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Imaging for the Pretreatment Staging of Small Cell Lung Cancer

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Imaging for the Pretreatment Staging of Small Cell Lung Cancer

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None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information (i.e., in the context of available resources and circumstances presented by individual patients).

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site www.effectivehealthcare.ahrq.gov to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input.

We welcome comments on this systematic review. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

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Acknowledgments

Key Informants

In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

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In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

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Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report does not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential non-financial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential non-financial conflicts of interest identified.

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Imaging for the Pretreatment Staging of Small Cell Lung Cancer

Structured Abstract

Objectives. For small cell lung cancer (SCLC), several imaging modalities can be used to determine cancer staging, which is important to ensure optimal management. Our aim was to synthesize the literature on whether some imaging modalities are better than others for the pretreatment staging of small cell lung cancer. We searched for evidence on comparative accuracy (sensitivity, specificity) as well as subsequent clinical outcomes (choice of treatment, survival, and quality of life).

Data sources. We searched EMBASE, MEDLINE, PubMed, and the Cochrane Library from 2000 through June 15, 2015, for full-length articles on the use of multidetector computed tomography (MDCT), positron emission tomography/computed tomography (PET/CT), magnetic resonance imaging (MRI), combined PET/MRI, endobronchial ultrasound (EBUS), endoscopic ultrasound with fine-needle aspiration (EUS-FNA), and bone scintigraphy in the pretreatment staging of small cell lung cancer.

Review methods. We included studies of pertinent imaging tests on SCLC patients before treatment that reported one or more of the outcomes of interest (studies did not have to directly compare two or more imaging modalities). We extracted data from the included studies and constructed evidence tables. Comparative outcomes of interest included test concordance, staging accuracy (sensitivity and specificity), choice of treatment, timeliness of treatment, tumor response, harms due to overtreatment or undertreatment, survival, and quality of life. For each pair of tests and each assessed aspect (e.g., determination of metastases), we determined whether the evidence was sufficient to permit a conclusion of a difference, a conclusion of similar accuracy, or neither (i.e., insufficient). We rated the risk of bias of individual studies using an internal validity instrument and graded the overall strength of evidence of conclusions using Evidence-Based Practice Center guidance.

Results. The searches identified 2,880 citations; after screening against the inclusion criteria, we included seven primary studies that enrolled a total of 408 patients. Six of the seven studies were deemed moderate risk of bias (principally due to failure to report on patient selection, reader blinding to results of comparator tests, and possible spectrum bias), and one was deemed high risk of bias (due to failure to blind readers to results of comparator tests and presence of spectrum bias). One of the studies reported test concordance, three studies reported the comparative accuracy of two or more testing strategies (one of which had also reported test concordance), and four studies reported the accuracy of a single imaging modality. Staging determinations included limited versus extensive disease, osseous (bone or bone marrow) metastases, lymph node involvement, liver metastases, spleen metastases, adrenal metastases, brain metastases, and any distant metastases. The most frequently reported imaging tests were MDCT, [^{18}F]-fluorodeoxyglucose (FDG) PET/CT, and bone scintigraphy. No studies were included for any other outcomes or for associations with patient comorbidity, body habitus, or tumor characteristics.

Conclusions. Evidence is sparse on imaging modalities in the pretreatment staging of small cell lung cancer. Nevertheless, we drew three conclusions about comparative accuracy: (1) FDG PET/CT is more sensitive than MDCT for detecting osseous metastases; (2) FDG PET/CT is more sensitive than bone scintigraphy for detecting osseous metastases; (3) Standard staging plus FDG PET/CT is more sensitive than standard staging alone for detecting any distant metastases. We assigned a grade of low to the strength of evidence for these conclusions, mostly due to risk of bias and a small number of studies. Research gaps include the dearth of evidence on several tests of interest (particularly MRI, EBUS, EUS, and PET/MRI), a lack of study designs to compare tests on patient-oriented outcomes such as survival, and a lack of data on whether comparative accuracy or effectiveness are associated with patient factors.

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Executive Summary

Background

Lung cancer is the leading cause of cancer-related mortality, estimated to account for about 27 percent of cancer deaths in the United States in 2015.[1] Small cell lung cancer (SCLC) is an aggressive subset of lung cancer characterized by rapid doubling time, high growth fraction, and early development of metastatic disease. This histologic subset of lung cancer is primarily seen in smokers[2] and comprises approximately 15 percent of all lung cancers.[3] Despite advances in diagnosis, treatment, and management of lung cancer, the 5-year survival rate for SCLC remains dismal at about 6 percent.[1]

Staging involves determining the extent of disease and guides the choice of treatment. SCLC is often staged using the Veterans Administration Lung Study Group (VALSG) system,[4] which classifies SCLC as either "limited stage" or "extensive stage" disease with the following definitions:

- Limited stage disease (LD): Cancer is confined to one hemithorax and may be present in the regional lymph nodes or in ipsilateral supraclavicular nodes, all of which can be encompassed in a safe radiotherapy field.
- Extensive stage disease (ED): Cancer that cannot be classified as LD, such as when contralateral hilar or supraclavicular nodes, malignant pericardial or pleural effusions, or distant metastatic disease are present.

The revised AJCC TNM system[5] can also be used; however, it is used less commonly for SCLC than in non-small cell lung cancer. Lung cancers are classified based on the size of the main tumor, whether it has locally invaded other organs/tissues, spread to lymph nodes, and metastasized to other parts of the body. This information is used to assign a stage between I and IV. A higher stage represents more extensive spread.

The National Cancer Institute reported that from 1975–2008, about 70 percent of SCLC cases presented with extensive stage disease, another 21 percent had regional spread such as mediastinal nodal involvement, and only 5 percent were localized (the other 4 percent were unstaged).[6] The most common sites of metastases for SCLC are the liver, adrenal glands, bone, bone marrow, and brain.[7]

Patients with SCLC who have extensive disease at diagnosis have an estimated 5-year survival of only 1 percent.[8] Chemotherapy has been shown to extend overall survival and improve quality of life. Patients with LD are treated more aggressively with concurrent chemotherapy and radiation with curative intent. After completion of first-line therapy, even without evidence of metastases in the brain, prophylactic cranial irradiation has been demonstrated to prolong survival in both LD and ED.

"Standard" staging of SCLC is not a precisely defined term, but may involve numerous investigations including history, physical exam, chest x-ray, chest CT, bone scan, bone marrow aspiration, and/or MRI or CT of the brain. Accurate staging of patients is essential to select the optimal treatment plan that will maximize a patient's chances of survival. On the one hand, overstaging of SCLC risks denies the patient potentially life-saving treatment, while understaging risks subjects the patient to the unnecessary risk of complications from more aggressive treatment. Given the rapid progression of SCLC, timely diagnosis and staging is important; performing potentially unnecessary tests during the diagnostic and staging process could delay treatment initiation, compromising treatment efficacy.

Multidetector computed tomography (MDCT) of the chest is typically the first test performed to diagnose lung cancer. For staging SCLC, additional MDCT images are taken of the abdomen, pelvis, or head to detect distant metastases. MDCT has general strengths of widespread availability, high spatial resolution, and high speed and is particularly useful for evaluating the lungs, airways, bowel, and cortical bone. However, because it is a structural imaging modality, it may not detect early metastatic disease involving sites such as the bone marrow or lymph nodes and is not always able to characterize lesions as benign or malignant based on their morphologic properties. In addition, some patients cannot receive iodinated contrast material due to allergy or renal insufficiency, limiting evaluation for presence of hilar lymphadenopathy, vascular abnormalities, and lesion characterization; for these patients, the sensitivity of CT may be lower.

Positron emission tomography (PET) is an imaging modality that localizes the uptake of a positron-emitting radioisotope in the body. [^{18}F]-fluorodeoxyglucose (FDG) is the most commonly used PET radiotracer. Because FDG-PET identifies anatomic sites that harbor metabolically active malignant areas, FDG-PET helps distinguish malignant tumors from benign nodules or masses. FDG-PET can also uniquely detect metabolically active metastases that have not caused anatomic changes. Because PET images lack anatomic detail, combined PET/CT scanners have been developed so the molecular information from PET can be anatomically localized with CT. As of 2014, PET without a concurrent CT is no longer the state of the art. Even though they are widely used, PET/CT scans are not perfect, and are associated with false negative and false positive results. False negative scans usually result from non-metabolically active sites of tumor or from suboptimal quality studies. False positives scans can occur due to sites of metabolically active infection or inflammation.

Magnetic resonance imaging (MRI) is a structural and functional imaging technique that measures the biophysical properties of tissue. MRI has widespread availability, high spatial resolution, and high soft-tissue contrast resolution; this imaging modality is particularly useful for detection and characterization of lesions within tissues even when subcentimeter in size, as well as for evaluation of the internal architecture of organs/tissues such as the brain, spinal cord, breasts, bone marrow, muscles, tendons, ligaments, cartilage, and other solid organs. Also, functional imaging capabilities such as diffusion-weighted imaging and magnetic resonance spectroscopy may be used to improve diagnostic accuracy. MRI examinations take longer to perform and generally cost more than MDCT, patients with certain types of implanted electronic or metallic devices cannot undergo MRI. Newer devices, including some pacemakers, are increasingly MRI-compatible. Some patients with claustrophobia may have difficulty tolerating an MRI examination. Combined PET and MRI scanners are a recent technical development; they promise the sensitivity of PET combined with the anatomic detail of MRI.

Endobronchial ultrasound (EBUS) is a bronchoscopic technique utilizing ultrasonography to visualize structures within and adjacent to the airway wall, whereas endoscopic ultrasound (EUS) is an endoscopic technique that uses ultrasonography to visualize structures within and adjacent to the esophageal wall. These techniques are minimally invasive and can be performed on an outpatient basis. EBUS-guided transbronchial needle aspiration (EBUS-TBNA) is generally performed if suspected lymph nodes are in the anterior or superior mediastinum and appear to be accessible based on prior cross-sectional imaging, whereas EUS-guided fine needle aspiration (EUS-FNA) may initially be used for nodes that are paraesophageal or subaortic in location or located in the posterior or inferior mediastinum. EBUS-TBNA can also be used to sample hilar lymph nodes. A typical EBUS procedure for lung cancer staging involves

standardized sampling of multiple nodal stations that have >5 mm lymph nodes that are detectable and accessible via the EBUS scope.

Bone scintigraphy is a planar molecular imaging technique with widespread availability, high contrast resolution, and relatively low cost compared with FDG-PET/CT. However, false-negative results can occur since bone scintigraphy only indirectly detects the effects of metastatic lesions upon bone turnover. False-positive results can also occur due to visualization of increased bone turnover caused by non-neoplastic etiologies such as fractures and osteomyelitis.

Regarding patient subgroups, performance of various imaging modalities may be affected by comorbidities such renal insufficiency, which potentially limits use of contrast for MDCT or MRI. Generally, body habitus may limit the diagnostic quality and accuracy for any imaging modality. Many scanners are unable to safely accommodate patients above a particular weight or girth. Tumor characteristics may be associated with comparative accuracy and/or effectiveness.

A 2013 guideline from the American College of Chest Physicians recommended that patients with either proven or suspected SCLC undergo CT of the chest and abdomen or CT of the chest extending through the liver and adrenal glands, as well as MRI of the brain and bone scintigraphy.[9] In patients with limited stage SCLC, PET was also suggested. In 2014, the American College of Radiology (ACR) appropriateness criteria review gave the highest rating of "usually appropriate" (with regard to staging SCLC) to the following specific modalities: CT of the chest and abdomen with contrast, MRI of the head with and without contrast, and FDG-PET/CT from skull base to mid-thigh.[10] Bone scintigraphy was rated as "may be appropriate" and considered unnecessary if PET/CT had been performed.

Scope and Key Questions

The scope of this report is to compare imaging modalities in the context of pretreatment staging for SCLC. The Key Questions (KQs) we addressed were as follows:

KQ 1: What are the test concordance and comparative accuracy of imaging tests (MDCT, PET/CT, MRI, PET/MRI, EBUS, EUS, bone scintigraphy) for the pretreatment staging of SCLC?
   a. Test concordance
   b. Sensitivity
   c. Specificity
   d. Positive predictive value
   e. Negative predictive value
   f. Positive likelihood ratio
   g. Negative likelihood ratio

KQ 2: When used for the pretreatment staging of SCLC, what is the comparative effectiveness of imaging tests (MDCT, PET/CT, MRI, PET/MRI, EBUS, EUS, bone scintigraphy) on later outcomes?
   a. Choice of treatment (e.g., surgery, chemotherapy, radiation)
   b. Timeliness of treatment

c. Tumor response

d. Harms due to overtreatment or undertreatment

e. Survival

f. Quality of life

KQ 3. To what extent are the following factors associated with the comparative accuracy or effectiveness of imaging tests (MDCT, PET/CT, MRI, PET/MRI, EBUS, EUS, bone scintigraphy) when used for the pretreatment staging of SCLC?

a. Comorbidities

b. Body habitus

c. Tumor characteristics

Note that two terms above, "accuracy" and "effectiveness", are used as overarching labels for different sets of outcomes. The "accuracy" outcomes (which are part of KQ 1), involve an accurate determination of the patient's stage, whereas the "effectiveness" outcomes (which are listed for KQ 2), involve the post-staging outcomes such as clinical management and response to treatment. For comparing the *effectiveness* of two imaging modalities, we required that studies make direct comparisons between two or more modalities, whereas for *accuracy*, we included studies that only used one imaging modality. Our full list of inclusion criteria appear in the section below called "Study Selection".

Methods

Literature Search

With general guidance from the review team, literature searches were performed by medical librarians within the Evidence-Based Practice Center (EPC) Information Center; searches followed established systematic review methods. We searched the following databases using controlled vocabulary and text words: EMBASE, MEDLINE, PubMed, and the Cochrane Library. The complete search strategy is available in the full report. Each article was screened by at least two people using the database Distiller SR (Evidence Partners, Ottawa, Canada). The last search date was June 15, 2015.

For our gray literature searches, we searched for relevant devices on the FDA Web site (i.e., EUS, EBUS, bronchoscopes, CT scanning systems, bone scintigraphy, bone scan). We also browsed ECRI Institute publications including Healthcare Product Comparison Systems reports, Health Technology Forecast and Hotline reports, and ECRI Institute Sourcebase. On the Internet, we searched clinicaltrials.gov, professional organization Web sites for relevant disease information including prevalence statistics, standards and guidelines, and manufacturer information for relevant diagnostic devices. Professional organization Web sites were identified via Google and National Guideline Clearinghouse (NGC) searches for relevant SCLC screening/diagnostic/staging guidelines. These Web sites were browsed for disease-specific information: National Comprehensive Cancer Network (NCCN), Society of Nuclear Medicine, and the American College of Radiology.

Study Selection

Our inclusion criteria are listed below in five categories: Publication criteria, study design criteria, patient criteria, test criteria, and data criteria.

Publication Criteria

a. Full-length articles: The article must have been published as a full-length, peer-reviewed study.
b. Redundancy: To avoid double-counting patients, in instances in which several reports of the same or overlapping groups of patients were available, only outcome data based on the larger number of patients were included. However, we included data from publications with lower numbers of patients when either (1) a publication with lower patient enrollment reported an included outcome that was not reported by other publications of that study, or (2) a publication with lower patient enrollment reported longer followup data for an outcome.
c. Publication date: We included studies published since January 1, 2000. Technical progress in all the imaging modalities under consideration means that older studies are likely to underestimate the diagnostic performance of these modalities.
d. We initially had excluded studies not published in English, but after identifying a relatively low number of qualifying studies, we removed that requirement.

Study Design Criteria

a. The study must have provided data on at least one test of interest. Ideally, studies would directly compare two or more tests (or test strategies). The comparison may also be addressed indirectly by comparing one set of studies of one imaging test and another set of studies of another imaging test (e.g., a set of studies reporting the accuracy of MRI at mediastinal node staging of SCLC compared with a separate set of studies reporting the accuracy of CT at mediastinal node staging of SCLC). This is an indirect comparison of modalities, so conclusions based on it are weaker.
b. For comparisons of variants of a given modality, and studies of patient factors or tumor characteristics for KQ3, the comparison must have been planned in advance.
c. For comparative accuracy (KQ1), the study must have compared both tests to a common reference standard. The reference standard must not have been defined by either imaging test being assessed. We set no requirements on what the reference standard must be (e.g., biopsy, clinical followup).
d. For comparative effectiveness (KQ2), some patients must have received one of the imaging tests (or test strategies), and a separate group of patients must have received a different imaging test (or test strategy). This design permits a comparison of how the choice of test (or test strategy) might influence choice of treatment, timeliness of treatment, harms due to over/undertreatment, survival, and/or quality of life.
e. For the influence of patient factors or tumor characteristics (KQ3), the study must have reported comparative accuracy data stratified by patient/tumor factor or comparative-effectiveness data stratified by patient/tumor factor.

Patient Criteria

   a. The study reported data specifically on patients undergoing staging for SCLC, or if the data were combined with other types of patients, at least 85 percent of the patients in the reported data were undergoing staging for SCLC.
   b. Adults. At least 85 percent of patients must have been aged 18 years or older or data must have been reported separately for those aged 18 years or older.
   c. Studies of the staging of *primary* SCLC were included. Studies for the staging of *recurrent* SCLC were excluded.
   d. Data on imaging tests performed after any form of treatment (e.g., chemotherapy) were excluded, but pretreatment imaging data were considered.

Test Criteria

   a. Type of test. Only studies of the imaging tests of interest were included (listed in the KQs above). Studies of CT that did not explicitly specify whether CT or MDCT was used were assumed to be MDCT. Given our publication date of 2000 and later, we believe it is safe to assume that CT performed in such studies was MDCT.
   b. PET/CT must have been based on a dedicated PET/CT machine. We excluded studies in which PET and CT were acquired separately and later fused for the following reasons. First, methods for image fusion can vary widely. Since accurate staging relies on accurate localization of the of area of increased FDG uptake, inclusion of less-precise means of combining PET and CT images would underestimate the performance of PET/CT. Second, image fusion is no longer the state of the art in PET/CT, and since this report is intended to guide use of imaging technologies in the future, it should reflect the technology presently in use.

Data Criteria

   a. The study must have reported data pertaining to one of the outcomes of interest (see the KQs).
      o For test concordance (part of KQ1), this means reporting the number of patients for whom the two tests provided the same or different results.
      o For comparative accuracy (part of KQ1), this means reporting enough information to calculate both sensitivity and specificity, along with their corresponding confidence intervals (CIs).
      o For comparative choice of treatment (part of KQ2), this means reporting the percentage of patients who received a specific treatment choice for one test or test strategy compared with another test or test strategy.
      o For comparative timeliness of treatment (part of KQ2), this means reporting the duration of time elapsed before the initiation of treatment for one test or test strategy compared with another test or test strategy.
      o For comparative tumor response (part of KQ2), this means reporting the percentage of patients whose tumor responded to treatment for one test or test strategy compared with another test or test strategy.
      o For comparative harms of over- or undertreatment (part of KQ2), this means reporting the percentage of patients who were over- or undertreated (based on authors' judgment) for one test/test strategy compared with another test or test strategy.

- o For comparative survival (part of KQ2), this means either reporting median survival after each imaging test or test strategy, mortality rates at a given time point, or other patient survival such as a hazard ratio.
- o For quality of life (part of KQ2), this means reporting data on a previously tested quality-of-life instrument (such as the Short Form-36) separately for each imaging test or test strategy.
- o For patient factors or tumor characteristics (KQ3), this means reporting data on whether such factors are associated with either comparative accuracy and/or comparative effectiveness.

b. Regarding the minimum patient enrollment, we required data on at least 10 patients per imaging test or test strategy.

c. For all KQs, the reported data must have included at least 50 percent of the patients who had initially enrolled in the study.

Data Extraction and Management

Abstraction forms were constructed in Microsoft Excel, and the data were abstracted into these forms. Elements abstracted include general study characteristics (e.g., country, setting, study design, enrolled N, funding source), patient characteristics (e.g., enrollment criteria, age, sex, final diagnoses including tumor characteristics), details of the imaging methodology (e.g., radiotracer, timing of test, readers, elapsed time between imaging tests, what reference standard was used), risk of bias items, and outcome data. Study methods and outcome data were abstracted by experienced research analysts, in duplicate to ensure accuracy, with discrepancies resolved by consensus. Multiple publications of the same study were grouped as a single study. Duplicates were identified by examination of author names, study centers, patient enrollment dates, and imaging technologies.

Risk-of-Bias Evaluation

For studies directly comparing two or more imaging tests, we applied a set of nine items involving risk of bias (listed in Appendix D). These items were selected from items in the QUADAS-2 instrument,[11] as well as additional items that specifically address bias in the comparison of imaging tests. For studies of only a single imaging test of interest, the critical issue is whether the study's quantitative estimates could be biased, and we used 14 items that are listed in Appendix D (also based largely on the QUADAS-2 instrument.[11] Each study was assessed by two analysts independently, with disagreements resolved by consensus. Once all individual items were resolved, two analysts assigned each study to a risk-of-bias category (low, moderate, or high), with disagreements resolved by consensus.

Data Synthesis

Decisions about whether meta-analysis was appropriate for a particular data set depended on the judged clinical homogeneity of the different study populations, imaging and treatment protocols, and outcomes. When meta-analysis was not appropriate (due to limitations of reported data), the data were synthesized using a descriptive narrative review approach. We avoided specific numerical thresholds for defining clinical importance of differences because the potential clinical impact of a particular difference in test performance varies according to the particular clinical circumstances of each patient case.

Grading the Body of Evidence for Each Outcome

We used the system for grading evidence on diagnostic tests described in the EPC guidance chapter by Singh et al. (2012).[12] This system uses up to eight domains as inputs (study limitations, directness, consistency, precision, reporting bias, dose-response association, all plausible confounders would reduce the effect, and strength of association). The output is a grade for the strength of evidence: high, moderate, low, or insufficient. This grade is provided separately for each outcome of each comparison of each KQ. The grade refers to our confidence in the direction of effect when comparing two imaging technologies, not to the magnitude of the difference between technologies.

A grade was determined separately for each modality comparison (e.g., CT vs. PET/CT). For accuracy, we examined sensitivity and specificity separately. We did not separately grade other accuracy-related outcomes (i.e., predictive values, likelihood ratios) as these grades would be redundant with the grades already assigned for accuracy, since our estimates would be based on the same studies and quantitative syntheses.

A grade of Insufficient was given when evidence did not permit a conclusion for the two modalities being compared with respect to the outcome of interest. For example, if the outcome was comparative sensitivity of CT versus PET/CT, the evidence could support a conclusion that either (1) CT is more sensitive, (2) PET/CT is more sensitive, or (3) the tests are similarly sensitive. If none of these three conclusions could be drawn (as judged by three independent analysts), evidence was graded Insufficient for that comparison. In order to conclude that two modalities differ for an outcome, we used a p value less than 0.05 two-tailed (i.e., the standard value for alpha). In order to conclude that two modalities are approximately equivalent for an outcome, we used the independent judgment of three analysts (with disagreements resolved by discussion).

If the evidence was sufficient to permit a conclusion, the grade was deemed high, moderate, or low. The grade was provided by three independent raters, with discrepancies resolved by consensus. Specifically, each of three analysts considered all strength of evidence domains listed earlier, and decided on a rating for each evidence base, without knowledge of the ratings of the other two analysts. If any of the three ratings differed, a single rating was reached based on consensus discussion.

Peer Review and Public Commentary

Peer reviewers were invited to provide written comments on the draft report based on their clinical, content, or methodologic expertise. Peer-review comments on the preliminary draft of the report will be considered by the EPC in preparation of the final report. The dispositions of the peer-review comments are documented and will be published 3 months after the publication of the evidence report.

Results

Our searches identified 2,880 citations, of which we excluded 2,637. The most common reasons for exclusion were: studies of other conditions (e.g., non-small cell lung cancer), studies of treatments, and studies not addressing staging. We retrieved the remaining 243 articles, of which we excluded 236. The most common reasons were: studies with fewer than 10 SCLC patients and studies of other conditions. We included the remaining seven publications. Our search of ClinicalTrials.gov identified no additional relevant ongoing studies.

All seven studies were included for KQ1, and none were included for KQs 2 or 3. Two studies were conducted in South Korea, and one each in Japan, Taiwan, Spain, Germany, and Denmark. The only study not published in English was one from Spain.[13] The studies enrolled a total of 408 patients with SCLC. Of the seven studies, three[14-16] reported the comparative accuracy of two or more tests, and four[13,17-19] reported single-test accuracy. One[16] of the comparative accuracy studies also reported concordance data.

Of the three studies reporting comparative accuracy, we rated two as moderate risk of bias, and one as high risk of bias. The moderate ratings were due to a variety of factors including unknown spectrum bias, failure to report whether test readers had the same clinical information available when interpreting different tests, and the use of test results in determining the reference standard. For instance, Lee et al.[14] assessed the comparative accuracy of bone scan and FDG-PET for bone marrow metastases. However, the study failed to report whether all patients meeting selection criteria during study period were enrolled. Furthermore, study authors did not specify whether nuclear medicine physicians evaluating FDG-PET images for bone marrow metastases had access to results from the prior bone scan, or additional clinical information which could potentially impact their interpretation. In addition, the study did not specify whether both interpreters had access to the same clinical information before interpreting the images.

The one high risk-of-bias rating was assigned due to the above problems as well as the probability of spectrum bias, failure to report the elapsed time between imaging tests, and clear acknowledgement that test readers had non-complementary knowledge. The four single-test accuracy studies were all rated as moderate risk of bias. Reasons for the moderate rating varied across studies, but common problems included failure to account for inter-reader differences and not blinding the reference standard assessment to test results or other clinical information.

Results of Literature Searches

We depict the literature selection process in Figure A. Searches identified 2,880 citations, of which we excluded 2,637 based on abstracts. The most common reasons for exclusion were studies of other conditions (e.g., non-small-cell lung cancer), case reports, studies of treatments, and other studies not addressing staging. We retrieved the other 243 articles, of which we excluded 236. The most common reasons were studies with fewer than 10 patients with SCLC and studies of other conditions.

Figure A. Literature flow diagram


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┌─────────────────┐
│ 2,880 publications │
│    identified    │
└─────────────────┘
        │
        ▼
   ◇ Abstracts screened ◇ ──────►  ┌──────────────────────────────────────────┐
                                    │ 2,637 excluded                            │
                                    │ 953: Not SCLC                             │
                                    │ 322: Case report                          │
                                    │ 269: Treatment study                      │
                                    │ 254: Narrative review                     │
                                    │ 232: Not staging                          │
                                    │ 170: Screening                            │
                                    │ 129: Opinion/editor/news/letter           │
                                    │ 118: None of the modalities of interest   │
                                    │ 47: Duplicate article                     │
                                    │ 40: Prognosis                             │
                                    │ 27: Animals/in vitro/phantom              │
                                    │ 18: Fewer than 10 patients with SCLC      │
                                    │ 18: Systematic review                     │
                                    │ 17: Guideline                             │
                                    │ 23: Other reason                          │
                                    └──────────────────────────────────────────┘
        │
        ▼
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│ 243 full articles │
│    retrieved     │
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   ◇ Full articles reviewed ◇ ─────► ┌──────────────────────────────────────────┐
                                     │ 236 excluded                             │
                                     │ 64: Fewer than 10 SCLC patients          │
                                     │ 42: Not SCLC                             │
                                     │ 31: One test of interest, but no data on staging accuracy │
                                     │ 26: No separate SCLC data                │
                                     │ 22: Not a study (review, opinion)        │
                                     │ 10: Unclear whether any patients had SCLC│
                                     │ 10: None of the modalities of interest   │
                                     │ 9: No outcomes of interest               │
                                     │ 9: Not staging before treatment          │
                                     │ 2: Duplicate of already-identified article│
                                     │ 11: Other reason                         │
                                     └──────────────────────────────────────────┘
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        ▼
┌─────────────────┐
│ 7 studies included, all │
│  for Key Question 1   │
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SCLC = small cell lung cancer

KQ 1: Concordance and Comparative Accuracy

We first briefly summarize test concordance data, then discuss our findings on comparative accuracy.

Test Concordance

One study[16] reported test-test concordance data for three imaging tests (MDCT, FDG PET/CT, and bone scintigraphy). The data appear in Table C-5 of Appendix C. For various staging determinations (T stage, N stage, pleural effusion, metastases to ipsilateral lung, metastases to contralateral lung, metastases to the liver, metastases to the adrenal glands and metastases to extra-thoracic lymph nodes), authors reported high agreement between MDCT and FDG PET/CT, ranging from 86 percent to 97 percent. For the assessment of osseous involvement, however, agreement was lower (83 percent between MDCT and FDG PET/CT; 46 percent between MDCT and bone scintigraphy; 57 percent between FDG PET/CT and bone

scintigraphy). The same study also reported the accuracy of these modalities for the assessment of osseous metastases, and we discuss these data (along with all other accuracy data) in the next section.

Comparative Accuracy

An overview of the included accuracy data appears in Table A. Studies reported many different staging determinations (e.g., whether the patient had limited or extensive disease, whether there was metastasis to the brain), but the evidence for any given determination and modality comparison was limited. The largest evidence base involved the comparison of FDG PET/CT to bone scintigraphy for detection of osseous (bone or bone marrow) metastases; this evidence base comprised two studies making direct comparisons (combined n=123) and a single study reporting only bone scintigraphy accuracy data (n=76).

Below, we discuss the results separately for each of eight staging determinations (LD/ED, metastases to osseous structures (bone or bone marrow), lymph node involvement, metastases to adrenal glands, metastases to the liver, metastases to the spleen, any distant metastases, and metastases to the brain). Each of these findings is made even more uncertain by the absence of a consistent and reliable reference method for diagnosis in the studies.

Table A. Overview of included accuracy data

Staging Determination	Studies Making Direct Comparisons in Accuracy Between Imaging Modalities	Studies Reporting Accuracy Data on a Single Imaging Modality (i.e., for indirect comparisons)
Limited or extensive disease	Standard staging* vs. FDG PET/CT; 1 study, n=28	Standard staging* only; 1 study, n=25
Presence of metastases to osseous structures (bone or bone marrow)	MDCT vs. Bone scintigraphy; 1 study, n=28 MDCT vs. FDG PET/CT; 1 study, n=29 Bone scintigraphy vs. FDG PET/CT; 2 studies, n=123	Bone scintigraphy only; 1 study, n=76
Presence of lymph node involvement	None	MDCT only; 1 study, n=118 EBUS only; 1 study, n=36
Presence of metastases to adrenal glands	None	MDCT only; 1 study, n=120
Presence of metastases to the liver	None	MDCT only; 1 study, n=120
Presence of metastases to the spleen	None	MDCT only; 1 study, n=120
Presence of any distant metastases	Standard staging vs. standard staging plus FDG PET/CT; 1 study, n=73	None
Presence of metastases to the brain	None	FDG PET/CT only; 1 study, n=21

FDG PET/CT = [18F]-fluorodeoxyglucose positron emission tomography/computed tomography; MDCT = multidetector computed tomography

* The study's definition of "standard staging" involved any of the following: clinical exam, blood test, chest x-ray, bronchoscopy, and bone marrow biopsy.

