N1, N2, and N3 disease, respectively. Verhagen et al assessed the reliability of PET for staging mediastinal lymph nodes in 66 patients with NSCLC (36). The study found that, although the negative predictive value for staging mediastinal lymph nodes was 71%, the negative predictive value was only 17% for patients with positive N1 nodes and/or a centrally located primary tumour, compared to 96% for patients with negative N1 nodes and a non-centrally located primary tumour (36). Nomori et al measured the size of metastatic foci in lymph nodes with true-positive and false-negative results to determine the lower size limit of metastatic lymph nodes that PET can detect (37). Metastatic foci in the lymph nodes with true-positive results had a mean size of 10 mm (range 4-18 mm), and false-negative results had a mean size of 3 mm (range 0.5-9 mm). Lymph nodes with false-positive results had a mean size of 12 mm (range 9-16 mm), and true-positive results had a mean size of 10 mm (range 6-15 mm). PET did not detect any metastatic foci less than 4 mm in size. Lardinois et al compared integrated PET-CT to dedicated PET and found that integrated PET-CT improved the accuracy of staging mediastinal metastases (30). Pozo-Rodriguez et al evaluated contrast-enhanced helical CT and ^{18}FDG-PET, alone and combined. Helical CT and ^{18}FDG-PET performed similarly in mediastinal staging (p=0.32), although the authors concluded that both tests are conditionally dependent and provide complementary information (42).

(c) Primary NSCLC—Extrathoracic Staging: Accuracy of PET

Findings of ICES and Other Reports

Although the ICES report did not address this topic, extrathoracic staging was addressed in four other evidence-based reports. The Health Technology Board for Scotland (HTBS) report (83) was the most comprehensive and evaluated 19 studies on the detection of distant metastases (20,23,25,26,33,51,54,60,76,79,84-92). They concluded that there is evidence that ^{18}FDG-PET may be a useful tool in staging in patients believed to be free of distant metastases, specifically for adrenal glands and bone metastases, but this needs to be confirmed in controlled trials. In addition, a review by NICE (93) provided an SROC curve for the detection of distant metastases, and calculated a summary sensitivity of 93% and specificity of 96%. They also found that an average of 15% of patients had unexpected distant metastases detected by ^{18}FDG-PET.

Results of Primary Studies

Only one prospective study retrieved in the update search reported on the staging of extrathoracic metastases. Verhagen et al assessed the value of PET in detecting extrathoracic metastases in 72 patients with NSCLC (36). In this study, PET detected extrathoracic metastases in 15% (10/66) of patients in whom conventional staging showed no evidence of metastases.

Table 6: Characteristics of prospective studies for staging primary NSCLC.

Trial (ref.)	N	Eligibility	Method of Analysis	Reference Standard
Trials included in ICES Report				
Reed (31)	287[a]	Suspected or confirmed NSCLC found to be surgical candidates (stage I, II or IIIA) by routine staging procedures	Visual with and without CT and other conventional imaging results	Confirmatory procedures [b]
Kahn (32)	157	Suspected of having operable and potentially curable lung cancer by abnormal CT scan	Visual and SUV	Histology
Saunders (25)	97[c]	Biopsy proven or strongly suspected lung cancer by clinical and CT criteria, and judged to be operable (< Stage IIIA)	Visual and SUV	Histology, CT, and follow up
Vesselle (27)	142	Potentially resectable NSCLC based on CT. Patients with lesions <1cm or insufficient cellularity, or with unknown histological type were excluded	Visual, read with thoracic CT scans	Histology, additional imaging
Poncelet (29)	64	Potentially resectable NSCLC based on CT. Excluded patients with N3 or M1 as detected by PET	NR	Histology
Pieterman (26)	102	Potentially resectable NSCLC	Visual	Histology, follow up, additional imaging
Gupta (23)	103	Suspected or proven NSCLC considered to be surgically resectable	SUV	Histology
Gupta (24)	118	Suspected or proven NSCLC considered to be surgically resectable	Visual and SUV	Histology, CT
Bury (33)	110	Histological diagnosis of NSCLC	Visual	Bone scintigraphy, histology, additional radiology
Bury (20)	50	Potentially resectable NSCLC	Visual	Histology
Chin (21)	43	Potentially resectable NSCLC. Excluded patients with obvious stage IIIB or IV	Visual	Histology
Stokkell (22)	33	Newly diagnosed patients with NSCLC	Visual with dual-headed gamma camera	Histology
Albes (28)	40	Suspected or proven NSCLC. Excluded patients with distant metastases.	SUV	Histology
Lardinois (30)	50	Suspected or proven NSCLC.	Integrated PET-CT, or visually correlated PET & CT, or PET alone	Histology
Trials published after completion of the ICES review				
Halter (35)	155	Suspected lesions of the lung based on helical CT	NR	Histology
Cerfolio (38)	129	Patients with an indeterminate pulmonary nodule or biopsy-proven NSCLC	Integrated PET-CT, visually correlated PET & CT	Histology
Oturai (39)	86	Suspected lung cancer based on the radiograph	Visual dedicated-PET, gamma camera PET	Histology, follow-up
Nomori (37)	80	Patients with peripheral-type lung cancer	Semiquantitatively using contrast ratio	Histology
Verhagen (36)	66	Suspected or proven primary NSCLC	Visual	Histology
Halpern (40)	36	Suspected or biopsy proven NSCLC	Visual	Histology
Shim (41)	106	Histopathologically proven NSCLC	SUV	Histology
Pozo-Rodriguez (42)	132	Histologically diagnosed potentially respectable stage I, II and selected stage II NSCLC	Visual, plus in parallel with helical CT	Histology and follow up

N: number of patients, NR: not reported, NSCLC: non-small cell lung cancer, SUV: standardized uptake value.
[a] 445 patients were registered. 303 underwent PET, but only 287 were evaluable for metastatic disease.
[b] Included biopsy, additional imaging, judgement of the surgeon and 6 month follow up.
[c] 13 patients had distant metastases and did not undergo mediastinal sampling.

Table 7: Diagnostic accuracy of ^{18}FDG-PET for staging primary NSCLC.

Trial (ref.)	N	Test	Prev %	Acc %	Se %	Sp %	PPV %	NPV %
Trials included in ICES Report								
Reed (31)	287	Detection of Distant Metastases ^{18}FDG-PET vs. Biopsy/additional imaging/judgement of the surgeon[a]/6-month follow-up	6	90	83	90	36	99
	302	Staging Mediastinal (N0/N1 vs.N2/N3) Disease ^{18}FDG-PET vs.Histology	25	78	61	84	56	87
Kahn (32)	157	Primary Lung Lesion Visual ^{18}FDG-PET vs.Histology/12 mo follow-up	-	-	96	71	92	83
		SUV vs.Histology/12 month follow-up	-	-	90	80	-	-
	128	Hilar/Mediastinal Lymph Nodes ^{18}FDG-PET vs.Histology	-	-	81	77	53	93
	139	Detecting Stage <IIIB vs. IIIB/IV ^{18}FDG-PET vs.Histology or CT or MRI or bone scintigraphy	-	-	63	84	-	-
Saunders (25)	84	Staging Mediastinal (N0/N1 vs.N2/N3) Disease ^{18}FDG-PET vs.Histology	21	92	71	97	86	93
Vesselle (27)	118	Staging Mediastinal (N0/N1 vs.N2/N3) Disease ^{18}FDG-PET vs.Histology	36	91	81	96	92	90
Poncelet (29)	62	Staging Mediastinal (N0/N1 vs.N2/N3) Disease ^{18}FDG-PET vs.Histology	15	82	67	85	43	94
Pieterman (26)	102	Detection of Distant Metastases ^{18}FDG-PET vs.Histology	-	-	82	93	-	-
		Detection of Mediastinal (N0/N1 vs.N2/N3) Disease						
		^{18}FDG-PET vs.Histology	31	87	91	86	74	95
		CT & ^{18}FDG-PET vs.Histology	31	88	94	86	75	97
Gupta (23)	Lymph nodes 126	Detection of Mediastinal (N0/N1 vs.N2/N3) Disease ^{18}FDG-PET vs.Histology	40	94	93	94	92	94
Gupta (24)	Lymph nodes	Staging Mediastinal Metastases						
	168	^{18}FDG-PET vs.Histology	-	94	96	93	-	-
	53	Lymph nodes <1 cm	-	92	80	95	-	-
	107	Lymph nodes 1-3 cm	-	95	100	91	-	-
	8	Lymph nodes >3	-	88	100	75	-	-
Bury (33)	110	Detection of Bone Metastases ^{18}FDG-PET vs. Bone Scan, Histology, additional imaging	-	96	90	98	90	98
Bury (20)[b]	50	Detection of Mediastinal (N0 vs.N1/N2/N3) Disease FDG-PET vs.Histology	58	84	83	86	89	78
Chin (21)	30	Detection of N2 Status ^{18}FDG-PET vs.Histology	30	80	78	81	64	89
		Primary Lung Lesion ^{18}FDG-PET vs.Histology	-	89	94	33	94	33
Stokkell (22)	Lymph nodes 187	Mediastinal Lymph Node Involvement (N0/N1 vs.N2) ^{18}FDG-PET vs.Histology	-	96	90	97	85	98

