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Office of Patient Care Services

UPDATED INFORMATION FOR VA TECHNOLOGY ASSESSMENT PROGRAM (VATAP) REPORTS

In June 2000, VATAP was relocated within the Veterans Health Administration from the Office of Research & Development to the Office of Patient Care Services. The following report was produced prior to the relocation of VATAP.

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Appendix 6

**Systematic Review:
PET as a Diagnostic Test in
Lung Cancer**

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*Appendix 6***Systematic Review:
PET as a Diagnostic Test in Lung Cancer**

The final literature database searches for the systematic reviews were performed on September 10, 1996; the assessment represents peer-reviewed literature published and indexed as of that date.

This Appendix to the PET assessment presents the results of the systematic review of PET in lung cancer. A general rationale for the use of PET in oncology is supplied by Hawkins, et al., (1994) and Hoh, et al., (1994):

- many forms of cancer characteristically perturb tissue biochemical and physiological processes and PET imaging can be expected to detect the resulting abnormalities;
- reliance on tumor histology and anatomy limits the oncologist's tools for selecting optimal treatment;
- the ability to monitor metabolic responses to treatment could allow the early re-direction of therapy in patients who fail to respond to the first attempt at radiation or chemotherapy.

These and other authors (e.g., Price and Jones, 1995) report that PET studies in cancer are emerging as a major focus of the technology, both in basic research and in clinical investigations. Information gathered by the MDRC Technology Assessment Program from VA PET facilities corroborates that perception (see *Appendix 9: Experience With PET in VHA*).

Fluorine-18-fluorodeoxyglucose (FDG) is the most commonly employed radiopharmaceutical in PET cancer studies. Many neoplasms have high glycolytic rates, resulting in intracellularly trapped phosphorylated FDG that can be imaged with PET. Hawkins, et al., (1994), note that tumor-specific biochemical characteristics of glucose transport and phosphorylation may affect quantitative estimates of tumor glucose metabolism with FDG PET, and that investigations are under way to define these characteristics. However, these uncertainties may be of less concern with qualitative or semiquantitative FDG PET cancer studies because the primary intent of such studies is to detect and map tumor foci, not to rigorously quantify tumor glycolytic rates.

In some instances, PET imaging techniques have been modified to meet the needs of cancer diagnosis. Most PET systems allow axial fields of view (the length of the body encompassed by a series of cross sectional images) of approximately 10 cm. Cancer is frequently distributed beyond this field of view, and whole body image acquisition procedures have been developed (Hoh, et al., 1993). Since it is impractical to apply standard transmission scanning attenuation correction methods to these procedures, whole body PET imaging is primarily useful as a qualitative indicator of disease distribution.

Nieweg (1994) and Price and Jones (1995) define a number of potential applications for PET in oncology. These include:

- tumor detection (although PET images offer insufficient structural detail and should not be used to visualize anatomy; registration techniques to combine PET and anatomic imaging into a single image are under development to circumvent this limitation);
- staging (particularly using whole-body imaging methods) although there is a lower limit to the size of metastases that can be detected by PET;
- detection of local recurrence of disease, since anatomically-based imaging is often limited by the effects of treatment;
- prediction of tumor response to chemotherapy;
- treatment monitoring.

I. BACKGROUND

A. General sources

The information in this section, unless otherwise noted, is based on Minna (1994). Additional sources are referenced in the text.

B. Description

Bronchogenic carcinoma, classified as either small cell or non-small cell, comprises 95% of all primary lung cancers. Three-fourths of all bronchogenic carcinomas are of the non-small cell varieties and include cell types which, when localized, have the potential for cure with surgical resection. They include adenocarcinoma (including bronchiolalveolar), squamous (or epidermoid) cell carcinoma, and large cell (including large cell anaplastic) carcinoma. This report will not address small cell lung carcinomas, because they occur less frequently and are staged and treated differently than non-small cell types.

C. Epidemiology

Bronchogenic carcinoma is the leading cause of cancer death in the United States. In 1996 it is estimated that there will be 177,000 new cases of primary lung carcinoma and 158,700 deaths from lung cancer (American Cancer Society, 1996). Within the Veterans Health Administration, malignant neoplasms of the bronchus and lung accounted for a total of 14,749 patients discharged (1.75% of all patients discharged within the system) with an average length of stay of 18.0 days in fiscal year 1994 (Annual Report of the Secretary of Veterans Affairs, 1994).

The overall incidence is increasing, causing the age-adjusted lung cancer death rate to double every 15 years. The major risk factor for all lung cancers is smoking. The contribution of second-hand smoke is controversial, but is estimated to be responsible for 15% to 20% of lung cancers in non-smokers (Filderman, 1994). There is a dose-response correlation between lung cancer death rate and the total amount of cigarettes smoked. Likewise, cessation of smoking decreases the risk of developing lung cancer, although the risk may never return to normal levels. Additional risk factors may include exposure to: asbestos, chromium, nickel, mustard gas, vinyl chloride, arsenic, isopropyl oil, hydrocarbons, radon, and chloromethyl ether, and ionizing radiation from occupational, medical, and environmental sources (Filderman, 1994). Most, and perhaps all, of these materials are additive or synergistic with cigarette smoke in the development of lung cancer.

Evidence suggesting a genetic predisposition to lung cancer has been reported, but the underlying mechanisms have not yet been identified (Samet, 1993). Because lung cancer rarely occurs in the absence of tobacco exposure, host characteristics may be expressed only in the presence of an environmental insult, such as tobacco.

Dietary factors may contribute independently to the incidence of lung cancer in some populations. While a direct association between increased consumption of dietary cholesterol and animal fat and increased lung cancer risk has been reported, current evidence supports neither benefit nor harm from the use of supplemental beta carotene (Kabat, 1993; Zagonel, 1994; Hennekens, 1996).

D. Diagnosis

In unscreened and asymptomatic patients, 5-15% of non-small cell lung cancers are detected on a routine chest radiograph usually ordered for other reasons. However, the vast majority of patients are symptomatic, indicating advanced disease at clinical presentation.

The clinical manifestations of lung cancer vary with cell type and extent of tumor spread (stage), and may be confused with paraneoplastic syndromes (a group of symptoms resulting from nonmetastatic complications that may mimic metastatic disease). Signs and symptoms resulting from local tumor spread include pain and discomfort resulting from tumor involvement of adjacent thoracic structures such as the heart, esophagus, trachea and chest wall. More severe symptoms may include respiratory insufficiency and impaired oxygenation.