Limited or Extensive Disease

Two moderate risk-of-bias studies[16,18] reported data on the ability of imaging tests to determine whether patients with SCLC had LD or ED. Both reported the use of "standard staging," which is a combination of multiple testing procedures such as chest x-ray, bone marrow biopsy, and possibly MRI or CT of the brain. In addition, Fischer et al. (2007)[16] reported data on the performance of FDG PET/CT in determining LD/ED. The data suggest that both standard

staging and FDG PET/CT had good results (e.g., 86 percent or 95 percent for the sensitivity at detecting ED, and specificity of 90 percent or more at ruling out ED). However, both studies were small (n=28 and n=25, respectively), and the overall data were too imprecise to permit any conclusions about relative accuracy.
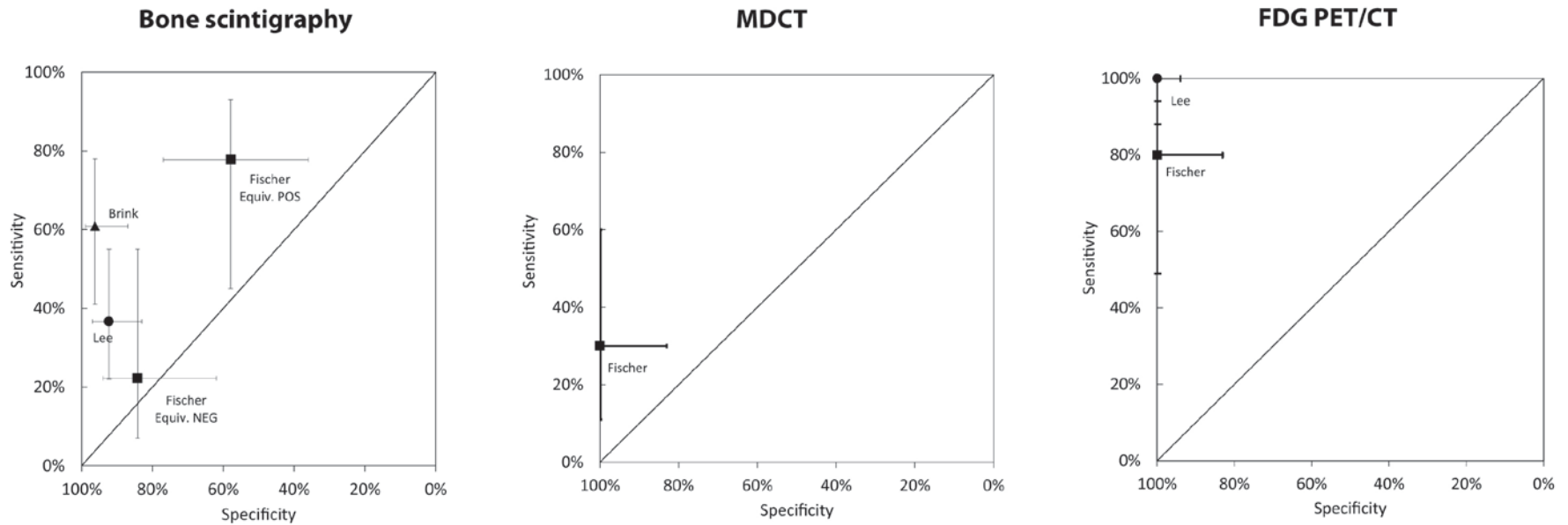
Metastases to Osseous Structures (Bone or Bone Marrow)

Three moderate risk-of-bias studies reported data on the accuracy of imaging tests to determine whether patients had metastases to osseous structures (bone or bone marrow). One study compared FDG PET/CT to bone scintigraphy;[14] another study compared CT to FDG PET/CT to bone scintigraphy;[16] the third study provided data only on bone scintigraphy.[19] The accuracy data are shown in Figure B. For bone scintigraphy, the data from Fischer et al. (2007)[16] are plotted twice: once in which equivocal bone scans are treated as positive tests and a second time if equivocal bone scans are treated as negative tests.

Our statistical tests of these data indicated FDG PET/CT was more sensitive than bone scintigraphy in the Lee study, a finding also replicated by the Fischer study if equivocal bone scans were treated as negative tests. If they were considered positive tests, then FDG PET/CT was more specific than bone scintigraphy for the Fischer study. These are direct comparisons. Considered together with the bone scintigraphy results in the Brink study, we concluded that FDG PET/CT is more sensitive than bone scintigraphy for detecting osseous metastases.

Comparing FDG PET/CT to MDCT, only the Fischer study made a direct comparison, and FDG PET/CT was more sensitive but not more specific. Thus, we concluded that FDG PET/CT is more sensitive than MDCT for detecting osseous metastases.

Finally, turning to the comparison of MDCT with bone scintigraphy, treating equivocal bone scans as positive meant a statistical advantage in sensitivity for bone scintigraphy but a statistical advantage in specificity for MDCT. By contrast, if we treated equivocal bone scans as negatives in Fischer, we found no statistical differences in sensitivity or specificity. Other data on bone scintigraphy from Brink and Lee do not suggest marked differences from MDCT. However, the data were too imprecise to permit any conclusions about the comparison of MDCT and bone scintigraphy with respect to osseous metastases.

Figure B. ROC plots of accuracy data for osseous metastases

Note: The three plots show the data on osseous metastases in ROC space. The left plot is for bone scintigraphy, the middle plot is for MDCT, and the right plot is for FDG PET/CT. They each show two accuracy measures; sensitivity and specificity. Sensitivity is the percentage of patients who are deemed by the test to have osseous metastases, among those who truly do have osseous metastases. Specificity, by contrast, is the percentage of patients who are deemed by the test to not have osseous metastases, among those who truly do not have osseous metastases. The best possible score for both measures is 100 percent. In each plot, the horizontal axis is specificity (with higher specificity as one moves to the left in the plot), and the vertical axis is sensitivity (with higher sensitivity as one moves up in the plot). The 45 degree line is chance. Thus, an optimal modality would have data in the upper left corner of the plot. Each point is a study (with different studies represented by different shapes). The error bars represent 95% confidence intervals. The study by Brink provided data only on bone scintigraphy, which explains why it does not appear in the other two plots. The study by Lee compared bone scintigraphy and FDG-PET/CT, and the study by Fischer compared all three modalities. The Fischer data are further complicated by the fact that some bone scintigraphy results were considered equivocal by the authors (i.e., neither clearly positive nor clearly negative). Treating equivocal results as positive (as shown with the point labeled "Fischer Equiv. POS") results in higher sensitivity than treating equivocal bone scan results as negative (as shown with the point labeled "Fischer Equiv. NEG"), but lower specificity. For PET/CT, both studies had point estimates for specificity of 100 percent, but the confidence intervals around those estimates were too wide to permit conclusions about relative specificity.

ES-13

Lymph Node Involvement

Two moderate risk-of-bias studies reported data on the accuracy of imaging tests to determine whether patients had lymph node involvement. One study used EBUS for this purpose,[17] and the other used MDCT.[19] The EBUS study reported better accuracy (96 percent sensitivity and 100 percent specificity) than the CT study (70 percent sensitivity, 94 percent specificity). However, patients in the CT study may have been more difficult to assess for lymph node involvement (as not all lymph nodes were histologically assessed), which would bias the comparison against CT. The indirect nature of the comparison precludes conclusions.

Metastases to Adrenal Glands, Liver, or Spleen

A single moderate-risk-of-bias study[19] reported the single-test accuracy of MDCT for detecting metastases to the adrenal glands, liver, or spleen (separate accuracy data for each of these three types). Because such data were not reported for other imaging modalities by this or other studies, we drew no conclusions about how different modalities compare.

Any Distant Metastases

A single high-risk-of-bias study[15] reported the comparative accuracy of standard staging versus standard staging plus FDG PET/CT for detecting any distant metastases. This study's version of standard staging involved history, physical exam, chest x-ray, chest CT, bone scintigraphy, bone marrow aspiration, and either MRI or CT of the brain. The study reported a large difference in sensitivity (92 percent for standard staging plus FDG PET/CT vs. only 46 percent for standard staging), and this difference was statistically significant. The specificities were similar (96 percent for standard staging plus FDG PET/CT vs. 100 percent for standard staging), but the precision was too low to permit a conclusion of equivalence on specificity. We deemed the evidence sufficient to permit the conclusion that standard staging plus FDG PET/CT is more sensitive than standard staging alone for detecting any distant metastases. Given that it was only a single high-risk-of-bias study, we rated the strength of the evidence as low.

Metastases to the Brain

A single moderate-risk-of-bias study[13] reported the single-test accuracy of FDG PET/CT of the brain for detecting brain metastases. Because this and others studies did not report such data for other modalities, we drew no conclusions about how different modalities compare in the assessment of brain metastases.

KQ 2: Comparative Effectiveness

No studies were included for this question.

KQ 3: Factors Associated with Comparative Outcomes

No studies were included for this question.

Discussion

Key Findings and Strength of Evidence

Based on the evidence we reviewed, we concluded the following:

- FDG PET/CT is more sensitive than bone scintigraphy at detecting osseous metastases (Strength of Evidence: low)
- FDG PET/CT is more sensitive than CT at detecting osseous metastases (Strength of Evidence: low)
- Standard staging plus FDG PET/CT is more sensitive than standard staging alone at detecting any distant metastases (Strength of Evidence: low)

Our strength-of-evidence judgments for these conclusions, along with other evidence we identified, but deemed insufficient to permit conclusions, are listed in Table B below. Note that all three of our conclusions involve the superior sensitivity of FDG PET/CT. We discuss this finding below in the section "Implications for Clinical and Policy Decisionmaking."

Table B. Strength of evidence grades

Staging Determination	Test Comparison	Number of Studies and Number of Patients	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Magnitude of Effect	SOE Grade*	Conclusion
LD vs. ED	Standard staging[†] vs. FDG PET/CT	Direct comparison: 1 study[16] of 28 patients. Indirect comparison: 1 study[18] of standard staging of 25 patients	Moderate	Mixed	Unknown	Imprecise	None suspected	Not large	Insufficient	NA
Osseous metastases	FDG PET/CT vs. bone scintigraphy	Direct comparison: 2 studies[14,16] of 123 patients. Indirect comparison: 1 study[19] of bone scintigraphy of 76 patients	Moderate	Mixed	Consistent	Imprecise	None suspected	Large	Low	FDG PET/CT more sensitive
Osseous metastases	CT vs. FDG PET/CT	Direct comparison: 1 study[16] of 29 patients	Moderate	Direct	Unknown	Imprecise	None suspected	Large	Low	FDG PET/CT more sensitive
Osseous metastases	CT vs. bone scintigraphy	Direct comparison: 1 study[16] of 28 patients. Indirect comparison: 1 study[19] of bone scintigraphy of 76 patients	Moderate	Mixed	Unknown	Imprecise	None suspected	Not large	Insufficient	NA
Lymph node involvement	CT vs. EBUS	Indirect comparison: 1 study[19] of CT of 118 patients, and 1 study[17] of EBUS of 36 patients	Moderate	Indirect	Unknown	Imprecise	None suspected	Not large	Insufficient	NA
Metastases to adrenal glands	CT vs. anything else	Indirect comparison: 1 study[19] of CT of 120 patients	Moderate	Indirect	Unknown	Unknown	None suspected	Unknown	Insufficient	NA
Metastases to liver	CT vs. anything else	Indirect comparison: 1 study[19] of CT of 120 patients	Moderate	Indirect	Unknown	Unknown	None suspected	Unknown	Insufficient	NA
Metastases to spleen	CT vs. anything else	Indirect comparison: 1 study[19] of CT of 120 patients	Moderate	Indirect	Unknown	Unknown	None suspected	Unknown	Insufficient	NA

Staging Determination	Test Comparison	Number of Studies and Number of Patients	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Magnitude of Effect	SOE Grade*	Conclusion
Any distant metastasis	Standard staging[†] vs. standard staging[†] plus FDG PET/CT	Direct comparison: 1 study[15] of 73 patients	High	Direct	Unknown	Imprecise	None suspected	Large	Low	Standard staging[†] plus FDG PET/CT more sensitive
Metastases to brain	FDG PET/CT of the brain vs. anything else	Indirect comparison: 1 study[13] of FDG PET/CT of 21 patients	Moderate	Indirect	Unknown	Imprecise	None suspected	Unknown	Insufficient	NA

FDG PET/CT = [^{18}F]-fluorodeoxyglucose positron emission tomography/computed tomography; NA = not applicable since evidence was insufficient to permit a conclusion for this staging determination for this test-test comparison; SOE = strength of evidence

* The SOE grade indicates our confidence in the conclusion about the direction of the effect, not about the magnitude of the difference.

[†] Standard" staging of SCLC is not a precisely defined term, but may involve numerous investigations including history, physical exam, chest x-ray, chest CT, bone scan, bone marrow aspiration, and/or MRI or CT of the brain.

Implications for Clinical and Policy Decisionmaking

Based on our review of the current evidence, our results suggest two overall conclusions. First, compared with CT and bone scintigraphy (imaging modalities commonly used for staging), FDG PET/CT is more sensitive for detecting osseous metastases in patients with SCLC. Our findings suggest that clinicians evaluating patients for the presence of osseous metastases may consider forgoing bone scintigraphy and routinely using FDG PET/CT instead. Second, for patients with SCLC who have undergone standard staging, the addition of FDG PET/CT increases sensitivity for detecting any distant metastases overall at the patient level.

The evidence base did not allow us to draw conclusions about the comparative specificity of FDG PET/CT compared with these other modalities; thus, we acknowledge that any of the modalities could yield false positives. If a false positive led to inaccurate "upstaging" to extensive disease, a patient might only receive a palliative regimen instead of aggressive chemotherapy aimed at cure. Unfortunately, as we found only one study evaluating EBUS and no studies evaluating EUS, MRI, or PET/MRI meeting inclusion criteria, we were unable to assess their comparative accuracy with regard to FDG PET/CT.

Our findings regarding FDG-PET are aligned with recent guidelines from the ACR and ACCP: in 2014, the ACR gave the highest rating of "usually appropriate" to the following specific modalities for staging SCLC: CT of the chest and abdomen with contrast, MRI of the head with and without contrast, and FDG-PET/CT from skull base to mid-thigh.[10] Bone scintigraphy was rated as "may be appropriate" and considered unnecessary if PET/CT had been performed. Similarly, the 2013 ACCP guideline recommended a staging workup consisting of CT of the chest and abdomen or CT of the chest extending through the liver and adrenal glands, as well as MRI of the brain and bone scintigraphy. For limited disease patients, the guideline "suggested" FDG-PET" as a replacement for bone scan.

SCLC is an aggressive cancer, and timely staging is important to determine treatment decisions based on whether patients have limited or extensive disease. Currently, as part of the standard staging process, patients may undergo bone scintigraphy, CT of the abdomen and pelvis, brain MRI, and FDG PET/CT. Reducing the total number of tests may improve the timeliness of staging and permit faster initiation of treatment.

Higher sensitivity also has other potential important implications for patient care. First, better detection of metastases can improve patient selection for optimal therapy. The higher sensitivity of FDG PET/CT would provide clinicians more confidence to offer a comprehensive stage-based treatment plan. Second, earlier detection of extensive disease allows patients to be spared from more aggressive concurrent chemotherapy and radiation protocols used for patients with limited disease. Earlier initiation of palliative measures may result in improved quality of life, an important consideration given the current poor prognosis of this disease. Third, improved sensitivity and timeliness of staging may potentially improve the ability of ongoing research trials to prognosticate and detect therapeutic efficacy.

Finally, our results suggest potential resource implications. Although FDG PET/CT may be more expensive than CT and bone scintigraphy, some patients may undergo all three tests when being evaluated for osseous and other distant metastases outside the brain. Eliminating routine use of bone scintigraphy from SCLC staging protocols in favor FDG-PET/CT could potentially result in some cost savings.

Research Gaps

For characterizing gaps, we used the EPC framework proposed by Robinson et al. (2011).[20] This system suggests that reviewers identify a set of important gaps and determine the most important reason for each gap. Each gap should be assigned one of the following reasons for the inability to draw conclusions:

a. Insufficient or imprecise information: no studies, limited number of studies, sample sizes too small, estimate of effect is imprecise
b. Information at risk of bias: inappropriate study design; major methodologic limitations in studies
c. Inconsistency or unknown consistency: consistency unknown (only 1 study); inconsistent results across studies
d. Not the right information: results not applicable to population of interest; inadequate duration of interventions/comparisons; inadequate duration of followup; optimal/most important outcomes not addressed; results not applicable to setting of interest

We found three primary gaps in the literature on imaging tests for the pretreatment staging of SCLC. The first concerns the dearth of evidence on several tests of interest, particularly MRI, EBUS, EUS, and PET/MRI. This gap exists due to reason a, Insufficient information. Note that we did not restrict our search to studies of particular staging purposes even though some are typically used for specific targets (e.g., brain MRI). EBUS and EUS may be used as much for diagnosis as for staging, which may partially explain the lack of direct evidence on staging SCLC. PET/MRI is a relatively new technology, and we predicted that little would be identified, but future systematic reviews may uncover evidence as it becomes more widespread.

The second gap concerns the absence of study designs to inform the optimal imaging plan for the pretreatment staging of SCLC. Thus, the reason for this gap is reason b, Information at risk of bias. At least three underlying sources exist for the gap: (1) the general lack of direct comparisons of different imaging modalities; (2) the use of mixed reference standards (based on partial histology, other imaging tests, and clinical followup) since not all patients' true stage can be determined before treatment; and (3) the complete lack of studies of comparative effectiveness with patient-oriented outcomes such as management strategy or survival after receiving different test strategies. We recognize that some of these problems are due to the clinical reality that SCLC is fast-growing, necessitating timely initiation of treatment.

The third gap concerns KQ3, which addressed the extent to which comparative accuracy or effectiveness are associated with patient factors (comorbidities, body habitus, tumor characteristics). We identified no studies for this question, so this gap exists due to reason a, Insufficient information. Addressing this problem would be easier than addressing the problems listed in the previous paragraph. Most patient records already contain information on patient characteristics; future research could stratify accuracy results accordingly. Armed with this more detailed data, clinicians and policymakers could possibly recommend tailoring specific strategies for different patient subgroups.

Conclusions

Comparative evidence on the pretreatment staging of SCLC is sparse. We found some low-strength evidence suggesting that FDG PET/CT is more sensitive than CT and bone scintigraphy for assessing osseous metastases, and that standard staging plus FDG PET/CT is more sensitive than standard staging alone at detecting any distant metastases.

References

1. American Cancer Society (ACS). Cancer facts & figures 2015. Atlanta, GA: American Cancer Society (ACS); 2015. 56 p.

2. American Cancer Society. Cancer prevention & early detection facts & figures 2013. Atlanta, GA: American Cancer Society; 2013. 65 p.

3. National Cancer Institute (NCI). Small cell lung cancer treatment (PDQ) health professional version. Bethesda, MD: National Cancer Institute (NCI), National Institutes of Health (NIH); 2014 Feb 21. http://www.cancer.gov/cancertopics/pdq/treatment/small-cell-lung/healthprofessional/page1. Accessed 2014 Jun 11.

4. Micke P, Faldum A, Metz T, et al. Staging small cell lung cancer: Veterans Administration Lung Study Group versus International Association for the Study of Lung Cancer--what limits limited disease? Lung Cancer. 2002 Sep;37(3):271-6. PMID: 12234695

5. Rusch VW, Rice TW, Crowley J, et al. The seventh edition of the American Joint Committee on Cancer/International Union Against Cancer Staging Manuals: the new era of data-driven revisions. J Thorac Cardiovasc Surg. 2010 Apr;139(4):819-21. PMID: 20304130

6. Trends in lung cancer morbidity and mortality. Chicago (IL): American Lung Association; 2012 Apr. 34 p.

7. Glisson BS, Byers LA. Pathobiology and staging of small cell carcinoma of the lung. In: Lilenbaum RC, Nicholson A, Jett JR, editors. UptoDate. Waltham, MA: UptoDate; 2013 May 07. http://www.uptodate.com/contents/pathobiology-and-staging-of-small-cell-carcinoma-of-the-lung?source=search_result&search=sclc&selectedTitle=2%7E150#H7. Accessed 2014 Jun 12.

8. Shepherd FA, Crowley J, Van Houtte P, et al. The International Association for the Study of Lung Cancer Lung Cancer Staging Project: proposals regarding the clinical staging of small cell lung cancer in the forthcoming (seventh) edition of the tumor, node, metastasis classification for lung cancer. J Thorac Oncol. 2007 Dec;2(12):1067-77. PMID: 18090577

9. Jett JR, Schild SE, Kesler KA, et al. Treatment of small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013 May;143(5 Suppl):e400S-19S. PMID: 23649448

10. Ravenel JG, Rosenzweig KE, Kirsch J, et al. ACR appropriateness criteria non-invasive clinical staging of bronchogenic carcinoma. J Am Coll Radiol. 2014 Sep;11(9):849-56. PMID: 25086958

11. Whiting P, Rutjes AW, Reitsma JB, et al. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. BMC Med Res Methodol. 2003 Nov 10;3(1):25. PMID: 14606960

12. Singh S, Chang S, Matchar DB, et al. Grading a body of evidence on diagnostic tests (AHRQ publication no. 12-EHC079-EF). Chapter 7 of Methods Guide for medical test reviews. AHRQ publication no. 12-EHC017. Rockville, MD: Agency for Healthcare Research and Quality; 2012 Jun 1. http://effectivehealthcare.ahrq.gov/ehc/products/246/558/Methods-Guide-for-Medical-Test-Reviews_Full-Guide_20120530.pdf.

13. Palomar Munoz A, Garcia Vicente AM, Bellon Guardia ME, et al. Is a selective brain (18)F-FDG PET/CT study profitable in patients with small cell lung cancer? Rev Esp Med Nucl Imagen Mol. 2012 May;31(3):124-9. PMID: 21722995

14.   Lee JW, Lee SM, Lee HS, et al. Comparison of diagnostic ability between (99m)Tc-MDP bone scan and 18F-FDG PET/CT for bone metastasis in patients with small cell lung cancer. Ann Nucl Med. 2012 Oct;26(8):627-33. PMID: 22729551

15.   Sohn BS, Lee DH, Kim EK, et al. The role of integrated 18F-FDG PET-CT as a staging tool for limited-stage small cell lung cancer: a retrospective study. Onkologie. 2012 Aug;35(7):432-8. PMID: 22846975

16.   Fischer BM, Mortensen J, Langer SW, et al. A prospective study of PET/CT in initial staging of small-cell lung cancer: comparison with CT, bone scintigraphy and bone marrow analysis. Ann Oncol. 2007 Feb;18(2):338-45. PMID: 17060487

17.   Wada H, Nakajima T, Yasufuku K, et al. Lymph node staging by endobronchial ultrasound-guided transbronchial needle aspiration in patients with small cell lung cancer. Ann Thorac Surg. 2010 Jul;90(1):229-34. PMID: 20609781

18.   Shen YY, Shiau YC, Wang JJ, et al. Whole-body 18F-2-deoxyglucose positron emission tomography in primary staging small cell lung cancer. Anticancer Res. 2002;22(2):1257-64. PMID: 12168935

19.   Brink I, Schumacher T, Mix M, et al. Impact of [(18)F]FDG-PET on the primary staging of small-cell lung cancer. Eur J Nucl Med Mol Imaging. 2004 Dec;31(12):1614-20. PMID: 15258700

20.   Robinson KA, Saldanha IJ, Mckoy NA. Frameworks for determining research gaps during systematic reviews. Methods Future Research Needs Report No. 2. (Prepared by the Johns Hopkins University Evidence-based Practice Center under Contract No. HHSA 290-2007-10061-I.) AHRQ Publication No. 11-EHC043-EF. Rockville, MD: Agency for Healthcare Research and Quality. June 2011. http://www.effectivehealthcare.ahrq.gov/ehc/products/201/735/FRN2_Frameworks_20110726.pdf.

Introduction

Background

Epidemiology

Lung cancer is the leading cause of cancer-related mortality, accounting for about 27 percent of cancer deaths in the United States in 2015.[1] In 2011 (the most recent year for which U.S. prevalence data are available), an estimated 402,236 people in the United States were living with lung cancer.[2] In 2015, an estimated 221,200 new cases of lung cancer will be diagnosed.[1] Small cell lung cancer (SCLC) is an aggressive subset of lung cancer that is characterized by rapid doubling time, high growth fraction, and early development of metastatic disease. This histologic subset of lung cancer is primarily seen in smokers[3] and composes approximately 15 percent of all lung cancers.[4] Despite advances in diagnosis, treatment, and management of lung cancer, the 5-year survival rate for SCLC remains dismal at about 6 percent.[1]

The majority of the patients with SCLC (approximately 70 percent) present with metastatic disease, and about 20 to 30 percent have brain metastases at presentation.[5,6] Patients with metastatic SCLC have a poor prognosis, with a median survival of only 9–11 months despite aggressive initial treatment. The high rate of distant failure after completion of treatment suggests that systemic micrometastatic spread is common at the time of initial diagnosis but poorly captured by available imaging and surveillance. Platinum-based chemotherapy in combination with etoposide has been the standard of care for over 25 years, with virtually no headway in research. As we pursue novel therapies for this disease, it is imperative that we concurrently pursue strategies that enable us to diagnose and stage these patients' disease in a timely fashion, to guide selection of suitable patients for specific therapy, and to predict clinical outcome.

Diagnosis

SCLC remains a pathologic diagnosis requiring tissue obtained via biopsy. Most cases are diagnosed after patients become symptomatic with cough, shortness of breath, weight loss, or hemoptysis. Imaging, often performed as a first diagnostic step usually reveals a suspicious nodule or mass. Thus, while imaging plays a key role in the diagnostic workup, these tests cannot be used to definitively distinguish SCLC from other types of lung cancer or from other noncancerous conditions (i.e., differential diagnosis). Multidetector computed tomography (MDCT) is widely used as the initial imaging test to determine whether, where, and how to perform a biopsy. Biopsy may be performed via one of several methods (e.g., bronchoscopy, CT-guided percutaneous biopsy, endobronchial ultrasound [EBUS], endoscopic ultrasound [EUS]), depending on the location and size of the mass and patient factors like body mass index and presence of other comorbidities. In a minority of patients, SCLC can also be detected incidentally. In these asymptomatic patients, a chest x-ray or chest CT ordered for other reasons may reveal a nodule or suspicious mass requiring further investigation.

Staging

Staging involves determining the extent of disease and to direct the choice and goals of therapy. SCLC is typically staged using one of two systems, with the Veterans Administration

Lung Study Group (VALSG) system or the less commonly used American Joint Committee on Cancer (AJCC) TNM (T stands for primary tumor, N stands for regional lymph nodes, and M stands for distant metastasis system):

- The VALSG system[7] classifies SCLC as either "limited stage" or "extensive stage" disease with the following definitions:
  - Limited stage disease (LD): Cancer is confined to one hemithorax and may be present in the regional lymph nodes or in ipsilateral supraclavicular nodes, all of which can be encompassed in a safe radiotherapy field.
  - Extensive stage disease (ED): Cancer that cannot be classified as LD, such as when contralateral hilar or supraclavicular nodes, malignant pericardial or pleural effusions, or distant metastatic disease are present.
- The AJCC TNM system is used less commonly for SCLC but often used for other types of cancer. Lung cancers are classified based on the size of the main tumor, whether it has locally invaded other organs/tissues, spread to lymph nodes, and metastasized to other parts of the body. This information is used to assign a stage between I and IV. A higher stage represents a more extensive spread.

The National Cancer Institute reported that from 1975–2008, about 70 percent of SCLC cases presented with ED, another 21 percent had regional spread such as mediastinal nodal involvement, and only 5 percent were localized (the other 4 percent were unstaged).[8] The most common sites of metastases for SCLC are liver, adrenal glands, bone, bone marrow, and brain.[9]

Some debate exists about which system should be used. The International Association for the Study of Lung Cancer recommended in 2007 that clinicians use the AJCC system.[5] This recommendation was based on an analysis of more than 8,000 patients with SCLC, which found that both tumor stage and lymph node status were associated with survival. By contrast, others have noted that since approximately two-thirds of patients with SCLC present with advanced disease,[9] the simpler VALSG system is sufficient to guide treatment. A 2013 guideline from the American College of Chest Physicians recommended that SCLC be staged using both systems.[10] Staging involves evaluating disease in the abdomen, pelvis, bones, and brain.

More than two-thirds of patients with SCLC present with extensive stage and have a poor prognosis with a median survival of only 9–11 months. Despite initial response to chemotherapy, most patients become refractory to therapy or relapse shortly thereafter. Platinum-based chemotherapy in combination with etoposide has been the standard of care for over 25 years, with virtually no headway in research. Patients with LD are treated more aggressively with concurrent chemotherapy and radiation with curative intent. After completion of first-line therapy, prophylactic cranial irradiation (i.e., without evidence of metastases in) has been demonstrated to prolong survival in both LD and ED.

"Standard" staging of SCLC is not a precisely defined term, but may involve numerous investigations including history, physical exam, chest x-ray, chest CT, bone scan, bone marrow aspiration, and/or MRI or CT of the brain. Accurate staging of patients is essential to select the optimal treatment plan that will maximize a patient's chances of survival. On the one hand, overstaging risks denying the patient potentially life-saving treatment, while understaging risks subjecting the patient to unnecessary risk of complications from more aggressive treatment. Given the rapid progression of SCLC, timely diagnosis and staging is important; performing potentially unnecessary tests during the diagnostic and staging process could delay treatment initiation, compromising treatment efficacy.

Imaging Tests

This section discusses several types of imaging tests used to stage SCLC.

Multidetector Computed Tomography

CT scanners acquire cross-sectional images (slices) of the body using x-rays. While early CT scanners could acquire only one slice at a time, current state of the art MDCT scanners can acquire as many as 640 slices at a time. These images can be reconstructed for viewing in any desired plane (multiplanar reconstruction). Since single-detector CT scanners are now obsolete, our report excluded clinical studies using single-detector CT.