Trial (ref.)	N	Test	Prev %	Acc %	Se %	Sp %	PPV %	NPV %
Albes (28)		Primary Tumour						
	38	T0: ^{18}FDG-PET vs.Histology	-	-	67	100	100	-
		T1/2: ^{18}FDG-PET vs.Histology	-	-	79	83	92	-
		T3: ^{18}FDG-PET vs.Histology	-	-	83	88	56	-
		T4: ^{18}FDG-PET vs.Histology	-	-	67	89	33	-
	38	Mediastinal Lymph Node Involvement						
		N0: ^{18}FDG-PET vs.Histology	-	-	89	86	84	-
		N1/2: ^{18}FDG-PET vs.Histology	-	-	71	86	80	-
		N3: ^{18}FDG-PET vs.Histology	-	-	80	94	67	-
Lardinois (30)	40	Tumour Stage c						
		PET Alone	-	40	-	-	-	-
		Visual correlation of PET & CT	-	65	-	-	-	-
		Integrated PET-CT	-	88	-	-	-	-
		Node Stage c						
		PET Alone	-	49	-	-	-	-
		Visual correlation of PET & CT	-	59	-	-	-	-
		Integrated PET-CT	-	81	-	-	-	-
Trials published after completion of the ICES review								
Halter (35)	116	Lymph Node Status (N0 vs. N1/N2/N3)	71	89	88	91	96	76
	155	Primary Tumour	75	91	91	90	96	78
Cerfolio (38)		Stage		(PET-CT vs. PET))				
	10	0	-	90/70	-	-	-	-
	42	I	-	**52/33**	-	-	-	-
	17	II	-	**70/36**	-	-	-	-
	23	IIIA	-	70/48	-	-	-	-
	9	IIIIB	-	56/33	-	-	-	-
	19	IV	-	89/84	-	-	-	-
	91	T Status (overall)	-	**70/47**	-	-	-	-
	11	T0	-	100/81	-	-	-	-
	21	T1	-	76/57	-	-	-	-
	39	T2	-	**65/41**	-	-	-	-
	12	T3	-	**58/8**	-	-	-	-
	8	T4	-	63/63	-	-	-	-
	110	N Status (overall)	-	**78/56**	-	-	-	-
	55	N0	-	**76/56**	-	-	-	-
	15	N1	-	**93/53**	-	-	-	-
	35	N2	-	77/57	-	-	-	-
	5	N3	-	60/60	-	-	-	-
	129	M Status (overall)	-	92/87	-	-	-	-
	110	M0	-	93/88	-	-	-	-
	19	M1	-	89/79	-	-	-	-
Oturai (39)		Detection of Primary Lung Lesion						
	84	gPET vs. histology	62	82	98	56	78	95
		^{18}FDG-PET vs. histology	62	81	100	50	76	100
	67	Regional Lymph nodes (N0 vs.N1/N2/N3)						
		gPET vs. histology	27	82	61	90	69	86
		^{18}FDG-PET vs. histology	27	82	78	84	64	91
Nomori (37)	564 lymph nodes	Mediastinal Lymph Node Involvement ^{18}FDG-PET vs. histology	-	97	78	98	74	98
Verhagen (36)	66	Mediastinal lymph node status (N0 vs.N1/N2/N3) ^{18}FDG-PET vs. histology	-	-	58	90	83	71

Trial (ref.)	N	Test	Prev %	Acc %	Se %	Sp %	PPV %	NPV %
Halpern (40)	36	Mediastinal lymph node status (N0 vs.N1/N2/N3)						
		^{18}FDG-PET vs. histology	-	69	50	77	45	80
		Integrated PET-CT vs. histology	-	78	60	85	60	85
		T Stage						
		^{18}FDG-PET vs. histology	-	67	-	-	-	-
		Integrated PET-CT vs. histology	-	97	-	-	-	-
		TNM Stage						
		^{18}FDG-PET vs. histology	-	57	-	-	-	-
		Integrated PET-CT vs. histology	-	83	-	-	-	-
Shim (41)		Integrated PET-CT vs. histology						
		Mediastinal lymph node status	-	84	85	84	-	-
		T Stage	-	86	-	-	-	-
		Overall Stage	-	87	-	-	-	-
		Stage I	-	89	-	-	-	-
		Stage II	-	94	-	-	-	-
		Stage III	-	71	-	-	-	-
Pozo-Rodriguez (42)	132	Mediastinal lymph node status (N0/N1 vs.N2/N3)						
		^{18}FDG-PET vs. histology	28	77	81	76	56	91
		^{18}FDG-PET and helical CT vs. histology	28	65	92	55	43	95

Notes: Values in **Bold** are significant at the p<.05 confidence level. Acc = Accuracy, Se = Sensitivity, Sp = Specificity, Prev = Prevalence, PPV = Positive Predictive Value, NPV = Negative Predictive Value, N: number of patients (unless specified as lymph node), gPET = Gamma Pet, dPET = dedicated PET, vs. = versus.
[a] Judgment of the surgeon was not specified in the protocol as a confirmatory procedure
[b] Values were calculated based on results given, however are different from what the study reported
[c] Results that were correct, but equivocal, were not included in calculating diagnostic accuracy. FP and FN were not reported.

Table 8: Characteristics of RCTs on preoperative staging.

Trial (ref.)	N	Test	Method of Analysis	Reference Standard
Trials included in ICES Report				
Van Tinteren (18)	188	Suspected or proven NSCLC judged to be medically operable & potentially resectable based on clinical staging	Visual correlation with CT	Conventional Work-up including CT
Viney (19)	183	Histologically or cytologically proven stage I-II NSCLC	Visual analysis	Conventional Work-up including CT
Trials published after completion of the ICES review				
Herder (34)	465	Suspected NSCLC based on history, physical exam and chest x-ray Excluded patients with overt disseminated disease at first presentation	Visual analysis	Traditional workup

N: Number of patients, NR: Not Reported, NSCLC: Non-small cell lung cancer

Table 9: Outcomes of RCTs on preoperative staging

Trial (ref.)	N	Outcome	Results		
Trials included in ICES Report			CWU	CWU + PET	p value
Van Tinteren (18)	188	Futile thoracotomies			
		Relative Reduction	51% *(95% CI 32-80)*		p=0.003
		Absolute difference	41% (39/96)	21% (19/92)	
		Stage I/II	46% (31/68)	29% (8/28)	NR
		Stage III	29% (8/28)	11% (3/27)	NR
Viney (19)	183	Thoracotomy rate	98% (90/92)	96% (87/91)	p=0.2

		One year survival	77% *(95% CI 67-85)*	80% *(95% CI 70-87)*	NR
Trials published after completion of the ICES review			**TWU**	**PET**	**p value**
Herder (34)	465	Mean # of all tests	7.88 *(SD 1.95)*	7.90 (*SD 1.88)*	p=0.90
		Mean # of functional tests	2.13 (SD 0.91)	2.23 (SD 0.94)	P=0.27
		Mean # of staging tests	4.75 (SD 0.91)	4.69 (SD 1.52)	P=0.66
		Mean # of imaging tests	3.74 (SD 1.16)	3.80 (SD 1.09)	P=0.54
		Mean # of invasive tests	0.96 (SD 0.95)	0.85 (SD 0.79)	P=0.18
		≥1 invasive test for N staging (No.)	92 (39%)	52 (22%)	P<0.0001
		Thoracotomy (No.)	88 (38%)	96 (41%)	p=0.43
		Mediastinoscopy (No.)	79 (34%)	31 (13%)	p>0.05[a]
		Proportion of patients requiring at least 3 tests	52%	51%	P=0.82
		Agreement between clinical and final stage	κ 0.85 *(95% CI 0.80-0.90)*	κ 0.78 *(95% CI 0.72-0.84)*	p= 0.073
		Median time to diagnosis (days)	23	14	p<0.0001

[a] Abstract reported that mediastinoscopies occurred significantly less often in the PET arm.
CI: confidence interval, CWU: conventional workup, N: number of patients, No: number, NS: not statistically significant NR: not reported, PET: Position Emission Tomography, SD: standard deviation, TWU: Traditional workup, κ: Kappa,

Question 3: Staging of Primary Small Cell Lung Cancer (SCLC)

Very few primary studies have evaluated the accuracy of PET in the diagnosis and staging of SCLC. This topic was not covered by the ICES report (46,47), although the Agency for Healthcare Research and Quality (AHRQ) report (94) provided an assessment of the available evidence (see Appendices C and D).

Results of Primary Studies

In all, three prospective studies (43-45) examined the use of ^{18}FDG-PET in staging primary SCLC and are summarized in Table 11 and 12. The reference standards varied between the studies, and none of the studies confirmed all lesions with histological results. Brink et al confirmed only 20% of lesions with histopathological results (45). PET was evaluated independently of the reference standard in two of the studies (43,45). Only one study clearly specified explicit criteria for defining a positive PET test result (45). Sensitivity for staging extensive versus limited stage disease ranged from 89% to 100%, and specificity ranged from 78% to 95%. Chin et al compared ^{18}FDG-PET to conventional staging and reported that PET agreed with conventional staging in 15 of 18 cases (83%). PET up-staged two patients to extensive disease, of which one was confirmed to have extensive disease, and down-staged one patient to limited disease. There was insufficient information to verify the other two discrepant results.

Table 11: Characteristics of prospective studies for staging primary SCLC.

Trial (ref.)	N	Eligibility	Method of Analysis	Reference Standard
Bradley (43)	24	Histologically or cytologically confirmed limited SCLC based on conventional imaging	Visual and SUV	Biopsy and additional imaging [a]
Chin (44)	18	Newly diagnosed SCLC	NR	Conventional staging [b]
Brink (45)	120	Histologically confirmed SCLC	Visual	Histology or consensus based on sum of available data [c]

N: number of patients, NR: not reported, SCLC: small cell lung cancer, SUV: standardized uptake value.
[a] Biopsy was not conducted for lesions that were not visible on anatomic imaging or that were < 1 cm in size.
[b] Conventional staging included chest CT, abdominal CT, cranial CT or MRI, bone scan and bone marrow biopsy.
[c] Conventional staging included patient history, physical findings, bronchoscopy, and thoracic and abdominal contrast-enhanced CT scans in all patients. Cranial MRI, cranial CT, bone marrow biopsy, or bone scintigraphy were conducted in some patients. If conventional staging and PET disagreed, selective additional examinations, pre-existing files, or results of follow up examinations were used.

Table 12: Diagnostic accuracy of ^{18}FDG-PET for staging primary SCLC.