Initial diagnosis is based on a complete history, physical examination, and chest radiography (planar x-ray). If results of the chest film increase the likelihood of cancer, resulting in a high post-test probability of disease, other tests are needed to determine stage, cell type, and subsequent treatment. Patient tolerance, tumor accessibility, and the risks and costs associated with each available test will determine the best method(s) (i.e., degree of invasiveness needed) for obtaining tissue specimens to optimize diagnostic certainty. Any one or combination of the following methods may be used to obtain tissue specimens: sputum sampling, diagnostic bronchoscopy, percutaneous transthoracic biopsy, mediastinoscopy, thoracoscopy, and thoracotomy (Kaplan, 1991). These endoscopic procedures and thoracotomy are also used to further visualize extent of disease.

E. Staging, treatment, and survival

Lung cancer staging assesses the extent of local and distant disease and involves two parts: 1) anatomic staging, and 2) physiologic staging or the ability of the patient to tolerate specific therapeutic interventions (performance status). Illustrated below is the TNM International Stage System (ISS) developed by the American Joint Committee on End Results Reporting used to describe the extent of primary tumor involvement (T stage), lymph node involvement (N stage) and distant metastasis (M stage), and to reflect prognosis and survival among homogenous patient groups with non-small cell lung carcinomas (Mountain, 1993).

Table 1 Lung Cancer TNM Staging System

	N ₀	N ₁	N ₂	N ₃	
T ₀	carcinoma <i>in situ</i>				Roman numerals represent stages
T ₁					Occult stage=T _x N ₀ M ₀
T ₂	I	II			Occult stage through stage IIIb are without distant metastases (M ₀)
T ₃			III a		All M ₁ tumors (with distant metastases) are stage IV
T ₄				III b	

subscripted numbers=degree of involvement; 0=least to 4=most

Source: Mountain, 1993

The data in the following table were provided by NCI through its on-line Physician Data Query (PDQ) system to present staging, treatment, and survival data for patients with non-small cell lung cancer.

Table 2 Lung Cancer Staging, Treatment, and Survival

Primary Site	Staging	Standard Therapy	5-Year Survival (Other Therapy-Specific Survival Data, Where Indicated)
Lung Parenchyma	Occult	Surgery	70-80%, overall for occult
	0= <i>in situ</i>	surgery with curative intent photodynamic therapy	not available
	I	surgery with curative intent radiotherapy with curative intent, depending on T-stage neoadjuvant therapy <i>5-10% of patients may develop second lung cancers within 5 years</i>	50% overall for stage 1 10-60%
	II	surgery with curative intent radiotherapy with curative intent, depending on T-stage surgery and/or radiotherapy and/or chemotherapy	30% overall for stage 11 10-60%
	IIIa	surgery surgery and radiotherapy radiotherapy surgery and/or radiotherapy plus chemotherapy	10-30% overall for stage 111a
	IIIb	radiotherapy with curative intent chemotherapy plus radiotherapy chemotherapy plus radiotherapy followed by surgery chemotherapy alone radiotherapy followed by surgery	< 5% overall for stage 111b
	IV	radiotherapy with palliative intent chemotherapy, depending on performance status chemo- and radiation therapy	< 2% overall for stage IV
	Recurrence	radiotherapy chemotherapy both	not available

Source: NCI, 1995

At the time of diagnosis approximately 55% of patients with lung cancer will have stage IV disease; 25% will have either stage II, IIIa or IIIb disease; and 20% will have local stage I disease. Surgical resection is the treatment of choice for patients with operable lung cancer (occult carcinoma through stage IIIa). For inoperable stage IIIa, IIIb and IV cancer, radiotherapy is the preferred option for palliation in patients with poor performance status or in patients who refuse multimodality regimens, but it results in cure for only a small minority of patients. In stage IIIb and IV disease chemotherapy offers modest improvements in patients with a good performance status, although overall survival is poor. The effect of chemotherapy on survival in patients with poor performance status is unknown (Souquet, 1993). Multimodality treatment in more advanced stages of disease to improve survival is being studied.

Recent advances in endoscopic surgical equipment, surgical techniques, and neoadjuvant (preoperative) chemotherapy with and without radiotherapy aid in converting some patients from unresectable to resectable status. Unfortunately, advances in staging methods and surgical treatment of lung cancer have had little impact on overall mortality rates, although more accurate staging, particularly of the mediastinum, has significantly reduced the incidence of unbeneficial exploratory thoracotomy (Pearson, 1993). Two ongoing randomized trials, one evaluating extensive versus limited resection and the other evaluating

the effect of surgery in more extensive disease, may provide insight into the effectiveness of surgery in the treatment of localized non-small cell lung cancer (Lederle, 1994).

Prognostic factors of patients with non-small cell lung cancer have been identified as those predictive of treatment response and those predictive of survival (Shepherd, 1994). As in all malignancies, the primary predictor of response to treatment is the stage of disease at diagnosis; others include performance status and chemotherapeutic regimen (eg., single agent versus combination therapy). The most significant factors predictive of survival are stage at diagnosis and performance status followed by gender, history of pretreatment weight loss, and/or elevated blood lactate dehydrogenase levels. Since the majority of patients present with advanced stage disease, there is a need to identify (or “screen”) individuals, particularly those at high risk, at a point early in tumor development with the hope that the tumor would still be amenable to curative surgical resection.

Lung cancer screening is usually performed using serial chest radiography (x-ray) and sputum sampling. However, studies using these screening tools have not demonstrated a clear survival benefit because of their low sensitivity. Moreover, results were confounded by the effects of either the surgical intervention, lead time bias (the interval between the diagnosis of a disease at screening and when it would have been detected due to development of symptoms), or length-time bias (overrepresentation among screen-detected cases of slower growing tumors which have a more favorable prognosis). Accordingly, there is a need to develop other technologies to overcome these limitations.

The prognostic role of molecular diagnostics as an adjunct to lung cancer screening tools represents a significant portion of research activity to date. Tumor biomarkers may provide insight into the natural history of occult or pre-cancerous tumor development and their corresponding treatment. Advancements in fiberoptic technology enhanced with laser (eg., fluorescence bronchoscopy) are being developed to locate pre-cancerous cells in the airways, which would enable the patient to undergo curative resection much earlier in the course of the disease. Methods for detecting genetic alterations, including oncogene anomalies and deoxyribonucleic acid (DNA) mutations in sputum and bronchoscopic specimens, in patients with lung cancer are areas of active investigation.

F. Potential roles for PET

Currently, CT is the preferred diagnostic imaging test and is used at several points in the initial work up and treatment of a patient with lung cancer. Its roles include staging, evaluating treatment response, and differentiating recurrent tumor from fibrosis after treatment. However, its limitations are well known. CT provides morphologic (typically size), not histologic, detail of the disease site. Therefore, biopsy confirmation of the primary site and metastases is required to determine the most appropriate treatment.