Intravenous injection of a radiopaque contrast agent should be performed whenever not contraindicated in CT examinations for lung cancer staging. Contrast-enhanced CT can provide additional information about the characteristics of a mass seen in the unenhanced scan, which may facilitate characterization of the mass as probably malignant or probably benign.

MDCT has general strengths of widespread availability, high spatial resolution, and high speed and is particularly useful for evaluating the lungs, airways, bowel, and cortical bone. However, because it is a structural imaging modality, it may not detect early metastatic disease involving sites such as the bone marrow or lymph nodes and is not always able to characterize lesions as benign or malignant based on their morphologic properties. In addition, some patients cannot receive iodinated contrast material due to renal insufficiency, limiting evaluation for presence of hilar lymphadenopathy, vascular abnormalities, and lesion characterization. The major risks of iodinated contrast material include contrast allergic-like reactions (most often mild and self-limited in nature, less commonly moderate or severe requiring therapeutic intervention), contrast-induced nephropathy (most commonly in patients with pre-existing renal insufficiency), and extravasation injury (occurring in up to approximately 1 percent of scans, most often in the superficial soft tissues and typically self-limited, rarely leading to compartment syndrome). One potential concern about MDCT is patient exposure to ionizing radiation. However, given the poor prognosis for SCLC when it is typically diagnosed, this concern is relatively unimportant.

MDCT of the chest is often one of the first tests performed to diagnose possible lung cancer. For staging SCLC, additional MDCT images are taken of the abdomen, pelvis, or head to detect distant metastases.

Positron Emission Tomography/Computed Tomography

Positron emission tomography (PET) is an imaging modality that localizes the uptake of a positron-emitting radioisotope in the body. [^{18}F]-fluorodeoxyglucose (FDG) is the most commonly used PET radiotracer. Because FDG-PET identifies anatomic sites that harbor metabolically active malignant areas, FDG-PET helps distinguish malignant tumors from benign nodules or masses. FDG-PET can also detect metabolically active metastases that may not be detected by structural imaging modalities (e.g., MDCT, magnetic resonance imaging [MRI]).

Because PET images lack anatomic detail, combined PET/CT scanners have been developed so the molecular information from PET can be anatomically localized with CT. As of 2015, PET without a concurrent CT is rarely performed. Therefore, our analysis of PET data included only studies in which patients were imaged using a combined PET/CT scanner.

FDG-PET/CT is sometimes available (but less often than CT) and has high contrast resolution. Because it is quantitative, measurements of the specific uptake in individual lesions or global disease burden may be performed. However, FDG uptake within a lesion does not always indicate malignancy. Infectious and no-infectious inflammatory lesions may also

demonstrate FDG uptake, potentially leading to false-positive results. Furthermore, some small or indolent malignant lesions (such as lung adenocarcinoma in situ or carcinoid tumor) may have little to no radiotracer uptake, potentially leading to false-negative results. Lastly, patients with elevated serum glucose levels (greater than 200 mg/dl) do not generally undergo FDG-PET/CT, given the potential for false-negative results. Again, one potential concern about FDG-PET/CT is patient exposure to ionizing radiation. However, given the poor prognosis for SCLC when it is typically diagnosed, this concern is relatively unimportant.

Magnetic Resonance Imaging

MRI uses magnetic fields and radio waves to generate three-dimensional images of the body. Unlike PET and CT, MRI does not use ionizing radiation and thus poses no radiation-related risks to the patient. Paramagnetic contrast agents can be administered during the MRI examination to give additional information about the nature of a mass in the same way that iodinated contrast agents can enhance a CT scan.

MRI is a structural and functional imaging technique with widespread availability, high spatial resolution, and high soft-tissue contrast resolution; this imaging modality is particularly useful for detecting and characterizing lesions within tissues even when subcentimeter in size, as well as for evaluating the internal architecture of organs/tissues such as the brain, spinal cord, breasts, bone marrow, muscles, tendons, ligaments, cartilage, and other solid organs. Also, functional imaging capabilities such as diffusion-weighted imaging and magnetic resonance spectroscopy may be used to improve diagnostic accuracy. MRI examinations take longer to perform and generally cost more than MDCT, and some patients with implanted electronic or metallic devices or with claustrophobia cannot undergo MRI.

Positron Emission Tomography/Magnetic Resonance Imaging

Combined PET and MRI scanners are a recent technical development: they promise the sensitivity of PET combined with the anatomic detail of MRI. PET/MRI is a hybrid molecular/structural imaging technique that possesses the general strengths provided by PET and MRI listed above, along with a lower radiation dose compared with PET/CT, and potentially improved PET quantification and motion compensation. However, in addition to the weaknesses of PET and MRI listed above, it is not widely available; not currently reimbursed for by insurance companies; more expensive in terms of instrumentation than PET/CT, MDCT, and MRI; involves longer examination times; and requires additional training of personnel in terms of safety, protocol optimization, and study interpretation.

Endobronchial Ultrasound and Endoscopic Ultrasound

EBUS is a bronchoscopic technique utilizing ultrasonography to visualize structures within and adjacent to the airway wall, whereas EUS is an endoscopic technique that uses ultrasonography to visualize structures within and adjacent to the esophageal wall. These techniques are minimally invasive and can be performed on an outpatient basis. Patients with suspected spread of lung cancer to mediastinal lymph nodes may undergo preoperative (or intraoperative) EBUS-guided biopsy and/or EUS-guided biopsy for real-time, minimally invasive pathologic mediastinal N staging, even for lymph nodes that are subcentimeter in size or located near blood vessels. EBUS is used to sample hilar and mediastinal lymph nodes that surround the tracheal bronchial tree, whereas EUS can be used to sample other lymph nodes in

proximity to the esophagus. These techniques are used during the staging workup of patients with lung cancer, as accurate N staging is important to determine optimal therapy.

EBUS-guided transbronchial needle aspiration (EBUS-TBNA) is generally performed if suspected lymph nodes are in the anterior or superior mediastinum and appear to be accessible based on prior cross-sectional imaging. EUS-guided fine-needle aspiration (EUS-FNA) may initially be used for nodes that are paraesophageal or subaortic in location or located in the posterior or inferior mediastinum. EBUS-TBNA can also be used to sample hilar lymph nodes or biopsy the left adrenal gland, left hepatic lobe and celiac axis lymph nodes.

EBUS can also be used to inform T staging of lung cancer and may potentially improve the determination of the distance between the tumor and the carina, which is a determinant of T stage. Furthermore, it may help distinguish between airway invasion by tumor compared with airway compression by tumor. EBUS is also used for diagnostic evaluation of endobronchial lesions, peripherally located pulmonary nodules, and mediastinal lesions, as well as for guiding endobronchial therapy.

Bone Scintigraphy

Bone scintigraphy uses a gamma camera or SPECT (Single Photon Emission Computed Tomography) scanner to create two-dimensional images of the distribution of a radiotracer, typically technetium-99m methylene diphosphonate (Tc99m-MDP). Scintigraphy of radiotracers that localize to the bones is useful in cancer staging because areas of high radiotracer uptake could represent metastases; however, uptake occurs with other common conditions as well, meaning that false-positive findings are not unusual.

Bone scintigraphy is a two-dimensional molecular imaging technique with widespread availability, high contrast resolution, and relatively low cost compared with FDG-PET/CT. However, false-negative results can occur, particularly when lytic osseous lesions are present, as bone scintigraphy indirectly reveals sites of metabolic bone turnover in reaction to bone marrow metastatic disease rather than the metastatic lesions directly. False-positive results can also occur due to other nonmalignant conditions that lead to increased bone turnover, such as fractures and osteomyelitis. Also, this technique has only planar capability (compared with tomographic capability of the other imaging techniques described above), further limiting its diagnostic capability. Lastly, bone scintigraphy is less quantitative than PET/CT and does not allow evaluation of non-osseous structures of the body (in contrast to MDCT, MRI, and PET).

Test Utilization and Costs

Based on an evaluation of a 20 percent sample of Medicare fee-for-service claims from 2008, Hillner and colleagues calculated the combined annual imaging days per person-year (i.e., the average number of days imaging was performed each year per patient) in beneficiaries with cancer as 2.3 for CT, 0.49 for MRI, 0.70 for PET, and 0.13 for bone scintigraphy.[11] The annual rates of imaging from 2004 to 2008 increased 0.5 percent for CT, 3.2 percent for MRI, and 18.0 percent for PET, and decreased 12.7 percent for bone scintigraphy. PET continues to grow rapidly with evidence that it is replacing bone scintigraphy without a decline in CT.[11] Regarding PET or PET/CT, an estimated 1.62 million clinical PET and PET/CT scans were performed in 2014, representing a net decrease of about 13 percent compared with 2011.[12] About 94 percent of all PET studies in 2012 were for cancer (19 percent for diagnosis, 38 percent for staging, 13 percent for treatment planning, and 30 percent for follow up).[13] Regarding combined MRI/CT, utilization rates have increased from 64.3 to 109.1 per 1,000 person years from 2000 to 2009.[14]

However, growth has slowed in recent years, with an average annual decline in the imaging growth rate of 4.7 percent between 2000 and 2009.[14]

Regarding costs, we searched the CMS Web site (http://www.cms.gov/apps/physician-fee-schedule/search/search-criteria.aspx) for Medicare rates (national payment amounts, based on 2015 CPT codes and CMS.gov physician fee schedule) for specific procedures and found the following:

- CT chest with contrast: $229.55
- CT abdomen and pelvis with contrast: $312.50
- CT head/ brain wo contrast: $116.20
- FDG-PET/CT (skull base to thigh): $1523.19
- MRI chest w/wo contrast: $581.37
- MRI abdomen w/wo contrast: $508.43
- MRI pelvis w/wo contrast: $507.36
- MRI head (or brain) w/wo contrast: $378.28
- Bone scintigraphy: $261.37
- Bronchoscopy with EBUS/TBNA: $281.39

Patient Subgroups of Particular Interest

We are unaware of patient factors that might differentially affect the accuracy of imaging modalities specifically for SCLC. As previously noted, performance of various imaging modalities may be affected by comorbidities such renal insufficiency, which potentially limits the use of contrast for MDCT. Generally speaking, body habitus may limit the diagnostic quality and accuracy for any imaging modality. Many scanners are unable to safely accommodate patients above a particular weight or girth. However, these are general patient considerations, not specific to the use of imaging for SCLC.

Recent Guidance From Professional Societies and Need for Future Work

In 2014, the American College of Radiology (ACR) appropriateness criteria review gave the highest rating of "usually appropriate" (with regard to staging SCLC) to the following specific modalities: CT of the chest and abdomen with contrast, MRI of the head with and without contrast, and FDG-PET/CT from skull base to mid-thigh.[15] Bone scintigraphy was rated as "may be appropriate" and considered unnecessary if PET/CT had been performed. ACR noted that PET/CT is often helpful in staging SCLC and may result in a change in staging in up to 17 percent of cases, mostly cases in which PET/CT detects extensive disease that was not detected by other modalities. It may also detect additional involved lymph nodes, leading to revisions in treatment plans for patients scheduled to receive radiotherapy. As PET/CT has already become frequently adopted as part of the SCLC staging process, it is important to establish whether evidence exists to support this practice.

Similarly, a 2013 guideline from the American College of Chest Physicians recommended that patients with either proven or suspected SCLC undergo CT of the chest and abdomen or CT of the chest extending through the liver and adrenal glands, as well as MRI of the brain and bone scintigraphy.[10] Furthermore, in patients thought to have limited disease, the guideline suggested FDG-PET/CT imaging to improve detection of metastases (with the potential to increase the stage and change the treatment choice). However, the evidence underlying this recommendation

of PET for potential upstaging is limited and considered weak. The last search date of the guideline was 2011; therefore, approximately 3.5 years of additional literature were available for our report (2012 through June 15, 2015 when searches were performed). A primary objective of this report is to update the evidence base by including more recent studies.

Scope and Key Questions

Key Questions

Key Question 1: What are the test concordance and comparative accuracy of imaging tests (MDCT, PET/CT, MRI, PET/MRI, EBUS, EUS, bone scintigraphy) for the pretreatment staging of SCLC?
   a. Test concordance
   b. Sensitivity
   c. Specificity
   d. Positive predictive value
   e. Negative predictive value
   f. Positive likelihood ratio
   g. Negative likelihood ratio

Key Question 2: When used for the pretreatment staging of SCLC, what is the comparative effectiveness of imaging tests (MDCT, PET/CT, MRI, PET/MRI, EBUS, EUS, bone scintigraphy) on later outcomes?
   a. Choice of treatment (e.g., surgery, chemotherapy, radiation)
   b. Timeliness of treatment
   c. Tumor response
   d. Harms due to overtreatment or undertreatment
   e. Survival
   f. Quality of life

Key Question 3. To what extent are the following factors associated with the comparative accuracy or effectiveness of imaging tests (MDCT, PET/CT, MRI, PET/MRI, EBUS, EUS, bone scintigraphy) when used for the pretreatment staging of SCLC?
   a. Comorbidities
   b. Body habitus
   c. Tumor characteristics

Note that two terms above, "accuracy" and "effectiveness", are used as overarching labels for different sets of outcomes. The "accuracy" outcomes (which are part of Key Question 1), involve an accurate determination of the patient's stage, whereas the "effectiveness" outcomes (which are listed for Key Question 2), involve the post-staging outcomes such as clinical management and response to treatment. For comparing the *effectiveness* of two imaging modalities, we required that studies make direct comparisons between two or more modalities, whereas for *accuracy*, we included studies that only used one imaging modality. Our full list of inclusion criteria appear in the section below called "Study Selection".

Populations, Interventions, Comparators, and Outcomes

Populations
- Adult patients with known SCLC or combined SCLC who are undergoing imaging test(s) for staging and who have not yet received treatment.

Interventions
Imaging using one or more of the following tests:
- Multidetector computed tomography (MDCT)
- PET/CT
- MRI
- PET/MRI
- EBUS
- EUS-FNA
- Bone scintigraphy

Comparators
- Any direct comparisons of the imaging tests of interest
- Any combination of the imaging test of interest

Outcomes
- Test concordance
- Sensitivity
- Specificity
- Positive predictive value
- Negative predictive value
- Positive likelihood ratio
- Negative likelihood ratio
- Choice of treatment (e.g., surgery, chemotherapy, radiation)
- Timeliness of treatment
- Tumor response
- Harms due to overtreatment or undertreatment
- Survival
- Quality of life

Conceptual Framework

The conceptual framework for this review appears in Figure 1. This figure depicts the key questions within the context of the PICOTS listed in the previous section. The figure shows that the populations of interest (patients with either SCLC or Combined SCLC) are staged using various imaging modalities, which leads to choices in patient management, leading (hopefully) to tumor response, and finally to patient-oriented outcomes of survival and quality of life. Key harms of interest are the harms due to overtreatment or undertreatment.

Figure 1. Conceptual framework
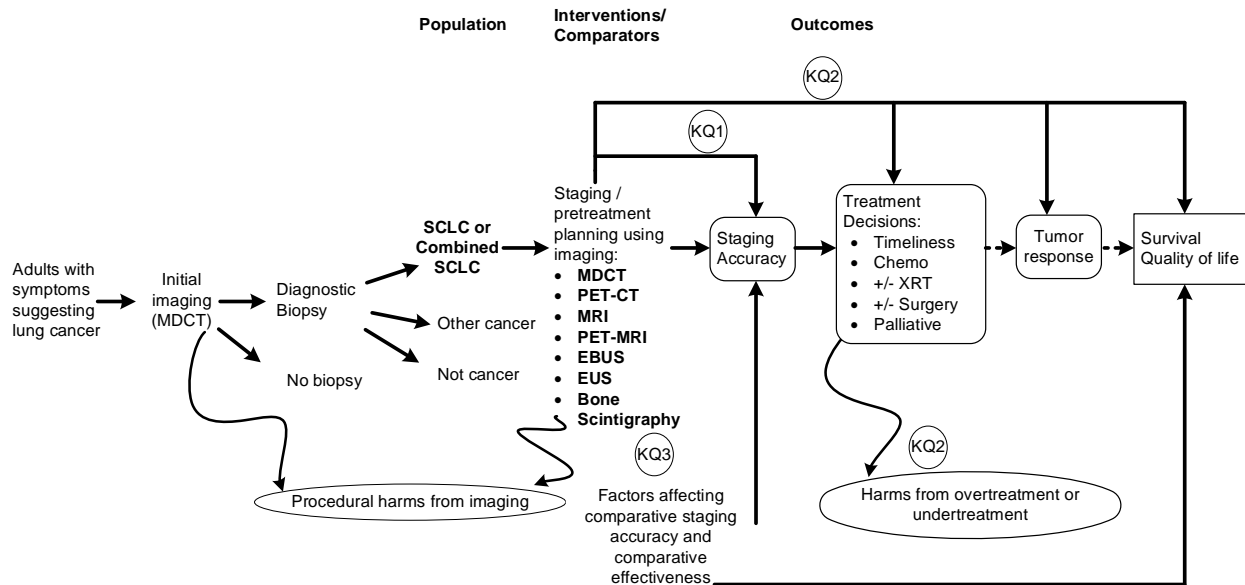
Chemo = chemotherapy; EBUS = endobronchial ultrasound; EUS = endoscopic ultrasound; KQ = Key Question; MDCT = multidetector computed tomography; MRI = magnetic resonance imaging; PET-CT = positron emission tomography/computed tomography; PET-MRI = positron emission tomography/magnetic resonance imaging; SCLC = small cell lung cancer; XRT = radiotherapy

Organization of This Report

In the remaining three chapters of this report, we present the methods for this systematic review, the results for each key question, and a discussion of the findings. Within the Results chapter, we provide the results of the literature searches and selection procedures, then the results for Key Question 1. The Discussion section provides an overview of our findings and how they relate to what is already known. In that section, we also discuss clinical and policy decisionmaking, the applicability of the evidence, limitations of our review as well as limitations of the evidence we reviewed, and any major gaps in existing research.

Methods

Topic Development and Refinement

Initially a panel of key informants gave input on the Key Questions (KQs) to be examined; these KQs were posted on AHRQ's Web site for public comment between September 4, 2014, and September 24, 2014, and revised as needed. We then drafted a protocol for the Comparative Effectiveness Review and recruited a panel of technical experts to provide high-level content and methodologic expertise throughout the development of the review. The protocol is registered with PROSPERO (http://www.crd.york.ac.uk/PROSPERO/) as review # CRD42014015429.

Literature Search Strategy

Literature searches were performed by medical librarians within the Evidence-Based Practice Center (EPC) Information Center; searches followed established systematic review methods. We searched the following databases using controlled vocabulary and text words: EMBASE, MEDLINE, PubMed, and the Cochrane Library. The following grey literature sources were searched using text words: ClinicalTrials.gov, Centers for Medicare & Medicaid Medicare Coverage Database, ECRI Institute Health Devices, Healthcare Standards, Internet, Medscape, National Guideline Clearinghouse™, and the U.S. Food and Drug Administration. The search strategy appears in Appendix A. The last search date was June 15, 2015.

Literature screening was performed by experienced research analysts using the database Distiller SR (Evidence Partners, Ottawa, Canada). Literature search results were initially screened for relevancy. Relevant abstracts were screened against the study inclusion criteria in duplicate. Studies that appeared to meet the study inclusion criteria were retrieved in full and screened in duplicate against the study inclusion criteria. All disagreements were resolved by consensus discussion among the two original screeners or a third screener.

Study Selection

Our inclusion criteria are listed below in five categories: Publication criteria, study design criteria, patient criteria, test criteria, and data criteria.

Publication Criteria

a. Full-length articles: The article must have been published as a full-length, peer-reviewed study.
b. Redundancy: To avoid double-counting patients, in instances in which several reports of the same or overlapping groups of patients were available, only outcome data based on the larger number of patients were included. However, we included data from publications with lower numbers of patients when either (a) a publication with lower patient enrollment reported an included outcome that was not reported by other publications of that study, or (b) a publication with lower patient enrollment reported longer followup data for an outcome.
c. Publication date: We included studies published since January 1, 2000. Technical progress in all the imaging modalities under consideration means that older studies are likely to underestimate the diagnostic performance of these modalities.

d. We initially had excluded studies not published in English, but after identifying a relatively low number of qualifying studies, we removed that requirement.

Study Design Criteria

a. The study must have provided data on at least one test of interest. Ideally, studies would directly compare two or more tests (or test strategies). The comparison may also be addressed indirectly by comparing one set of studies of one imaging test and another set of studies of another imaging test (e.g., a set of studies reporting the accuracy of MRI at mediastinal node staging of SCLC compared with a separate set of studies reporting the accuracy of CT at mediastinal node staging of SCLC). This is an indirect comparison of modalities, so conclusions based on it are weaker.
b. For comparisons of variants of a given modality, and studies of patient factors or tumor characteristics for KQ3, the comparison must have been planned in advance.
c. For comparative accuracy (KQ1), the study must have compared both tests to a common reference standard. The reference standard must not have been defined by either imaging test being assessed. We set no requirements on what the reference standard must be (e.g., biopsy, clinical followup).
d. For comparative effectiveness (KQ2), some patients must have received one of the imaging tests (or test strategies), and a separate group of patients must have received a different imaging test (or test strategy). This design permits a comparison of how the choice of test (or test strategy) may influence choice of treatment, timeliness of treatment, harms due to over-/undertreatment, survival, and/or quality of life.
e. For the influence of patient factors or tumor characteristics (KQ3), the study must have reported comparative accuracy data stratified by patient/tumor factor or comparative-effectiveness data stratified by patient/tumor factor.

Patient Criteria

a. The study reported data specifically on patients undergoing staging for SCLC, or if the data were combined with other types of patients, at least 85 percent of the patients in the reported data were undergoing staging for SCLC.
b. Adults. At least 85 percent of patients must have been aged 18 years or older, or data must have been reported separately for those aged 18 years or older.
c. Studies of staging for *primary* SCLC were included. Studies of staging for *recurrent* SCLC were excluded.
d. Data on imaging tests performed after any form of treatment (e.g., chemotherapy) were excluded, but pretreatment imaging data were considered.

Test Criteria

a. Type of test. Only studies of the imaging tests of interest were included (listed in the key questions above). Studies of CT that did not explicitly state (or we could not determine) whether they used CT or MDCT were assumed to be MDCT. Given our publication date of 2000 and later, we believe it is safe to assume that CT performed in such studies was MDCT.
b. PET/CT must have been based on a dedicated PET/CT machine. We excluded studies in which PET and CT were acquired separately and later fused for the following reasons.

First, methods for image fusion can vary widely. Since accurate staging relies on precise localization of the margin of tumor or metastasis, inclusion of less precise means of combining PET and CT images would underestimate the performance of PET/CT. Second, image fusion is no longer the state of the art in PET/CT, and since this report is intended to guide use of imaging technologies in the future, it should reflect the technology presently in use.

Data Criteria

a. The study must have reported data pertaining to one of the outcomes of interest (see the KQs).
- o For test concordance (part of KQ1), this means reporting the number of patients for whom the two tests provided the same or different results.
- o For comparative accuracy (part of KQ1), this means reporting enough information to calculate both sensitivity and specificity, along with their corresponding confidence intervals (CIs).
- o For comparative choice of treatment (part of KQ2), this means reporting the percentage of patients who received a specific treatment choice for one test or test strategy compared with another test or test strategy.
- o For comparative timeliness of treatment (part of KQ2), this means reporting the duration of time elapsed before the initiation of treatment for one test or test strategy compared with another test or test strategy.
- o For comparative tumor response (part of KQ2), this means reporting the percentage of patients whose tumor responded to treatment for one test or test strategy compared with another test or test strategy.
- o For comparative harms of overtreatment or undertreatment (part of KQ2), this means reporting the percentage of patients who were overtreated or undertreated (based on authors' judgment), for one test/test strategy compared with another test/test strategy.
- o For comparative survival (part of KQ2), this means either reporting median survival after each imaging test or test strategy, or mortality rates at a given time point, or other patient survival such as a hazard ratio.
- o For quality of life (part of KQ2), this means reporting data on a previously tested quality-of-life instrument (such as the Short-Form 36) separately for each imaging test or test strategy.
- o For patient factors or tumor characteristics (KQ3), this means reporting data on whether such factors are associated with either comparative accuracy and/or comparative effectiveness.

b. Regarding the minimum patient enrollment, we required data on at least 10 patients per imaging test or test strategy.

c. For all KQs, the reported data must have included at least 50 percent of the patients who had initially enrolled in the study.

Data Extraction and Management

Abstraction forms were constructed in Microsoft Excel, and the data were abstracted into these forms. Elements abstracted included general study characteristics (e.g., country, setting, study design, enrolled N, funding source), patient characteristics (e.g., enrollment criteria, age,

sex, final diagnoses including tumor characteristics), details of the imaging methodology (e.g., radiotracer, timing of test, readers, elapsed time between imaging tests, what reference standard was used), risk-of-bias items, and outcome data. Outcome data were dual abstracted to ensure accuracy, with discrepancies resolved by consensus. Multiple publications of the same study were grouped as a single study. We identified these by examining author names, study centers, patient enrollment dates, and imaging technologies.

Risk-of-Bias Evaluation

For studies directly comparing two or more imaging tests, we applied a set of nine items involving risk of bias (listed in Appendix D). We devised these items after considering the QUADAS-2 instrument,[16] as well as additional issues that specifically address bias in the comparison of imaging tests. For studies of only a single imaging test of interest, the critical issue was whether the study's quantitative estimates could be biased, and we used 14 items, which are listed in Appendix D (also based on considering the QUADAS-2 instrument.)[16] Two analysts independently assessed each study, with disagreements resolved by consensus. Once all individual items were resolved, two analysts assigned each study to a risk-of-bias category (low, moderate, or high), with disagreements resolved by consensus.

Data Synthesis

Decisions about whether meta-analysis is appropriate depended on the judged clinical homogeneity of the different study populations, imaging and treatment protocols, and outcomes. When meta-analysis was not appropriate (due to limitations of reported data), the data were synthesized using a descriptive narrative review approach.

For KQ1 on comparative accuracy, we had planned to synthesize sensitivity and specificity of each test on its own using a bivariate mixed-effects binomial regression model as described by Harbord et al.[17] If appropriate, all such analyses were performed using the STATA 13 statistical software package (StataCorp, College Station, Texas) using the "midas" command.[18] To compare two tests, we used the EPC methods described in equation 39 of Trikalinos et al. (2013).[19]

For KQ2 on comparative effectiveness, if meta-analysis had been appropriate, we planned to compute effect sizes and measures of variance using standard methods and to perform Knapp-Hartung random-effects meta-analysis. If heterogeneity was encountered, we planned to use meta-regression to explore possible causes.

For KQ3 on patient factors and tumor characteristics, we planned to calculate for each study the association between a patient factor (e.g., age) and comparative accuracy or effectiveness (e.g., the difference in sensitivity between two tests). If appropriate, we would have meta-analyzed the correlations using standard techniques and Knapp-Hartung standard errors.

We refrained from specifying a numerical threshold for clinical significance of results in either sensitivity or specificity in this report, for two reasons. First, there is no agreement in the field on what threshold is appropriate. Second, clinical importance is a clinical judgment that is sensitive to numerous clinicians and patient factors.

Grading the Body of Evidence for Each Outcome

We determined the strength-of-evidence grade for the following outcomes:
- Comparative sensitivity (KQ1)

- Comparative specificity (KQ1)
- Comparative timeliness of treatment (KQ2)
- Comparative choice of treatment (KQ2)
- Comparative tumor response (KQ2)
- Comparative survival (KQ2)
- Comparative quality of life (KQ2)
- Comparative harms due to overtreatment (KQ2)
- Comparative harms due to undertreatment (KQ2)
- Association between age and comparative accuracy (KQ3)
- Association between body habitus and comparative accuracy (KQ3)
- Association between tumor characteristics and comparative accuracy (KQ3)
- Association between age and comparative effectiveness (KQ3)
- Association between body habitus and comparative effectiveness (KQ3)
- Association between tumor characteristics and comparative effectiveness (KQ3)

We determined each grade separately for each modality comparison (e.g., CT vs. PET/CT). For accuracy, we examined both sensitivity and specificity. We did not separately grade other accuracy-related outcomes (i.e., predictive values or likelihood ratios) because these grades would be redundant with the grades for accuracy since our estimates would be based on the same studies and the same quantitative syntheses.

We used the EPC system for grading evidence on diagnostic tests as described in the EPC guidance chapter by Singh et al. (2012).[20] This system uses up to eight domains as inputs (study limitations, directness, consistency, precision, publication bias, dose-response association, all plausible confounders would reduce the effect, and strength of association). The output is a grade for the strength of evidence: high, moderate, low, or insufficient (see Table 1). This grade is provided separately for each outcome of each comparison of each KQ. The grade refers to our confidence in the direction of effect when comparing two imaging technologies, not to the magnitude of the difference between technologies.

Table 1. Strength of evidence grades and definitions

Grade	Definition
High	**We are very confident that the estimate of effect lies close to the true effect for this outcome.** The body of evidence has few or no deficiencies. We believe that the findings are stable, that is, another study would not change the conclusions.
Moderate	**We are moderately confident that the estimate of effect lies close to the true effect for this outcome.** The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
Low	**We have limited confidence that the estimate of effect lies close to the true effect for this outcome.** The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
Insufficient	**We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome.** No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

Source: Singh et al. (2012).[20]

A grade of Insufficient was given when the evidence did not permit a conclusion for the outcome of interest and the two modalities being compared. For example, if the outcome is test accuracy and the comparison is CT to PET/CT, the evidence may permit a conclusion that either

1) CT is more accurate, 2) PET/CT is more accurate, or 3) the tests are similarly accurate. If none of these three conclusions could be drawn (as judged by three independent analysts), then evidence was graded Insufficient for that comparison. In order to conclude that two modalities differ for an outcome, we used a p value less than 0.05 two-tailed (i.e., the standard value for alpha). In order to conclude that two modalities are approximately equivalent for an outcome, we used the independent judgment of three analysts (with disagreements resolved by discussion).

If the evidence was sufficient to permit a conclusion, then the grade was deemed high, moderate, or low. The grade was provided by three independent raters, with discrepancies resolved by consensus. Specifically, each of three analysts considered all strength of evidence domains listed earlier, and decided on a rating for each evidence base, without knowledge of the ratings of the other two analysts. If any of the three ratings differed, a single rating was reached based on consensus discussion.