Trial (ref.)	N	Test	Prev %	Acc %	Se %	Sp %	PPV %	NPV %
Bradley (43)	24	Staging Extensive vs. Limited Disease ^{18}FDG-PET vs. Biopsy and additional imaging	8	96	100	95	67	100
Chin (44)	18	Staging Extensive vs. Limited Disease ^{18}FDG-PET vs. Conventional Staging	50	83	89	78	80	88
Brink (45)		^{18}FDG-PET vs.Histology or consensus						
	120	Staging Extensive vs. Limited Disease	63	99	100	98	99	100
	118	Detection of lymph node metastases	45	99	100	98	98	100
	70	Detection of distant metastases (except	66	96	98	92	96	96
	91	brain)	14	90	46	97	75	92
		Detection of brain metastases						

Acc = Accuracy, N: number of patients, SCLC: small cell lung cancer, Se = Sensitivity, Sp = Specificity, Prev = Prevalence, PPV = Positive Predictive Value, NPV = Negative Predictive Value, vs. = versus.

DISCUSSION

The accurate diagnosis and staging of lung cancer patients is vital for the selection of appropriate treatment. In recent years, ^{18}FDG-PET scanning has emerged as a potential non-invasive imaging technique for the diagnosis and staging of lung cancer. Many studies have evaluated the accuracy of ^{18}FDG-PET in the diagnosis and staging of lung cancer; however, there is limited evidence to determine the impact of PET on clinical management and on patient outcomes.

The majority of studies examining PET have been diagnostic accuracy studies; however, these studies are highly susceptible to bias, which can result in unreliable estimates of accuracy. Diagnostic studies with methodological limitations tend to overestimate the diagnostic performance of the test (95). In evaluating the evidence for PET in lung cancer, a number of limitations were present in the accuracy studies, including differences in patient selection, the use of different reference standards for verification of results, and biases in the evaluation of test results. These shortcomings in study design can affect the estimates of diagnostic accuracy. In addition, it is not clear how results from diagnostic accuracy studies translate into changes in patient management. The DSG placed considerable weight on the findings of the randomized utility studies for the staging of primary NSCLC. For other issues, accuracy of the evidence was used to support what are largely consensus recommendations.

The determination as to whether an SPN is benign or malignant can be problematic as certain lesions cannot be diagnosed by conventional means other than surgical resection. To ensure that only patients with a potentially resectable lung cancer are taken to thoracotomy, histologic or cytologic evidence of malignancy is needed. For patients with an SPN, percutaneous FNAB is usually performed. However, FNAB may be contraindicated because there may be an underlying medical condition, the lesion may be inaccessible to FNAB, prior attempts at FNAB may have failed, or the patient may refuse the procedure.

Meta-analyses of studies evaluating the ability of PET to differentiate benign from malignant lesions have found the sensitivity of PET to range from 96%-97% and specificity to range from 78%-86% (48,49). Accuracy studies have confirmed that PET appears to have a high sensitivity, and a reasonable specificity for differentiating benign from malignant lesions as small as 1 cm in size. A mass of metabolically active cells is needed for PET to be positive

and to suggest that a lesion may be malignant. With current PET scanners, it is difficult to detect malignancy in nodules that are less than 1 cm. The studies by Normori et al suggest that pulmonary nodules less than 1 cm or with faint or ground-glass opacity images on CT cannot be evaluated accurately by PET and that both CT and PET findings should be considered to determine if surgical biopsy is necessary for small pulmonary nodules (16,17). False-negative results can also occur with low-grade malignant tumours such as well-differentiated adenocarcinomas, including bronchoalveolar cell carcinomas, due to their lower metabolic activity. False-positive results can occur in inflammatory conditions such as granulomatous disease due to the increased metabolic activity of inflammatory cells. Infection with histoplasmosis is common in Ontario and could increase the rate of false-positive PET scans.

Based on this evidence, PET is recommended for patients with SPN 1.0 cm or greater in size who cannot undergo FNAB or who have failed a prior attempt at FNAB. If the PET is positive, the probability is high that the lesion is malignant, and the patient should proceed to thoracotomy. A negative PET scan suggests that the lesion is benign but careful follow-up is indicated, as PET can be falsely negative in slow growing adenocarcinomas and bronchoalveolar carcinoma.

A study by Lardinois et al (96), that did not meet the inclusion criteria for this report, reviewed cases of NSCLC solitary extrapulmonary FDG accumulations in patients with NSCLC. Solitary extrapulmonary lesions were found in 72 of 350 patients (21%) with PET-CT imaging. 54% of lesions were solitary metastases and 46% were lesions unrelated to the primary lung tumour. This trial supports the conclusions that SPN require histopathologic diagnosis as up to half solitary extrapulmonary FDG accumulations may represent unrelated malignancies or benign disease.

After lung cancer has been diagnosed, accurate staging is essential for appropriate treatment decisions to be made. Conventional staging procedures are currently imperfect in their ability to spare patients from the morbidity and mortality of stage inappropriate therapies. Health technology assessment reports have concluded that it is difficult to quantify the improvement in diagnostic accuracy of PET in staging NSCLC due to the variations in study quality and the lack of direct evidence on whether PET improves patient outcomes (83,97). Meta-analyses found sensitivity to range from 81%-90% and specificity to range from 89%-90% for the distinction between N0-1 and N2-3 patients (50,63,98). Accuracy studies had similar results, with PET results found to be superior to CT imaging for mediastinal staging. Studies that interpreted PET images with CT results had higher accuracy than when PET was interpreted independently (26,30). Integrated PET-CT scanners also improved accuracy (30,38); however, additional studies on this type of imaging are needed as only a few small single-centre prospective studies have evaluated the accuracy of integrated PET-CT scanners, and there are no studies on the impact of PET-CT on patient outcomes. The results from Nomori et al suggest that PET is unable to detect metastatic foci smaller than 4 mm (37). False positives with respect to staging the mediastinum also occur with infection and inflammation. The trials suggest that a positive test result should be confirmed to ensure that patients are not denied potentially curative surgery. False-negative results can occur when the primary tumour obscures mediastinal lymph nodes, as the ^{18}FDG uptake in the lymph nodes may not be distinguished from the avid uptake in the primary tumour. PET has also been used to detect distant metastases, but additional research is needed in this area. PET has been found to have high accuracy (89%-96%) for detecting distant metastases and has also detected extrathoracic metastases in patients in whom conventional imaging showed no evidence of distant metastases. The role of PET in the evaluation of distant metastases appears to be greatest for adrenal and bone metastases. PET is not useful for detection of brain metastases due to the high glucose uptake of normal brain tissue.

Three randomized controlled trials have evaluated the value of preoperative PET assessment; however, two of these trials had conflicting results. These two trials randomized patients to conventional workup with or without PET. The PLUS trial reported a 51% relative reduction in futile thoracotomies (p=0.003) when PET was added to conventional work up (18), whereas the Australian trial found no difference in the number of thoracotomies avoided (p=0.2) (19). A number of factors contribute to the apparent discrepancy between these trials. One factor is the difference in the patient populations between the trials. The PLUS trial included patients with suspected or proven NSCLC based on clinical, not surgical staging and as a result included patients with both benign and malignant lesions, whereas the Australian trial only included patients with histologically or cytologically proven NSCLC prior to randomization. However, the reduction in futile thoracotomies was still significant for PET (53% relative reduction, 95% CI 32%-88%) when patients with benign lesions were excluded from the analysis in the PLUS study. In addition, 29% of patients in the PLUS trial had clinical stage III disease at baseline, whereas the Australian trial only included patients demonstrating clinical stage I or II disease. Another explanation for the difference in results is that the approach to the management of patients with early stage lung cancer differed. Patients in the Australian trial with stage IIIA disease underwent surgery without further evaluation, while thoracotomy was considered futile in the PLUS trial if the patients had stage IIIA/N2 disease. Finally, the definition of futile thoracotomies (benign disease, exploratory thoracotomy, pathological stage IIIA [mediastinal node positive] or IIIB disease, or postoperative relapse or death within 12 months of randomization) in the PLUS study differed from the Australian trials definition of avoided thoracotomies (patients who were able to avoid thoracotomy as determined by the surgeon). Thus, the different designs of these studies might explain the contradicting results, demonstrating that the impact of PET on patient outcomes depends on the treatment decision-making process.

The recent POORT trial randomized patients with suspected NSCLC to traditional staging workup or up-front PET (34). PET did not decrease the number of staging tests required, and the agreement between the clinical and final stage were similar for both analyses. PET shortened the time to diagnosis by nine days, decreased the number of mediastinoscopies, and decreased the percentage of patients who needed one or more invasive tests for nodal staging. This is the first trial to compare conventional imaging to PET on clinically important aspects of clinical management.

^{18}FDG-PET has not been studied as extensively in staging patients with SCLC. PET appears to have good accuracy (83%-99%) in staging extensive versus limited stage disease (43-45), but further trials are needed to determine the role of PET in this setting.

Evaluation of new imaging techniques is important as “high costs, increasing demand for healthcare, increasing medical abilities and limited budgets have necessitated prioritisation” (99). PET scanning could improve the results of surgical therapy for early stage lung cancer by excluding patients from surgical resection who have evidence of metastatic disease beyond the scope of surgical resection and not evident by standard preoperative staging procedures. Similarly, the results for the management of locally advanced disease might also be expected to improve because of the addition of patients with minimal contralateral nodal disease that precluded surgery. Moreover, if PET imaging spares patients from the potential morbidity and risk of mortality from an unnecessary surgical procedure or chemo-radiotherapeutic intervention, it would not only have a significant impact on individual patients but would allow for more efficient and effective utilization of limited health care resources. Future research is needed to determine not only if PET should be integrated into the standard staging and diagnosis process of lung cancer but also how PET would be incorporated into the diagnostic algorithm. The Ontario Clinical Oncology Group (OCOG) is currently conducting two prospective randomized controlled trials on the use of

PET that have been approved by the Ontario Ministry of Health and Long-Term Care and a registry study of PET in patients with SPN. The randomized trials are examining the impact of PET on improving the management of patients with potentially surgically resectable NSCLC and the impact of PET on improving the management of patients with stage III NSCLC.

This systematic review only evaluated the role of ^{18}FDG-PET in lung cancer. There are many other radioisotopes and biological markers that may in the future find utility in lung cancer imaging.