The wide range of reported accuracies makes the contribution of CT to lung cancer staging difficult to quantify. The following factors are likely to influence the reported characteristics of CT: differences in disease prevalence among study populations; cell type; scanning techniques; definition of the boundary between adjacent node structures; criteria for lymph node enlargement; data analysis (by patient or nodal station); and extent of node sampling performed either pre- or peri-operatively (Quint, 1995 and Seely, 1993). The contribution of interobserver variability in image interpretation has also been identified (Guyatt, 1995 and Webb, 1993).

Detection of cancer in mediastinal lymph nodes is particularly problematic. CT of the mediastinum may demonstrate the presence of enlarged but benign lymph nodes, and may

often appear normal in the presence of micrometastases. A meta-analysis assessing the use of CT in staging lung cancer found CT to be 80% accurate in evaluating mediastinal lymph nodes, and advances in CT staging techniques in recent years have had little measurable effect on accuracy (Dales, 1990). While predictive values are generally more helpful in the clinical management of these patients, the range of prevalence of malignancy in these studies precluded the use of predictive values in their analysis. Using data based on sensitivity, specificity, and accuracy the authors recommended that an indicator other than lymph node size be used to determine lymph node pathology.

Determination of distant metastases (M stage) may require multiple scans, which can be very resource-intensive. Brain and abdominal CT and radionuclide bone scanning are most often employed as part of the work up for metastatic disease. Standard practice supports the use of scanning those organs in patients demonstrating symptoms of metastatic disease, but routine use in patients with an otherwise unremarkable clinical exam remains controversial. A systematic review conducted by Hillers, et al. (1994) confirmed the controversial nature of the metastatic work up in these patients, although the prevalence of unsuspected brain metastases in patients with lung cancer may provide the rationale among some clinicians for routine brain CT scanning.

A meta-analysis conducted by Silvestri, et al., (1995) concluded that the negative predictive value of an unremarkable clinical evaluation when compared with brain CT, abdominal CT, or radionuclide bone scanning consistently exceeded 90%. The negative predictive value exceeded 97% when an expanded pre-defined set of criteria was added to the routine clinical evaluation of metastatic disease to the brain or abdomen. A decision analysis conducted by this same group further supported not using brain CT scans routinely in the presence of normal findings on clinical examination (Colice, 1995). Both studies reemphasized the importance of a standardized physical examination, history, and basic lab tests in staging these patients.

Use of other diagnostic imaging technologies in the staging of lung cancer is circumscribed largely because of technical limitations, availability, and cost. Whereas MRI has not demonstrated additional benefit over CT or in combination with CT in staging, it may help in delineating vascular structures within the hila and mediastinum and in detecting aortopulmonary and subcarinal lymphadenopathy. Excellent visualization provided by coronal, sagittal, and oblique views of the chest does offer MRI several advantages over CT in staging Pancoast tumors and imaging tumor invasion of both diaphragmatic surfaces and the chest wall. Ultrasonography may also have a limited role in detecting tumors invading the chest wall.

Advances in nuclear medicine imaging have focused on qualitative and quantitative physiologic, rather than morphologic, determination of disease status with the intent to improve the accuracy of diagnosis. So far, the results of nuclear medicine studies using Gallium-67, Thallium-201, and Technetium-99m-sestaMIBI (Chiti, 1996) to stage lung cancer have not demonstrated marginal benefit over CT. The use of immunoscintigraphy (radiolabelled monoclonal antibodies) in early detection of lung cancer is being applied, but validation with larger trials is needed.

Potential roles for whole body FDG PET in lung cancer have been noted in the literature (Nieweg, 1994 and Gupta, 1993). PET has been evaluated in the detection of the primary tumor, staging, and distinguishing recurrent disease from scar tissue. Interpretation of these PET studies is accomplished by visual inspection and by various quantitative or semiquantitative analyses used to characterize disease status.

Results of FDG PET imaging in patients with lung cancer were first published by Nolop, et al., (1987) from the Royal Postgraduate Medical School, London, England. This study

demonstrated that the quantitative assessment of glucose utilization in pulmonary neoplasms is feasible and may have important therapeutic implications. Rege, et al., (1993) from UCLA School of Medicine were the first to demonstrate the feasibility and potential utility of the whole body PET method to image primary and metastatic chest tumors.

Additional roles for PET have been suggested. They include:

- analyzing tumor biology;
- predicting tumor response by measuring uptake of chemotherapeutic agents;
- quantitatively monitoring tumor response to therapy.

The MDRC TA Program was unable to identify any studies which evaluated these roles in lung cancer and which met the screening criteria for this assessment.

II. RESULTS

Thirty-seven articles were selected from the MEDLINE and other database searches and from the bibliographies of initially retrieved articles as meeting the screening criteria. After review, 21 (57%) were found to meet the criteria for assignment to the following levels of the diagnostic efficacy hierarchy (Fryback and Thornbury, 1991; *Appendix 2: Assessing Diagnostic Technologies*): 9 met the definition of technical efficacy (see Reference List; full data abstraction tables for Technical Efficacy studies are on file with the MDRC Technology Assessment Program); 11 met most or all of the criteria for studies of diagnostic efficacy; 1 met the criteria for studies of diagnostic efficacy and attempted to address diagnostic thinking efficacy hypothetically.

Tables 4 and 5 abstracted data from studies of diagnostic accuracy of PET for certain lung cancer applications. Table 3 summarizes cross-study findings on PET and alternative technologies. The MDRC Technology Assessment Program was unable to locate any studies using PET in lung cancer at the patient outcome or societal levels.

Gambhir, et al., (1996) presented a decision analysis for the cost-effectiveness of FDG-PET in the staging and management of non-small cell lung cancer. This study was not included in the tables because of the preliminary nature of the assumptions upon which the analysis was based, which may affect the stability of the conclusions. Sensitivity and specificity values used in the analysis were derived from 3 small preliminary studies (two abstracts, one peer-reviewed) comprising 96 total patients analyzed by nodal station and mediastinal side. Cost data were based on billable costs (charges) that may not adequately reflect true costs, and that may not have been sufficiently comprehensive with respect to inclusion of other costs related to the work-up and to patients with unresectable metastases. The results from this analysis may not be valid and should be viewed with caution.

All currently available data on the use of PET in diagnosing lung cancer are derived from case series studies. These studies provide Level V (i.e., the weakest) evidence of any association between the use of a technology and improved patient outcomes. All studies included patients with a high index of suspicion for lung cancer and used internal controls (patients with benign masses). Accordingly, no predictive values were reported, with the exception of Knight, et al., (1996), who had an equivalent array of subjects with which to calculate predictive values for a small subset of patients.