Below, we discuss the eight domains and how they were considered as inputs to the grade:

Study Limitations (see the section Assessment of Methodological Risk of Bias of Individual Studies above). If the evidence permits a conclusion, and all else being equal, a set of studies with low limitations yield a higher strength of evidence grade than a set of studies with moderate or high limitations.

Directness. Our initial inclusion criteria required direct comparisons between modalities, but we subsequently included studies of single modalities. Indirect comparisons meant downgrades to the strength of the evidence. This is because different sets of studies may have enrolled slightly different types of patients or used slightly different reference standards for determining patients' true SCLC stages.

Consistency. Consistency among study results was judged based on whether the studies' findings suggest the same direction of effect (e.g., that one test is better than another).

Precision. Precision of the combined study results was judged by an assessment of the meta-analytic CI, or if meta-analysis was not performed, by an assessment of the precision of the individual studies (based on CIs or numbers of patients).

Reporting bias. This was addressed by noting the presence of abstracts or ClinicalTrials.gov entries describing studies that did not subsequently appear as full published articles. If many such studies exist, this tends to decrease the strength of the evidence. We also considered the funding sources of the studies in determining the risk of reporting bias.

Dose-response association. This factor is used for studies of treatments and is not relevant for this topic.

All plausible confounders would reduce the effect. This domain acknowledged that a set of studies may be biased *against* finding a difference between two modalities, and yet the studies still found an important difference. Thus, if the studies had controlled for the confounders, the effect would have been even larger. This domain will generally increase the strength-of-evidence grade.

Strength of association. While the Cochrane Collaboration and other reviewers have objective criteria for defining this domain in the context of treatments, no such criteria exist for diagnostic test accuracy. Therefore, this domain was judged by EPC team members based on whether the strength of the effect (e.g., the extent of difference in accuracy between two tests) is so large that the potential study biases could not explain it. If true, this domain will generally increase the strength-of-evidence grade.

Peer Review and Public Commentary

Peer reviewers were invited to provide written comments on the draft report based on their clinical, content, or methodologic expertise. Peer-review comments on the preliminary draft have been be considered by the EPC in preparation of the final version of the report. Dispositions of the peer- review comments are documented and will be published 3 months after publication of the evidence report.

Results

Results of Literature Searches

We depict the literature selection process in Figure 2. Searches identified 2,880 citations, of which we excluded 2,637. The most common reasons for exclusion were studies of other conditions (e.g., non-small-cell lung cancer), case reports, studies of treatments, and other studies not addressing staging. We retrieved the other 243 articles, of which we excluded 236. The most common reasons were studies with fewer than 10 patients with SCLC and studies of other conditions. See Appendix B for a list of the publications excluded at the full article level. We included the remaining seven publications. Our search of Clinicaltrials.gov identified no additional relevant studies.

All seven studies were included for KQ1, and none were included for KQs 2 or 3. Two studies were conducted in South Korea, and one each in Japan, Taiwan, Spain, Germany, and Denmark. The only study not published in English was one from Spain.[21] The studies enrolled a total of 408 patients with SCLC, with average ages ranging from 56 to 68, and the percentage of patients who were female ranged from 15 percent to 62 percent. Start dates ranged from 1999 to 2008, and the median duration of patient enrollment was about 5 years. Four studies were retrospective, and three were prospective. Only one study[22] reported its funding source (the German Cancer Foundation, which likely would not have a vested interest in some imaging technologies over others), and two other studies[23,24] reported that there were no financial conflicts of interest to disclose.

All evidence tables appear in Appendix C, including general study information (Table C-1), patient characteristics (Table C-2), general test details (Table C-3), readers and reference standards (Table C-4), concordance data (Table C-5), accuracy data (Table C-6), and our analyses of accuracy data (Table C-7). Of the seven studies, three[23-25] reported the comparative accuracy of two or more tests, and four[21,22,26,27] reported single-test accuracy. One[25] of the comparative accuracy studies also reported concordance data.

Regarding the imaging tests performed:

- Three studies[24,25,27] reported data on "standard staging" or "conventional staging." This involved multiple tests, typically history, clinical exam, chest x-ray, bone marrow biopsy, and possibly MRI or CT of the brain.
- Three studies[22,23,25] reported data on whole-body bone scintigraphy with Tc99m-MDP, using a dose of 500-900 MBq 2 to 3 hours before the scan, and a dual-head camera
- Two studies[22,25] reported data on MDCT, but authors provided few details.
- Four studies[21,23-25] reported data on PET/CT using FDG (dose range 400–550 MBq). One was specifically of the brain,[21] and the others three were presumably whole body. All were dedicated PET/CT scanners: two were the GE Discovery system, one was the Phillips Gemini scanner, and one was the Siemens Biograph Sensation.
- One study[26] reported data on EBUS, using a convex probe integrated with convex transducer; a 22-gauge needle was used for needle aspiration.
- No studies reported data on MRI, PET/MRI, or EUS.

For three studies of comparative accuracy of imaging tests, the elapsed time between the tests was a median of 5 days in one study,[23] a maximum of 7 days in another study,[25] and not reported by the third study.[24] Test readers were generally experienced, but authors mentioned little about resolving difference among different readers. Reference standards were based on multiple

considerations such as histology if available, clinical followup, progression on subsequent scans, and other imaging results such as MRI.

Our risk-of-bias assessments appear in Appendix D in Figure D-1 and Figure D-2. Of the three studies reporting comparative accuracy, we rated two as moderate risk of bias and one as high risk-of-bias. The moderate ratings were due to unknown spectrum bias, lack of reporting of whether test readers had the same clinical information available when interpreting different tests, and the use of test results in determining the reference standard. The one high-risk-of-bias rating was due to the above problems as well as the probability of spectrum bias, not reporting the elapsed time between imaging tests, and non-complementary knowledge available to different test readers.

The four single-test accuracy studies were all rated as moderate risk of bias. Reasons for the moderate rating varied across studies, but common problems were not accounting for inter-reader differences and not blinding the reference standard assessment to test results or other clinical information.

Figure 2. Literature flow diagram
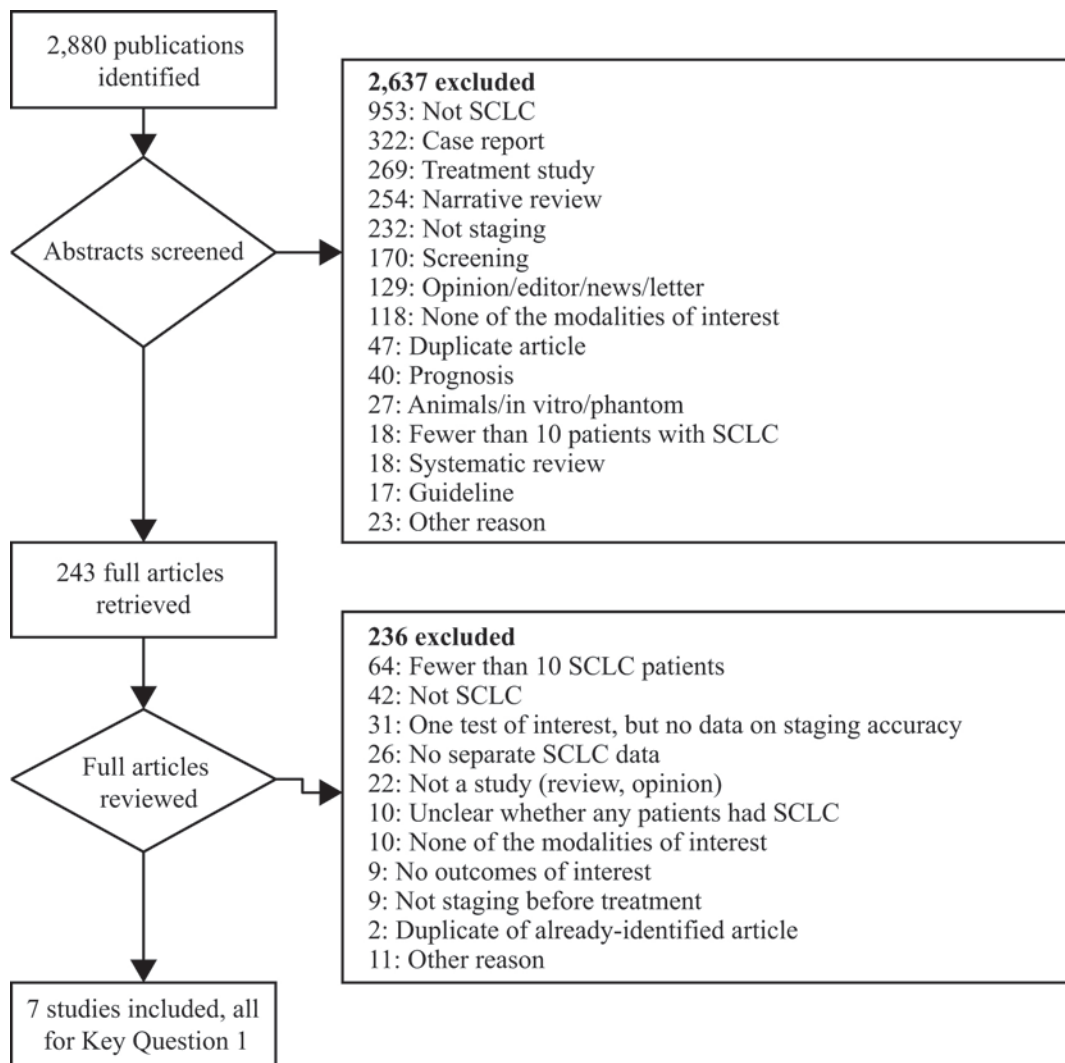
SCLC = small cell lung cancer

Key Question 1: Concordance and Comparative Accuracy

In this section, we address the following KQ:

KQ1: What are the test concordance and comparative accuracy of imaging tests (MDCT, PET/CT, MRI, PET/MRI, EBUS, EUS, bone scintigraphy) for the pretreatment staging of SCLC?

We first briefly summarize test concordance data, and then the rest of the section concerns comparative accuracy.

Test Concordance

One study[25] reported test-test concordance data for three imaging tests (MDCT, FDG PET/CT, and bone scintigraphy). The data appear in Table C-5 of Appendix C. For various staging determinations (T stage, N stage, pleural effusion, metastases to ipsilateral lung, metastases to contralateral lung, metastases to the liver, metastases to the adrenal glands, and metastases to extra-thoracic lymph nodes), authors reported high agreement between MDCT and FDG PET/CT, ranging from 86 to 97 percent. For the assessment of osseous involvement, however, agreement was lower (83 percent between MDCT and FDG PET/CT; 46 percent between MDCT and bone scintigraphy; 57 percent between FDG PET/CT and bone scintigraphy). The same study also reported the accuracy of these modalities for assessing osseous metastases, and these data are discussed (along with all other accuracy data) in the next section.

Comparative Accuracy

An overview of the included accuracy data appears in Table 2. Studies reported numerous staging determinations (e.g., whether the patient has limited or extensive disease), but the evidence for any given determination and modality comparison was limited. The largest evidence base involved the comparison of FDG PET/CT to bone scintigraphy in the determination of osseous (bone or bone marrow) metastases; this evidence base comprised two studies making direct comparisons (combined n=123) and a single study reporting only bone scintigraphy accuracy data (n=76).

Below, we discuss the results separately for each of eight staging determinations (LD/ED, metastases to osseous structures (bone or bone marrow), lymph node involvement, metastases to adrenal glands, metastases to the liver, metastases to the spleen, any distant metastases, and metastases to the brain).

Table 2. Overview of included accuracy data

Staging Determination	Studies Making Direct Comparisons in Accuracy Between Imaging Modalities	Studies Reporting Accuracy Data on a Single Imaging Modality (i.e., for indirect comparisons)
Limited or extensive disease	Standard staging* vs. FDG PET/CT; 1 study, n=28	Standard staging only*; 1 study, n=25
Presence of metastases to osseous structures (bone or bone marrow)	MDCT vs. Bone scintigraphy; 1 study, n=28 MDCT vs. FDG PET/CT; 1 study, n=29 Bone scintigraphy vs. FDG PET/CT; 2 studies, n=123	Bone scintigraphy only; 1 study, n=76

Staging Determination	Studies Making Direct Comparisons in Accuracy Between Imaging Modalities	Studies Reporting Accuracy Data on a Single Imaging Modality (i.e., for indirect comparisons)
Presence of lymph node involvement	None	MDCT only; 1 study, n=118 EBUS only; 1 study, n=36
Presence of metastases to adrenal glands	None	MDCT only; 1 study, n=120
Presence of metastases to the liver	None	MDCT only; 1 study, n=120
Presence of metastases to the spleen	None	MDCT only; 1 study, N=120
Presence of any distant metastases	Standard staging* vs. standard staging* plus FDG PET/CT; 1 study, N=73	None
Presence of metastases to the brain	None	FDG PET/CT only; 1 study, N=21

FDG PET/CT = [18F]-fluorodeoxyglucose positron emission tomography/computed tomography; MDCT = multidetector computed tomography

* Standard" staging of SCLC is not a precisely defined term, but may involve numerous investigations including history, physical exam, chest x-ray, chest CT, bone scan, bone marrow aspiration, and/or MRI or CT of the brain.

A detailed description of reference standards for each study is provided in Appendix C, Table C-4. As a reminder, studies utilizing an imaging test *alone* as a reference standard were considered to provide information regarding test concordance, but not comparative accuracy. Reference standards for comparative accuracy studies varied widely, from clinical follow up to composite measures consisting of several possible elements (i.e., positive biopsy *or* confirmation by CT *or* MRI *or* progression on subsequent imaging).

Limited or Extensive Disease

Two studies[25,27] with moderate risk of bias reported data on the ability of imaging tests to determine whether patients with SCLC had LD or ED. Both reported the use of "standard staging," which is a combination of multiple testing procedures such as chest x-ray, bone marrow biopsy and possibly MRI or CT of the brain. In addition, Fischer et al. (2007)[25] reported data on the performance of FDG PET/CT in staging disease as LD or ED. The data suggest that both standard staging and FDG PET/CT performed well (e.g., 86 percent or 95 percent for the sensitivity at detecting ED, or specificity of 90 percent or more at ruling out ED). However, both studies were small (n=28 and n=25, respectively), and the overall data were too imprecise to permit any conclusions about relative accuracy.

Metastases to Osseous Structures (Bone or Bone Marrow)

Three studies with moderate risk of bias reported data on the ability of imaging tests to determine whether patients had metastases to osseous structures (bone or bone marrow). One study compared FDG PET/CT to bone scintigraphy;[23] another study compared CT to FDG PET/CT to bone scintigraphy;[25] the third study provided data only on bone scintigraphy.[22] The sensitivity and specificity data are shown in Figure 3. For bone scintigraphy, the data from Fischer et al. (2007)[25] are shown twice: once if equivocal bone scans are treated as positive tests and another if equivocal bone scans are treated as negative tests.

Our statistical tests of these data indicated FDG PET/CT was more sensitive than bone scintigraphy in the Lee study; the Fischer study replicated this finding if equivocal bone scans were treated as negative tests. If they were considered positive tests, then for the Fischer study FDG PET/CT was more specific than bone scintigraphy. These are direct comparisons. Considered together with the bone scintigraphy results in the Brink study, we concluded that FDG PET/CT is more sensitive than bone scintigraphy for detecting osseous metastases. There was not sufficient data to allow us to assess comparative sensitivity by metastasis site.

Comparing FDG PET/CT to MDCT, only the Fischer study made a direct comparison, and FDG PET/CT was more sensitive, but not more specific. Thus, we concluded that FDG PET/CT is more sensitive than MDCT for detecting osseous metastases. Too little data exist to permit a conclusion on specificity, so we cannot rule out FDG PET/CT being less specific than MDCT.

Finally, with regard to comparing MDCT with bone scintigraphy, treating equivocal bone scans as positive resulted in a statistical advantage in sensitivity for bone scintigraphy but a statistical advantage in specificity for MDCT. By contrast, if equivocal bone scans were treated as negatives in Fischer, we found no statistical differences in sensitivity or specificity. Other data on bone scintigraphy from Brink and Lee do not suggest marked differences from MDCT. However, the data were too imprecise to permit any conclusions about the comparison of MDCT and bone scintigraphy with respect to osseous metastases.

Figure 3. ROC plots of accuracy data for osseous metastases

Note: The three plots show the data on osseous metastases in ROC space. The left plot is for bone scintigraphy, the middle plot is for MDCT, and the right plot is for FDG PET/CT. They each show two accuracy measures; sensitivity and specificity. Sensitivity is the percentage of patients who are deemed by the test to have osseous metastases, among those who truly do have osseous metastases. Specificity, by contrast, is the percentage of patients who are deemed by the test to *not* have osseous metastases, among those who truly do not have osseous metastases. The best possible score for both measures is 100 percent. In each plot, the horizontal axis is specificity (with higher specificity as one moves to the left in the plot), and the vertical axis is sensitivity (with higher sensitivity as one moves up in the plot). The 45-degree line represents chance. Thus, an optimal modality would have data in the upper left corner of the plot. Each point is a study (with different studies represented by different shapes). The error bars represent 95% confidence intervals. The study by Brink provided data only on bone scintigraphy, which explains why it does not appear in the other two plots. The study by Lee compared bone scintigraphy and FDG- PET/CT, and the study by Fischer compared all three modalities. The Fischer data are further complicated by the fact that some bone scintigraphy results were considered equivocal by the authors (i.e., neither clearly positive nor clearly negative). Treating equivocal results as positive (as shown with the point labeled "Fischer Equiv. POS") results in higher sensitivity than treating equivocal bone scan results as negative (as shown with the point labeled "Fischer Equiv. NEG"), but lower specificity. For PET/CT, both studies had point estimates for specificity of 100 percent, but the confidence intervals around those estimates were too wide to permit conclusions about relative specificity.

Lymph Node Involvement

Two moderate-risk-of-bias studies reported data on the ability of imaging tests to determine whether patients had lymph node involvement. One study used EBUS for this purpose;[26] the other used MDCT.[22] The EBUS study reported better results (96 percent sensitivity, 100 percent specificity) than the CT study (70 percent sensitivity, 94 percent specificity). However, patients in the CT study (which defined a positive lymph node as >1cm) may have had cancers that were more difficult to assess for lymph node involvement, which would bias the comparison against CT. The indirect nature of the comparison precludes conclusions.

Metastases to Adrenal Glands, Liver, or Spleen

A single study[22] with moderate risk of bias reported the single-test performance of MDCT for detecting metastases to the adrenal glands, liver, or spleen (separate results for each of these three types). Because such data were not reported for other imaging modalities by this or other studies, we drew no conclusions about how different modalities compare.

Any Distant Metastases

A single study[24] with high risk of bias reported the comparative performance of standard staging versus standard staging plus FDG PET/CT for detecting any distant metastases. The study reported a large difference in sensitivity (92 percent for standard staging plus FDG PET/CT vs. only 46 percent for standard staging), and this difference was statistically significant. The specificities were similar (96 percent for standard staging plus FDG PET/CT vs. 100 percent for standard staging), but the precision was too high to permit a conclusion of equivalence on specificity. We deemed the evidence sufficient to permit the conclusion that standard staging plus FDG PET/CT is more sensitive than standard staging alone for detecting any distant metastases. Given that it was only a single study that had a high risk of bias, we rated the strength of evidence as low.

Metastases to the Brain

A single study with moderate risk of bias reported the single-test performance of FDG PET/CT of the brain for detecting brain metastases. Because such data were not reported for other modalities by this or other studies, we drew no conclusions about how different modalities compare in the assessment of brain metastases.

Key Question 2: Comparative Effectiveness

In this section, we address the following KQ:

KQ2: When used for the pretreatment staging of SCLC, what is the comparative effectiveness of imaging tests (MDCT, PET/CT, MRI, PET/MRI, EBUS, EUS, bone scintigraphy) on later outcomes?

No studies were included for this question.

Key Question 3: Factors Associated with Comparative Outcomes

In this section, we address the following KQ:

KQ3. To what extent are the following factors associated with the comparative accuracy or effectiveness of imaging tests (MDCT, PET/CT, MRI, PET/MRI, EBUS, EUS, bone scintigraphy) when used for the pretreatment staging of SCLC?

No studies were included for this question. No studies had been excluded due to the fact that we required such comparisons to be planned in advance.

Discussion

Key Findings and Strength of Evidence

Based on the evidence we reviewed, we concluded the following:

- FDG PET/CT is more sensitive than bone scintigraphy at detecting osseous metastases (Strength of Evidence: low)
- FDG PET/CT is more sensitive than CT at detecting osseous metastases (Strength of Evidence: low)
- Standard staging plus FDG PET/CT is more sensitive than standard staging alone at detecting any distant metastases (Strength of Evidence: low)

Our strength-of-evidence judgments for these conclusions, along with the other evidence that was insufficient to permit conclusions, are listed in Table 3 below. Note that all three of our conclusions involve the superior sensitivity of FDG PET/CT. We discuss this commonality below in the sections "Finds in Relationship to What Is Already Known" and "Implications for Clinical and Policy Decisionmaking."

Table 3. Strength of evidence grades

Staging Determination	Test Comparison	Number of Studies and Number of Patients	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Magnitude of Effect	SOE Grade*	Conclusion
LD vs. ED	Standard staging[†] vs. FDG PET/CT	Direct comparison: 1 study[25] of 28 patients Indirect comparison: 1 study[27] of standard staging of 25 patients	Moderate	Mixed	Unknown	Imprecise	None suspected	Not large	Insufficient	NA
Osseous metastases	FDG PET/CT vs. bone scintigraphy	Direct comparison: 2 studies[23,25] of 123 patients Indirect comparison: 1 study[22] of bone scintigraphy of 76 patients	Moderate	Mixed	Consistent	Imprecise	None suspected	Large	Low	FDG PET/CT more sensitive
Osseous metastases	CT vs. FDG PET/CT	Direct comparison: 1 study[25] of 29 patients	Moderate	Direct	Unknown	Imprecise	None suspected	Large	Low	FDG PET/CT more sensitive
Osseous metastases	CT vs. bone scintigraphy	Direct comparison: 1 study[25] of 28 patients Indirect comparison: 1 study[22] of bone scintigraphy of 76 patients	Moderate	Mixed	Unknown	Imprecise	None suspected	Not large	Insufficient	NA
Lymph node involvement	CT vs. EBUS	Indirect comparison: 1 study[22] of CT of 118 patients, and 1 study[26] of EBUS of 36 patients	Moderate	Indirect	Unknown	Imprecise	None suspected	Not large	Insufficient	NA
Metastases to adrenal glands	CT vs. anything else	Indirect comparison: 1 study[22] of CT of 120 patients	Moderate	Indirect	Unknown	Unknown	None suspected	Unknown	Insufficient	NA
Metastases to liver	CT vs. .anything else	Indirect comparison: 1 study[22] of CT of 120 patients	Moderate	Indirect	Unknown	Unknown	None suspected	Unknown	Insufficient	NA
Metastases to spleen	CT vs. anything else	Indirect comparison: 1 study[22] of CT of 120 patients	Moderate	Indirect	Unknown	Unknown	None suspected	Unknown	Insufficient	NA

Staging Determination	Test Comparison	Number of Studies and Number of Patients	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Magnitude of Effect	SOE Grade*	Conclusion
Any distant metastasis	Standard staging[†] vs. Standard staging[†] plus FDG PET/CT	Direct comparison: 1 study[24] of 73 patients	High	Direct	Unknown	Imprecise	None suspected	Large	Low	Standard staging[†] plus FDG PET/CT more sensitive
Metastases to brain	FDG PET/CT of the brain vs. anything else	Indirect comparison: 1 study[21] of FDG PET/CT of 21 patients	Moderate	Indirect	Unknown	Imprecise	None suspected	Unknown	Insufficient	NA

EBUS = endobronchial ultrasound; ED = extensive stage disease; FDG PET/CT = [^{18}F]-fluorodeoxyglucose positron emission tomography/computed tomography; LD = limited stage disease; NA = not applicable since evidence was insufficient to permit a conclusion for this staging determination for this test-test comparison; SOE = strength of evidence

* The SOE grade indicates our confidence in the conclusion about the direction of the effect, not about the magnitude of the difference.

[†] Standard" staging of SCLC is not a precisely defined term, but may involve numerous investigations including history, physical exam, chest x-ray, chest CT, bone scan, bone marrow aspiration, and/or MRI or CT of the brain.

Findings in Relationship to What Is Already Known

Our searches found eight previous systematic reviews that evaluated imaging modalities for pretreatment staging of SCLC. We found no previous systematic reviews of evidence on CT, MRI, or bone scintigraphy for SCLC staging. Thus, our conclusions for these modalities (and documentation of lack of evidence in many instances) represent new knowledge that can guide future investigations.

All prior systematic reviews on imaging modalities for SCLC staging focused on PET. Some reviews included studies using combined PET/CT scanners, but most had data only from standalone PET scanning, which is no longer the current standard of practice. Our review focuses on PET/CT, which will more accurately reflect choices available today.

The most relevant previous reviews were undertaken in the development of American College of Chest Physicians (ACCP) guidelines for management of SCLC. Two editions of these guidelines included reviews meeting our inclusion criteria. In the review by Samson et al. (2007),[28] for the second edition of the guidelines, only one KQ addressed the role of imaging tests in SCLC staging. This question asked whether the addition of PET scanning improved staging of SCLC. The authors identified six studies of PET for various staging indications, deemed the evidence to be poor quality, and drew no conclusions from it. This and the previous reviews could not use a consistent reference standard for comparison to PET; they had to use the reference standards reported by the investigators of each study.

Since the publication of that review, combined PET/CT systems have replaced standalone PET scanners at most U.S. hospitals, so our review excluded standalone PET, which resulted in exclusion of all the studies Samson et al. cited.[28] Like Samson et al, we also found the evidence on PET/CT to be weak, but nevertheless concluded that PET/CT has superior sensitivity compared with either CT alone or bone scintigraphy for detecting osseous metastases; we also concluded that PET/CT has superior sensitivity to standard staging for detecting any distant metastases overall at the patient level. Samson et al. saw a similar trend in the standalone PET studies they reviewed.[28] We are more willing to state conclusions from the weak evidence because the AHRQ evidence grading system expresses the degree of weakness and makes clear that additional evidence could overturn our conclusions.

The third edition of the ACCP guidelines included the KQ "what is the ability of PET imaging to determine the stage of cancer?" The review concluded that PET was superior to standard staging modalities for detecting metastases, with the exception of brain metastases, where PET was inferior to CT and MR. The resulting guideline recommended PET for patients with SCLC clinically diagnosed as limited-stage.

While the review for ACCP by Jett et al. (2013)[10] was published relatively recently, it included studies dating back as far as 2001; nearly all the studies used standalone PET. Direct integration of anatomic data from CT in combined PET/CT may mitigate some inaccuracy of PET in diagnosing brain metastases. Indeed, when looking only at PET/CT compared with standard staging, we could not conclude that PET/CT was inferior.

The Jett review also analyzed how often PET resulted in a change of management plans for patients with SCLC.[10] All but one study used standalone PET, but a substantial number of patients remained whose management was changed as the result of PET findings. Like we did, Jett et al. recognized that the absence of a reliable reference diagnosis in most of these studies precludes determination that PET is the superior imaging modality. Jett et al. also commented on

the lack of uniformity in study methods and data analysis; these issues persist in the evidence base for PET/CT and hindered our ability to draw any conclusions.

Neither of the ACCP guideline reviews offered a granular categorization and analysis of data such as we have provided. Therefore, although we were unable to draw many conclusions about the comparative effectiveness of PET/CT, we have provided a thorough and detailed description of the current available evidence that future investigators can use to address these important evidence gaps.

The two other systematic reviews of SCLC staging—Lu et al. (2014)[29] and Ruben et al (2012)[30] –were similar in that the majority of studies in both were small and included standalone PET. However, the focus of the two reviews differed. Lu et al. sought to determine a summary sensitivity and specificity of PET for distinguishing between patients with LD and ED, concluding that the sensitivity of PET was 98.1 percent (95% CI 94.7%–99.6%) and the specificity was 97.5 percent (95% CI 93.0%–99.5%). We did not find sufficient data to permit similar summary estimates for PET/CT. Ruben et al. studied the effect of PET on patient management, concluding that changes to treatment plans occurred in nearly one-third of patients having PET scans. Jett et al. arrived at a similar conclusion.[10] In the absence of a gold standard reference, it is not possible to ascertain whether those changes resulted in better or worse outcomes for the patient due to denial of potentially valuable treatment (false-positive PET) or avoidance of unnecessary treatment and its side effects (true-positive PET).

Three previous reviews—Ravanal (2012),[31] Helwig et al. (2009),[32] and Ung et al. (2007)[33]— covered lung cancer staging in general, making little reference to SCLC in particular. As the clinical course of SCLC is considerably different from that of other forms of lung cancer, decisions on staging and treatment should be based on evidence specific to SCLC. The effects of differences between cancer types could outweigh the differences in effectiveness between one modality and another as seen in a study of mixed types of lung cancer. The systematic review published by the U.K. National Health Service on PET for various cancer indications[34] reported that as of the time of their searches (August 2005) no published studies existed on combined PET/CT for diagnosis, staging, or restaging of SCLC.

Implications for Clinical and Policy Decisionmaking

Based on our review of the current evidence, our results suggest two overall conclusions. First, compared with CT and bone scintigraphy (imaging modalities commonly used for staging) FDG PET/CT is more sensitive for detecting osseous metastases in patients with SCLC. Our findings suggest that clinicians evaluating patients for the presence of osseous metastases may consider forgoing bone scintigraphy and routinely use FDG PET/CT instead. Second, for patients with SCLC who have undergone standard staging, the addition of FDG PET/CT increases sensitivity for detecting any distant metastases overall at the patient level.

The evidence base did not allow us to draw conclusions about the comparative specificity of FDG PET/CT compared with these other modalities; thus, we acknowledge that any of the modalities could yield false positives. If a false positive led to inaccurate "upstaging" to extensive disease, a patient might only receive a palliative regimen instead of aggressive chemotherapy aimed at cure. Unfortunately, as we found only 1 study addressing EBUS and no studies evaluating EUS, MRI, or PET/MRI for inclusion we were unable to assess their comparative accuracy for FDG PET/CT.

SCLC is an aggressive cancer, and timely staging is important to determine treatment decisions based on whether patients have limited or extensive disease. Currently, as part of the

standard staging process, patients may undergo bone scintigraphy, CT of the abdomen and pelvis, brain MRI, and FDG-PET/CT. Reducing the total number of tests may improve the timeliness of staging and permit faster initiation of treatment.