ONGOING TRIALS

The National Cancer Institute (NCI) clinical trials database on the Internet (http://www.cancer.gov/search/clinical_trials/) was searched for ongoing trials.

Protocol IDs	Title and details of trial
NCT00136890 (ELPET Trial)	Tamber MS, Maziak DE, Darling GE, Evans WK, Ginsberg R, and the Cancer Care Ontario Provincial Lung Cancer Disease Site Group. The Impact of PET imaging in staging potentially surgically resectable NSCLC: a prospective multicentre randomized clinical trial. Funding: Ontario Ministry of Health and Canadian Institutes of Health Research Objective: To improve the management of patients with potentially surgically curable NSCLC by comparing PET to conventional staging procedures Projected accrual: 322 patients
NCT00136864 (PET START Trial)	Ung YC, Darling G, Ehrlich L, Evans WK, Leighl N, Levine M, MacRae R, Roberts R, Shulman H, Sun A, Wright J, and Yu E. The Impact PET Imaging in Stage III NSCLC : A Prospective Randomized Clinical Trial. Funding: Ontario Ministry of Health Objective: To improve the management of patients with stage III NSCLC by using PET to improve the identification of those patients who can receive potentially curative combined modality surgery Projected accrual: 400 patients
NA	Maziak DE, et al. The use of PET for solitary lung nodules. Funding: Ontario Ministry of Health Objective: To determine whether PET scanning alters the management of the SPN that cannot be diagnosed by FNA
SP-11-0035 NCT00123760	Study of 18F-Fluorodeoxyglucose (FluGlucoScan) in Patients with Cancer or Suspected Cancer Objective: To demonstrate the safety of 18F-FDG and to confirm the diagnostic effectiveness of 18F-FDG in subjects with known or suspected oncologic disease Projected accrual: 3000 patients
ACRIN-6668 NCT00083083 RTOG-0235	Diagnostic Study of Fluorodeoxyglucose F18 PET for Pre- and Post-treatment Assessment in Patients with Locally Advanced NSCLC Funding: National Cancer Institute Projected accrual: 250 patients
R05-0076 NCT00207298	Phase III open label study of 18F-FDG PET in Oncology Objective: To evaluate 18F-FDG PET as a decision making and diagnostic tool in the management of oncology patients in British Columbia Projected accrual: 5000 patients
ASOSOG Trial	The utility of PET in staging of patients with potentially operable NSCLC [a] Objective: To ascertain whether ^{18}FDG-PET scanning can detect lesions that would preclude pulmonary resection in patients found to be surgical candidates by standard imaging procedures Project accrual: 235 patients

NA: Not Applicable.

[a] Reported on the American College of Surgeons Oncology group Web site (www.acosog.org) and accessed on March 22, 2006

CONFLICT OF INTEREST

The members of the Lung DSG disclosed potential conflict of interest relating to this practice guideline. Two of the guideline lead authors are primary investigators for the OCOG PET-START and ELPET trials.

JOURNAL REFERENCE

The systematic review has been published in the peer-reviewed journal *Journal of the National Cancer Institute* (http://jnci.oxfordjournals.org/):

- Ung YC, Maziak DE, Vanderveen JA, Smith CA, Gulenchyn K, Lacchetti C, et al. ^{18}Fluorodeoxyglucose positron emission tomography in the diagnosis and staging of lung cancer: a systematic review. J Natl Cancer Inst. 2007;99(23):1753-67. doi: 10.1093/jnci/djm232.

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Appendix A. Glossary of terms.

False negative	A negative finding in a patient in whom the disease is present
False positive	A positive finding in a patient in whom the disease is absent
Negative predictive value (NPV)	The proportion of people with a negative test who are free of disease
Positive predictive value (PPV)	The proportion of people with a positive test who have the disease
Prevalence	The proportion of individuals with a disease in a given population at a specified time
Sensitivity	The proportion of people with disease who have a positive test result
Specificity	The proportion of people without disease who have a negative test result

Diagnostic Test Accuracy Measure Calculations

	Reference Standard	
Test Results	*Disease Present*	*Disease Absent*
Disease Present	True Positive (a)	False Positive (b)
Disease Absent	False Negative (c)	True Negative (d)

Sensitivity = a ***/*** (a + c)

Specificity = d ***/*** (b + d)

Positive predictive value = a ***/*** (a + b)

Negative predictive value = d ***/*** (c + d)

Prevalence = (a + c) ***/*** (a + b + c + d)

Source: Adapted from Gordon Guyatt G, Drummond Rennie D, editors. Users' guides to the medical literature, Chicago (IL): AMA Press; 2002.

Appendix B. Glossary of organizations.

ACCP	American College of Chest Physicians
AETMIS	Agence d'Évaluation des Technologies et des Modes Intervention en Santé
AHRQ	Agency for Healthcare Research and Quality
ASCO	American Society of Clinical Oncology
FNCLCC	French National Federation of Comprehensive Cancer Centres
HTBS	Health Technology Board for Scotland
ICES	Institute for Clinical Evaluative Sciences
MSAC	Medical Services Advisory Committee
NICE	National Institute for Clinical Excellence

Appendix C. Characteristics of evidence-based reports included in this guideline report.

Trial (ref.)	Report type	Search sources	Timeframe	Literature selection criteria
ICES, 2004 (46,47)	HTA/SR	MEDLINE Cochrane Library HealthStar CANCER Gray literature Review articles	1975-Sep 2004	English language Primary data Peer-reviewed N>12, human Focus on prospective trials
AHRQ, 2004 (94)	HTA/SR	MEDLINE	1990-Apr 2003	Similar to ICES except: Include only SCLC trials and include retrospective data Excluded feasibility trials (category 1) and abstract reports
HTBS 2002 (83)	HTA/SR	Based on an earlier HTA published in Danish (100) Update search in: MEDLINE & PreMEDLINE EMBASE Cochrane Library Current Controlled Trials register Gray literature (experts; Internet) Bibliographies	Original HTA, 1990-May 2001 Updated through Oct 2001	English language Used ^{18}FDG-PET Human Report change in pt outcomes or management
AÉTMIS 2001 (100)	HTA/SR	Based on two earlier technology reports including one HTA (97) with an update search in: PubMed The Cochrane Library Current Contents EMBASE and CANCERLIT Internet	Earlier HTA, 1966-2000 Updated from 1999-Feb 2001	English or French language N≥10, human Used ^{18}FDG-PET Provided sufficient information to determine data quality Consecutive eligible patients included Stated patient selection criteria Conducted independent blinded comparisons with a reference standard PET results did not influence the decision to use the reference standard Sufficient detail provided to allow for replication of the test
MSAC 2000 (97)	HTA/SR	The Cochrane Library MEDLINE Internet HTA agency sources and studies from MSAC applications and members	1966-Jan 2000	English language Primary, peer-reviewed data Studies not duplicated or superseded by a subsequent study with the same purpose from the same institution N≥10, human Used ^{18}FDG-PET Clear description of study design, methods, and patient entry criteria Consecutive eligible patients included Independent, blind comparison with a reference standard PET results did not influence decision to perform reference standard Sufficient detail provided to permit replication of test
NICE 2005 (93)	PG/SR	Cochrane Library MEDLINE EMBASE CINAHL PsycInfo	1966-Dec 2003	English language Excluded if true positives, true negative, false positives, and false negatives could not be calculated.

Trial (ref.)	Report type	Search sources	Timeframe	Literature selection criteria
		HEED (Jessica/Jean to clarify) ASCO conference proceedings Internet Bibliographies		
ASCO 2003 (101)	PG/SR	MEDLINE Cochrane Library Bibliographies ASCO conference proceedings	1996-Mar 2003	English Language Human
FNCLCC 2002 (102)	PG/SR	MEDLINE Cochrane Library CANCERLIT ASCO conference proceedings Experts Three earlier HTA reports (103) and German consensus conference (98,104)	1996-Nov 2001	English and French Language Human ^{18}FDG-PET
ACCP 2003 (98,104)	PG/SR	MEDLINE HealthStar Cochrane Library References	1991-July 2001	English Peer-reviewed n>20 patient group not included in a subsequent update of study histologic or cytologic confirmation of mediastinal nodes or extrathoracic sites in addition to the primary tumour availability of the raw data for calculations
Fischer, B et al 2001 (48)	SR/MA	MEDLINE EMBASE Cochrane Controlled Trials register References	1993-June 2000	English, German and French Original data assessing the diagnostic performance of dedicated ^{18}FDG-PET and gamma-camera ^{18}FDG-PET Adequate description of methods and results N > 10
Birim, O et al 2005 (50)	SR/MA	Medline References	NR-Jan 2003	English Primary NSCLC only N >15 Evaluated the correlation of ^{18}FDG-PET and mediastinal lymph node metastases Peer reviewed Availability of raw data for calculations Abstracts excluded
Gould, M. et al 2003 (63)	SR/MA	MEDLINE CANCERLIT EMBASE Current Contents BIOSIS References	1966-Mar 2003	Any language Excluded abstracts Availability of raw data for calculations Examined ^{18}FDG-PET imaging for mediastinal lymph node staging in patients with NSCLC N>10 (≥5 with lymph node metastases) Excluded review or case reports
Gould, M et al 2001 (49)	SR/MA	MEDLINE CANCERLIT Conference Proceedings References	1966-Sep 2000	Any language Examined ^{18}FDG-PET or ^{18}FDG with a gamma camera in coincidence mode for diagnosis of pulmonary nodules or

Trial (ref.)	Report type	Search sources	Timeframe	Literature selection criteria
		Experts Review		mass lesions N>10 (≥5 with malignant lesions) Adequate raw data for calculations

Abbreviations: ACCP – American College of Chest Physicians, AÉTMIS – Agence d'évaluation des technologies et des modes d'intervention en santé, AHRQ – Agency for Healthcare Research and Quality, ASCO – American Society of Clinical Oncology, FNCLCC – French National Federation of Comprehensive Cancer Centres, HTA – health technology assessment, HTBS – Health Technology Board for Scotland, ICES – Institute for Clinical Evaluative Sciences, MA – meta-analysis, MSAC – Medical Services Advisory Committee, NICE – National Institute for Clinical Excellence, N.R. – Not reported, PG – practice guideline, Pl – pleural, SCLC – small cell lung cancer, SPN – solitary pulmonary nodule, SR – systematic review.