PET was evaluated at various points in the test sequence in the diagnosis of lung cancer either as an addition to or as a substitute for CT. Results for the use of PET in detecting unknown primary

disease, nodal metastases, and recurrent disease are presented below. Anecdotal data on the use of PET in detecting distant metastases were presented by Valk, et al., (1995) in Table 4, but were not included in Table 3 because of the small number of patients.

A. Detecting unknown primary disease

Table 4 lists six preliminary studies using PET in the diagnosis of primary lung cancer, of which two (Wahl, 1994; Sazon, 1996) assessed PET and CT independently. The remaining four studies evaluated the complementary role of PET with CT in the diagnostic process. One study by Valk, et al., (1995) did not report operating characteristics for either PET or CT in detecting primary disease and was not included. Only two studies (Wahl, 1994 and Knight, 1996) presented CT data for comparison; limitations in study design and small study size call for cautious interpretation of these results.

In most studies the extent to which the PET results influenced determination of disease (eg., to proceed to thoracotomy versus follow-up) could not be ascertained. Of interest is a finding by Kubota, et al., (1990), who noted that the differences in operating characteristics between the two PET models used in their study may have affected the generalizability of reported results.

Table 5 lists one study (Slosman, 1993) that assessed the impact of PET on diagnostic thinking efficacy using Bayesian analysis in patients seen at a satellite center for a diagnostic work up of lung cancer. Using sensitivity figures derived from their own study population, but specificity from Kubota, et al., (1990), and varying the prevalence of disease, the authors hypothesized the impact of PET on diagnostic certainty. While they illustrated that PET would have the greatest impact in a population with a low prevalence of disease, and in whom a positive test could lead to more aggressive therapy than one would otherwise plan, further study in larger populations is needed to define the role of PET in the diagnostic work-up.

B. Detecting hilar and mediastinal metastases

Several studies evaluated PET at various points in the test sequence for staging mediastinal involvement in lung cancer. Most studies evaluated PET qualitatively, while Scott, et al., (1996) evaluated PET quantitatively using a cut-off value based on unpublished data.

Variations in study design influenced the range of reported results and contributed to the degree of bias found in these studies. These relatively small studies comprised a narrow range of patients restricted to biopsy-proven cases with a high index of suspicion for metastases. In three studies (Patz, 1995; Sazon, 1996; Scott, 1996) the choice of patients included for mediastinal staging was influenced by the PET results.

CT and PET are limited in their ability to detect micrometastases and require histologic confirmation of disease. In most, and perhaps all, of these studies there was a strong association between the test result and choice of biopsy site. Variations in biopsy sampling procedures and the thoroughness of sampling, often left to the discretion of the surgeon, occurred across all studies and typically was not reported with sufficient detail to be reproducible. While standard practice supports the use of imaging by surgeons either pre- or peri-operatively, knowledge of imaging test results may favor nodes that appear suspicious on imaging, resulting in biased test characteristics.

Differences in methods of data analysis reported by patient, by mediastinal side, and by node were presented and may contribute to the range of reported results. Scott and

associates (1996) presented data by both patient and node. Operating characteristics from all of these studies should be interpreted cautiously, as the degree of bias is significant.

C. Detecting recurrent disease

Two studies (Patz, 1994 and Inoue, 1995) used PET with CT to distinguish recurrent or residual cancer from fibrosis. Both studies incorporated a semiquantitative methodology to characterize comparison groups. The preliminary nature of these studies must be stressed because of variations in cut-off points, one which was determined retrospectively, and low number of study subjects.

III. SUMMARY

Preliminary studies of the potential roles of FDG PET in diagnosing lung cancer using visual inspection, semiquantitative analysis, and Bayesian analysis were presented. None of these studies demonstrated the incremental value of PET in the sequence of tests used to diagnose and stage lung cancer or to distinguish local cancer recurrence from fibrosis. All were relatively small case series using internal controls with a disproportionately high number of malignant cases, and may not provide reliable estimates of accuracy. The MDRC Technology Assessment Program was unable to locate any studies in lung cancer that evaluated the incremental value of PET information on treatment planning or patient outcome. Gambhir and associates (1996) presented a decision analysis to assess the cost-effectiveness of PET in the work-up of non-small cell lung cancer, but the underlying assumptions used in the study may not be valid.

None of the studies met strict evidence-based medicine criteria for blinding, and there is a strong likelihood that the test results may have influenced the determination of disease status. However, all studies presented information on the comprehensiveness of blinding of the test interpreters to the diagnostic gold standard (i.e., biopsy confirmation). One small, hypothetical diagnostic thinking efficacy study (Slosman, 1994) was included, but further validation with larger study populations is needed. Table 3 summarizes the findings from studies assessing the diagnostic accuracy of PET. These findings received low methodologic quality grades because of small study size, retrospective design, and a significant degree of bias.

IV. DISCUSSION

The attempt by some of these studies to characterize comparison groups quantitatively warrants further discussion. Consideration of the cut-off point used in quantitative analysis will depend on the consequences of limiting false negative results and of accepting false positive results. This value will also be influenced by the pre-test probability of disease of the study population and the heterogeneity of both normal and cancerous lung tissue. In a recently published case control study Miyauchi, et al., (1996) demonstrated the effect of regional variations of FDG uptake within normal lungs on the range of reported results, particularly with respect to small lung nodules found in lower lung fields. Variations in normalization procedures used in semi-quantitative analyses may further influence the choice of cut-off (Schomburg, 1996). Determination of the clinical efficacy of PET using quantitative methods requires first standardizing the technique, defining the optimal cut-off point from a much larger and broader study population, and subsequently applying it to studies designed to determine diagnostic accuracy.

One study attempted to evaluate the impact of PET on diagnostic certainty using Bayesian analysis (Slosman, et al., 1993). Although this study has methodologic shortcomings (i.e., an insufficient

number of controls with which to determine specificity), it does illustrate the importance of defining the baseline prevalence of disease within the study population of interest when evaluating operating characteristics of a test.

As modifications of more widely available and less costly alternatives are refined and evaluated, their contribution to the medical workup may affect the utility of PET as a diagnostic tool for lung cancer. Over the last two decades, there have been considerable developments in medical imaging, many of which use variations of the techniques used in CT to improve diagnostic accuracy. An increased understanding of the physics underlying imaging, enhanced computer capabilities, and applied mathematical-reconstruction techniques have made a significant contribution to improved image generation and analysis (Greenes and Brinkley, 1990). Most, if not all, of the techniques described below are in the preliminary stage of evaluation, and their contribution to the diagnostic process has not been quantified.