Higher sensitivity also has other potential important implications for patient care. First, better detection of metastases can improve patient selection for optimal therapy. The higher sensitivity of FDG PET/CT would provide clinicians the confidence to offer a comprehensive stage-based treatment plan. Second, earlier detection of extensive disease would spare patients from more aggressive chemotherapy and radiation protocols used for patients with LD. Earlier initiation of palliative measures may result in improved quality of life, an important consideration given the current poor prognosis of this disease. Third, improved sensitivity and timeliness of staging may potentially improve the ability of ongoing research trials to prognosticate and detect therapeutic efficacy.

Finally, our results suggest potential resource implications. Although FDG PET/CT may be more expensive than CT and bone scintigraphy, some patients may undergo all three tests when evaluated for osseous and other distant metastases outside the brain. Eliminating routine use of bone scintigraphy from SCLC staging protocols in favor FDG-PET/CT could potentially result in some cost savings.

Applicability

We judged the applicability of the evidence based on comparison of the patients, interventions, and settings found in the research studies to those typically used in clinical practice. The typical mean age of patients in our included studies was in the seventh decade of life. Based on the National Cancer Institute's (NCI) Surveillance Epidemiology and End Results (SEER) database, in 2011, 82 percent of those living with lung cancer were 60 years of age or older.[35] Six of seven studies included mostly males (72 percent to 86 percent), and one included more females (62 percent). Based on the NCI SEER database, in 2011, men develop lung cancer more often than women (1.3:1 male/female ratio).[35] Overall, the applicability of evidence in the included studies to typical patients appears reasonable.

With regard to imaging tests, the studies of FDG-PET/CT employed patient preparation and acquisition parameters typical of those used in clinical practice,[36] despite minor variations in image-acquisition parameters used in these included studies. Similarly, bone scintigraphy performed in these studies was obtained with techniques typical of those used in clinical practice.[37] EBUS-FNA is also frequently used as a diagnostic test for staging SCLC, and the one study addressing this technique described it similarly to that used in clinical practice.

Studies were conducted in university-based academic or teaching hospitals outside the United States, which may limit the applicability of the results to community hospitals and hospitals in the United States. Community hospitals may differ from the settings in the included studies with respect to the experience of the technicians administering the imaging test or the interpretation skills of those reading the imaging results. U.S. hospitals may differ from those outside the United States in terms of their specified protocols for the diagnostic workup and management of patients with SCLC.

Limitations of the Comparative-Effectiveness Review Process

In this section, we discuss three challenges we faced in developing this review: (1) whether to include the concept of diagnosis, (2) whether to include non-English studies, and (3) how to assess the risk of bias of comparative accuracy studies.

The first challenge arose from the fact that imaging tests often serve the dual purpose of diagnosing and staging lung cancer. By definition, when imaging is used for diagnosis, it remains unknown whether the patient has SCLC. Lung symptoms may be due to a variety of causes, including SCLC, but also NSCLC or metastases from another site, in addition to noncancerous causes. As all these etiologies are possibilities during the process of diagnosis, including the concept of diagnosis would have required including studies of imaging tests for diagnosing any of these possibilities. Given the defined time and budget, such a scope was untenable, and so we chose to focus on the staging of SCLC.

A second challenge involved whether to include non-English studies. We initially excluded them due to the cost of translation and the possibility that the design and results of such studies may not be applicable to the United States. However, when confronted with the small size of the resulting literature (5 studies), we reconsidered the 28 studies that we had excluded for this reason. Of those, two studies met our inclusion criteria.

A third challenge involved assessing the risk of bias of comparative accuracy studies. The basic target for this assessment is whether a study comparing the staging accuracy of test A to that of test B (measuring both against a common reference standard) was biased in favor of one of the two tests. Ideally, we could have used an existing off-the-shelf assessment instrument. However, current risk-of-bias instruments for diagnostic studies (e.g., QUADAS-2) do not sufficiently address this topic because they were designed for single-test accuracy studies (e.g., did this study provide unbiased estimates of test accuracy). We thought carefully about potential areas of bias and devised our own instrument for this purpose. The instrument has not been tested by others, and its appropriateness should be verified.

Limitations of the Evidence Base

The seven included studies were limited in numerous ways. The most prominent ways were (1) lack of test-test comparisons, (2) small sample sizes, (3) questionable reference standards, and (4) lack of comparative-effectiveness designs.

First, only three studies directly compared the accuracy of different imaging tests. More test-test comparisons might have permitted us to draw more conclusions from the evidence. Indirect comparisons are fraught with difficulty because important inter-study differences in patient populations could confound any comparisons.

Second, the seven studies were generally small (the median sample size was 36, with a range from 21 to 120). This means large imprecision in statistical results may result, which in turn means insufficient evidence to make claims about test-test comparisons.

Third, studies' reference standards were often suboptimal. Studies generally used a combination of clinical history, cell pathology (only obtained for a portion of patients), other imaging tests, and clinical followup. These reflect the clinical reality of the process of staging SCLC, since it would be unethical to perform a biopsy on all possible sites of metastases in a patient. Thus, the test accuracy estimates reported by all studies are tentative. The direction of possible bias resulting from the lack of good reference standards in these studies is not

predictable, so it simply increases the uncertainty of the results. For instance, incorporation of the study test into the reference standard (incorporation bias) would tend to increase positive predictive value, but other shortcomings such as lack of histologic verification of positives could decrease positive predictive value.

Fourth, and perhaps most important, none of the studies were designed to allow inferences about *comparative effectiveness*. Generally, all patients in a given study received the same battery of imaging tests; thus, subsequent outcomes (e.g., management strategies, survival time and quality of life) could not be attributed to any single test or test strategy. The clinical value of an imaging test is best measured by using it for only some of the patients and comparing their health outcomes to a carefully matched group of other patients who did not receive that imaging test. Granted, such a design is exceedingly rare in the medical literature. Without such designs, however, the true patient-oriented value of any give staging modality cannot be determined.

Research Gaps

For characterizing gaps, we used the EPC framework proposed by Robinson et al. (2011).[38] That system suggests that reviewers identify a set of important gaps and determine the most important reason for each gap. Each gap should be assigned one of the following reasons for the inability to draw conclusions:

a. Insufficient or imprecise information: no studies, limited number of studies, sample sizes too small, estimate of effect is imprecise
b. Information at risk of bias: inappropriate study design; major methodologic limitations in studies
c. Inconsistency or unknown consistency: consistency unknown (only 1 study); inconsistent results across studies
d. Not the right information: results not applicable to population of interest; inadequate duration of interventions/comparisons; inadequate duration of followup; optimal/most important outcomes not addressed; results not applicable to setting of interest

We found three primary gaps in the literature on imaging tests for the pretreatment staging of SCLC. The first concerns the dearth of evidence on several tests of interest, particularly MRI, EBUS, EUS, and PET/MRI. This gap exists due to reason a, Insufficient information. Note that we did not restrict our search to studies of particular staging purposes of these tests even though some are typically used for specific targets (e.g., brain MRI). EBUS and EUS may be used as much for diagnosis as for staging, so that may partially explain the lack of direct evidence on staging SCLC. PET/MRI is a relatively new technology, and we predicted that little would be identified, but future systematic reviews may uncover evidence as it becomes more widespread.

The second gap concerns the absence of study designs to inform the optimal imaging plan for the pretreatment staging of SCLC. Thus, the reason for this gap is reason b, Information at risk of bias. At least three underlying sources exist for the gap: (1) the general lack of direct comparisons of different imaging modalities; (2) the use of mixed reference standards (based on partial histology, other imaging tests, and clinical followup) since not all patients' true stage can be determined before treatment; and (3) the complete lack of studies of comparative effectiveness with patient-oriented outcomes such as management strategy or survival after receiving different test strategies. We recognize that some of these problems are due to the clinical reality that SCLC is fast-growing, necessitating timely initiation of treatment.

The third gap concerns KQ3, which addressed the extent to which comparative accuracy or effectiveness are associated with patient factors (comorbidities, body habitus, tumor

characteristics). We identified no studies for this question, so this gap exists due to reason a, Insufficient information. Addressing this problem would be easier than addressing the problems listed in the previous paragraph. As most patient records already contain information on patient characteristics, future research could stratify their accuracy results accordingly. Armed with this more detailed data, clinicians and policymakers could possibly recommend tailoring specific strategies for different patient subgroups.

Our knowledge of the biology of SCLC has increased tremendously over the past few decades. Many molecular targets have been identified. These have been used as potential targets for diagnostic and therapeutic intervention. Despite several attempts, these advances have not translated into a meaningful survival benefit. Future advances in SCLC should focus on efforts to refine imaging strategies to identify patients with actionable mutations, and identify specific sub-populations within SCLC suitable for targeted therapy.

Conclusions

Comparative evidence on the pretreatment staging of SCLC is sparse. We found some low-strength evidence suggesting that FDG PET/CT is more sensitive than CT and bone scintigraphy for assessing osseous metastases, and that standard staging plus FDG PET/CT is more sensitive than standard staging alone at detecting any distant metastases.

References

1. American Cancer Society (ACS). Cancer facts & figures 2015. Atlanta, GA: American Cancer Society (ACS); 2015. 56 p.

2. SEER Cancer Statistics Review, 1975-2011. Bethesda, MD: National Cancer Institute; 31 p.

3. American Cancer Society. Cancer prevention & early detection facts & figures 2013. Atlanta (GA): American Cancer Society; 2013. 65 p.

4. National Cancer Institute (NCI). Small cell lung cancer treatment (PDQ) health professional version. Bethesda, MD: National Cancer Institute (NCI), National Institutes of Health (NIH); 2014 Feb 21. http://www.cancer.gov/cancertopics/pdq/treatment/small-cell-lung/healthprofessional/page1. Accessed 2014 Jun 11.

5. Shepherd FA, Crowley J, Van Houtte P, et al. The International Association for the Study of Lung Cancer Lung Cancer Staging Project: proposals regarding the clinical staging of small cell lung cancer in the forthcoming (seventh) edition of the tumor, node, metastasis classification for lung cancer. J Thorac Oncol. 2007 Dec;2(12):1067-77. PMID: 18090577

6. Kalemkerian GP, Akerley W, Bogner P, et al. Small cell lung cancer. JNCCN J Natl Compr Canc Netw. 2013 Jan 1;11(1):78-98. PMID: 23307984

7. Micke P, Faldum A, Metz T, et al. Staging small cell lung cancer: Veterans Administration Lung Study Group versus International Association for the Study of Lung Cancer--what limits limited disease? Lung Cancer. 2002 Sep;37(3):271-6. PMID: 12234695

8. Trends in lung cancer morbidity and mortality. Chicago, IL: American Lung Association; 2012 Apr. 34 p.

9. Glisson BS, Byers LA. Pathobiology and staging of small cell carcinoma of the lung. In: Lilenbaum RC, Nicholson A, Jett JR, editors. UptoDate. Waltham, MA: UptoDate; 2013 May 07. http://www.uptodate.com/contents/pathobiology-and-staging-of-small-cell-carcinoma-of-the-lung?source=search_result&search=sclc&selectedTitle=2%7E150#H7. Accessed 2014 Jun 12.

10. Jett JR, Schild SE, Kesler KA, et al. Treatment of small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013 May;143(5 Suppl):e400S-19S. PMID: 23649448

11. Hillner BE, Tosteson AN, Song Y, Et al. Growth in the use of PET for six cancer types after coverage by medicare: additive or replacement? J Am Coll Radiol. 2012 Jan;9(1):33-41. PMID: 22221634

12. 2014 PET market summary report. Greenbelt, MD: IMV Info; 2014. http://www.imvinfo.com/index.aspx?sec=pet&sub=dis&itemid=200083. Accessed 2015 May 15.

13. New IMV survey shows slowing growth in PET medical imaging scans. Des Plaines (IL): PRWeb; 2012 Aug 12. http://www.prweb.com/releases/2012/8/prweb9820176.htm. Accessed 2015 May 18.

14. Lang K, Huang H, Lee DW, et al. National trends in advanced outpatient diagnostic imaging utilization: an analysis of the medical expenditure panel survey, 2000-2009. BMC Med Imag. 2013;13:40. PMID: 24279724

15. Ravenel JG, Rosenzweig KE, Kirsch J, et al. ACR appropriateness criteria non-invasive clinical staging of bronchogenic carcinoma. J Am Coll Radiol. 2014 Sep;11(9):849-56. PMID: 25086958

16. Whiting P, Rutjes AW, Reitsma JB, et al. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. BMC Med Res Methodol. 2003 Nov 10;3(1):25. PMID: 14606960

17. Harbord RM, Deeks JJ, Egger M, et al. A unification of models for meta-analysis of diagnostic accuracy studies. Biostatistics. 2007 Apr;8(2):239-51. PMID: 16698768

18. STATA statistics/data analysis. MP parallel edition. Ver. 10.0. College Station (TX): StataCorp; 1984-2007. Single user Stata for Windows. http://www.stata.com.

19. Trikalinos TA, Hoaglin DC, Small KM, et al. Evaluating practices and developing tools for comparative effectiveness reviews of diagnostic test accuracy: methods for the joint meta-analysis of multiple tests. Methods research report. (Prepared by the Tufts Evidence-based Practice Center, under Contract No. 290-2007-10055-I.) AHRQ publication no. 12(13)-EHC151-EF. Rockville, MD: Agency for Healthcare Research and Quality; 2013 Jan. 49 p. http://effectivehealthcare.ahrq.gov/ehc/products/291/1380/Methods%20Report_Evaluating-Practices-Developing-Tools_Final_01-14-2013.pdf.

20. Singh S, Chang S, Matchar DB, et al. Grading a body of evidence on diagnostic tests (AHRQ publication no. 12-EHC079-EF). Chapter 7 of Methods guide for medical test reviews (AHRQ publication no. 12-EHC017). Rockville, MD: Agency for Healthcare Research and Quality; 2012 Jun 1. http://effectivehealthcare.ahrq.gov/ehc/products/246/558/Methods-Guide-for-Medical-Test-Reviews_Full-Guide_20120530.pdf.

21. Palomar Munoz A, Garcia Vicente AM, Bellon Guardia ME, et al. Is a selective brain (18)F-FDG PET/CT study profitable in patients with small cell lung cancer? Rev Esp Med Nucl Imagen Mol. 2012 May;31(3):124-9. PMID: 21722995

22. Brink I, Schumacher T, Mix M, et al. Impact of [(18)F]FDG-PET on the primary staging of small-cell lung cancer. Eur J Nucl Med Mol Imaging. 2004 Dec;31(12):1614-20. PMID: 15258700

23. Lee JW, Lee SM, Lee HS, et al. Comparison of diagnostic ability between (99m)Tc-MDP bone scan and 18F-FDG PET/CT for bone metastasis in patients with small cell lung cancer. Ann Nucl Med. 2012 Oct;26(8):627-33. PMID: 22729551

24. Sohn BS, Lee DH, Kim EK, et al. The role of integrated 18F-FDG PET-CT as a staging tool for limited-stage small cell lung cancer: a retrospective study. Onkologie. 2012 Aug;35(7):432-8. PMID: 22846975

25. Fischer BM, Mortensen J, Langer SW, et al. A prospective study of PET/CT in initial staging of small-cell lung cancer: comparison with CT, bone scintigraphy and bone marrow analysis. Ann Oncol. 2007 Feb;18(2):338-45. PMID: 17060487

26. Wada H, Nakajima T, Yasufuku K, et al. Lymph node staging by endobronchial ultrasound-guided transbronchial needle aspiration in patients with small cell lung cancer. Ann Thorac Surg. 2010 Jul;90(1):229-34. PMID: 20609781

27. Shen YY, Shiau YC, Wang JJ, et al. Whole-body 18F-2-deoxyglucose positron emission tomography in primary staging small cell lung cancer. Anticancer Res. 2002;22(2):1257-64. PMID: 12168935

28. Samson DJ, Seidenfeld J, Simon GR, et al. Evidence for management of small cell lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). Chest. 2007 Sep;132(3 Suppl):314S-23S. PMID: 17873177

29. Lu YY, Chen JH, Liang JA, et al. 18F-FDG PET or PET/CT for detecting extensive disease in small-cell lung cancer: a systematic review and meta-analysis. Nucl Med Commun. 2014 Jul;35(7):697-703.

30. Ruben JD, Ball DL. The efficacy of PET staging for small-cell lung cancer: a systematic review and cost analysis in the Australian setting. J Thorac Oncol. 2012 Jun;7(6):1015-20. PMID: 22534816

31. Ravenel JG. Evidence-based imaging in lung cancer: a systematic review. J Thorac Imaging. 2012 Sep;27(5):315-24. PMID: 22914125

32. Hellwig D, Baum RP, Kirsch C. FDG-PET, PET/CT and conventional nuclear medicine procedures in the evaluation of lung cancer: a systematic review. Nuklearmedizin. 2009;48(2):59-69. PMID: 19333516

33. Ung YC, Maziak DE, Vanderveen JA, et al. 18Fluorodeoxyglucose positron emission tomography in the diagnosis and staging of lung cancer: a systematic review. J Natl Cancer Inst. 2007 Dec 5;99(23):1753-67. PMID: 18042932

34. Facey F, Bradbury I, Laking G, et al. Overview of the clinical effectiveness of positron emission tomography imaging in selected cancers. Health Technol Assess. 2007 Oct;11(44):iii-85. PMID: 17999839

35. Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review (CSR) 1975-2011. Bethesda, MD: National Cancer Institute (NCI); 2014 Dec 17. http://seer.cancer.gov/csr/1975_2011/. Accessed 2015 Feb 2.

36. American College of Radiology (ACR), Society for Pediatric Radiology (SPR). ACR-SPR practice parameter for performing FDG-PET in oncology. Reston, VA: American College of Radiology (ACR); 2014. 14 p. http://www.acr.org/~/media/71B746780F934F6D8A1BA5CCA5167EDB.pdf.

37. American College of Radiology (ACR), Society for Pediatric Radiology (SPR). ACR-SPR practice parameter for the performance of skeletal scintigraphy (bone scan). Reston, VA: American College of Radiology (ACR); 2014. 9 p. http://www.acr.org/~/media/839771405B9A43F7AF2D2A9982D81083.pdf.

38. Robinson KA, Saldanha IJ, Mckoy NA. Frameworks for determining research gaps during systematic reviews. Methods Future Research Needs Report No. 2. (Prepared by the Johns Hopkins University Evidence-based Practice Center under Contract No. HHSA 290-2007-10061-I.) AHRQ Publication No. 11-EHC043-EF. Rockville, MD: Agency for Healthcare Research and Quality. June 2011. http://www.effectivehealthcare.ahrq.gov/ehc/products/201/735/FRN2_Frameworks_20110726.pdf.

Abbreviations and Acronyms

95% CI	95% confidence interval
CT	Computed tomography
EBUS	Endobronchial ultrasound
EUS	Endoscopic ultrasound
FDG	Fluorodeoxyglucose
MBq	Megabecquerel
MHz	Megahertz
MRI	Magnetic resonance imaging
NA	Not applicable
NR	Not reported
PET/CT	Combined positron emission tomography and computed tomography
QUADAS	Quality assessment tool for diagnostic accuracy studies
SCLC	small cell lung cancer
SD	Standard deviation
TBNA	transbronchial needle aspiration
Tc99m-MDP	Technetium-99m methylene diphosphonate

Appendix A. Search Strategy

Search Strategies

The strategy below is presented in EMBASE syntax; the search was simultaneously conducted across EMBASE and MEDLINE. A similar strategy was used to search the databases comprising the Cochrane Library, and PubMed.

EMBASE/MEDLINE (2000–2014)

Set Number	Concept	Search Statement	Retrieval
1	Small cell lung cancer	'small cell lung carcinoma'/exp OR 'small cell lung carcinoma' OR 'carcinoma small cell'/exp OR 'carcinoma small cell' OR 'lung small cell cancer':de AND [2000-2014]/py	20,124
2		'small-cell lung cancer' OR 'small cell lung cancer' OR 'oat cell' OR sclc AND [2000-2014]/py	71,843
3		#1 OR #2	75,550
4		#3 NOT ('non-small cell':ti OR 'non-small-cell':ti OR 'non small cell':ti OR 'nonsmall cell':ti OR nsclc:ti) AND [2000-2014]/py	44,281
5	Lung Symptoms	'lung disease'/mj OR 'lung tumor'/mj AND [2000-2014]/py	24,811
6		lung*:ti OR pulmonary:ti OR bronch*:ti OR chest:ti AND (age*:ab,ti OR smok*:ab,ti OR symptom*:ab,ti OR wheez*:ab,ti OR cough*:ab,ti OR edema:ab,ti OR fibrosis:ab,ti OR asthma:ab,ti OR 'shortness of breath':ab,ti OR pain*:ab,ti OR nodule*:ab,ti)	130,089
7		#5 OR #6	147,159
8		#7 NOT ('non-small cell':ti OR 'non-small-cell':ti OR 'non small cell':ti OR 'nonsmall cell':ti OR nsclc:ti) AND [2000-2014]/py	133,916
9	Imaging	'computer assisted tomography'/exp OR 'emission tomography'/de OR 'nuclear magnetic resonance imaging'/exp OR 'diagnostic imaging'/exp OR 'tomography'/de OR 'respiratory-gated imaging' OR 'bone scintiscanning' AND [2000-2014]/py	910,744
10		pet NEXT/1 ct OR sdct:ab,ti mdct:ab,ti OR mri:ab,ti OR ct:ab,ti OR cat:ab,ti OR pet:ab,ti OR fdg NEAR/1 pet OR 'computed tomography':ab,ti OR 'positron emission':ab,ti OR 'magnetic resonance':ab,ti OR multislice:ab,ti OR 'multi slice':ab,ti OR bone NEXT/2 scan* AND [2000-2014]/py	704,685
11		'endosonography'/exp OR 'endosonography' OR 'eus' OR endoscop* NEXT/1 (ultrasound OR ultrasonography* OR echograph*) AND [2000-2014]/py	22,797
12		'endobronchial ultrasonography'/exp OR 'endobronchial echography' OR 'endobronchial ultrasound' OR 'ebus'/exp OR 'ebus' OR endobronch* NEXT/1 (ultrasound OR ultrasonography* OR echograph*) AND [2000-2014]/py	2,889
13		#9 OR #10 OR #11 OR #12	1,129,897

Set Number	Concept	Search Statement	Retrieval
14	Pretreatment staging and planning	'cancer classification'/mj OR 'cancer classification' OR 'cancer staging'/exp OR cancer NEAR/2 stag* AND [2000-2014]/py	170,380
15		(cancer OR tumor* OR tumour* OR mass* OR neoplasm*) NEAR/2 (stage OR staging OR class*) AND [2000-2014]/py	194,534
16		'pre-treatment':ab,ti OR pretreatment:ab,ti OR 'pretreatment' NEXT/2 staging OR 'pre-treatment' NEXT/2 plan* AND [2000-2014]/py	114,512
17		#14 OR #15 OR #16	307,057
18	Prognosis	'cancer prognosis'/exp OR 'cancer prognosis' OR prognos* OR predict* OR outcome* OR 'survival'/de OR survival OR 'quality of life'/de OR 'quality of life' OR qol AND [2000-2014]/py	3,322,222
19	Combine Small Cell Lung Cancer AND Imaging	#4 AND #13	8,415
20	Combine Lung Symptoms AND Imaging	#7 AND #13	33,186
21	Combine SCLC AND Imaging AND Pretreatment staging and planning (KQ 1)	#17 AND #19	2,470
22	Combine Lung Symptoms AND Imaging AND Pretreatment staging and planning (KQ 1)	#17 AND #20	2,860
23	Combine SCLC AND Imaging AND Pretreatment staging and planning AND prognosis (KQ 2)	#18 AND #21	1,412
24	Combine Lung Symptoms AND Imaging AND Pretreatment staging and planning AND prognosis (KQ 2)	#18 AND #22	1,694
25	Combine final sets	#21 OR #22 OR #23 OR #24	4,660
26	Apply limits	#25 AND [humans]/lim AND [2000-2014]/py	4,442

Set Number	Concept	Search Statement	Retrieval
27	Limit by publication and study type	#26 AND ('clinical article'/exp OR 'clinical article' OR 'clinical trial'/exp OR 'clinical trial' OR 'controlled study'/exp OR 'controlled study' OR 'intermethod comparison'/exp OR 'intermethod comparison' OR 'major clinical study'/exp OR 'major clinical study' OR 'retrospective study'/exp OR 'retrospective study')	2,029
28	Guidelines	#26 AND ('practice guideline'/exp OR 'practice guideline' OR 'professional standard':de OR 'practice parameter' OR 'position statement' OR 'position paper' OR 'policy statement' OR standard*:ti OR guideline*:ti OR 'white paper' OR 'clinical pathway'/exp OR 'clinical pathway' OR 'clinical guideline' OR 'consensus development'/exp OR 'consensus development')	218
29	Systematic Reviews	#26 AND ('research synthesis' OR pooled OR 'systematic review'/de OR 'meta analysis'/de OR ('evidence base' OR 'evidence based' OR methodol* OR systematic OR quantitative* OR studies OR search* AND ('review'/de OR review/it)))	340
30	Remove unwanted publication types	#26 NOT ('conference abstract'/it OR 'conference paper'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'case report'/de)	2,632
31	Combine final sets	#27 OR #28 OR #29 OR #30	2,931

EMBASE.com Syntax:

*   = truncation character (wildcard)

NEAR/*n* = search terms within a specified number (*n*) of words from each other in any order

NEXT/*n* = search terms within a specified number (*n*) of words from each other in the order specified

/   = search as a subject heading

exp   = "explodes" controlled vocabulary term (e.g., expands search to all more specific related terms in the vocabulary's hierarchy)

mj   = denotes a term that has been searched as a major subject heading

:de   = search in the descriptors field

:lnk   = floating subheading

:it,pt. = source item or publication type

:ti.   = limit to title

:ti,ab. = limit to title and abstract fields

PUBMED (PreMEDLINE)

Set Number	Concept	Search Statement
1	Small cell lung cancer	(("small-cell" OR "small cell") AND (lung OR bronch*)) OR "oat cell" OR sclc
2		2 NOT ("non-small cell"[ti] OR "non-small-cell"[ti] OR "non small cell"[ti] OR "nonsmall cell"[ti] OR nsclc[ti])
3	Lung Symptoms	(lung*[ti] OR pulmonary[ti] OR bronch*[ti] OR chest[ti]) AND (age* OR smok* OR symptom* OR wheez* OR cough* OR edema OR fibrosis OR asthma OR "shortness of breath" OR pain* OR nodule*)
4	Imaging	sdct OR mdct OR mri OR ct OR (cat AND scan*) OR pet OR (fdg AND pet) OR "computed tomography" OR "positron emission" OR "magnetic resonance" OR "multislice" OR "multi slice" OR "bone scan" OR "bone scintigraphy" OR (bone AND scan*)
5		"endosonography" OR "eus" OR (endoscop* AND (ultrasound OR ultrasonography* OR echograph*))
6		"endobronchial echography" OR "endobronchial ultrasound" OR "ebus" OR (endobronch* AND (ultrasound OR ultrasonography* OR echograph*))
7		#4 OR #5 OR #6
8	Pretreatment staging and planning	(cancer OR tumor* OR tumour* OR mass* OR neoplasm*) AND (stage OR staging OR class*)
9		(cancer[tiab] OR neoplasm[tiab] OR tumor*[tiab] OR tumour*[tiab]) AND (care[tiab] OR treatment[tiab] OR therapy[tiab] OR pretreatment[tiab] OR "pre-treatment"[tiab] OR plan[tiab])
10		#8 OR #9
11	Prognosis	"cancer prognosis" OR prognos* OR predict* OR outcome* OR survival OR "quality of life" OR qol
12	Combine SCLC OR Lung Symptoms	#2 OR #3
13	Combine SCLC OR Lung Symptoms with imaging	#7 AND #12
14	Combine SCLC OR Lung Symptoms with imaging and pretreatment planning	#10 AND #13
15	Combine with prognosis	#11 AND #14
16	In process	#15 AND (pubmednotmedline[sb] OR inprocess[sb] OR [publisher[sb])
17	English	#16 AND English[la]

PubMed Syntax:

*   = truncation character (wildcard)

[ti]   = limit to title field

[tiab] = limit to title and abstract fields

[tw] = text word

Appendix B. List of Excluded Full Articles

Alatas F, Dundar E, Yildirim H, et al. Role of real-time endobronchial ultrasound-guided transbronchial needle aspiration in the diagnosis and mediastinal staging of lung cancer. Turk Klin J Med Sci. 2012;32(2):407-14. ***One test of interest, but no data on SCLC staging accuracy.***

Al-Kadi OS, Watson D. Texture analysis of aggressive and nonaggressive lung tumor CE CT images. IEEE Trans Biomed Eng. 2008 Jul;55(7):1822-30. PMID: 18595800. ***Unclear whether any patients had SCLC.***

Allen-Auerbach M, Yeom K, Park J, et al. Standard PET/CT of the chest during shallow breathing is inadequate for comprehensive staging of lung cancer. J Nucl Med. 2006 Feb 1;47(2):298-301. PMID: 16455636. ***Not SCLC.***

An YS, Sheen SS, Oh YJ, et al. Nonionic intravenous contrast agent does not cause clinically significant artifacts to 18F-FDG PET/CT in patients with lung cancer. Ann Nucl Med. 2007 Dec;21(10):585-92. Epub 2007 Dec 25. PMID: 18092135. ***Fewer than 10 patients with SCLC.***

Anantham D, Koh MS. Endobronchial Ultrasound-guided Tranbronchial Needle Aspiration (EBUS-TBNA) in the diagnosis and staging of lung cancer. Chin J Lung Cancer. 2010 May;13(5):418-23. PMID: 20677635. ***Not a study (e.g., review, opinion).***

Andrade RS, Groth SS, Rueth NM, et al. Evaluation of mediastinal lymph nodes with endobronchial ultrasound: the thoracic surgeon's perspective. J Thorac Cardiovasc Surg. 2010 Mar;139(3):578-83. ***Fewer than 10 patients with SCLC.***

Annema JT, Versteegh MI, Veselic M, et al. Endoscopic ultrasound-guided fine-needle aspiration in the diagnosis and staging of lung cancer and its impact on surgical staging. J Clin Oncol. 2005;23(33):8357-61. PMID: 16219935. ***No separate SCLC data.***

Aquino SL, Fischman AJ. Does whole-body 2-[18F]-fluoro-2-deoxy-D-glucose positron emission tomography have an advantage over thoracic positron emission tomography for staging patients with lung cancer? Chest. 2004 Sep;126(3):755-60. PMID: 15364753. ***Not SCLC.***