Appendix D. Findings of evidence-based reports on the use of PET for staging and diagnosis.

Appraisal

Five reports used a meta-analytic method to construct summary receiver operating characteristic (SROC) curves (49,50,63,83,98). This method recognizes that sensitivity and specificity are a function of the threshold that defines an abnormal test and should not be considered independently (105). One report estimated the mean sensitivity and specificity independently (48) and did not recognize that sensitivity and specificity are related. Pooling mean specificities and sensitivities independently can lead to biased estimates of test performance, and generally underestimates the accuracy of the test (105).

Question 1: Diagnosis of Solitary Pulmonary Nodules (SPN)

Six evidence-based reports examined the effectiveness of PET in identifying malignant SPN and its appropriateness for the diagnosis of solitary pulmonary nodules. The MSAC (See Appendix B for a Glossary of Organizations) report cited three SPN studies (12,106,107) and concluded that "the potential value for PET in this indication is in the avoidance of biopsy in negative lesions. However, since FNAB is still a reasonably low-risk procedure, PET would mainly be of value for lesions considered to be unsuitable for FNAB [due to severe lung disease or location of the lesion] or for those with a very low post-test probability of malignancy" (97). The AÉTMIS endorsed the MSAC conclusion and stated that characterization of SPN by PET is considered a recognized use. The FNCLCC recommended that ^{18}FDG-PET be used in the diagnosis of malignancy in solitary pulmonary lesions larger than 1 cm and suspicious of malignancy on initial imaging (102). The NICE report evaluated 13 studies (13,77,108-118) and one meta-analysis (49), and concluded that PET has a good sensitivity and reasonable specificity for detection of malignant SPN and masses, but may be less reliable for nodules smaller than 1.5 cm in diameter. NICE recommended that "an ^{18}FDG-PET scan should be performed to investigate SPN in cases where a biopsy is not possible or has failed, depending on nodule size, position and CT characterisation" (93).

Question 2: Staging of Non-Small Cell Lung Cancer (NSCLC) at Initial Diagnosis

(a) Primary NSCLC Staging: Utility and Accuracy of PET

A number of evidence-based reports reviewed studies on the utility and accuracy of PET for the staging of primary NSCLC. The AÉTMIS report (100) reviewed the MSAC report (97), as well as four primary studies (24,26,119,120) and two meta-analyses (49,121). It concluded that "the clinical utility of PET in staging NSCLC is supported by new data demonstrating superior sensitivity and equal or superior specificity, which facilitates patient management in the immediate term." The MSAC report (97) cited 17 primary studies (23,25,33,51-55,59,61,64,65,84-86,90,122) and concluded that PET can change management in patients before planned surgery or radiotherapy, however there is not clear evidence that PET improves patient outcomes.

The FNCLCC report (102) recommended the use of ^{18}FDG-PET for staging and assessing locoregional involvement. The NICE report (93) evaluated four primary studies (31,123-125) and two meta-analyses (83,98). The report had the following recommendations: patients who are staged as surgical candidates by CT should have an ^{18}FDG-PET scan to look for intrathoracic lymph nodes and distant metastases. Surgical candidates who have limited N2/3 disease of uncertain pathological significance on CT should also have an ^{18}FDG-PET scan. Patients staged as N0/N1 and M0 by ^{18}FDG-PET and CT do not require cytological/histological confirmation of lymph nodes. Patients with a positive ^{18}FDG-PET scan for N2/N3 disease should have histological/cytological confirmation, except if there is definite distant

metastatic disease or a high probability that the N2/3 disease is metastatic. Patients with a negative ^{18}FDG-PET scan for N2/N3 disease do not require biopsy, even if the CT shows enlarged nodes.

(b) Primary NSCLC: Mediastinal Staging: Accuracy of PET

The ACCP report evaluated the results of 18 studies (20,21,25,26,51,52,54,56,58,59,62,64,65,70,73,74,77,82) on the accuracy of PET for mediastinal staging. The pooled sensitivity and specificity values for staging the mediastinum (N0/N1 vs.N2/N3) were 0.84 (95% CI, 0.78 to 0.89) and 0.89 (95% CI, 0.83 to 0.93), respectively (98). It concluded that "for patients who are candidates for surgery, a whole-body ^{18}FDG-PET scan is recommended to evaluate the mediastinum" and that "in patients with abnormal ^{18}FDG-PET scan findings, further evaluation of the mediastinum with sampling of the abnormal lymph nodes should be performed prior to surgical resection of the primary tumor" (104). The HTBS evaluated 33 studies on staging the mediastinum (20-26,29,51-56,58-62,64,65,70,73,76,77,79,82,85,86,122,126-128) and stated that most studies reported that ^{18}FDG-PET is more specific and more sensitive than CT; however, many of the studies were methodologically flawed (83). Pooled specificity in CT-positive patients was 0.76, (95% CI, 0.69-0.82) with a derived sensitivity of 0.92 (95% CI, 0.87-0.95). The pooled specificity in CT-negative patients was 0.90 (95% CI, 0.87-0.93) with a derived sensitivity of 0.86 (95% CI, 0.79-0.91). The authors concluded from these meta-analyses that PET appears to have substantial value in discriminating between nodes containing cancer from those that do not contain cancer, for both CT-positive and CT-negative patients; but that the pooled estimate of specificity for PET in CT-positive patients was much lower than in CT-negative patients. ASCO recommends ^{18}FDG-PET as a complement to CT scanning for staging locoregional disease, when there is no evidence of distant metastatic disease by CT (101). Data from nonrandomized studies is cited to show the superiority of ^{18}FDG-PET in comparison to CT scanning alone, and the ASCO guideline authors also note that the anatomic information provided by CT scanning is vital to treatment planning. In addition, they state that biopsy is still recommended for mediastinal lymph nodes that are positive on ^{18}FDG-PET scanning, and a negative ^{18}FDG-PET result should not preclude biopsy of radiographically enlarged mediastinal lymph nodes.

(c) Primary NSCLC: Extrathoracic Staging: Accuracy of PET

In addition to the HTBS report, extrathoracic staging was addressed in three other evidence-based reports. The MSAC report (97) concluded that PET is more accurate than conventional imaging in the detection of distant metastases, particularly when PET is supplementary. ASCO also recommended ^{18}FDG-PET for staging distant metastatic disease, when there is no evidence of distant metastatic disease by CT (101).

Question 3: Staging of Primary Small Cell Lung Cancer (SCLC)

The AHRQ report cited five studies that examined staging at initial diagnosis of SCLC (44,129-132). Three of the studies did not provide information on the comparison test or did not provide data to calculate test accuracy. The evidence was inconsistent for the studies that compared PET with CT. Due to the limited evidence, no recommendations were provided by the AHRQ.

Evidence-Based Series 7-20 Version 2: Section 3

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

18-Fluorodeoxyglucose Positron Emission Tomography in the Diagnosis and Staging of Lung Cancer: Guideline Development and External Review—Methods and Results

Y.C. Ung, D.E. Maziak, J.A. Vanderveen, C.A. Smith, K. Gulenchyn, W.K. Evans, and the Lung Cancer Disease Site Group

These guideline recommendations have been ENDORSED, which means that the recommendations are still current and relevant for decision making. Please see Section 4: Document Summary and Review Tool for a summary of updated evidence published between 2006 and 2012, and for details on how this Clinical Practice Guideline was ENDORSED.

Report Date: April 27, 2007

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative 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 PEBC supports a network of disease-specific panels, called Disease Site Groups (DSGs) and Guideline Development Groups (GDGs), mandated to develop the PEBC products. These panels are comprised of clinicians, other health care providers, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based practice guideline reports, using the methods of the Practice Guidelines Development Cycle (1,2). The PEBC reports consist of a comprehensive systematic review of the clinical evidence on a specific cancer care topic, an interpretation of and consensus agreement on that evidence by our DSGs and GDGs, the resulting clinical recommendations, and an external review by Ontario clinicians in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each clinical practice guideline report, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original clinical practice guideline information.

The Evidence-Based Series: A New Look to the PEBC Practice Guidelines

Each Evidence-Based Series is comprised of three sections.

- *Section 1: Clinical Practice Guideline*. This section contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the DSG or GDG involved and a formalized external review by Ontario practitioners.
- *Section 2: Systematic Review.* This section presents the comprehensive systematic review of the clinical and scientific research on the topic and the conclusions reached by the DSG or GDG.
- *Section 3: Guideline Development and External Review: Methods and Results.* This section summarizes the guideline development process and the results of the formal external review by Ontario practitioners of the draft version of the clinical practice guideline and systematic review.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES

Development and Internal Review

This evidence-based series was developed and approved by the members of the Lung DSG of CCO's PEBC. The series is a convenient and up-to-date source of the best available evidence on 18-fluorodeoxyglucose positron emission tomography in the diagnosis and staging of lung cancer, developed through systematic review, evidence synthesis, and input from practitioners in Ontario.

Report Approval Panel

Prior to the submission of this evidence-based series 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 Panel included the use and presentation of evidence contained in health technology assessments apart from primary studies and the need for distinguishing studies of imaging diagnostic accuracy from those investigating utility.

External Review by Ontario Clinicians

Following the review and discussion of Sections 1 and 2 of this evidence-based series and the review and approval of the report by the PEBC Report Approval Panel, the Lung Cancer DSG circulated the clinical practice guideline and systematic review to clinicians in Ontario for review and feedback. Box 1 summarizes the draft clinical recommendations and supporting evidence developed by the panel.

BOX 1:
DRAFT RECOMMENDATIONS (approved for external review Jan 30, 2007)

Target Population
Adult patients with lung cancer.