New approaches in standard radiographic image generation (x-ray) have been described (Kaplan, 1995). Scanning equalization radiography is a term used to describe a family of techniques designed to improve image quality, but systems that use this technique have limited commercial availability. Developments in the use of neural networks to decrease the number of false positive findings have been reported (Wu, 1995). Advances in radiology for use in lung cancer have focused largely on improving the image generating capabilities of CT (through the use of contrast media, reduced scanning time, and spiral volumetric technologies to improve image resolution) and developing other modalities such as MRI and ultrasonography to overcome the limitations of CT.

Recent advances in nuclear medicine instrumentation include multi-headed gamma cameras and higher efficiency computers for single-photon emission computed tomography (SPECT). New computer techniques in anatomometabolic fusion imaging, which combine the images of CT, MRI, SPECT, or PET, are used to compare structural abnormalities with physiologic or metabolic information. These advances offer potential advantages over older procedures and other structural imaging techniques, not only in the diagnosis and staging of cancer, but also as tools for monitoring and predicting the effects of therapy on cancer biochemistry and metabolism.

Technologies designed to improve diagnostic accuracy are also being developed in areas other than imaging. In addition to the advances in early detection described previously, procedures and instrumentation used in sampling and analysis are being enhanced to increase diagnostic yield. Newer endoscopes with smaller diameters and greater flexibility have been developed in an attempt to improve access to and visualization of tumors. Local practices which use these other technologies may affect the utility of PET in the diagnostic work up.

Although advances in diagnostic imaging in lung cancer have focused mainly on improving earlier detection of disease and the accuracy of staging, the benefit of more accurate lung cancer staging has not been clearly demonstrated. The radiologic improvement of CT over standard x-ray is not disputed, and it has only been in recent years that CT has become sufficiently available and accepted as part of the routine diagnostic work up for lung cancer. However, the impact of CT on the reported prevalence of lung cancer and corresponding pre-test probability of disease has not been quantified. With respect to advances in staging using CT and alternatives such as PET, methods of reporting statistics on prevalence, natural history, and therapeutic effectiveness, and evaluations of diagnostic accuracy according to lesion size have been suggested to better define the impact of these advances (Black and Welch, 1993).

The effects of many therapeutic interventions for lung cancer are under investigation. The rationale for using PET in the clinical management of patients with an overall poor five year survival may be difficult to define. Any analysis of the effect of PET on the outcomes of treatment which might be attempted, based on other follow up of patients who have been reported in the existing literature, would be further complicated by the range of stages and histologies of non-small cell lung cancer included in the case series, and the associated range of treatment and outcomes.

V. SUGGESTIONS FOR FURTHER PET RESEARCH

Preliminary data have been published to date, and have attempted to define the operating characteristics of PET as a diagnostic test. Contributions from other investigators working with larger patient populations comparing PET to existing modalities will be needed to refine the characteristics of PET as a diagnostic tool in lung cancer, and to establish a base for further research.

In this context, future research within VA should focus on:

- establishing a PET registry, which would provide a range of data on demographic and clinical characteristics of patients on whom PET studies are performed, and on their clinical outcomes in a variety of settings;
- defining the role of PET as part of a diagnostic test battery;
- studies defining the impact of PET on treatment decision making and on outcomes such as survival, in comparison with existing technologies such as CT, MRI, and endoscopic procedures.

Table 3 Summary of the Literature: Diagnostic accuracy efficacy studies of PET and alternatives in lung cancer

Notes: All of the studies in the table are case series (Level V evidence) with internal controls (i.e. those with benign masses) used as a comparison group. All patients in these studies had suspected or biopsy-proven lung cancer (i.e. the pre-test probability of disease in the study populations was very high). Results from Knight, et al., 1996 and Inoue, et al., 1995 were reported as ranges to include data from all subgroup analyses.

None of these studies met strict evidence-based medicine criteria for blinding, but all studies presented information on blinding of the test interpreters to the biopsy gold standard. Blinding of the PET interpreters to other clinical and radiologic data varied across studies and is reflected in the columns designated "Operating Characteristics"; "PET + CT" indicates a complementary role of PET with CT, and PET alone indicates a substitutive role of PET for CT.

Where substantial duplication in purpose of study, patients studied, and results in multiple studies from the same institution could be inferred, only the most recent, largest, most rigorously designed, or most comprehensive was included in the table. Studies reviewed but not included are listed under "References".

Abbreviations are listed at the end of the table.

Role <i>(Note: Some studies assessed multiple roles)</i>	Study	N	Operating Characteristics*			Evidence-Based Medicine Criteria**			Methodologic Quality Grade***
			PET	PET + CT	CT	comparison group	histologic gold standard	blinding	
Defining unknown primary disease	Kubota, et al., 1990	12 malignant cases 10 benign cases		Se=83% Sp=90% accuracy=86%	no data reported	+ internal	+	+	C
	Scott, et al., 1994	47 malignant cases 15 benign cases		Se=94% Sp=80%	no data reported	+ internal	+	+	C
	Slosman, et al., 1994	31 malignant cases 5 benign cases		Se=93.5%	no data reported	+ internal	+ & follow-up	+	C
	Wahl, et al., 1994	19 malignant cases 4 benign cases	Se=100%		Se=100%	+ internal	+	+	C
	Sazon, et al., 1996	82 malignant cases 25 benign cases	Se=100% Sp=52%		no data reported	+ internal	+	+	C
	Knight, et al., 1996	32 malignant cases 16 benign cases		Se=100% Sp=58%-63% PPV=75% NPV=100%	Se=33%-41% Sp=52% PPV=83% NPV=52%	+ internal	+	+	D

Role <i>(Note: Some studies assessed multiple roles)</i>	Study	N	Operating Characteristics*			Evidence-Based Medicine Criteria**			Methodologic Quality Grade***
			PET	PET + CT	CT	comparison group	histologic gold standard	blinding	
Detecting overall lymph adenopathy	Patz, et al., 1995	42 patients with: 23 malignant nodes 39 benign nodes	Se=83% Sp=82%		Se=43% Sp=85%	+ internal	+	+	D
Detecting hilar/lobar lymph adenopathy	Patz, et al., 1995	42 patients with : 11 malignant nodes 29 benign nodes	Se=73% Sp=76%		Se=27% Sp=86%	+ internal	+	+	D
Detecting mediastinal lymph adenopathy	Patz, et al., 1995	42 patients with: 12 malignant nodes 10 benign nodes	Se=92% Sp=100%		Se=58% Sp=80%	+ internal	+	+	D
	Wahl, et al., 1994	23 patients with: 11 malignant sides 16 benign sides	Se=82% Sp=81% accuracy=81%		Se=64% Sp=44% accuracy=52%	+ internal	+	+	C
	Chin, et al., 1995	9 malignant cases 21 benign cases		Se=70% Sp=81% accuracy=80%	Se=56% Sp=86% accuracy=77%	+ internal	+	+	D
	Valk, et al., 1995	24 malignant sides 52 benign sides		Se=83% Sp=94% accuracy=91%	Se=63% Sp=73% accuracy=70%	+ internal	+ & follow-up	+	D
	Sazon, et al., 1996	32 patients with: 16 malignant sides 16 benign sides	Se=100% Sp=100%		Se=81% Sp=56%	+ internal	+	+	C
	Scott, et al., 1996	10 malignant nodes 65 negative nodes within: 9 malignant cases 18 benign cases		Se=100% Sp=98%-100%	Se=60% Sp=83%-94%	+ internal	+	+	D
Distinguishing local cancer recurrence from fibrosis	Patz, et al., 1994	35 recurrence cases 8 fibrosis cases		Se=97.1% Sp=100%	no data reported	+ internal	+ & follow-up	+	D
	Inoue, et al., 1995	23 recurrence cases 13 fibrosis cases		PET + x-ray, CT, MRI Se=100% Sp=56%-78% accuracy=86%	no x-ray, CT, or MRI data reported	+ internal	+ & follow-up	+	D