Araz O, Demirci E, Ucar EY, et al. Roles of Ki-67, p53, transforming growth factor-β and lysyl oxidase in the metastasis of lung cancer. Respirology. 2014 Oct;19(7):1034-9. Epub 2014 Jul 3. PMID: 24995672. ***One test of interest, but no data on SCLC staging accuracy.***

Araz O, Demirci E, Yilmazel Ucar E, et al. Roles of Ki-67, p53, transforming growth factor-ß and lysyl oxidase in the metastasis of lung cancer. Respirology. 2014 Oct;19(7):1034-9. Epub 2014 Jul 3. ***Not staging before treatment.***

Ardengh JC, Bammann RH, de Giovani M, et al. Endoscopic ultrasound-guided biopsies for mediastinal lesions and lymph node diagnosis and staging. Clinics. 2011;66(9):1579-83. PMID: 22179163. ***Fewer than 10 patients with SCLC.***

Arslan N, Tuncel M, Kuzhan O, et al. Evaluation of outcome prediction and disease extension by quantitative 2-deoxy-2-[18F] fluoro-D-glucose with positron emission tomography in patients with small cell lung cancer. Ann Nucl Med. 2011 Jul;25(6):406-13. PMID: 21409347. ***One test of interest, but no data on SCLC staging accuracy.***

Azad A, Chionh F, Scott AM, et al. High impact of 18F-FDG-PET on management and prognostic stratification of newly diagnosed small cell lung cancer. Mol Imaging Biol. 2010 Aug;12(4):443-51. PMID: 19921339. ***None of the modalities of interest.***

Bae W, Kim H, Kim YA, et al. Diagnostic concordance rate between histologic and cytologic specimens of endobronchial ultrasound-guided transbronchial needle aspiration in lung cancer: a single institution experience. Thorac Cancer. 2014 Mar;5(2):174-8. ***No separate SCLC data.***

Bayrak SB, Ceylan E, Serter M, et al. The clinical importance of bone metabolic markers in detecting bone metastasis of lung cancer. Int J Clin Oncol. 2012 Apr;17(2):112-8. PMID: 21691728. ***None of the modalities of interest.***

Bayram N, Borekci S, Uyar M, et al. Transbronchial needle aspiration in the diagnosis and staging of lung cancer. Indian J Chest Dis Allied Sci. 2008 Jul-Sep;50(3):273-6. PMID: 18630793. ***Fewer than 10 patients with SCLC.***

Behrendt FF, Temur Y, Verburg FA, et al. PET/CT in lung cancer: Influence of contrast medium on quantitative and clinical assessment. Eur Radiol. 2012 Nov;22(11):2458-64. Epub 2012 Jun 4. http://dx.doi.org/10.1007/s00330-012-2515-1. PMID: 22661058. *Unclear whether any patients had SCLC.*

Benveniste H, Zhang S, Reinsel RA, et al. Brain metabolomic profiles of lung cancer patients prior to treatment characterized by proton magnetic resonance spectroscopy. Int J Clin Exp Med. 2012;5(2):154-64. PMID: 22567176. *Not SCLC.*

Biersack HJ, Bender H, Ruhlmann J, et al. Clinical PET in oncology. Rev Esp Med Nucl. 2000 Jun 1;19(3):219-24. *Not SCLC.*

Bilaceroglu S, Chhajed P, Mavis A, et al. Computed tomography-guided transthoracic needle aspiration in diagnosing and staging hilar and mediastinal masses of lung cancer after negative bronchoscopy. J Bronchol. 2007 Jul;14(3):149-55. *None of the modalities of interest.*

Block MI. Transition from mediastinoscopy to endoscopic ultrasound for lung cancer staging. Ann Thorac Surg. 2010 Mar;89(3):885-90. PMID: 20172149. *Fewer than 10 patients with SCLC.*

Blum R, MacManus MP, Rischin D, et al. Impact of positron emission tomography on the management of patients with small-cell lung cancer: preliminary experience. Am J Clin Oncol. 2004 Apr;27(2):164-71. PMID: 15057156. *None of the modalities of interest.*

Bocchino M, Valente T, Somma F, et al. Detection of skeletal muscle metastases on initial staging of lung cancer: a retrospective case series. Jpn J Radiol. 2014 Mar;32(3):164-71. PMID: 24452325. *Fewer than 10 patients with SCLC.*

Bocchino M, Valente T, Somma F, et al. Detection of skeletal muscle metastases on initial staging of lung cancer: a retrospective case series. Jpn J Radiol. 2014 Mar;32(3):164-71. PMID: 24452325. *Fewer than 10 patients with SCLC.*

Bolton WD, Johnson R, Banks E, et al. Utility and accuracy of endobronchial ultrasound as a diagnostic and staging tool for the evaluation of mediastinal adenopathy. Surg Endosc. 2013 Apr;27(4):1119-23. PMID: 23239294. *Fewer than 10 patients with SCLC.*

Bradley JD, Dehdashti F, Mintum MA, et al. Positron emission tomography in limited-stage small-cell lung cancer: a prospective study. J Clin Oncol. 2004;22(16):3248-54. PMID: 15310768. *One test of interest, but no data on SCLC staging accuracy.*

Brakel K, Van Overhagen H, Heijenbrok MW, et al. Detection and diagnosis of supraclavicular lymph node metastases in patients with symptoms of lung cancer by palpation, ultrasound and CT. Nederlands Tijdschrift Voor Geneeskunde. 2005 Jan 22;149(4):189-95. *No separate SCLC data.*

Buchbender C, Hartung-Knemeyer V, Beiderwellen K, et al. Diffusion-weighted imaging as part of hybrid PET/MRI protocols for whole-body cancer staging: does it benefit lesion detection? Eur J Radiol. 2013 May;82(5):877-82. Epub 2013 Feb 18. PMID: 23428414. *Not SCLC.*

Buck AK, Herrmann K, Schreyogg J, et al. PET/CT for staging lung cancer: costly or cost-saving? Eur J Nucl Med Mol Imaging. 2011 May;38(5):799-801. Epub 2011 Mar 26. PMID: 21442260. *Not a study (e.g., review, opinion).*

Bugalho A, Ferreira D, Barata R, et al. Endobronchial ultrasound-guided transbronchial needle aspiration for lung cancer diagnosis and staging in 179 patients. Rev Port Pneumol. 2013 Sep/Oct;19(5):192-9. PMID: 23850376. *Fewer than 10 patients with SCLC.*

BuilBruna N, Sahota T, López-Picazo JM, et al. Early Prediction of Disease Progression in Small Cell Lung Cancer: Toward Model-Based Personalized Medicine in Oncology. Cancer Research. 2015. *None of the modalities of interest.*

Chan WL, Freund J, Pocock NA, et al. Coincidence detection FDG PET in the management of oncological patients: attenuation correction versus non-attenuation correction. Nucl Med Commun. 2001;22(11):1185-92. *Not SCLC.*

Chin R Jr, McCain TW, Miller AA, et al. Whole body FDG-PET for the evaluation and staging of small cell lung cancer: a preliminary study. 2002;37(1):1-6. PMID: 12057859. *One test of interest, but no data on SCLC staging accuracy.*

Cho AR, Lim I, Na II, et al. Evaluation of adrenal masses in lung cancer patients using F-18 FDG PET/CT. Nucl Med Mol Imaging. 2011 Mar;45(1):52-8. *Fewer than 10 patients with SCLC.*

Chodorowska A, Rzechonek A, Dyla T, et al. CT-guided fine-needle biopsy of focal lung lesions as the method for reducing the number of invasive diagnostic procedures. Polish J Radiol. 2010 Apr;75(2):55-7. *None of the modalities of interest.*

Chong S, Lee KS, Kim BT, et al. Integrated PET/CT of pulmonary neuroendocrine tumors: diagnostic and prognostic implications. AJR Am J Roentgenol. 2007 May;188(5):1223-31. PMID: 17449764. *One test of interest, but no data on SCLC staging accuracy.*

Chooi WK, Matthews S, Bull MJ, et al. Multislice computed tomography in staging lung cancer: the role of multiplanar image reconstruction. J Comput Assist Tomogr. 2005 May/Jun;29(3):357-60. PMID: 15891507. *Unclear whether any patients had SCLC.*

Chou PC, Lin SM, Lo CY, et al. Endobronchial mucosa invasion predicts survival in patients with small cell lung cancer. PLoS ONE. 2012 Oct 4;7(10):e47613. Epub 2012 Oct 4. PMID: 23056644. *No outcomes of interest.*

Claessens NJ, Maas KW, Kummer JA, et al. [Lung cancer staging by endobronchial ultrasound with transbronchial needle aspiration]. Nederlands Tijdschrift Voor Geneeskunde. 2012;156(46):A4741. PMID: 23151327. *Other: Full article no obtainable.*

Cucuruz B, Dango S, Jurinovic V, et al. MAGE qPCR improves the sensitivity and accuracy of EBUS-TBNA for the detection of lymphatic cancer spread. J Thorac Oncol. 2012 Apr;7(4):690-7. PMID: 22237266. *Fewer than 10 patients with SCLC.*

Cullen JP, Glynn C, Murtagh E, et al. Auditing a new lung cancer service. Ir Med J. 2004 Oct;97(9):281-3. PMID: 15568588. *No separate SCLC data.*

Dane F, Turk HM, Sevinc A, et al. The markers of bone turnover in patients with lung cancer. J Natl Med Assoc. 2008 Apr;100(4):425-8. PMID: 18481482. *No outcomes of interest.*

Dango S, Cucuruz B, Mayer O, et al. Detection of disseminated tumour cells in mediastinoscopic lymph node biopsies and endobronchial ultrasonography-guided transbronchial needle aspiration in patients with suspected lung cancer. 2010 Jun;68(3):383-8. PMID: 19733415. *One test of interest, but no data on SCLC staging accuracy.*

Debevec L, Erzen J, Debeljak A, et al. Exploratory thoracotomy and its influence on the survival of patients with lung cancer. Wiener Klinische Wochenschrift. 2006 Aug;118(15):479-84. PMID: 16957979. *Fewer than 10 patients with SCLC.*

DeLappe E, Dunphy M. 18F-2-Deoxy-d-Glucose positron emission tomography-computed tomography in lung cancer. Semin Roentgenol. 2011 Jul;46(3):208-23. PMID: 21726705. *Not a study (e.g., review, opinion).*

Delattre C, Fournier C, Bouchindhomme B, et al. Endoscopic ultrasound guided transbronchial fine needle aspiration: a French Department of Pathology's 4-year experience. J Clin Pathol. 2011 Dec;64(12):1117-22. Epub 2011 Sep 30. PMID: 21965831. *No separate SCLC data.*

Dubey S, Powell CA. Update in lung cancer 2006. Am J Respir Crit Care Med. 2007 May 1;175(9):868-74. PMID: 17446343. *Not a study (e.g., review, opinion).*

Evison M, Crosbie PA, Martin J, et al. EBUS-TBNA in elderly patients with lung cancer: safety and performance outcomes. J Thorac Oncol. 2014 Mar;9(3):370-6. PMID: 24518088. *No separate SCLC data.*

Evison M, Crosbie PA, Martin J, et al. EBUS-TBNA in elderly patients with lung cancer: Safety and performance outcomes. J Thorac Oncol. 2014 Mar;9(3):370-6. *No separate SCLC data.*

Farjah F, Flum DR, Ramsey SD, et al. Multi-modality mediastinal staging for lung cancer among Medicare beneficiaries. J Thorac Oncol. 2009 Mar;4(3):355-63. PMID: 19156000. *Not SCLC.*

Feller-Kopman D, Yung RC, Burroughs F, et al. Cytology of endobronchial ultrasound-guided transbronchial needle aspiration: a retrospective study with histology correlation. Cancer Cytopathol. 2009 Dec 25;117(6):482-90. PMID: 19834962. *Fewer than 10 patients with SCLC.*

Fernandez FG, Kozower BD, Crabtree TD, et al. Utility of mediastinoscopy in clinical stage I lung cancers at risk for occult mediastinal nodal metastases. J Thorac Cardiovasc Surg. 2015 Jan;149(1):35-41, 42.e1. ***Not SCLC.***

Figueiredo VR, Cardoso PF, Jacomelli M, et al. Endobronchial ultrasound-guided transbronchial needle aspiration for lung cancer staging: early experience in Brazil. Jornal Brasileiro De Pneumologia : Publicaça O Oficial Da Sociedade Brasileira De Pneumologia E Tisilogia. 2015;41(1):23-30 ***Fewer than 10 patients with SCLC.***

Flechsig P, Kratochwil C, Schwartz LH, et al. Quantitative volumetric CT-histogram analysis in N-staging of 18F-FDG-equivocal patients with lung cancer. J Nucl Med. 2014 Apr 1;55(4):559-64. Epub 2014 Feb 13. PMID: 24525209. ***Fewer than 10 patients with SCLC.***

Flechsig P, Kratochwil C, Schwartz LH, et al. Quantitative volumetric CT-histogram analysis in N-staging of 18F-FDG-equivocal patients with lung cancer. J Nucl Med. 2014 Apr 1;55(4):559-64. Epub 2014 Feb 13. ***Fewer than 10 patients with SCLC.***

Fournel P. Criteria of choice for 1(st) line CT. Rev Pneumol Clin. 2004 Nov;60(5). PMID: 15687986. ***Not SCLC.***

Fujiwara T, Yasufuku K, Nakajima T, et al. The utility of sonographic features during endobronchial ultrasound-guided transbronchial needle aspiration for lymph node staging in patients with lung cancer: a standard endobronchial ultrasound image classification system. Chest. 2010 Sep 1;138(3):641-7. PMID: 20382710. ***No separate SCLC data.***

Fukushima T, Tateishi K, Hanaoka M, et al. Clinical outcomes in patients with small cell lung cancer in a single institute: Comparative analysis of radiographic screening with symptom-prompted patients. Lung Cancer. 2015; 88(1):48-51 **No outcomes of interest.**

Fukushima T, Tateishi K, Hanaoka M, et al. Clinical outcomes in patients with small cell lung cancer in a single institute: Comparative analysis of radiographic screening with symptom-prompted patients. Lung Cancer. 2015 Feb 9. **Duplicate of already-identified article.**

Fusaroli P, Caletti G. Endoscopic ultrasonography. Endoscopy. 2007 Jan;39(1):17-20. PMID: 17252454. ***Not a study (e.g., review, opinion).***

Garcia-Olive I, Monso E, Andreo F, et al. Sensitivity of linear endobronchial ultrasonography and guided transbronchial needle aspiration for the identification of nodal metastasis in lung cancer staging. Ultrasound Med Biol. 2009 Aug;35(8):1271-7. PMID: 19540652. ***No separate SCLC data.***

Gerke O, Hermansson R, Hess S, et al. Cost-effectiveness of PET and PET/computed tomography: A systematic review. Pet Clinics. 2015;10(1):105-24 ***Not SCLC.***

Go SI, Song HN, Kang JH, et al. The clinical impact of the sum of the maximum standardized uptake value on the pretreatment with F-FDG-PET/CT in small-cell lung cancer. Oncology. 2014 Jan;86(1):1-9. Epub 2013 Dec 10. PMID: 24335538. ***One test of interest, but no data on SCLC staging accuracy.***

Gomez DR, Gladish GW, Wei X, et al. Prognostic value of positron emission tomography/computed tomography findings in limited-stage small cell lung cancer before chemoradiation therapy. Am J Clin Oncol. 2014 Feb;37(1):77-80. ***One test of interest, but no data on SCLC staging accuracy.***

Graeter TP, Hellwig D, Hoffmann K, et al. Mediastinal lymph node staging in suspected lung cancer: comparison of positron emission tomography with F-18-fluorodeoxyglucose and mediastinoscopy. Ann Thorac Surg. 2003 Jan 1;75(1):231-6. PMID: 12537221. ***Fewer than 10 patients with SCLC.***

Grahek D, Tofighi M, Montravers F, et al. 18FDG CDET in staging of lung cancer. Med Nucl. 2000;24(2):99-106. ***Fewer than 10 patients with SCLC.***

Gregory DL, Brennan SM, Stillie A, et al. Impact of 18F-fluorodeoxyglucose positron emission tomography in the staging and treatment response assessment of extra-pulmonary small-cell cancer. J Med Imaging Radiat Oncol. 2010 Apr;54(2):100-7. ***Not SCLC.***

Guerra L, Meregalli S, Zorz A, et al. Comparative evaluation of CT-based and respiratory-gated PET/CT-based planning target volume (PTV) in the definition of radiation treatment planning in lung cancer: Preliminary results. Eur J Nucl Med Mol Imag. 2014 Apr;41(4):702-10. ***Fewer than 10 patients with SCLC.***

Halter G, Buck AK, Schirrmeister H, et al. Lymph node staging in lung cancer using [18F]FDG-PET. Thorac Cardiovasc Surg. 2004 Apr;52(2):96-101. PMID: 15103582. ***Not SCLC.***

Halter G, Buck AK, Schirrmeister H, et al. [18F] 3-deoxy-3'-fluorothymidine positron emission tomography: alternative or diagnostic adjunct to 2-[18f]-fluoro-2-deoxy-D-glucose positron emission tomography in the workup of suspicious central focal lesions? J Thorac Cardiovasc Surg. 2004 Apr;127(4):1093-9. PMID: 15052207. ***Fewer than 10 patients with SCLC.***

Han TJ, Kim HJ, Wu HG, et al. Comparison of treatment outcomes between involved-field and elective nodal irradiation in limited-stage small cell lung cancer. Jpn J Clin Oncol. 2012 Oct;42(10):948-54. PMID: 22811409. ***Other: Did not separate data of standalone PET patients from PET/CT patients.***

Harders SW. Lucis: Lung Cancer Imaging Studies. Dan Med J. 2012;59(11):1-30. PMID: ***Not a study (e.g., review, opinion).***

Hashizume T, Yamada K, Suzuki R, et al. Correlation between clinical characteristics, radiological findings, pathological findings, and prognosis in patients with a peripheral lung adenocarcinoma less than 15 mm in diameter. Jpn J Lung Cancer. 2005 Aug;45(4):311-7. PMID: ***Not SCLC.***

Hattori A, Suzuki K, Maeyashiki T, et al. The presence of air bronchogram is a novel predictor of negative nodal involvement in radiologically pure-solid lung cancer. Eur J Cardiothorac Surg. 2014 Apr;45(4):699-702. PMID: 24135955. ***Not SCLC.***

Hattori A, Suzuki K, Matsunaga T, et al. Tumour standardized uptake value on positron emission tomography is a novel predictor of adenocarcinoma in situ for c-Stage IA lung cancer patients with a part-solid nodule on thin-section computed tomography scan. Interact Cardiovasc Thorac Surg. 2014 Mar;18(3):329-34. ***Not SCLC.***

Hauber HP, Bohuslavizki KH, Lund CH, et al. Positron emission tomography in the staging of small-cell lung cancer: a preliminary study. Chest. 2001;119(3):950-4. PMID: 11243980. ***Fewer than 10 patients with SCLC.***

Henschke CI, Yankelevitz DF, Miettinen OS. Computed tomographic screening for lung cancer: the relationship of disease stage to tumor size. Arch Intern Med. 2006 Feb 13;166(3):321-5. PMID: 16476872. ***One test of interest, but no data on SCLC staging accuracy.***

Herth FJ, Becker HD, Ernst A, et al. Ultrasound-guided transbronchial needle aspiration: an experience in 242 patients. Chest. 2003 Feb 1;123(2):604-7. PMID: 12576386. ***No separate SCLC data.***

Herth FJF, Krasnik M, Vilmann P. EBUS-TBNA for the diagnosis and staging of lung cancer. Endoscopy. 2006 Jun;38 Suppl 1:S101-5. PMID: 16802239. ***Not a study (e.g., review, opinion).***

Herth FJF, Schuler H, Gompelmann D, et al. Endobronchial ultrasound-guided lymph node biopsy with transbronchial needle forceps: a pilot study. Eur Respir J. 2012 Feb 1;39(2):373-7. PMID: 21700609. ***Fewer than 10 patients with SCLC.***

Herth R, Becker HD, Manegold C, et al. Endobronchial ultrasound (EBUS)--assessment of a new diagnostic tool in bronchoscopy for staging of lung cancer. Onkologie. 2001 Apr;24(2):151-4. PMID: 11441295. ***Unclear whether any patients had SCLC.***

Hillner BE, Tosteson AN, Tosteson TD, et al. Intended versus inferred care after PET performed for initial staging in the national oncologic PET registry. J Nucl Med. 2013 Dec 1;54(12):2024-31. PMID: 24221994. ***One test of interest, but no data on SCLC staging accuracy.***

Hochstenbag MMH, Twijnstra A, Wilmink JT, et al. Asymptomatic brain metastases (BM) in small cell lung cancer (SCLC): MR-imaging is useful at initial diagnosis. J Neurooncol. 2000;48(3):243-8. PMID: 11100822. ***One test of interest, but no data on SCLC staging accuracy.***

Hsu LH, Ko JS, You DL, et al. Transbronchial needle aspiration accurately diagnoses subcentimetre mediastinal and hilar lymph nodes detected by integrated positron emission tomography and computed tomography. Respirology. 2007 Nov;12(6):848-55. PMID: 17986113. ***Not SCLC.***

Hu Y, Puri V, Crabtree TD, et al. Attaining proficiency with endobronchial ultrasound-guided transbronchial needle aspiration. J Thorac Cardiovasc Surg. 2013 Dec;146(6):1387-1392.e1. PMID: 24075565. ***No separate SCLC data.***

Huang D, Zhang Y, Zhao F, et al. Clinical significance of (99m)Tc-tetrofosmin SPECT in the diagnosis of lung neoplasms and mediastinal lymph node involvement. Chin J Lung Cancer. 2007 Feb 20;10(1):25-38. *No separate SCLC data.*

Huang D, Zhang Y, Zhao F, et al. Clinical significance of 99mTc-tetrofosmin SPECT in the diagnosis of lung neoplasms and mediastinal lymph node involvement. Chin J Lung Cancer. 2007 Feb;10(1):25-38. *Fewer than 10 patients with SCLC.*

Huang GJ, Zhang DC, Mao YS, et al. Comparison of clinical and surgico-pathological TNM stage of 2007 lung cancer patients. Zhonghua Zhong Liu Za Zhi. 2005 Sep;27(9):551-3. PMID: 16438855. *No separate SCLC data.*

Huellner MW, Collen TD, Gut P, et al. Multiparametric PET/CT-perfusion does not add significant additional information for initial staging in lung cancer compared with standard PET/CT. EJNMMI Res. 2014;4(1):6. PMID: 24450990. *Fewer than 10 patients with SCLC.*

Huellner MW, Collen TD, Gut P, et al. Multiparametric PET/CT-perfusion does not add significant additional information for initial staging in lung cancer compared with standard PET/CT. Ejnmmi Research. 2014;4(1):1-13. *Fewer than 10 patients with SCLC.*

Igdem T, Alco G, Ercan T, et al. The application of positron emission tomography/computed tomography in radiation treatment planning: effect on gross target volume definition and treatment management. Clin Oncol (R Coll Radiol). 2010 Apr;22(3):173-8. *Fewer than 10 patients with SCLC.*

Imamura F, Kuriyama K, Seto T, et al. Detection of bone marrow metastases of small cell lung cancer with magnetic resonance imaging: early diagnosis before destruction of osseous structure and implications for staging. 2000 Mar;27(3):189-97. PMID: 10699692. *Other: Authors analyzed only a component of the full MR imaging procedure.*

Ippolito D, Capraro C, Guerra L, et al. Feasibility of perfusion CT technique integrated into conventional 18FDG/PET-CT studies in lung cancer patients: clinical staging and functional information in a single study. Eur J Nucl Med Mol Imaging. 2013 Jan;40(2):156-65. Epub 2012 Nov 10. PMID: 23143661. *Fewer than 10 patients with SCLC.*

Iwano S, Ito S, Tsuchiya K, et al. What causes false-negative PET findings for solid-type lung cancer? Lung Cancer. 2013 Feb;79(2):132-6. PMID: 23177277. *Fewer than 10 patients with SCLC.*

Jacob T, Grahek D, Kerrou K, et al. Usefulness of [18F]-FDOPA pet as an adjunct to [18F]-FDG PET in the imaging of small cell lung carcinoma. Preliminary results. Med Nucl. 2003 Jul 1;27(7):353-8. *Fewer than 10 patients with SCLC.*

Jennings SG, Winer-Muram HT, Tann M, et al. Distribution of stage I lung cancer growth rates determined with serial volumetric CT measurements. Radiology. 2006 Nov;241(2):554-63. Epub 2006 Sep 27. PMID: 17005771. *Fewer than 10 patients with SCLC.*

Jernlas B, Nyberger H, Ek L, et al. Diagnostic yield and efficacy of endobronchial ultrasound-guided transbronchial needle aspiration in mediastinal lymphadenopathy. Clin Respir J. 2012 Apr;6(2):88-95. PMID: 21651742. *One test of interest, but no data on SCLC staging accuracy.*

Jerusalem G, Hustinx R, Beguin Y, et al. The value of positron emission tomography (PET) imaging in disease staging and therapy assessment. Ann Oncol. 2002;13(Suppl 4):227-34. *Not a study (e.g., review, opinion).*

Jeyabalan A, Shelley-Fraser G, Medford AR. Impact of needle gauge on characterization of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) histology samples. Respirology. 2014 Jul;19(5):735-9. *No separate SCLC data.*

Kamel EM, Kamel EM, McKee TA, et al. Occult lung infarction may induce false interpretation of 18F-FDG PET in primary staging of pulmonary malignancies. Eur J Nucl Med Mol Imaging. 2005 Jun;32(6):641-6. Epub 2005 Feb 22. PMID: 15726357. *Unclear whether any patients had SCLC.*

Kamel EM, Zwahlen D, Wyss MT, et al. Whole-body (18)F-FDG PET improves the management of patients with small cell lung cancer. J Nucl Med. 2003 Dec;44(12):1911-7. PMID: 14660716. *One test of interest, but no data on SCLC staging accuracy.*

Kamiyoshihara M, Kawashima O, Ishikawa S, et al. Mediastinal lymph node evaluation by computed tomographic scan in lung cancer. J Cardiovasc Surg (Torino). 2001;42(1):119-24. PMID: 11292919. *Not SCLC.*

Kandemir O, Karakus K, Katrancioglu O, et al. Semi-quantitative investigation of primary tumor and bone metastasis in lung cancer patients using the PET-CT approach. Int J Clin Exp Med. 2014 Sep 30;7(9):2624-31. *No separate SCLC data.*

Karathanos E, Datseris I, Vlontzou E, et al. Contribution of (99m)Tc-depreotide (Neospect) scintigraphy in lung cancer staging. J BUON. 2010 Jan-Mar;15(1):147-52. PMID: 20414943. *None of the modalities of interest.*

Kazawa N, Kitaichi M, Hiraoka M, et al. Small cell lung carcinoma: eight types of extension and spread on computed tomography. J Comput Assist Tomogr. 2006 Jul/Aug;30(4):653-61. PMID: 16845299. *One test of interest, but no data on SCLC staging accuracy.*

Kies P, Schober O, Presselt N, et al. What role does FDG-PET play in staging bronchial carcinoma? Chir Prax. 2003 Oct;62(1):25-8. *Not a study (e.g., review, opinion).*

Kim HK, Ha SI, Kim YR, et al. The usefulness of ultrasound-guided fine needle aspiration cytology of impalpable neck nodes in patients with lung cancer. Tuberc Respir Dis (Seoul). 2004 May;56(5):505-13. *One test of interest, but no data on SCLC staging accuracy.*

Kim MA, Lee JC, Choi CM. Bronchial anthracofibrosis and macroscopic tissue pigmentation on EBUS-TBNA predict a low probability of metastatic lymphadenopathy in Korean lung cancer patients. J Korean Med Sci. 2013 Mar;28(3):383-7. PMID: 23486741. *Not staging before treatment.*

Kim TJ, Park CM, Goo JM, et al. Is there a role for FDG PET in the management of lung cancer manifesting predominantly as ground-glass opacity? AJR Am J Roentgenol. 2012 Jan;198(1):83-8. PMID: 22194482. *Not SCLC.*

Kirmani BH, Rintoul RC, Win T, et al. Stage migration: results of lymph node dissection in the era of modern imaging and invasive staging for lung cancer. Eur J Cardiothorac Surg. 2013 Jan;43(1):104-10. PMID: 22529185. *Not SCLC.*

Kitase M, Hara M, Katoh K, et al. [FDG-PET in patient with clinical T1N0 lung cancer; Determination of nodal status]. Rinsho Hoshasen. 2000;45(1):209-14. *Not SCLC.*

Kobayashi T, Tanaka N, Matsumoto T, et al. HRCT findings of small cell lung cancer measuring 30 mm or less located in the peripheral lung. Jpn J Radiol. 2015 Feb;33(2):67-75. *No outcomes of interest.*

Krupski W, Zlomaniec J. The usefulness of computed tomography spatial imaging in diagnosing lung tumours. Ann Univ Mariae Curie Sklodowska Med. 2002;57(2):112-8. PMID: 12898828. *Not staging before treatment.*

Kushibe K, Kawaguchi T, Nishimoto Y, et al. Operative indications for lung cancer with satellite lesions. Asian Cardiovasc Thorac Ann. 2006 Aug;14(4):316-20. PMID: 16868106. *Not SCLC.*

Kut V, Spies W, Spies S, et al. Staging and monitoring of small cell lung cancer using [18F]fluoro-2-deoxy- D-glucose-positron emission tomography (FDG-PET). Am J Clin Oncol. 2007 Feb;30(1):45-50. PMID: 17278894. *One test of interest, but no data on SCLC staging accuracy.*

La Fianza A, Pellegrini C, Berton F, et al. Diagnostic imaging of lung cancer after heart transplantation. Tumori. 2006 Sep/Oct;92(5):429-32. PMID: 17168437. *Not SCLC.*

Laking G, Price P. 18-Fluorodeoxyglucose positron emission tomography (FDG-PET) and the staging of early lung cancer. Thorax. 2001;56:ii38-44. PMID: 11514705. *Not a study (e.g., review, opinion).*

Ladrón de Guevara H D, Furnaro L F, et al. [Positron emission tomography/computed tomography for lung cancer staging]. Revista Médica De Chil. 2015;143(1):22-9 *No separate SCLC data.*

Lannes D, Monteiro AS, Toscano E, et al. Transbronchial needle aspiration of hilar and mediastinal lymph nodes. Rev Port Pneumol. 2007 Sep/Oct;13(5):651-8. PMID: 17962884. *Not staging before treatment.*