Recommendation

There is limited randomized controlled trial evidence related to the clinical questions. Based on the interpretation of available evidence and expert consensus opinion, the Lung Cancer Disease Site Group recommends the following:

- **Diagnosis of Solitary Pulmonary Nodules (SPN)**
  - Fine needle aspiration (FNA) biopsy is recommended as the first-line diagnostic approach in the workup of SPN. PET should be reserved for those situations in which a biopsy is inconclusive or contraindicated
    - PET appears to have a high sensitivity and specificity to differentiate benign from malignant lesions as small as 1 cm in size. Lesions less than 1 cm are difficult to categorize as they lack a sufficient mass of metabolically active cells. False-negative results can occur with low-grade malignant tumours due to their lower metabolic activity or with ground-glass opacities as may be seen in bronchoalveolar carcinomas.
  - The impact of PET on clinical management and patient outcomes cannot be defined from the current evidence

- **Staging of Primary NSCLC**
  - In the opinion of the Lung DSG, there is currently no definitive evidence to show that the addition of PET to conventional staging or the up-front use of PET in mediastinal and extrathoracic staging improves patient outcomes
  - Prospective studies have found that PET detects unexpected distant metastases in 15% of patients, which may lead to changes in patient management.
  - For potential surgical candidates, mediastinoscopy is recommended to verify that PET positive mediastinal lesions are due to cancer in view of the potential for false positive results. Mediastinoscopy is necessary to ensure that a patient is not denied potentially curative surgery. A solitary extrathoracic site should also be confirmed to be metastatic, if possible, in order that a patient not be denied the chance of curative therapy.

- **Diagnosis and Staging SCLC**
  - The lack of evidence on the use of PET in the diagnosis and staging of SCLC precludes definitive recommendations being made.

Methods

Feedback was obtained through a mailed survey of 208 practitioners in Ontario (including 34 medical oncologists, 22 radiation oncologists, 25 surgeons, and 82 nuclear medicine specialists). The survey 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 practice guideline. Written comments were invited. The survey was mailed out on January 30, 2007. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The survey was closed for responses at the end of March 2007. The Lung Cancer DSG reviewed the results of the survey.

Results

Seventy responses were received out of the 208 surveys sent (34% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. Of the practitioners who responded, 45 indicated that the report was relevant to their clinical practice, and they completed the survey. Key results of the practitioner feedback survey are summarized in Table 1.

Table 1. Responses to eight items on the practitioner feedback survey.

Item	Number (%)		
	Strongly agree or agree	**Neither agree nor disagree**	**Strongly disagree or disagree**
The rationale for developing a guideline, as stated in the "Introduction" section of the report, is clear.	39 (87%)	3 (7%)	3 (7%)
There is a need for a guideline on this topic.	39 (89%)	3 (7%)	2 (5%)
The literature search is relevant and complete.	37 (84%)	4 (9%)	3 (7%)
The results of the trials described in the report are interpreted according to my understanding of the data.	33 (73%)	7 (16%)	5 (11%)
The draft recommendations in the report are clear.	36 (80%)	4 (9%)	5 (11%)
I agree with the draft recommendations as stated.	29 (64%)	3 (7%)	13 (29%)
This report should be approved as a practice guideline.	25 (56%)	6 (13%)	14 (31%)
If this report were to become a practice guideline, how likely would you be to make use of it in your own practice?	**Very likely or likely**	**Unsure**	**Not at all likely or unlikely**
	10 (23%)	6 (14%)	28 (64%)

Given the relatively low approval rating for the report, an additional analysis by practitioner speciality was conducted. Approval of the report varied by speciality; 83% of respirologists and 75% of radiation oncologists agreed the report should be approved, while only 46% of nuclear medicine specialists, and 17% of surgeons agreed the report should be approved (Table 2).

Table 2. Approval of the report by speciality.

Item	Strongly agree or agree	Neither agree nor disagree	Strongly disagree or disagree
This report should be approved as a practice guideline.	%	%	%
Medical Oncologists (n=14)	*64*	*14*	*21*
Nuclear Medicine Specialists (n=13)	*46*	*23*	*31*
Respirologists (n=6)	*83*	*-*	*17*
Surgeons (n=6)	*17*	*-*	*83*
Radiation Oncologists (n=4)	*75*	*-*	*25*

Summary of Written Comments

22 respondents (49%) provided written comments. The main points contained in the written comments were:

(a) General comments on the recommendations

1. The recommendations are too restrictive and limited.
   ► Overall, the report understates the value of PET in NSCLC, and places too great an emphasis on short-term cost containment.

2. The recommendations should better correspond with practices and recommendations made in other jurisdictions (notably, the USA, but also other provinces such as Alberta, Manitoba, Quebec, and British Columbia).
   ► The adoption of PET is necessary to keep pace with technology in the rest of the world.

3. The guideline places too much focus on older technologies.

4. The emphasis on/language around patient 'outcomes' is problematic. PET alters patient management, this is where the emphasis should lie.

5. The discrepancy between the ICES and the Lung DSG recommendations for FDG-PET should be explained.

(b) Issues with recommending FNA as first line in diagnosing SPN.

6. FNA should not be the recommended first-line approach. PET should be performed first, and the FDG active areas subsequently biopsied.
   ► For many nodules it is common to proceed directly to resection (in the context of a practice with a very low benign rate).
   ► In terms of theoretic rationale: Why do a FNA biopsy first? If it is negative, then it needs PET for diagnosis. If it is positive, PET is still required for staging.

7. The recommendation for first-line FNA is open to manipulation in clinical settings or across centres.

(c) Issues with recommending CT follow-up every 3 months for 2 years for PET negative SPN.

8. It is not clear there is a reasonable basis for this recommendation.
   ► In general the recommendations for follow-up CT vary widely in the radiology literature, and there is unclear evidence to support the superiority of one particular approach.
   ► A recently published article provides greater clarity on the management of pulmonary nodules.

   MacMahon H, Austin JH, Gamsu G, Herold CJ, Jett JR, Naidich DP, et al. Guidelines for management of small pulmonary nodules detected on CT scans: a statement from the Fleischner Society. Radiology. 2005 Nov;237(2):395-400.

(d) Issues with the recommendation for PET in primary NSCLC staging:

9. PET should be used in the staging of NSCLC.
   ► There is sufficient data to warrant using PET in NSCLC staging.
   ► The tendency for PET to produce upstaging in 10-15% patients is non-negligible. PET should be regarded as appropriate in staging generally and in diagnosis for Stage III.

10. The role of PET in diagnosis should be more detailed. Specifically, it should emphasize the need to interpret the PET scan in conjunction with the CT scan.

(e) Issues in regard to the implications of the recommendations for the Ontario health system

11. The availability of PET is a limiting factor for the implementation of these recommendations. The system could be overwhelmed by if these recommendations were followed with current capacity.
    - ► More information should be provided in the report, specifically the numbers of patients who meet the recommendation criteria, and the distribution of patients in PET centres in the province.

12. PET scans should be available at each teaching hospital in the province.

Modifications/Actions

(a) General comments on the recommendations

1. The Lung DSG acknowledges that some practitioners may feel that its recommendations for ^{18}FDG-PET are restrictive. These recommendations are formulated in accordance with the best available clinical evidence, and reflect the findings of this evidence as well as the opinions of key clinical experts from across the province. The external review of this guideline and recommendations by a large sample of reviewers from across the province has highlighted some specific issues with the recommendations, and these are addressed below.

2. The Lung DSG establishes recommendations to improve lung cancer care in the province of Ontario. The DSG acknowledges that in some cases its recommendations differ from those established in other jurisdictions. As a general principle, the Lung DSG considers the recommendations of other bodies, specifically the evidence and rationale underlying those recommendations, and considers their applicability to the Ontario context. Ultimately, the recommendations of the Lung DSG are formulated with the concerns of patient care in Ontario being paramount. In response to suggestions that the Lung DSG recommendations need to "keep pace" with other jurisdictions, the DSG maintains that clinical guidance should be predicated on the best available evidence and clinical experience. The DSG strives to make the rationale for its recommendations transparent and explicit and seriously considers the feedback of practitioners from across the province in formulating its final recommendations. Bodies in other jurisdictions may have employed different processes, and placed values on different priorities in developing recommendations for ^{18}FDG-PET.

3. The DSG recognizes that PET is a rapidly evolving imaging technology, and, consequently, the available evidence is not always current with the state of the technology. This review of the evidence for ^{18}FDG-PET is comprehensive and up-to-date. For some recent advances, specifically hybrid PET/CT devices, the evidence is sparse. The DSG feels that the results are applicable to the current state of the technology in the province of Ontario and will update its report and recommendations as new evidence emerges.

4. The DSG acknowledged the term "outcome" can have various meanings in the context of diagnostic technologies. For the purposes of this systematic review, the term held dual meanings—the outcomes or findings of studies for specific measures (e.g., diagnostic specificity) and clinical outcomes of patients (e.g., survival). While the DSG was interested in ascertaining whether PET had an effect on tangible clinical outcomes such as survival, its recommendations were also predicated on other non-clinical indicators of potential superiority, including better accuracy for staging and diagnosis. In the view of the DSG, superiority in these areas would lead to changes in clinical management and provide information to inform guidance relating the use of PET in lung cancer. Revisions have been made throughout the report to better reflect this sentiment and to reinforce the fact that the recommendations of the DSG in regard to PET were not based solely on the presence or absence of a clear benefit in terms of hard clinical outcomes such as survival.

5. As stated in item #2 above, the Lung DSG does not generally justify its recommendations in relation to the recommendations of other bodies or organization (e.g., ICES), but does consider their suitability for

lung cancer practitioners in Ontario. On the issue of the correspondence between the Lung DSG recommendations and the recommendations of ICES, the DSG disagrees that its recommendations are in conflict with the ICES findings.

(b) Issues with recommending FNA as a first-line approach in diagnosing SPN

6. FNA is a safe procedure in the hands of experienced interventional radiologists and is successful in making a definitive diagnosis in approximately 85% of cases (3). Proceeding to thoracotomy without knowledge of whether a nodule is benign or malignant is not recommended by the Lung DSG as it exposes the patients to unjustifiable risk from a major surgical procedure while also contributing to excessive and unnecessary costs to the health care system. It is the expert opinion of the Lung DSG that PET be used to assess those nodules that cannot be diagnosed by FNA and cytological examination.