N, number of total study subjects included in analysis; unless otherwise noted, data are analyzed by subject
 Se, sensitivity
 Sp, specificity
 PPV, positive predictive value
 NPV, negative predictive value
 CT, computed tomography
 MRI, magnetic resonance imaging

* operating characteristics defined in Appendix 2: Assessing Diagnostic Technologies, Page 5-7
 ** Appendix 2, page 8
 *** Appendix 2, page 9

Table 4 Diagnostic Accuracy Efficacy of PET in Lung Cancer

Notes: All of the studies in this table met most of the evidence-based criteria for diagnostic test evaluations. None of these studies met strict evidence-based medicine criteria for blinding, but all studies presented information on the comprehensiveness of blinding of test interpreters to the gold standard. All of the studies in the table are case series (Level V evidence); internal controls (i.e. those with benign masses) were used in each study, and it was possible to calculate sensitivity and specificity for PET in those studies. All patients in these studies had suspected or biopsy-proven lung cancer (i.e. the pre-test probability of disease in the study populations was very high); therefore, predictive values were not reported.

Where substantial duplication in purpose of study, patients studied, and results in multiple studies from the same institution could be inferred, only the most recent, largest, most rigorously designed, or most comprehensive was included in the table. Studies reviewed but not included are listed under "References".

Abbreviations are listed at the end of the table.

Study	Patients/Methods	Results/Comments
Kubota, et al., 1990 (Tohoku University, Japan)	<p>Purpose to differentiate benign from malignant noncalcified lung tumors with PET using FDG and MET (MET data not reported)</p> <p>Cases 22 patients with unknown diagnosis presenting with a tumor shadow on chest x-ray</p> <p>Methods</p> <ul style="list-style-type: none"> •all received CT before PET for anatomical placement •PET interpreted visually and with tumor/muscle radioactivity (TUR) ratios; cut-off 2.0 chosen prospectively to define lesions •image interpreters blinded to histology results •PET compared to histology <p>Limitations of study design</p> <ul style="list-style-type: none"> •small sample sizes •two PET scanners used in study •independent determination of test result and final diagnosis unclear 	<p>Defining unknown primary disease (12 malignant cases, 10 benign cases)</p> <ul style="list-style-type: none"> •PET + CT: Se=83%; Sp=90%; accuracy=86% •TUR: malignant=4.4 ± 2.2 vs. benign=1.5 ± 0.3 (p<0.001) •CT: data not reported <p>Other findings</p> <ul style="list-style-type: none"> •using TUR tumors < 1 cm in diameter too small for accurate evaluation •one false positive attributed to granuloma •two false negatives attributed to a 0.5cm squamous cell carcinoma and liposarcoma •overall Se and Sp was higher in cases studied with Siemens model PT931/04 than with ECAT II model <p>Authors' Comments while metabolic diagnosis allows for detection of cancer with PET, metabolic diagnosis is limited by heterogeneity of tumor metabolism</p>

Study	Patients/Methods	Results/Comments
<p>Patz, et al., 1994 (Duke University, North Carolina)</p>	<p>Purpose to assess PET in differentiating recurrent or residual bronchogenic carcinoma from fibrosis after therapy</p> <p>Cases 43 patients with a persistent radiographic abnormality after treatment for bronchogenic carcinoma •35 recurrences documented by pathology (n=25) or by clinical and radiographic progression (n=10) •8 with fibrosis</p> <p>Methods •all patients had CXR and CT interpreted prior to PET •chest x-ray and CT used to locate abnormality on PET •all PET scans conducted at least 2 months after completion of therapy, blinded to biopsy •ROI defined and SURs calculated and compared to biopsy •SUR threshold of 2.5 empirically determined to provide optimal Se and Sp for malignant disease</p> <p>Limitations of study design •prospective determination of SUR threshold unclear •number of cases and internal controls not equivalent (high prevalence of malignancy) •independent determination of test result and final diagnosis unclear</p>	<p>Differentiating recurrence from fibrosis (35 recurrences, 8 fibrotic cases) •PET + CT: Se=97.1% (95% CI=85.1%-99.9%); Sp=100% (95% CI=63.1%-100) •CT: data not reported</p> <p>Semi-quantitative analysis [median (range)] •SUR: recurrence= 7.7 (1.9-18.7) vs. fibrosis= 1.6 (0.6-2.4) (P=.0001) •34/35 patients with recurrence had SUR > 2.5 •8/8 with no evidence of recurrence 16-124 months after initial diagnosis; 6 biopsy-confirmed, 2 radiographically stable for at least 2 years after treatment</p> <p>Authors' comments •authors acknowledge small number of patients, but data suggest the usefulness of PET in differentiating recurrence from fibrosis in these patients •further validation of PET including a cost-benefit analysis requires a larger patient population</p>
<p>Inoue, et al., 1995 (University of Texas, Houston, Texas)</p>	<p>Purpose to evaluate the diagnostic accuracy of PET in detecting recurrent lung cancer</p> <p>Cases 38 patients with clinically suspected recurrent or residual lung cancer on conventional imaging (CI) (39 total lesions) •26 malignant, 13 benign</p> <p>Methods •all PET images interpreted visually in conjunction with CI (CT, MRI, or chest x-ray) blinded to biopsy •SUVs compared retrospectively in 25 patients •imaging compared to biopsy (n=11) or clinical/radiographic follow-up > 6 months after PET (n=28)</p> <p>Limitations of study design •SUV threshold determined retrospectively •independent determination of test result and final diagnosis unclear •number of cases and internal controls not equivalent •temporal differences between PET and clinical/radiologic follow-up</p>	<p>Test characteristics based on visual inspection (23 recurrences, 13 fibrotic lesions) •PET + CI: *Se=100%; *Sp=61.5%; *accuracy=86% •CI: data not reported •3 small cell cases not included</p> <p>Semiquantitative analysis expressed as mean ± SD (16 recurrences, 9 benign cases) •SUV: recurrence= 11.2 ± 5.7 vs. benign = 3.5 ± 1.8 (p < 0.0001) •no significant differences among patients with squamous cell, adenocarcinoma, or small cell histologies</p> <p>Comparison of visual vs. quantitative PET results using SUV threshold of 5 defining non-small cell recurrence (13 recurrences, 9 benign cases) •visual: *Se= 100%; *Sp= 55.5%; *accuracy= 82% •SUV: *Se= 100%; *Sp= 78%; *accuracy= 91% •3 small cell cases not included</p> <p>Other findings •PET false positives attributed to acute inflammation and reactive mesothelial cells •curvilinear pattern of FDG uptake noted in inflammatory lesions; focal uptake noted in recurrences; further study of FDG distribution is needed</p> <p>Authors' comments •PET should be interpreted in conjunction with anatomical imaging •further studies are needed to assess PET in distinguishing non-small cell and small cell cancers</p>