Lee J, Kim JO, Jung CK, et al. Metabolic Activity on [(18)F]-Fluorodeoxyglucose-Positron Emission Tomography/Computed Tomography and Glucose Transporter-1 Expression might predict clinical outcomes in patients with limited disease small-cell lung cancer who receive concurrent chemoradiation. Clin Lung Cancer. 2014 Mar;15(2):e13-e21. *Not staging before treatment.*

Lee KJ, Suh GY, Chung MP, et al. Combined endobronchial and transesophageal approach of an ultrasound bronchoscope for mediastinal staging of lung cancer. PLoS ONE. 2014 Mar 14;9(3). *Fewer than 10 patients with SCLC.*

Lee KJ, Suh GY, Chung MP, et al. Combined endobronchial and transesophageal approach of an ultrasound bronchoscope for mediastinal staging of lung cancer. Plos One. 2014 Mar 14;9(3). *Fewer than 10 patients with SCLC.*

Lee ST, Berlangieri SU, Poon AMT, et al. Prevalence of occult metastatic disease in patients undergoing 18F-FDG PET for primary diagnosis or staging of lung carcinoma and solitary pulmonary nodules. Intern Med J. 2007 Nov;37(11):753-9. PMID: 17517082. *Unclear whether any patients had SCLC.*

Lennon AM, Rintoul RC, Penman ID. Competition for EUS (a) EBUS-TBNA (b) video assisted thoracoscopy. Endoscopy. 2006 Jun;38 Suppl 1:S80-3. PMID: 16802233. *Not a study (e.g., review, opinion).*

Lesser TG. Endothoracic sonography improves the estimation of operability in locally advanced lung cancer. Ann Thorac Surg. 2010 Jul;90(1):217-21. PMID: 20609778. *Not SCLC.*

Letonturier P. [What's new in lung cancer]. Presse Med. 2007 Mar;36(3 Pt 1):441-3. PMID: 17436450. *Not a study (e.g., review, opinion).*

Li S, Zhao B, Wang X, et al. Overestimated value of (18)F-FDG PET/CT to diagnose pulmonary nodules: analysis of 298 patients. Clin Radiol. 2014 Aug;69(8):e352-e357. PMID: 24877581. *Fewer than 10 patients with SCLC.*

Liao R, Yang X, Wang B, et al. Diagnosis and staging of mediastinal lymphadenopathy: EBUS-TBNA versus mediastinoscopy. Chin J Clin Oncol. 2011 Dec 30;38(24):1501-4. *Fewer than 10 patients with SCLC.*

Lin LF, Huang PT, Tsai MH, et al. Role of endoscopic ultrasound-guided fine-needle aspiration in lung and mediastinal lesions. J Chin Med Assoc. 2010 Oct;73(10):523-9. PMID: 21051029. *Fewer than 10 patients with SCLC.*

Lin WY, Hsu WH, Lin KH, et al. Role of preoperative PET-CT in assessing mediastinal and hilar lymph node status in early stage lung cancer. J Chin Med Assoc. 2012 May;75(5):203-8. PMID: 22632985. *Fewer than 10 patients with SCLC.*

Liu H, Liu Y, Yu T, et al. Evaluation of apparent diffusion coefficient associated with pathological grade of lung carcinoma, before therapy. J Mag Res Imag. 2014 Dec 24. *Fewer than 10 patients with SCLC.*

Liu Q, Peng Z, Liu Q, et al. Comparison of (11)C-choline PET/CT and enhanced CT in the evaluation of patients with pulmonary abnormalities and locoregional lymph node involvement in lung cancer. Clin Lung Cancer. 2012 Jul;13(4):312-20. PMID: 22182444. *Fewer than 10 patients with SCLC.*

Liu XG, Wang Y, Liang MZ, et al. The relationship between the peripheral lung cancer and the bronchi, pulmonary artery and vein: a multislice helical CT observation. Chin J Radiol. 2008 Jun;42(6):592-6. *No separate SCLC data.*

Luo J, Ni J, Zheng H, et al. Clinical analysis of 88 cases with combined small cell carcinoma. 2009 Feb;29(2):156-9. *No outcomes of interest.*

Mall JW, Schwenk W, Philipp AW, et al. Serum vascular endothelial growth factor levels correlate better with tumour stage in small cell lung cancer than albumin, neuron-specific enolase or lactate dehydrogenase. Respirology. 2002;7(2):99-102. PMID: 11985730. *One test of interest, but no data on SCLC staging accuracy.*

Matsuguma H, Yokoi K, Anraku M, et al. Proportion of ground-glass opacity on high-resolution computed tomography in clinical T1 N0 M0 adenocarcinoma of the lung: A predictor of lymph node metastasis. J Thorac Cardiovasc Surg. 2002 Aug;124(2):278-84. PMID: 12167787. *Not SCLC.*

Maya Martinez M, Carrion Valero F, Diaz Lopez J, et al. [Influence of computed tomography of the abdomen for staging lung cancer]. Arch Bronconeumol. 2002 Mar;38(3):123-9. PMID: 11900689. *Other: Outdated CT.*

Mazzone PJ, Marchi N, Fazio V, et al. Small vessel ischemic disease of the brain and brain metastases in lung cancer patients. PLoS ONE. 2009 Sep 30;4(9):e7242. PMID: 19789633. ***Unclear whether any patients had SCLC.***

Meyers BF, Haddad F, Siegel BA, et al. Cost-effectiveness of routine mediastinoscopy in computed tomography- and positron emission tomography-screened patients with stage I lung cancer. J Thorac Cardiovasc Surg. 2006 Apr;131(4). PMID: 16580440. ***Not SCLC.***

Mezzetti M, Calati AM, Schubert L, et al. Positron emission-computed tomography in diagnosis and staging of lung neoplasms. Personal experience. Minerva Chir. 2002;57(4):461-5. PMID: 12145576. ***None of the modalities of interest.***

Min JW, Um SW, Yim JJ, et al. The role of whole-body FDG PET/CT, Tc 99m MDP bone scintigraphy, and serum alkaline phosphatase in detecting bone metastasis in patients with newly diagnosed lung cancer. J Korean Med Sci. 2009 Apr;24(2):275-80. PMID: 19399270. ***No separate SCLC data.***

Mohan A, Naik S, Pandey RM, et al. Diagnostic utility of endobronchial ultrasound guided transbronchial needle aspiration for mediastinal lesions: a prospective three year, single centre analysis. Thorac Cancer. 2011 Nov;2(4):183-9. ***One test of interest, but no data on SCLC staging accuracy.***

Moodie K, Cherk M, Lau E, et al. Evaluation of pulmonary nodules and lung cancer with one-inch crystal gamma coincidence positron emission tomography/CT versus dedicated positron emission tomography/CT. J Med Imaging Radiat Oncol. 2009 Feb;53(1):32-9. PMID: 19453526. ***Unclear whether any patients had SCLC.***

Morimoto D, Takashima S, Sakashita N, et al. Differentiation of lung neoplasms with lepidic growth and good prognosis from those with poor prognosis using computer-aided 3D volumetric CT analysis and FDG-PET. Acta Radiol. 2014 Jun;55(5):563-9. ***Not SCLC.***

Mortensen J, Enevoldsen H, Friberg L, et al. 4. Preliminary findings of a prospective study of FDG-PET in patients with possible lung cancer. Clin Positron Imaging. 2000 Jul;3(4):158. PMID: 11150761. ***Other: Not a full length paper (e.g., abstract, poster).***

Mortensen J, Enevoldsen H, Friberg L, et al. Preliminary Findings of a Prospective Study of FDG-PET in Patients with Possible Lung Cancer. Clinical Positron Imaging: Official Journal Of The Institute For Clinical P.E.T. 2000 Jul;3(4):158. ***Not a full length paper (e.g., abstract, poster).***

Murakami Y, Oki M, Saka H, et al. Endobronchial ultrasound-guided transbronchial needle aspiration in the diagnosis of small cell lung cancer. Respir Investig. 2014 May;52(3):173-8. ***Not staging before treatment.***

Nabil H, Maher KM, Mahdy SAR. Follow up in chest tumors: value of integrated PET/CT. Egypt J Radiol Nucl Med. 2014 Sep;45(3):679-88. ***Fewer than 10 patients with SCLC.***

Nabil H, Maher KM, Mahdy SAR Follow up in chest tumors: value of integrated PET/CT. Egypt J Radiol Nucl Med. 2014 Sep;45(3):679-88. ***Fewer than 10 patients with SCLC.***

Nanguzgambo AB, Aubeelack K, Von Groote-Bidlingmaier F, et al. Radiologic features, staging, and operability of primary lung cancer in the Western cape, South Africa: a 1-year retrospective study. J Thorac Oncol. 2011 Feb;6(2):343-50. PMID: 21173714. ***One test of interest, but no data on SCLC staging accuracy.***

Natu S, Hoffman J, Siddiqui M, et al. The role of endobronchial ultrasound guided transbronchial needle aspiration cytology in the investigation of mediastinal lymphadenopathy and masses, the North Tees experience. J Clin Pathol. 2010 May;63(5):445-51. PMID: 20299387. ***One test of interest, but no data on SCLC staging accuracy.***

Niho S, Fujii H, Murakami K, et al. Detection of unsuspected distant metastases and/or regional nodes by FDG-PET [corrected] scan in apparent limited-disease small-cell lung cancer. Lung Cancer. 2007 Sep;57(3):328-33. Epub 2007 May 29. PMID: 17537538. ***One test of interest, but no data on SCLC staging accuracy.***

Nomori H, Ohtsuka T, Naruke T, et al. Histogram analysis of computed tomography numbers of clinical T1 N0 M0 lung adenocarcinoma, with special reference to lymph node metastasis and tumor invasiveness. J Thorac Cardiovasc Surg. 2003 Nov;126(5):1584-9. PMID: 14666037. ***Not SCLC.***

Oturai PS, Mortensen J, Enevoldsen H, et al. Gamma-camera 18F-FDG PET in diagnosis and staging of patients presenting with suspected lung cancer and comparison with dedicated PET. J Nucl Med. 2004 Aug;45(8):1351-7. PMID: 15299061. ***Fewer than 10 patients with SCLC.***

Ouboukdir R, Ghfir I, Rais NB. Bone scintigraphy with 99mTc-HMDP in the staging of lung cancer - about 136 cases. Med Nucl. 2011 Apr;35(4):219-23. *One test of interest, but no data on SCLC staging accuracy.*

Ost DE, Niu J, Elting LS, et al. Quality gaps and comparative effectiveness in lung cancer staging and diagnosis. Chest. 2014 Feb;145(2):331-45. *No outcomes of interest.*

Ozgul MA, Cetinkaya E, Tutar N, et al. Endobronchial ultrasound-guided transbronchial needle aspiration for the diagnosis of intrathoracic lymphadenopathy in patients with extrathoracic malignancy: a study in a tuberculosis-endemic country. J Cancer Res Ther. 2013 Jul-Sep;9(3):416-21. PMID: 24125976. *Not SCLC.*

Pandit N, Gonen M, Krug L, et al. Prognostic value of [18F]FDG-PET imaging in small cell lung cancer. Eur J Nucl Med Mol Imaging. 2003 Jan 1;30(1):78-84. Epub 2002 Oct 31. PMID: 12483413. *One test of interest, but no data on SCLC staging accuracy.*

Pauls S, Aschoff AJ, Wahl J, et al. Multi-detector row CT: is prospective electrocardiographic triggering improving the detection of small pulmonary tumors? Acad Radiol. 2005 May;12(5):614-9. PMID: 15866135. *Unclear whether any patients had SCLC.*

Pauls S, Schmidt SA, Juchems MS, et al. Diffusion-weighted MR imaging in comparison to integrated [(18)F]-FDG PET/CT for N-staging in patients with lung cancer. Eur J Radiol. 2012 Jan;81(1):178-82. Epub 2010 Oct 6. PMID: 20932700. *Fewer than 10 patients with SCLC.*

Pitman AG, Hicks RJ, Binns DS, et al. Performance of sodium iodide based (18)F-fluorodeoxyglucose positron emission tomography in the characterization of indeterminate pulmonary nodules or masses. Br J Radiol. 2002;75(890):114-21. PMID: 11893634. *Fewer than 10 patients with SCLC.*

Rakheja R, Ko JP, Friedman K. Lung cancer: positron emission tomography/computed tomography and the new staging system. Semin Roentgenol. 2013 Oct;48(4):308-22. PMID: 24034263. *Not a study (e.g., review, opinion).*

Razek AA, Fathy A, Gawad TA. Correlation of apparent diffusion coefficient value with prognostic parameters of lung cancer. J Comput Assist Tomogr. 2011 Mar-Apr;35(2):248-52. PMID: 21412099. *Fewer than 10 patients with SCLC.*

Remiszewski P, RoszkowskiSliz K, Wiatr E, et al. Prognosis in limited disease (LD) small cell lung cancer (SCLC) patients (PTS) according to status performance, local extension of lesions, type of treatment and the completeness of staging. Pneumonol Alergol Pol. 2003;71(3):139-47. PMID: 14587419. *No outcomes of interest.*

Ridge CA, Huang J, Cardoza S, et al. Comparison of multiplanar reformatted CT lung tumor measurements to axial tumor measurement alone: impact on maximal tumor dimension and T stage. AJR Am J Roentgenol. 2013 Nov;201(5):959-63. PMID: 24147464. *Not SCLC.*

Rintoul RC. Towards complete endoscopic staging of the mediastinum? Endoscopy. 2006 Jun;38 Suppl 1:S110-3. PMID: 16802241. *Not a study (e.g., review, opinion).*

Rintoul RC, Tournoy KG, El Daly H, et al. EBUS-TBNA for the clarification of PET positive intra-thoracic lymph nodes-an international multi-centre experience. J Thorac Oncol. 2009 Jan;4(1):44-8. PMID: 19096305. *Fewer than 10 patients with SCLC.*

Roman MR, Rossleigh MA, Angelides S, et al. Staging and managing lung tumors using F-18 FDG coincidence detection. Clin Nucl Med. 2001;26(5):383-8. PMID: 11317014. *Fewer than 10 patients with SCLC.*

Saadati K, Hashemzade S, Izadi S. The use of surgical methods in lung cancer staging and its impact on selection of treatment in 100 patients with lung cancer in Imam Khomeini hospital of Tabriz, Iran. J Zanjan Univ Med Sci Health Serv. 2014;23(97):14-20. *Fewer than 10 patients with SCLC.*

Sahiner I, Atasever T, Akdemir UO, et al. Relationship between primary lesion metabolic parameters and clinical stage in lung cancer. Rev Esp Med Nucl Imagen Mol. 2013 Nov-Dec;32(6):357-63. PMID: 23747221. *One test of interest, but no data on SCLC staging accuracy.*

Saisho S, Yasuda K, Maeda A, et al. Role of 2-[18F]fluoro-2-deoxyglucose positron emission tomography in preoperative management of solid-type small-sized lung cancer. Ann Nucl Med. 2013 Jul;27(6):515-22. PMID: 23504519. *Fewer than 10 patients with SCLC.*

de Cos Escuin JS, Menna DM, Gonzalez MA, et al. Silent brain metastasis in the initial staging of lung cancer. Evaluation by computed tomography and magnetic resonance imaging. Arch Bronconeumol. 2007 Jul;43(7):386-91. PMID: 17663891. *No separate SCLC data.*

Sanchez de Cos Escuin J, Serra Mitjans M, Hernandez Hernandez J, et al. The Spanish Society of Pulmonology and Thoracic Surgery Lung Cancer Cooperative Group-II registry. A descriptive study. Arch Bronconeumol. 2013 Nov;49(11):462-7. Epub 2013 Jul 6. PMID: 23838409. *No separate SCLC data.*

Sanz-Santos J, Andreo F, Sanchez D, et al. [Usefulness of a lung cancer rapid diagnosis specialist clinic. Contribution of ultrasound bronchoscopy]. Arch Bronconeumol. 2010 Dec;46(12):640-5. PMID: 20888680. *No separate SCLC data.*

Sarwate D, Sarkar S, Krimsky WS, et al. Optimization of mediastinal staging in potential candidates for stereotactic radiosurgery of the chest. J Thorac Cardiovasc Surg. 2012 Jul;144(1):81-5. PMID: 22498085. *Not SCLC.*

Sas-Korczynska B, Wojcik E, Luczynska E, et al. The diagnosis of limited stage small-cell lung cancer. Contemp Oncol (Pozn). 2008;12(1):1-5. *No outcomes of interest.*

Schmid RA, Hautmann H, Poellinger B, et al. Staging of recurrent and advanced lung cancer with 18F-FDG PET in a coincidence technique (hybrid PET). Nucl Med Commun. 2003 Jan;24(1):37-45. PMID: 12501018. *Fewer than 10 patients with SCLC.*

Schmid-Bindert G, Henzler T, Chu TQ, et al. Functional imaging of lung cancer using dual energy CT: how does iodine related attenuation correlate with standardized uptake value of 18FDG-PET-CT? Eur Radiol. 2012 Jan;22(1):93-103. PMID: 21822784. *Other: More than 3 weeks elapsed between imaging tests.*

Schmid-Bindert G, Jiang H, Kahler G, et al. Predicting malignancy in mediastinal lymph nodes by endobronchial ultrasound: a new ultrasound scoring system. Respirology. 2012 Nov;17(8):1190-98. PMID: 22789110. *Not SCLC.*

Schneider J. Early detection of lung cancers - Comparison of computed tomography, cytology and fuzzy-based tumor markers panels. Cancer Biomark. 2009;6(3):149-62. PMID: 20660961. *Not a study (e.g., review, opinion).*

Schumacher T, Brink I, Mix M, et al. FDG-PET imaging for the staging and follow-up of small cell lung cancer. Eur J Nucl Med. 2001;28(4):483-8. PMID: 11357499. *One test of interest, but no data on SCLC staging accuracy.*

Schwartz LE, Aisner DL, Baloch ZW, et al. The diagnostic efficacy of combining bronchoscopic tissue biopsy and endobronchial ultrasound-guided transbronchial needle aspiration for the diagnosis of malignant lesions in the lung. Diagn Cytopathol. 2013 Nov;41(11):929-35. PMID: 22362678. *No separate SCLC data.*

Schwenzer NF, Schraml C, Muller M, et al. Pulmonary lesion assessment: comparison of whole-body hybrid MR/PET and PET/CT imaging - pilot study. Radiology. 2012 Aug;264(2):551-8. *Not SCLC.*

Seemann MD, Schaefer JF, Englmeier KH. Virtual positron emission tomography/computed tomography-bronchoscopy: possibilities, advantages and limitations of clinical application. Eur Radiol. 2007 Mar;17(3):709-15. PMID: 16909219. *Not SCLC.*

Seidel C, Hambsch P, Hering K, et al. Analysis of frequency of deep white matter metastasis on cerebral MRI. J Neuro-Oncology. 2015;123(1):135-9. *No outcomes of interest.*

Shetty CM, Lakhkar BN, Gangadhar VSS, et al. Changing pattern of bronchogenic carcinoma: a statistical variation or a reality? Indian J Radiol Imaging. 2005 May;15(2):233-8. *Not staging before treatment.*

Shibata H, Nomori H, Uno K, et al. 11C-acetate for positron emission tomography imaging of clinical stage IA lung adenocarcinoma: comparison with 18F-fluorodeoxyglucose for imaging and evaluation of tumor aggressiveness. Ann Nucl Med. 2009 Sep;23(7):609-16. PMID: 19562438. *Not SCLC.*

Shinozaki T, Utano K, Fujii H, et al. Routine use of dual time (18)F-FDG PET for staging of preoperative lung cancer: does it affect clinical management? Jpn J Radiol. 2014 Aug;32(8):476-81. *Fewer than 10 patients with SCLC.*

Shinozaki T, Utano K, Fujii H, et al. Routine use of dual time (18)F-FDG PET for staging of preoperative lung cancer: does it affect clinical management? Jpn J Radiol. 2014 Aug;32(8):476-81. *Fewer than 10 patients with SCLC.*

Shirvani SM, Komaki R, Heymach JV, et al. Positron emission tomography/computed tomography-guided intensity-modulated radiotherapy for limited-stage small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2012 Jan 1;82(1):e91-7. Epub 2011 Apr 12. PMID: 21489716. *One test of interest, but no data on SCLC staging accuracy.*

Shweihat YR, Samant RS, Joshi M, et al. Endobronchial ultrasound-guided transbronchial needle aspiration in a geographical region with endemic histoplasmosis infection. J Bronchol Intervent Pulmonol. 2010 Oct;17(4):295-300. *Fewer than 10 patients with SCLC.*

Singh P, Camazine B, Jadhav Y, et al. Endoscopic ultrasound as a first test for diagnosis and staging of lung cancer: a prospective study. Am J Respir Crit Care Med. 2007 Feb 15;175(4):345-54. PMID: 17068326. *Not SCLC.*

Soja J, Szlubowski A, Kocon P, et al. Usefulness of transbronchial needle aspiration for initial lung cancer staging. Pol Arch Med Wewn. 2010 Jul-Aug;120(7):264-9. PMID: 20693956. *None of the modalities of interest.*

Stewart AG. Routine PET for early lung cancer. Thorax. 2010 Mar;65(3):279. *Not a study (e.g., review, opinion).*

Sun JY, Zhao H, Zhang J, et al. First 30 endobronchial ultrasound-guided transbronchial needle aspirations: a single institution's early experience. Chin Med J. 2011 Jun;124(12):1818-23. PMID: 21740839. *Fewer than 10 patients with SCLC.*

Sun R, Chen QS, Cai L, et al. Value of 18F-FDG PET/CT in staging and prognosis prediction of patients with small cell lung cancer. Chinese Journal of Medical Imaging Technology. 2011 Apr;27(4):743-6. *Not staging before treatment.*

Suzuki K, Yamamoto M, Hasegawa Y, et al. Magnetic resonance imaging and computed tomography in the diagnoses of brain metastases of lung cancer. Lung Cancer. 2004 Dec;46(3):357-60. PMID: 15541821. *Other: CT was single detector, and no accuracy data on MRI.*

Szlubowski A, Soja J, Kocon P, et al. A comparison of the combined ultrasound of the mediastinum by use of a single ultrasound bronchoscope versus ultrasound bronchoscope plus ultrasound gastroscope in lung cancer staging: a prospective trial. Interact Cardiovasc Thorac Surg. 2012 Sep;15(3):442-6. Epub 2012 May 23. PMID: 22623626. *Other: Less than 10 SCLC patients for each modality.*

Szlubowski A, Kuzdzal J, Pankowski J, et al. Ultrasound guided transbronchial needle aspiration as a diagnostic tool for lung cancer and sarcoidosis. Pneumonol Alergol Pol. 2008;76(4):229-36. PMID: 18785127. *Fewer than 10 patients with SCLC.*

Tamura M, Oda M, Matsumoto I, et al. Radiologic and nuclear medicine predictors of tumor invasiveness in patients with clinical stage IA lung adenocarcinoma. World J Surg. 2011 Sep;35(9):2010-5. PMID: 21633846. *Not SCLC.*

Tanaka R, Horikoshi H, Yoshida T, et al. Diffusion-weighted magnetic resonance imaging in differentiating the invasiveness of small lung adenocarcinoma. Acta Radiol. 2011 Sep 1;52(7):750-5. PMID: 21565888. *Not SCLC.*

Taneja S, Talwar V, Jena A, et al. Incidence of asymptomatic brain metastasis in lung cancer patients at initial staging work-up - a study of 211 cases. J Indian Acad Clin Med. 2007 Oct-Dec;8(4):312-5. *One test of interest, but no data on SCLC staging accuracy.*

Tatci E, Ozmen O, Gokcek A, et al. 18F-FDG PET/CT rarely provides additional information other than primary tumor detection in patients with pulmonary carcinoid tumors. Ann Thorac Med. 2014 Oct 1;9(4):227-31. *Not SCLC.*

Taulelle M. Lung cancer. Rev Mal Respir. 2004 Jun;21(4):5S54-5S61. *Not a study (e.g., review, opinion).*

Thatcher N, Faivre-Finn C, Blackhall F, et al. Small Cell Lung Cancer (SCLC); any progress? Eur J Cancer Suppl. 2007 Sep;5(5):398-9. *Not a study (e.g., review, opinion).*

Uemura S, Yasuda I, Kato T, et al. Preoperative routine evaluation of bilateral adrenal glands by endoscopic ultrasound and fine-needle aspiration in patients with potentially resectable lung cancer. Endoscopy. 2013;45(3):195-201. PMID: 23299524. *Fewer than 10 patients with SCLC.*

Ulger S, Demirci NY, Aydinkarahaliloglu E, et al. PET-CT guided curative conformal radiation therapy in limited stage small cell lung cancer. J Thorac Dis. 2015;7(3):295-302. *Not staging before treatment.*

Ulger S, Demirci NY, Aydinkarahaliloglu E, et al. PET-CT guided curative conformal radiation therapy in limited stage small cell lung cancer. J Thorac Dis. 2015;7(3):295-302. *Duplicate of already-identified article.*

Uramoto H, Sugio K, Nakata S, et al. Clinical usefulness of FDG-PET in the diagnosis of lung cancer. Jpn J Lung Cancer. 2006 Apr;46(2):127-31. *Fewer than 10 patients with SCLC.*

Usuda K, Sagawa M, Motono N, et al. Relationships between EGFR mutation status of lung cancer and preoperative factors - are they predictive? Asian Pac J Cancer Prev. 2014;15(2):657-62. PMID: 24568474. *Fewer than 10 patients with SCLC.*

Vaccarili M, Lococo A, Fabiani F, et al. Clinical diagnostic application of 111In-DTPA-octreotide scintigraphy in small cell lung cancer. Tumori. 2000 May/Jun;86(3):224-8. PMID: 10939603. *None of the modalities of interest.*

van Loon J, De Ruysscher D, Wanders R, et al. Selective nodal irradiation on basis of (18)FDG-PET scans in limited-disease small-cell lung cancer: a prospective study. Int J Radiat Oncol Biol Phys. 2010 Jun 1;77(2):329-36. PMID: 19782478. *Treatment study.*

van Loon J, Offermann C, Bosmans G, et al. 18FDG-PET based radiation planning of mediastinal lymph nodes in limited disease small cell lung cancer changes radiotherapy fields: a planning study. Radiother Oncol. 2008 Apr;87(1):49-54. Epub 2008 Mar 14. PMID: 18342967. *One test of interest, but no data on SCLC staging accuracy.*

Van Overhagen H, Brakel K, Heijenbrok MW, et al. Metastases in supraclavicular lymph nodes in lung cancer: assessment with palpation, US, and CT. Radiology. 2004 Jul;232(1):75-80. PMID: 15166326. *No separate SCLC data.*

Vansteenkiste J, Dooms C, Becker H, et al. Staging procedures. Eur J Cancer Suppl. 2005 Oct;3(3):7-19. *Not a study (e.g., review, opinion).*

Varadarajulu S, Schmulewitz N, Wildi SF, et al. Accuracy of EUS in staging of T4 lung cancer. Gastrointest Endosc. 2004 Mar;59(3):345-8. PMID: 14997129. *Not SCLC.*

Veronesi G, Maisonneuve P, Pelosi G, et al. Screening-detected lung cancers: is systematic nodal dissection always essential? J Thorac Oncol. 2011 Mar;6(3):525-30. PMID: 21289523. *Fewer than 10 patients with SCLC.*

Vilmann P, Krasnik M, Larsen SS, et al. Transesophageal endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) and endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) biopsy: a combined approach in the evaluation of mediastinal lesions. Endoscopy. 2005 Sep;37(9):833-9. PMID: 16116534. *Not SCLC.*

Vincent BD, El-Bayoumi E, Hoffman B, et al. Real-time endobronchial ultrasound-guided transbronchial lymph node aspiration. Ann Thorac Surg. 2008 Jan;85(1):224-30. PMID: 18154815. *Fewer than 10 patients with SCLC.*

Viney RC, Boyer MJ, King MT, et al. Staging lung cancer using positron emission tomography and the impact on care. J Clin Outcome Manag. 2004 Aug;11(8):486-8. *Not a study (e.g., review, opinion).*

Vinjamuri M, Craig M, Campbell-Fontaine A, et al. Can positron emission tomography be used as a staging tool for small-cell lung cancer? Clin Lung Cancer. 2008 Jan;9(1):30-4. PMID: 18282355. *Other: Clinical diagnosis reported only for select cases.*

Wang Memoli JS, El Bayoumi E, Pastis NJ, et al. Using endobronchial ultrasound features to predict lymph node metastasis in patients with lung cancer. Chest. 2011 Dec;140(6):1550-6. PMID: 21636663. *Fewer than 10 patients with SCLC.*

Wang F, Ma S, Shen L, et al. [Application of (18)F-FDG PET/CT in pulmonary disease: a report of 419 cases.] Chin J Lung Cancer. 2012;15(1):21-6. PMID: 22237120. *No separate SCLC data.*

Wang L, Hayes S, Paskalev K, et al. Dosimetric comparison of stereotactic body radiotherapy using 4D CT and multiphase CT images for treatment planning of lung cancer: evaluation of the impact on daily dose coverage. Radiother Oncol. 2009 Jun;91(3):314-24. PMID: 19111362. *Not SCLC.*

Wardeh R, Lee JG, Gu M. Endoscopic ultrasound-guided paracentesis of ascitic fluid: a morphologic study with ultrasonographic correlation. Cancer Cytopathol. 2011 Feb 25;119(1):27-36. PMID: 21072835. *Fewer than 10 patients with SCLC.*

Williamson S. Lung cancer diagnosis and management. Pharm Pract. 2008 Nov/Dec;18(8):265-71. *Not a study (e.g., review, opinion).*

Wong R. Are symptoms reliable as an indication for the necessity of bone scans in lung cancer metastases? Nat Clin Pract Oncol. 2004 Nov;1(1):18-9. PMID: 16264792. ***Not a study (e.g., review, opnion).***

Xanthopoulos EP, Corradetti MN, Mitra N, et al. Impact of PET staging in limited-stage small-cell lung cancer. J Thorac Oncol. 2013 Jul;8(7):899-905. PMID: 23608814. ***One test of interest, but no data on SCLC staging accuracy.***

Yang RM, Li L, Wei XH, et al. Differentiation of central lung cancer from atelectasis: comparison of diffusion-weighted MRI with PET/CT. PLoS ONE. 2013 Apr 4;8(4):e60279. PMID: 23593186. ***Fewer than 10 patients with SCLC.***

Yasufuku K, Chiyo M, Koh E, et al. Endobronchial ultrasound guided transbronchial needle aspiration for staging of lung cancer. Lung Cancer. 2005 Dec;50(3):347-54. PMID: 16171897. ***No separate SCLC data.***

Yasufuku K, Nakajima T, Motoori K, et al. Comparison of endobronchial ultrasound, positron emission tomography, and CT for lymph node staging of lung cancer. Chest. 2006 Sep;130(3):710-8. PMID: 16963667. ***Fewer than 10 patients with SCLC.***

Yildirim D, Tamam M, Sanli Y, et al. Virtual bronchoscopy using FDG-PET/CT images for the evaluation of lung cancer. Eur Rev Med Pharmacol Sci. 2012;16(14):1951-60. PMID: 23242722. ***Unclear whether any patients had SCLC.***

Yue L, Sun LL. Clinical application of CT eight-type classification of small cell lung cancer. Chin J Intervent Imaging Ther. 2012 Jun;9(6):459-62. ***One test of interest, but no data on SCLC staging accuracy.***

Zhang J, Cui LB, Tang X, et al. DW MRI at 3.0 T versus FDG PET/CT for detection of malignant pulmonary tumors. Int J Cancer. 2013;134(3):606-11. PMID: 23893610. ***No separate SCLC data.***

Zhao Y, De Bock GH, Vliegenthart R, et al. Performance of computer-aided detection of pulmonary nodules in low-dose CT: comparison with double reading by nodule volume. Eur Radiol. 2012 Oct;22(10):2076-84. PMID: 22814824. ***Not SCLC.***

Zimny M, Hochstenbag M, Lamers R, et al. Mediastinal staging of lung cancer with 2-[fluorine-18]-fluoro-2-deoxy-D-glucose positron emission tomography and a dual-head coincidence gamma camera. Eur Radiol. 2003 Apr 1;13(4):740-7. Epub 2002 Sep 7. PMID: 12664112. ***Fewer than 10 patients with SCLC.***

Appendix C. Evidence Tables

Table C-1. General study information of included studies

Study	Country	Name of Clinic(s)	Range of Dates When Patients Received Imaging Tests	Prospective or Retrospective	Funding Source and Disclosed Potential Conflicts of Interest
Lee et al. (2012)[1]	South Korea	Soonchunhyang University	Jan 2006–Oct 2011	Retrospective	Funding NR, No conflicts to disclose
Palomar Munoz et al. (2012)[2]	Spain	Ciudad Real	Jul 2008–Dec 2009	Retrospective	NR
Sohn et al. (2012)[3]	South Korea	Asan Medical Center	Jan 2002–Dec 2007	Retrospective	NR, but no conflicts to disclose
Wada et al. (2010)[4]	Japan	Chiba University	Nov 2002–Sep 2008	Retrospective	NR
Fischer et al. (2007)[5]	Denmark	Copenhagen University Hospital	Feb 2003–Dec 2004	Prospective	NR
Brink et al. (2004)[6]	Germany	Freiburg University Hospital	1999–2003	Prospective	Funded by German Cancer Foundation, conflicts NR
Shen et al. (2002)[7]	Taiwan	China Medical College	NR	Prospective	NR

NR=Not reported

Table C-2. Patient characteristics of included studies

Study	Patient Enrollment Criteria	Number of Patients Included	% Female	Age (Mean, Range)	Consecutivity
Lee et al. (2012)[1]	Diagnosed with SCLC, no treatment, no history of previous malignancy	95	25% (24/95)	Mean 68, SD 9, range NR	Did not report whether enrollment was consecutive
Palomar Munoz et al. (2012)[2]	Diagnosed with SCLC, had pre-treatment PET/CT, no neurologic symptoms	21	14% (3/21)	Mean 66.57 (range 45–83)	Excluded patients followed up less than 6 months. Does not explicitly say consecutive.
Sohn et al. (2012)[3]	Diagnosed with SCLC, no treatment, had initial CT and bone scan or neuro imaging	73	18% (13/73)	Mean NR, SD NR, median 62, range 27–83	Does not explicitly say consecutive.