7. The Lung DSG is uncertain to what types of manipulation the reviewer is referring. He/she could be concerned that some practitioners will simply claim that the lung lesion is inaccessible for FNA or contraindicated in order to make use of PET. The Lung DSG feels it is reasonable for practitioners to undertake those procedures that will provide accurate information to enable appropriate clinical management, which almost always means obtaining a histologic or cytologic diagnosis preoperatively.

(c) Issues with recommending CT follow-up every three months for two years for PET negative SPN

8. Member of the Lung DSG felt that a time interval of three months for CT follow-up of an apparently benign (PET negative SPN) was reasonable and safe. It acknowledges that the evidentiary basis for recommending any time interval for follow-up is weak.

9. The evidence review did not identify high-quality evidence that demonstrated that PET in addition to conventional staging, or the up-front use of PET for mediastinal or extra thoracic staging, improves clinical management or any specific patient outcomes. In fact, some of the evidence is contradictory. That is why Ontario has elected to undertake evaluative studies for both early potentially operable lung cancer and locally advanced NSCLC.

   The evidentiary review does not support this individual's stated opinion. While a number of studies suggest that up-staging can occur, currently accruing studies should answer this question more conclusively.

(d) Issues with the recommendation for PET in primary NSCLC staging

10. We agree that a PET scan should be interpreted in conjunction with a CT scan and that functional abnormalities can be correlated with anatomic structures and abnormalities. This is referenced in the introduction to the guideline (page 2).

(e) Issues in regard to the implications of the recommendations for the Ontario health system

11. & 12. Access to PET scans in Ontario is limited to five machines in the province for four indications and five evaluative studies. Despite relatively few machines, there is currently excess capacity in the system to absorb incremental volumes as new indications become well established. All of the current machines are associated with Academic Health Science Centres. As new machines are required to meet the need, they are likely to be first introduced in other academic teaching Centres.

Conclusion

The final published report reflects the integration of feedback obtained through the external review process with final approval given by the Lung DSG and the Report Approval Panel of the PEBC. Updates of the report will be conducted as new evidence informing the questions of interest emerge.

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3. Gong Y, Sneige N, Guo M, Hicks ME, Moran CA. Transthoracic fine-needle aspiration vs concurrent core needle biopsy in diagnosis of intrathoracic lesions: a retrospective comparison of diagnostic accuracy. Am J Clin Pathol. 2006;125(3):438-44.

Evidence-based Series 7-20 version 2: Section 4

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

18-Fluorodeoxyglucose Positron Emission Tomography in the Diagnosis and Staging of Lung Cancer

Guideline Summary Review

Y. Ung, N. Ismaila, and the Lung Cancer Disease Site Group

Review Date: October 1, 2012

The 2007 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 the Program in Evidence-based Care (PEBC), Cancer Care Ontario, in 2007. In September 2011, 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 conducted an updated search of the literature. A clinical expert (YU) reviewed and interpreted the new eligible evidence and proposed the existing recommendations could be endorsed. The Lung Cancer Disease Site Group (DSG) endorsed the recommendations found in Section 1 on October 1, 2012.

DOCUMENT ASSESSMENT AND REVIEW RESULTS

Question Considered

What is the role of 18-Fluorodeoxyglucose (18FDG) Positron Emission Tomography (PET) in:

1. The diagnosis of solitary pulmonary nodules (SPN)?
2. The staging of primary non-small cell lung cancer (NSCLC) at initial diagnosis?
3. The staging of primary small cell lung cancer (SCLC)?

Literature Search and New Evidence

The new search (June 2006 to May 2012) yielded 13 references representing one guideline, two systematic reviews, three randomized controlled trials (RCTs) (one RCT had three publications), four prospective clinical trials, and one retrospective study evaluating the role of positron emission tomography in the diagnosis and staging of lung cancer. Ten references are potentially new studies, of which eight had full text publications and two were in abstract form. There was no ongoing study identified from clinicaltrials.gov. Brief results of these searches are shown in the Document Review Tool.

Impact on Guidelines and Its Recommendations

The new data supports existing recommendations. Hence, the Lung Cancer DSG ENDORSED the 2007 recommendations on the use of 18-Fluorodeoxyglucose Positron Emission Tomography in the diagnosis and staging of lung cancer.

Document Summary and Review Tool

Number and title of document under review	7-20: 18-Fluorodeoxyglucose Positron Emission Tomography in the Diagnosis and Staging of Lung Cancer
Current Report Date	April 27, 2007
Clinical Expert	Dr. Yee Ung
Research Coordinator	Nofisat Ismaila
Date Assessed	September, 2011
Approval Date and Review Outcome (once completed)	Oct 1, 2012 (ENDORSE)

Original Question(s):

What is the role of 18-Fluorodeoxyglucose (18FDG) Positron Emission Tomography (PET) in:

4. The diagnosis of solitary pulmonary nodules (SPN)?
5. The staging of primary non-small cell lung cancer (NSCLC) at initial diagnosis?
6. The staging of primary small cell lung cancer (SCLC)?

Target Population:

- Adult patients with lung cancer

Study Section Criteria:

Inclusion Criteria

- Evidence-based reports were selected for inclusion in this practice guideline if they reported outcomes of interest and were the following: Health technology assessments or practice guidelines based on a systematic review of evidence, systematic reviews, or meta-analyses that evaluated the use of PET in the staging and diagnosis of lung cancer Reports fully published in English after 1999.
- Articles published as full reports or as abstracts after the completion of the ICES review or examining the use of PET in staging SCLC were selected if they were the following: Randomized or single-arm prospective studies that focused on 18FDG-PET scanning in the staging and diagnosis of lung cancer compared to an appropriate reference standard.
- Reports including at least one of the following measures of effectiveness/benefit: PET specificity and sensitivity, accuracy measures of staging, changes in patient management, or improvements in patient outcomes (survival).

Exclusion Criteria

1. Studies with ≤ 35 subjects. All sample sizes were included for SCLC trials.
2. Letters and editorials reporting clinical trials were not eligible.
3. Articles published in a language other than English.

Search Details:

- June 2006 to May 2012 (Medline May wk 1 + Embase week 18)
- June 2006 to May 2012 (ASCO Annual Meeting)
- June 2006 to May 2012 (Clinicaltrials.gov)

Brief Summary/Discussion of New Evidence:

Of 479 total hits from Medline + Embase and 10 total hits from ASCO + 79 total hits from clinicaltrials.gov, 13 references representing 1 guideline, 2 systematic reviews, 3 RCTs (I RCT had 3 publications), 4 prospective clinical trials and 1 retrospective study were found evaluating the role of positron emission tomography in the diagnosis and staging of lung cancer. Ten references are potentially new studies, of which 8 had full text publications and 2 were in abstract form. There was no ongoing study identified from clinicaltrials.gov.

Systematic reviews					
Interventions	**Type of studies**	**Population**	**Outcomes**	**Brief results**	**References**
PET/FDG uptake	9 retrospective, cross-sectional studies	Newly diagnosed patients with stage 1 NSCLC who had	Survival and recurrence	• Study quality of included studies was suboptimal. • In all studies, higher degrees of FDG uptake in the primary tumor were associated with worse overall or disease free survival after 2 to 5 years of follow-up, but these differences were statistically	Nair et al 2009

		surgery (N=1166) Median age range, 60-71 yrs		significant in only five studies. • Across studies, the median overall or disease free survival was 70% for patients with higher FDG uptake compared with 88% for patients with lower FDG uptake. • In three studies that performed multivariable analysis, the adjusted hazard of death or recurrence was 1.9 to 8.6 times greater in patients with higher FDG uptake.	
PET/CT screening	3 studies	Patients with Ling cancer (N=207)	Diagnostic performance	• The quality assessment of included studies was viewed as acceptable (> =75% of maximal score in each trial). • The estimated pooled sensitivity and specificity with 95% confidence interval was 86% (76−93%) and 92% (85−96%) respectively in the prevalent screen.	Chien wet al 2011 (Abstract)
Randomized control trials					
Interventions	**Population**	**Follow-up**	**Outcomes**	**Brief results**	**References**
PET-CT Vs. Conventional staging	Patients with confirmed clinical stage I, II, or IIIA NSCLC being considered for surgery (N=329) Mean age, 67 yrs	Total, 3 years	Correct upstaging of cancer and diagnostic accuracy	• Disease was correctly upstaged in 23 of 167 PET-CT recipients and 11 of 162 conventional staging recipients (13.8% vs. 6.8%; difference, 7.0 percentage points [95% CI, 0.3 to 13.7 percentage points]) • Disease was incorrectly upstaged in 8 PET-CT recipients and 1 conventional staging recipient (4.8% vs. 0.6%; difference, 4.2 percentage points [CI, 0.5 to 8.6 percentage points]), and it was incorrectly understaged in 25 and 48 patients, respectively (14.9% vs. 29.6%; difference, 14.7 percentage points [CI, 5.7 to 23.4 percentage points]). • At 3 years, 52 patients who had PET-CT and 57 patients who had conventional staging had died, mostly from lung cancer • In a sub analysis of 169 patients randomized to PET-CT alone (Darling et al 2011), 149 patients had mediastinal nodal staging at mediastinoscopy alone (14), thoracotomy alone (64), or both (71). • The sensitivity of PET-CT was 70% (95% confidence interval [CI], 48–85%), and specificity was 94% (95% CI, 88–97%). • Of 22 patients with a PET-CT interpreted as positive for mediastinal nodes, 8 did not have tumor. • The positive predictive value and negative predictive value were 64% (95% CI, 43–80%) and 95% (95% CI, 90–98%), respectively. • 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.	Maziak et al 2009, Gulenchyn et al 2010 (abstract) & Darling et al 2011
PET/CT Vs. CT	Patients with stage 3 NSCLC, who were considered candidates for CMT (N=310) Mean age, NR	Median, 17 months	OS	• The 2-year OS of the PET/CT group was 47% compared with 39% for the CT arm (hazard ratio [HR] = 0.8; 95% confidence interval [CI]: 0.6 - 1.0). • A multivariable analysis (MVA) for OS indicated that in addition to the intervention, stage (3B vs 3A; HR = 1.4, 95% CI: 1.1 - 1.9) and ECOG status (HR = 1.7 per unit increase, 95% CI: 1.3 - 2.6) were predictive of OS. • In the 142 PET/CT patients with complete PET scans, a MVA showed that SUV (HR = 1.03 per unit increase, 95% CI: 1.01 - 1.05) and stage (3B vs 3A; HR = 1.9, 95% CI: 1.2 - 3.0) were strong predictors of OS.	Ung et al, 2011
PET Vs. Conventional staging	Patients with histologically confirmed lung cancer deemed suitable for non surgical radical treatment (N=30)	Median, 62 months	Degree of upstaging	• Twenty patients were randomized to PET, two of these patients (10%, CI 3–30%) were found to have stage IV NSCLC or extensive stage SCLC. • Median overall survival of the group was 17 months and the median disease free survival was 13 months	Pulvirenti et al. 2010 (Abstract)
PET-CT Vs.	Patients who were referred	Mean, 27 months	Frequency of futile	• After PET–CT, 38 patients were classified as having inoperable NSCLC, and after conventional staging,	Fischer et al, 2009