Study	Patients/Methods	Results/Comments
<p>Wahl, et al., 1994 (Ann Arbor, Michigan and Orange Township Hospital, Australia)</p>	<p>Purpose to prospectively evaluate the use of PET with FDG in mediastinal staging in patients with non-small cell lung cancer</p> <p>Cases 23 patients with abnormality on chest x-ray or strong suspicion of non-small cell lung cancer (i.e. high pre-test probability of cancer) who were to have mediastinal staging •27 mediastinal sides assessed (11 malignant, 16 benign)</p> <p>Methods •time interval between imaging studies 0-23 days, mean 1.9 days •diameter of primary lesions determined by CT; > 1 cm on short axis considered positive for mediastinal nodal involvement •SUV-lean calculated for primary lung lesion, expressed as mean ± SEM •chest x-ray available to locate primary lung lesion on PET •PET diagnosis of primary and mediastinal/hilar lymph reached by consensus using a four-point scale •level of certainty of concordance and discordance between CT and PET reached by consensus for fusion and nonfusion images •fusion imaging assessed for technical accuracy and rated on visual quality using a four-point scale •blinded, independent visual analysis of CT alone, PET alone, CT and PET together (nonfusion), and anatometabolic (fusion) images by two readers reached by consensus •biopsy confirmation determined by needle biopsy, direct observation, and surgery</p> <p>Limitations of study design •small sample size •number of cases and internal controls not equivalent •variations in nodal sampling techniques •independence of test result and determination of final diagnosis unclear • SUV cut-off for primary disease not reported</p> <p><i>Note: Evaluation of diagnostic thinking efficacy (Level III) was attempted by authors when comparing diagnostic certainty of nonfused images and fusion images with CT and PET independently. However, results require histologic confirmation, and reconstruction of Se and Sp was not possible; therefore, inclusion of this study at a diagnostic efficacy level was felt to be warranted.</i></p>	<p>Defining unknown primary disease (19 malignant cases, 4 benign cases) PET: Se=100% (n=23) CT: Se=100% (n=22) •PET SUV-lean: malignant= 6.82 ± 0.983 vs. benign= 1.047 ± 0.268 (P < .04) •size on CT: malignant= 34.9mm ± 2.6 vs. benign=15.5mm ± 2.2 (P < .005)</p> <p>Mediastinal/Hilar nodal disease (11 malignant sides, 16 benign sides) •PET: Se=82%; Sp=81%; accuracy=81% •CT: Se=64%; Sp=44%; accuracy=52% •2 patients with hilar involvement not included in calculations •CT and PET false negatives attributed to close proximity of hilar and mediastinal nodes •PET and CT false positives attributed to granulomas, anthracotic disease; one on PET due to hilar proximity; seven on CT attributed to enlarged nodes</p> <p>Combined nonfused CT and PET images •CT + PET judged better than PET alone in 7/22 cases •CT + PET judged better than CT alone in 16/22 cases •one case not included in PET scan field of view</p> <p>PET anatometabolic fusion images (histologic proof for 7 cases) •visual or fusion images changed overall CT interpretation in 16/22 patients •on CT 3 negative node cases were changed to positive; in 11 node cases were changed from positive to negative •PET results correlated with all histologically confirmed cases •on CT 3 cases changed from tumor to nontumor on fusion image •one positive PET represented atelectasis on fusion image •one false positive fusion image due to mediastinal invasion not confirmed at surgery</p> <p>Other findings •experience too limited to comment on diagnosing hilar nodal involvement •additional data from larger studies needed to confirm results and demonstrate effect on treatment planning and patient outcomes •PET alone or with CT is preferred approach for noninvasive staging of metastatic mediastinal lymph nodes in patients with newly diagnosed or suspected non-small cell lung cancer</p>