Table C-2. Patient characteristics of included studies (continued)

Study	Patient Enrollment Criteria	Number of Patients Included	% Female	Age (Mean, Range)	Consecutivity
Wada et al. (2010)[4]	Limited disease SCLC patients who underwent EBUS-TBNA for lymph node staging because they were being considered for surgical resection	40	15% (6/40)	Mean 66.0, SD NR, range 37–79	Did not report whether enrollment was consecutive. Of note, although the demographic data describe 40 pts, only 36 were included in the denominator for sen, spec, calcs, since 4 patients who were considered "negative" by EBUS could not undergo surgery and confirmation of "negative" status. However, the demographics for these 4 are not provided separately.
Fischer et al. (2007)[5]	Patients with pathologically proven SCLC	34	62% (21/34)	Mean 63, range 47–77	Consecutive enrollment
Brink et al. (2004)[6]	Histologically confirmed SCLC, exclusion criteria not reported	120	25% (30/120)	Mean 60.8, SD 8.9	Consecutive enrollment
Shen et al. (2002)[7]	Diagnosed with SCLC, no treatment	25	28% (7/25)	Mean 56.4, SD 7.2, median 57, range 45–68	Did not report whether enrollment was consecutive.

NR=Not reported

Table C-3. General test details of included studies

Study	Number of SCLC Patients in This Study Who Received This Test	Imaging Test	Test Details	Order of Multiple Tests Performed	Elapsed Time Between Tests
Lee et al. (2012)[1]	95	Bone scintigraphy	Tc99m-MDP, 740-925 MBq 3 hours prior, GE Xeleris dual-head camera, continuous acquisition mode (12 cm/min), 20% symmetric window about 140 keV, whole-body and spot imaging	NR	Median 5 days, max 20 days
Lee et al. (2012)[1]	95	FDG PET/CT	FDG, 5.18 MBq/kg 1 hour prior, Philips Gemini scanner, 128 matrix, 3D reformatting	NR	Median 5 days, max 20 days
Palomar Munoz et al. (2012)[2]	21	FDG PET/CT of the brain	FDG, methods reported in previous article, GE Discovery DSTE 16 scanner	NA	NA
Sohn et al. (2012)[3]	73	FDG PET/CT	FDG, 550 MBq 1 hour prior, Siemens Biograph Sensation, 2 minutes per position	Conventional first	NR

Table C-3. General test details of included studies (continued)

Study	Number of SCLC Patients in This Study Who Received This Test	Imaging Test	Test Details	Order of Multiple Tests Performed	Elapsed Time Between Tests
Sohn et al. (2012)[3]	73	Standard staging	History, physical exam, chest x-ray, chest CT, bone scan, bone marrow aspiration, MRI or CT of the brain)	Conventional first	NR
Wada et al. (2010)[4]	40	EBUS	Convex probe EBUS (BF-UC260F-OL8; Olympus, Tokyo, Japan) integrated with convex transducer (7.5 MHz); ultrasound images processed with ultrasound scanner (EU-C2000;Olympus); a dedicated 22-gauge needle was used to perform transbronchial needle aspiration (NA-201SX-4022; Olympus)	NA	NA
Fischer et al. (2007)[5]	29	Standard staging	Any of the following: Clinical exam, blood test, chest x-ray, bronchoscopy, and bone marrow biopsy	NR	All exams performed within one week
Fischer et al. (2007)[5]	29	FDG PET/CT	400 MBq 18-F-FDG was given, scan performed on integrated PET/CT system (GE Discovery LS; General Electric Medical Systems, Milwaukee, WI). A standardized CT protocol (80–120 mAs, 140 kV, tube rotation time 0.5 s per rotation, pitch 6, and slice thickness of 5 mm) was applied followed by PET scan (3 or 5 min emission scan per table position)	Radiologist first read CT (blinded to PET), then nuclear medicine physician read PET (blinded to CT findings); then "fused PET/CT images were evaluated in consensus afterwards"	CT result was derived from PET/CT, thus no time lapse between PET/CT and CT. Bone scan was at most six days after PET/CT
Fischer et al. (2007)[5]	29	Bone scintigraphy	Whole body scan with dual head gamma camera (Geor ADAC) with high resolution low energy collimator was performed 2 hr after injection with 500-700 MBq 99m Tc-oxydronate (TechneScan HDP; Malinkrodt, Hazelwood, MO, USA)	NR	All exams performed within one week

Table C-3. General test details of included studies (continued)

Study	Number of SCLC Patients in This Study Who Received This Test	Imaging Test	Test Details	Order of Multiple Tests Performed	Elapsed Time Between Tests
Fischer et al. (2007)[5]	29	CT	Was performed using PET/CT scanner	Radiologist first read CT (blinded to PET), then nuclear medicine physician read PET (blinded to CT findings); then "fused PET/CT images were evaluated in consensus afterwards"	CT result was derived from PET/CT, thus no time lapse between PET/CT and CT. Bone scan was at most six days after PET/CT
Brink et al. (2004)[6]	120	CT	NR	NA	NA
Brink et al. (2004)[6]	76	Bone scintigraphy	Tc99m-MDP, 700 MBq 3 hours prior, dual-head camera, mfr. not reported, some SPECT as well	NR	NR
Shen et al. (2002)[7]	25	Standard staging	Standard staging assessment, which included history and physical exam, chest x-ray, possibly chest CT, brain CT, abdominal CT, possibly hepatic sonography, Tc-99m MDP bone scan, unilateral iliac crest bone marrow exam.	NA	NA

Note: This table includes details of only the imaging tests for which data met our inclusion criteria.

NA=Not applicable; NR=not reported

Table C-4. Imaging test readers and reference standards

Study	Imaging Test	Number of Test Readers Per Scan	Prior Experience of These Readers With This Imaging Test	Other Reported Details About the Readers	Reference Standard
Lee et al. (2012)[1]	Bone scintigraphy	2	Experienced	NM specialist, used 4-point scale. Consensus or independent reading NR, blinding NR	Positive biopsy OR CT or MRI confirmation OR progression seen on subsequent scan (any one sufficient to diagnose)
Lee et al. (2012)[1]	FDG PET/CT	2	Experienced	NM specialist, used 4-point scale. Consensus or independent reading NR, blinding NR	Positive biopsy OR CT or MRI confirmation OR progression seen on subsequent scan (any one sufficient to diagnose)

Table C-4. Imaging test readers and reference standards (continued)

Study	Imaging Test	Number of Test Readers Per Scan	Prior Experience of These Readers With This Imaging Test	Other Reported Details About the Readers	Reference Standard
Palomar Munoz et al. (2012)[2]	FDG PET/CT of the brain	NR	Nuclear medicine experts	NR	Minimum 6 month clinical follow-up including contrast CT, brain MRI.
Sohn et al. (2012)[3]	FDG PET/CT	2 (consensus)	Experienced	Not blinded to other results	Clinical follow-up
Sohn et al. (2012)[3]	Standard staging	NR	NR	Not blinded to other results	Clinical follow-up
Wada et al. (2010)[4]	EBUS	1	NR	Blinded to patient details	Negative nodes: surgical path; positive nodes: EBUS results
Fischer et al. (2007)[5]	Standard staging	NR	NR	NR	Reference standard based on four things: 1) histology if available; 2) concordance between different imaging modalities; 3) results of MRI or ultrasound; 4) clinical follow-up
Fischer et al. (2007)[5]	FDG PET/CT	2	Experienced	NR	See above
Fischer et al. (2007)[5]	Bone scintigraphy	1	"Experienced" nuclear medicine physician	NR	See above
Fischer et al. (2007)[5]	CT	1	"An experienced radiologist, blinded to PET findings interpreted the CT scan"	NR	See above
Brink et al. (2004)[6]	CT	NR	NR	NR	Consensus achieved by committee of 4 (2 clinicians, 2 nuclear medicine specialists)
Brink et al. (2004)[6]	Bone scintigraphy	Not reported	Not reported	NR	Committee decision
Shen et al. (2002)[7]	Standard staging (multiple tests)	NR	NR	NR	Based on several considerations including surgical findings, other imaging results, and one year clinical follow-up

Note: This table includes details of only the imaging tests for which data met our inclusion criteria.

NA=Not applicable; NR=not reported

Table C-5. Concordance data for tests of interest in included studies (Fischer et al. [2007])

Staging Determination	Test 1 Versus Test 2	Number With Both Tests Positive	Number With Both Tests Negative	Number With Where Test 1 Positive But Test 2 Negative	For These Discrepancies, How Many Were Stated by the Authors to be True Positives?	Number With Where Test 2 Positive and Test 1 Negative	For These Discrepancies, How Many Were Stated by the Authors to be True Positives?	% Agreement Between Tests	Comments
Tumor stage (T)	CT vs. PET/CT	28	0	1	NR	0	NR	97%	Out of 29 patients, CT and PET/CT agreed on T staging for 28. For 1 patient, CT found stage =3, while PET/CT found stage =2. PET/CT was assessed in consensus by two people (one who had previously viewed just the CT portion of PET/CT, and the other who previously viewed just the PET portion of PET/CT), whereas CT was assessed without reference to PET/CT.
N stage (N) Lymph nodes	CT vs. PET/CT	25	0	2	NR	2	NR	86%	Out of 29 patients CT and PET/CT agreed for 25 patients; for 2 patients CT had higher stage (Stages 3 vs. 2, Stage 2 vs. 0); for 2 patients PET/CT had higher stages (Stage 3 vs. 2 and Stage 3 vs. 2)
Pleural effusion	CT vs. PET/CT	9	20	0	NA	0	NA	100%	Out of 29 patients, complete agreement
Metastasis to ipsilateral lung	CT vs. PET/CT	4	23	2	NR	0	NR	93%	Out of 29 patients, 2 patients for whom CT found ipsilateral mets, but PET/CT did not
Metastasis to contralateral lung	CT vs. PET/CT	3	26	0	NR	0	NR	100%	Our of 29 patients there was complete agreement between these 2 tests

Table C-5. Concordance data for tests of interest in included studies (Fischer et al. [2007]) (continued)

Staging Determination	Test 1 Versus Test 2	Number With Both Tests Positive	Number With Both Tests Negative	Number With Where Test 1 Positive But Test 2 Negative	For These Discrepancies, How Many Were Stated by the Authors to be True Positives?	Number With Where Test 2 Positive and Test 1 Negative	For These Discrepancies, How Many Were Stated by the Authors to be True Positives?	% Agreement Between Tests	Comments
Metastasis to the liver	CT vs. PET/CT	10	16	1	NR	2	NR	90%	
Metastasis to adrenals	CT vs. PET/CT	3	24	2	NR	0	NR	93%	
Metastasis to extra-thoracic lymph nodes	CT vs. PET/CT	5	22	1	NR	1	NR	93%	
Metastasis to osseous structures	CT vs. PET/CT	3	21	0	NA	5	5	83%	All five discrepancies were called correctly by PET/CT and incorrectly by CT
Metastasis to osseous structures	CT vs. bone scint.	1	12	1	1	14	7	46%	Counting equivocal as + for Bone scan. The 14 includes 4 times where bone scintigraphy was positive and CT was negative. 10 times where bone scintigraphy was equivocal and CT was negative. Out of 15 total discrepancies, PET/CT was correct in 8 and bone scintigraphy was correct in 7.

Table C-5. Concordance data for tests of interest in included studies (Fischer et al. [2007]) (continued)

Staging Determination	Test 1 Versus Test 2	Number With Both Tests Positive	Number With Both Tests Negative	Number With Where Test 1 Positive But Test 2 Negative	For These Discrepancies, How Many Were Stated by the Authors to be True Positives?	Number With Where Test 2 Positive and Test 1 Negative	For These Discrepancies, How Many Were Stated by the Authors to be True Positives?	% Agreement Between Tests	Comments
Metastasis to osseous structures	FDG PET/CT vs. bone scint.	5	11	2	2	10	2	57%	Counting equivocal as + for Bone scan. The 10 includes 4 times where bone scintigraphy was positive and PET/CT was negative, and 6 times where bone scintigraphy was equivocal and PET/CT was negative. Out of 12 total discrepancies, PET/CT was correct in 10 and bone scintigraphy was correct in 2.

All included concordance data are from Fischer et al. (2007).[5]

NA=Not applicable; NR=not reported; scint.=scintigraphy.

Table C-6. Accuracy data for tests of interest in included studies

Study	Staging Determination	Test(s) of Interest (Test 1 vs. Test 2)	Test 1, True Positives	Test 1, False Positives	Test 1, False Negatives	Test 1, True Negatives	Test 2, True Positives	Test 2, False Positives	Test 2, False Negatives	Test 2, True Negatives	No Internal Discrepancies in Reported Data?	Comments
Fischer et al. (2007)[5]	LD/ED	Standard staging vs. FDG PET/CT	19	0	3	6	21	0	1	6	OK	
Shen et al. (2002)[7]	LD/ED	Standard staging only	14	1	1	9	NA	NA	NA	NA	OK	Data are from Table III in the article

Table C-6. Accuracy data for tests of interest in included studies (continued)

Study	Staging Determination	Test(s) of Interest (Test 1 vs. Test 2)	Test 1, True Positives	Test 1, False Positives	Test 1, False Negatives	Test 1, True Negatives	Test 2, True Positives	Test 2, False Positives	Test 2, False Negatives	Test 2, True Negatives	No Internal Discrepancies in Reported Data?	Comments
Lee et al. (2012)[1]	Metastasis to osseous structures	FDG PET/CT vs. Bone scintigraphy	30	0	0	65	11	5	19	60	OK	These data are on a per-patient basis
Fischer et al. (2007)[5]	Metastasis to osseous structures	CT vs. Bone scintigraphy	2	0	7	19	7	8	2	11	OK	These data treat equivocal bone scintigraphy results as positives
Fischer et al. (2007)[5]	Metastasis to osseous structures	CT vs. Bone scintigraphy	2	0	7	19	2	3	7	16	OK	These data treat equivocal bone scintigraphy results as negatives
Fischer et al. (2007)[5]	Metastasis to osseous structures	CT vs. FDG PET/CT	3	0	7	19	8	0	2	19	OK	
Fischer et al. (2007)[5]	Metastasis to osseous structures	FDG PET/CT vs. Bone scintigraphy	7	0	2	19	7	8	2	11	OK	These data treat equivocal bone scintigraphy results as positives
Fischer et al. (2007)[5]	Metastasis to osseous structures	FDG PET/CT vs. Bone scintigraphy	7	0	2	19	2	3	7	16	OK	These data treat equivocal bone scintigraphy results as negatives
Brink et al. (2004)[6]	Metastases to osseous structures	Bone scintigraphy only	14	2	9	51	NA	NA	NA	NA	OK	Subset of patients who had bone scan
Wada et al. (2010)[4]	Metastasis to mediastinal and hilar lymph nodes	EBUS only	27	0	1	8	NA	NA	NA	NA	OK	
Brink et al. (2004)[6]	Metastasis to lymph node(s) (>1cm defined positivity)	CT only	37	4	16	61	NA	NA	NA	NA	OK	Excluded two cases where CT and PET disagreed and no reference diagnosis was obtained
Brink et al. (2004)[6]	Metastases to adrenal glands	CT only	15	4	9	92	NA	NA	NA	NA	OK	

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Table C-6. Accuracy data for tests of interest in included studies (continued)

Study	Staging Determination	Test(s) of Interest (Test 1 vs. Test 2)	Test 1, True Positives	Test 1, False Positives	Test 1, False Negatives	Test 1, True Negatives	Test 2, True Positives	Test 2, False Positives	Test 2, False Negatives	Test 2, True Negatives	No Internal Discrepancies in Reported Data?	Comments
Brink et al. (2004)[6]	Metastases to liver	CT only	23	2	3	92	NA	NA	NA	NA	OK	
Brink et al. (2004)[6]	Metastases to spleen	CT only	3	0	1	116	NA	NA	NA	NA	OK	
Sohn et al. (2012)[3]	Distant metastasis	Standard staging vs. FDG PET/CT	12	0	14	47	24	2	2	45	Discrepancies	The two false positives were termed by authors as positives tests at first, but then termed equivocal tests; these data treat them as false positives
Palomar Munoz et al. (2012)[2]	Metastases to brain	FDG PET/CT of the brain only	3	0	2	16	NA	NA	NA	NA	OK	

NA=Not applicable; NR=not reported

Table C-7. Analyses of accuracy data for tests of interest in included studies

Study	Staging Determination	Test(s)	Sensitivity Test 1 (95% CI)[a]	Sensitivity Test 2 (95% CI)[a]	Specificity Test 1 (95% CI)[a]	Specificity Test 2 (95% CI)[a]	95% CI Around the Difference in Logit Sensitivities[a]	95% CI Around the Difference in Logit Specificities[a]
Fischer et al. (2007)[5]	LD/ED	Standard staging vs. FDG PET/CT	86% (66% to 95%) (19/22)	95% (78% to 99%) (21/22)	100% (60% to 100%) (6/6)	100% (60% to 100%) (6/6)	-3 to 1.1	-3.6 to 3.6
Shen et al. (2002)[7]	LD/ED	Standard staging only	93% (70% to 99%) (14/15)	NA	90% (59% to 98%) (9/10)	NA	NA	NA
Lee et al. (2012)[1]	Metastasis to osseous structures	FDG PET/CT vs. Bone scintigraphy	100% (88% to 100%) (30/30)	37% (22% to 55%) (11/30)	100% (94% to 100%) (65/65)	92% (83% to 97%) (60/65)	2.2 to 7.1 Favors FDG PET/CT	-0.1 to 4.9

Table C-7. Analyses of accuracy data for tests of interest in included studies (continued)

Study	Staging Determination	Test(s)	Sensitivity Test 1 (95% CI)[a]	Sensitivity Test 2 (95% CI) [a]	Specificity Test 1 (95% CI) [a]	Specificity Test 2 (95% CI) [a]	95% CI Around the Difference in Logit Sensitivities [a]	95% CI Around the Difference in Logit Specificities [a]
Fischer et al. (2007)[5]	Metastasis to osseous structures	CT vs. Bone scintigraphy (treating equivocals as positive)	22% (7% to 55%) (2/9)	78% (45% to 93%) (7/9)	100% (83% to 100%) (19/19)	58% (36% to 77%) (11/19)	-4.4 to -0.3 Favors bone scint.	0.8 to 5.9 Favors CT.
Fischer et al. (2007)[5]	Metastasis to osseous structures	CT vs. Bone scintigraphy (treating equivocals as negative)	22% (7% to 55%) (2/9)	22% (7% to 55%) (2/9)	100% (83% to 100%) (19/19)	84% (62% to 94%) (16/19)	-1.9 to 2.2	-0.7 to 4.6
Fischer et al. (2007)[5]	Metastasis to osseous structures	CT vs. FDG PET/CT	30% (11% to 60%) (3/10)	80% (49% to 94%) (8/10)	100% (83% to 100%) (19/19)	100% (83% to 100%) (19/19)	-3.9 to -0.1 Favors FDG PET/CT	-3.4 to 3.4
Fischer et al. (2007)[5]	Metastasis to osseous structures	FDG PET/CT vs. Bone scintigraphy (treating equivocals as positive)	78% (45% to 93%) (7/9)	78% (45% to 93%) (7/9)	100% (83% to 100%) (19/19)	58% (36% to 77%) (11/19)	-2.2 to 1.9	0.8 to 5.9 Favors FDG PET/CT.
Fischer et al. (2007)[5]	Metastasis to osseous structures	FDG PET/CT vs. Bone scintigraphy (treating equivocals as negative	78% (45% to 93%) (7/9)	22% (7% to 55%) (2/9)	100% (83% to 100%) (19/19)	84% (62% to 94%) (16/19)	0.3 to 4.4 Favors FDG PET/CT	-0.7 to 4.6
Brink et al. (2004)[6]	Metastases to osseous structures	Bone scintigraphy only	61% (41% to 78%) (14/23)	NA	96% (87% to 99%) (51/53)	NA	NA	NA
Wada et al. (2010)[4]	Metastasis to mediastinal and hilar lymph nodes	EBUS only	96% (82% to 99%) (27/28)	NA	100% (67% to 100%) (8/8)	NA	NA	NA
Brink et al. (2004)[6]	Metastasis to lymph node(s) (>1cm defined positivity)	CT only	70% (56% to 80%) (37/53)	NA	94% (85% to 97%) (61/65)	NA	NA	NA

Table C-7. Analyses of accuracy data for tests of interest in included studies (continued)

Study	Staging Determination	Test(s)	Sensitivity Test 1 (95% CI)[a]	Sensitivity Test 2 (95% CI) [a]	Specificity Test 1 (95% CI) [a]	Specificity Test 2 (95% CI) [a]	95% CI Around the Difference in Logit Sensitivities [a]	95% CI Around the Difference in Logit Specificities [a]
Brink et al. (2004)[6]	Metastases to adrenal glands	CT only	63% (43% to 79%) (15/24)	NA	96% (90% to 98%) (92/96)	NA	NA	NA
Brink et al. (2004)[6]	Metastases to liver	CT only	88% (71% to 96%) (23/26)	NA	98% (92% to 99%) (92/94)	NA	NA	NA
Brink et al. (2004)[6]	Metastases to spleen	CT only	75% (30% to 95%) (3/4)	NA	100% (97% to 100%) (116/116)	NA	NA	NA
Sohn et al. (2012)[3]	Distant metastasis	Standard staging vs. FDG PET/CT	46% (29% to 65%) (12/26)	92% (76% to 98%) (24/26)	100% (86% to 99%) (47/47)	96% (92% to 100%) (45/47)	-4.1 to -1.1 Favors FDG PET/CT	-1.2 to 4.1
Palomar Munoz et al. (2012)[2]	Metastases to brain	PET/CT of the brain only	60% (23% to 88%) (3/5)	NA	100% (80% to 100%) (16/16)	NA	NA	NA

[a] Calculated by investigators.

NA=Not applicable; NR=not reported

Appendix D. Risk of Bias Assessments

Figure D-1. Risk of bias assessments of comparative accuracy studies

Item	Lee et al. (2012)[1]	Fischer et al. (2007)[5]	Sohn et al. (2012)[3]
1. Did the study enroll all, consecutive, or a random sample of patients?	NR	Yes	Yes
2. Was the study unaffected by spectrum bias (e.g., patients with known status before the study, or patients selected for being difficult to diagnose/stage)?	NR	NR	No
3. Was prior experience with the test (technicians, readers) similar for the two imaging tests being compared in the study?	Yes	Yes	Yes
4. Were the imaging tests performed within one month of each other (to avoid the possibility that the patient's true condition changed between tests)?	Yes	Yes	Yes
5. Was knowledge of the other test complementary (either both tests were read with knowledge of the other results, or neither test was read with knowledge of the other)?	NR	Yes	No
6. Did the interpreters have the same other information available at the time of interpretation for the two imaging tests (other clinical information, 3rd test results)?	NR	NR	No
7. Was each test's accuracy measuring using the same reference standard (or a similar proportion of patients who underwent different reference standards such as clinical follow-up and surgical findings)?	Yes	Yes	Yes
8. Were readers of both tests of interest blinded to the results of the reference standard (or the reference standard was unknowable until after the tests were read)?	Yes	Yes	Yes
9. Were the people determining the reference standard unaware of the diagnostic test results?	No	No	No
Risk of Bias Category	**Moderate**	**Moderate**	**High**

Figure D-2. Risk of bias assessments of single test accuracy studies

Item	Wada et al. (2010)[4]	Brink et al. (2004)[6]	Shen et al. (2002)[7]	Palomar Munoz et al. (2012)[2]
1. Did the study enroll all, consecutive, or a random sample of patients?	Yes	Yes	NR	NR
2. Were more than 85 percent of the approached/eligible patients enrolled?	Yes	NR	NR	NR
3. Were the patient inclusion and exclusion criteria applied consistently to all patients?	Yes	Yes	NR	NR
4. Was the study unaffected by obvious spectrum bias?	Yes	Yes	Yes	Yes
5. Did the study account for inter-reader differences?	No	Yes	No	No
6. Were readers of the diagnostic test of interest blinded to the results of the reference standard?	NR	Yes	Yes	Yes
7. Were readers of the reference standard blinded to the results of the diagnostic test of interest?	No	No	NR	Yes
8. Were readers of the diagnostic test of interest blinded to all other clinical information?	Yes	Yes	NR	NR
9. Were readers of the reference standard blinded to all other clinical information?	NR	No	No	No
10. Were patients assessed by a reference standard regardless of the test's results?	No	Yes	Yes	Yes
11. Were all patients assessed by the same reference standard regardless of the test's results?	No	Yes	Yes	Yes
12. If the study reported data for a single diagnostic threshold, was the threshold chosen a priori?	NA	NA	NA	NA
13. Were the study results unaffected by intervening treatments or disease progression/regression?	Yes	Yes	Yes	No
14. Were at least 85 percent of the enrolled patients accounted for?	Yes	No	Yes	Yes
Risk of Bias Category	**Moderate**	**Moderate**	**Moderate**	**Moderate**

Appendix E. Appendix References

1. Lee JW, Lee SM, Lee HS, et al. Comparison of diagnostic ability between (99m)Tc-MDP bone scan and 18F-FDG PET/CT for bone metastasis in patients with small cell lung cancer. Ann Nucl Med. 2012 Oct;26(8):627-33. PMID: 22729551

2. Palomar Munoz A, Garcia Vicente AM, Bellon Guardia ME, et al. Is a selective brain (18)F-FDG PET/CT study profitable in patients with small cell lung cancer? Rev Esp Med Nucl Imagen Mol. 2012 May;31(3):124-9. PMID: 21722995

3. Sohn BS, Lee DH, Kim EK, et al. The role of integrated 18F-FDG PET-CT as a staging tool for limited-stage small cell lung cancer: a retrospective study. Onkologie. 2012 Aug;35(7):432-8. PMID: 22846975

4. Wada H, Nakajima T, Yasufuku K, et al. Lymph node staging by endobronchial ultrasound-guided transbronchial needle aspiration in patients with small cell lung cancer. Ann Thorac Surg. 2010 Jul;90(1):229-34. PMID: 20609781

5. Fischer BM, Mortensen J, Langer SW, et al. A prospective study of PET/CT in initial staging of small-cell lung cancer: comparison with CT, bone scintigraphy and bone marrow analysis. Ann Oncol. 2007 Feb;18(2):338-45. PMID: 17060487

6. Brink I, Schumacher T, Mix M, et al. Impact of [(18)F]FDG-PET on the primary staging of small-cell lung cancer. Eur J Nucl Med Mol Imaging. 2004 Dec;31(12):1614-20. PMID: 15258700

7. Shen YY, Shiau YC, Wang JJ, et al. Whole-body 18F-2-deoxyglucose positron emission tomography in primary staging small cell lung cancer. Anticancer Res. 2002;22(2):1257-64. PMID: 12168935