Conventional staging	for preoperative staging of NSCLC (N=189) Mean age, 64 yrs		thoracotomies and diagnostic accuracy	18 patients were classified thus. • Sixty patients in the PET–CT group and 73 in the conventional-staging group underwent thoracotomy (P = 0.004). Among these thoracotomies, 21 in the PET–CT group and 38 in the conventional-staging group were futile (P = 0.05). • The number of justified thoracotomies and survival were similar in the two groups. • For the PET–CT group, the diagnostic accuracy and sensitivity were 79% (95% CI, 69 to 86) and 64% (95% CI, 52 to 75), respectively. • For the conventional-staging group, the accuracy and sensitivity were 60% (95% CI, 50 to 70) and 32% (95% CI, 21 to 45), respectively	
Prospective clinical trials					
PET and CT scan	Patients with histologically confirmed NSCLC who had resectable disease, including stages IB, II, IIIA, or IIIB (N=89)	NR	Survival	• Patients with a partial or complete response based on Response Evaluation Criteria in Solid Tumors categories (n =33) had a better OS than those with stable or progressive disease (n=56; median survival time, not reached v 36 months, respectively; P=.04). • Of all patients, those with response in the highest quartile had 1- and 2-year survival rates of 100% and 81%, respectively, compared with 77% and 61%, respectively, among patients in the lowest quartile. • However, on the basis of visual analysis of PET scan, patients with a metabolic response (n = 28) had no significant difference in survival compared with patients without response (n=61; median survival time, 35.6 months v not reached, respectively; P=.94). • On the basis of a semiquantitative analysis of PET scan, using at least 30% reduction in tumor metabolism as a response (n = 59), no significant difference in survival among those with or without response was found.	Tanvetyanon et al, 2008
FDG-PET (Dual time point imaging)	Patients referred for characterization of lung lesions (N=83) Mean age, 69 yrs	NA	Improvement in sensitivity	• Sixty one lesions (74%) were non-small cell lung cancer, and 10 (12%) were other primary tumors or metastases. • Twelve lesions (14%) were benign. T:B ratios were significantly higher for early versus late scans (+ 5.1 ± 4.9 versus + 8.2 ± 8.7,p=0.01, n=71) for malignancies but not for benign lesions (+ 3.1 ± 3.4 versus + 2.6 ± 2.2, n=12). • The percent change of T:B ratios was higher for malignant than benign lesions (+ 48.3 ± 40.2% versus + 7.2 ± 22.8 %, 0.0009). • No malignant lesion of any type demonstrated a time-decrease in FDG T:B ratios. • The accuracy and sensitivity of lesion characterization were significantly higher for late scans than early scans for dichotomous visual readings. • Quantitative analysis was found to provide significantly higher sensitivity and accuracy than visual analysis for lesion characterization, with no significant difference in test specificity	Nunez et al, 2007
PET/CT Vs. Standard staging	Patients with histological or cytological proven SCLC (N=29) Mean age, 63 yrs	Median, 16.8 months	Staging	• PET/CT caused change of stage in 5/29 (17%). • Excluding patients with unconfirmed findings or pleural effusion, the sensitivity for accurate staging of patients with extensive disease was the following: for standard staging 79%, PET 93% and PET/CT 93%. Specificity was 100%, 83% and 100%, respectively. • McNemar's test was applied to test whether the possibility of a positive diagnosis (ED) was different between the three modalities; this difference was not significant	Fischer et al, 2007
FDG-PET VS CWU	Patients with histologically proven stage III NSCLC	Median, 35.3 months	OS & DFS	• Overall survival and metastasis-free survival were significantly longer in patients of group I stratified by FDG-PET than in group II (p=0.006 and 0.02 respectively).	Eschmann et al, 2007

	undergoing NARCT (N=188)			• Another significant factor for survival was complete tumor resection (p=0.02). • Gender, histological tumor type, tumor grade and UICC stage had no significant influence	
Retrospective study					
PET Vs. No PET	Patients who had undergone potentially curative resections for NSCLC (N = 1999)	NA	Survival	• Propensity matching revealed that the introduction of routine PET scanning did not result in improved survival in the short or long term, for patients undergoing resections for stage Ia (N = 271 in each matched group), p = 0.74, stage Ib (N = 321 in each matched group), p = 0.43 and stage II (N = 164 in each matched group), p = 0.06. • PET has however resulted in a significant increased survival for patients undergoing resections for stage III primary lung cancer (N = 68 in each matched group), p = 0.03	Fontaine et al, 2011

Acronyms: 18F-fluorodeoxyglucose positron emission tomography (FDG-PET); Tumor-to-background (T:B); Non-Small Cell Lung Cancer (NSCLC); Not Applicable (NA); Not Reported (NR); Overall survival (OS); Small-cell lung cancer (SCLC); Extensive Disease (ED); Conventional Workup (CWU); Neo-Adjuvant Radio-Chemotherapy (NARCT)

1. Does any of the newly identified evidence, on initial review, contradict the current recommendations, such that the current recommendations may cause harm or lead to unnecessary or improper treatment if followed? Answer Yes or No, and explain if necessary, citing newly identified references:	1. NO If Yes, the document will be immediately removed from the PEBC website, and a note as to its status put in its place. G**o to 2**.
2. On initial review, a. Does the newly identified evidence support the existing recommendations? b. Do the current recommendations cover all relevant subjects addressed by the evidence, such that no new recommendations are necessary? Answer Yes or No to each, and explain if necessary:	2. Yes to both questions. However, there might need for a rewrite with next update as the OCOG studies and the Fisher study are important and just attaching these tables to the original guideline doesn't do the studies justice. If both are Yes, the document can be **ENDORSED**. If either is No, **go to 3**.
3. Is there a good reason (e.g., new stronger evidence will be published soon, changes to current recommendations are trivial or address very limited situations) to postpone updating the guideline? Answer Yes or No, and explain if necessary:	3. Not Applicable If Yes, a final decision can be **DELAYED** up to one year. If No, **go to 4.**
4. Do the PEBC and the DSG/GDG responsible for this document have the resources available to write a full update of this document within the next year?	4. Not Applicable If Yes, the document needs an **UPDATE**. It can be listed on the website as IN REVIEW for one year. If a full update is not started within the year, it will be automatically **ARCHIVED**. If NO, go to 5.

5. If Q2, Q3, and Q4 were all answered NO, this document should be **ARCHIVED** with no further action.

Review Outcome	**ENDORSE**
DSG/GDG Approval Date	**Oct 1, 2012**
DSG/GDG Commentary	The established role of PET in staging the mediastinum still causes some confusion and it would help to clearly state in the summary the measure of positive and negative PET scans in as simple and explicit form as possible i.e the number of validated true positives per 100 +ve PETS and the number of validated true negatives per 100 –ve PETS

New References Identified (alphabetic order):

1. Chien CR, Liang JA, Wang HN, Lin CC, Kao CH. Diagnostic performance of selective positron emission tomography for lung cancer computed tomography screening: A meta-analysis. European Journal of Cancer. 2011;47:S211.
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Search strategy:

Embase

1. exp meta analysis/ or exp systematic review/
2. (meta analy$ or metaanaly$).tw.
3. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes?s or quantitative overview).tw.
4. (systematic adj (review$ or overview?)).tw.
5. exp review/ or review.pt.
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7. (study adj selection).ab.
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11. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
12. exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/
13. randomization/ or single blind procedure/ or double blind procedure/
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16. (phase II or phase 2).tw. or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/
17. 16 and random$.tw.
18. (clinic$ adj trial$1).tw.
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21. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
22. (allocated adj2 random).tw.
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25. practice guideline?.tw.
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28. 9 or 10 or 11 or 15 or 17 or 23 or 27
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Medline

1. meta-Analysis as topic.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
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31. practice guideline.pt.
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45. 41 or 44
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47. (PET? or tomography? or emission computed? or fluorodeoxyglucose F18?).tw.
48. 46 or 47
49. 45 and 48
50. 40 and 49
51. (200620: or 2007: or 2008: or 2009: or 2010: or 2011: or "2012").ed.
52. 50 and 51

ASCO Annual Meeting - searched http://www.ascopubs.org/search with keywords: Positron Emission Tomography AND (Lung cancer)
Clinicaltrials.gov – searched http://clinicaltrials.gov/ct2/home with keywords: Positron Emission Tomography AND (Lung cancer)

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3. **DELAY** – A Delay means that there is reason to believe new, important evidence will be released within the next year that should be considered before taking further action.

4. **UPDATE –** An Update means that the DSG/GDG recognizes that there is new evidence that 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 DSG/GDG will rewrite the guideline at the earliest opportunity to reflect this new evidence. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making.