Study	Patients/Methods	Results/Comments
<p>Scott, et al., 1994 (Creighton University Medical Center and Omaha Veterans Affairs Medical Center, Omaha, Nebraska)</p>	<p>Purpose</p> <ul style="list-style-type: none"> to retrospectively compare the accuracy of PET and CT to CT alone in imaging hilar and mediastinal lymph nodes to define the initial experience with PET imaging in patients with various lung tumors <p>Cases</p> <ul style="list-style-type: none"> 62 patients with various lung abnormalities all patients had biopsy confirmed primary disease (47 malignant, 15 benign) 25 patients had biopsy confirmation of mediastinal lymph nodes involvement (3 malignant, 22 benign) <p>Methods</p> <ul style="list-style-type: none"> all patients underwent CT before PET; CT or chest x-ray data used to locate lung mass on PET for visual analysis, but not always available for DUR calculations abnormal mediastinal node defined as > 1 cm in diameter on CT PET images analyzed visually by one reader, DURs calculated mean DURs for benign and malignant primary tumors compared, expressed as mean ± SEM PET images blinded to biopsy PET + CT and CT alone compared to biopsy results <p>Limitations of study design</p> <ul style="list-style-type: none"> limited histologic data available on mediastinal lymph nodes retrospective design number of cases and internal controls not equivalent 	<p>Detecting unknown primary disease (47 malignant cases, 15 benign cases)</p> <ul style="list-style-type: none"> PET + CT: Se=93.6%; Sp=80% CT: no data reported <p>Mediastinal lymph nodes (3 malignant cases, 22 benign cases)</p> <ul style="list-style-type: none"> PET correctly identified 19/22 benign cases PET correctly identified 2/3 malignant cases PET identified subcarinal lymph node metastases in 1 of 2 malignant cases with normal CT CT correctly identified 20/22 benign cases CT correctly identified 1/3 malignant cases <p>Quantitative analysis of PET for primary tumors (expressed as mean DUR ± SEM)</p> <ul style="list-style-type: none"> benign= 1.14 ± 0.26 vs. malignant=6.4 ± 0.56 (p < 0.0001) in retrospect, DUR cutpoint of 2.0 produced greatest accuracy (92%): *Se= 94%; *Sp=87% <p>Other findings</p> <ul style="list-style-type: none"> PET false positives attributed to granuloma or inflammatory disease PET false negatives attributed to small tumors < 1cm² and low grade malignancy <p>Authors' comments</p> <ul style="list-style-type: none"> no false negative PET findings occurred in patients with elevated glucose levels confirmation from larger series is needed PET most useful as adjunct to CT evaluation of PET in measuring treatment response is needed
<p>Patz, et al., 1995 (Duke University, North Carolina)</p>	<p>Purpose</p> <p>to assess prospectively the diagnostic accuracy of PET in detecting thoracic lymph node metastases in patients with bronchogenic carcinoma</p> <p>Cases</p> <ul style="list-style-type: none"> 42 patients with untreated bronchogenic carcinoma determined by chest x-ray, CT, bone scan and PET, who were to have nodal sampling 40 non-small cell; 1 small cell type; 1 undifferentiated type 62 total nodal stations sampled at surgery 40 hilar/lobar nodes; 22 mediastinal nodes <p>Methods</p> <ul style="list-style-type: none"> thoracic CT performed before PET lymph nodes on CT > 1 cm on short axis diameter classified as abnormal CT and qualitative PET results read independently and blinded to biopsy CT, PET, and surgical stage mapped according to ATS classification system limited, partial histologic sampling done in 40 patients; 2 patients had single nodal station sampled by thin-needle aspiration PET and CT scans compared to biopsy <p>Limitations of study design</p> <ul style="list-style-type: none"> source of cohort influenced by test results variations in comprehensiveness of nodal sampling test result and determination of final diagnosis not independent 	<p>Detecting hilar/lobar lymph node metastases (11 metastatic nodes, 29 benign nodes)</p> <p>PET: Se=73%; Sp=76% (p=0.009 PET compared with pathology) CT: Se=27%; Sp=86% (p=0.369 CT compared with pathology)</p> <p>Detecting metastatic lymph node metastases (12 metastatic nodes, 10 benign nodes)</p> <p>PET: Se=92%; Sp=100% (p<0.001 PET compared with pathology) CT: Se=58%; Sp=80% (p=0.099) CT compared with pathology</p> <p>Overall detection (23 metastatic nodes, 39 benign nodes)</p> <p>PET: Se=83%; Sp=82% (p<0.001 PET compared with pathology) CT: Se=43%; Sp=85% (p=0.019 CT compared with pathology)</p> <p>Other findings</p> <ul style="list-style-type: none"> false positive hilar nodes on PET due to inflammatory response

Study	Patients/Methods	Results/Comments
<p>Chin, et al., 1995 (Bowman Gray School of Medicine, Wake Forest University, North Carolina)</p>	<p>Purpose to assess prospectively the role of PET in evaluating mediastinal nodal metastases in patients with non-small cell lung cancer</p> <p>Cases •30 patients with potentially resectable tumors (N0-N1 and N2 disease) determined by CT</p> <p>Methods •lymph node on CT considered positive if long-axis diameter > 1.5 cm •CT and qualitative PET assessed independently according to ATS classification; results based on presence or absence of disease in mediastinum •SUVs calculated, but values not used to compute results •surgeons aware of clinical, radiologic, and PET results for mediastinal exploration; ipsilateral mediastinal explorations performed in all patients; contralateral explorations not routinely performed in absence of radiologic evidence •imaging results compared to biopsy</p> <p>Limitations of study design •number of cases and internal controls not equivalent •comprehensiveness of nodal sampling not noted •test result and determination of final diagnosis not independent for mediastinal evaluations</p>	<p>Detecting primary tumor (39 malignant cases, 0 benign cases) PET + CT: Se=94%; accuracy=89% CT: data not reported •data with which to perform calculations were not presented</p> <p>Detecting metastatic lymph node metastases (9 cases, 21 controls) PET + CT: Se=70%; Sp=81%; accuracy=80% CT: Se=56%; Sp=86%; accuracy=77% •agreement between CT and PET in 21 patients (70%) with a diagnostic accuracy of 90%; correlation between combined images and surgical results was statistically significant (p=0.004)</p> <p>Authors' comments •low Se of CT was a function of rigorous preoperative evaluation, limiting the number of true positives detected by either imaging modality and introducing a bias against CT •because of the number of false positive and false negative results, PET should not supplant histologic confirmation •lack of precise correlation of nodal stations between surgical results and both imaging modalities is unlikely to affect clinical management or outcome •low resolution of PET affects its ability to distinguish mediastinal tumors, but may be overcome by coregistration with CT •PET may contribute best in those patients whose CT image shows normal mediastinal adenopathy despite a high index of suspicion of N2 disease, persons with high operative risks, or low-risk patients whose lymph nodes meet size criteria (> 1 cm but < 2 cm) on CT, and may direct attention toward previously unsuspected areas of disease •role of PET may be influenced by local practices particularly with respect to the routine use of mediastinoscopy prior to surgery</p>
<p>Valk, et al., 1995 (Northern California PET Imaging Center and Radiologic Associates of Sacramento, Sacramento, California)</p>	<p>Purpose to assess prospective the role of PET with CT in staging patients with suspected or known lung cancer</p> <p>Cases 74 patients referred to the PET Center for staging of histologically diagnosed non-small cell lung cancer: •76 total mediastinal sides with histologic confirmation (24 positive, 52 negative) •7 patients with hilar node involvement •18 patients with distant metastases</p> <p>Methods •CT performed at referring site •criteria for positive nodes on CT defined as > 1 cm on short axis diameter •PET images interpreted visually and quantitatively; CT images used for localization and measurement of primary tumor, mediastinal CT findings were disregarded •SUVs calculated for primary lesions > 2 cm diameter •imaging correlated to biopsy obtained at mediastinoscopy or thoracotomy or to follow-up; analyzed by mediastinal side •effect of experience in PET interpretation during study evaluated; graded on a three-point visual scale •distant metastases determined by biopsy (n=6) or clinical follow up (n=19)</p> <p>Limitations of study design •number of cases and internal controls not equivalent (high index of suspicion for lung cancer) •test result and determination of final diagnosis not independent •comprehensiveness of nodal sampling unclear</p>	<p>Detecting primary tumor •authors reported a relative lack of anatomic information with PET •no operating characteristics reported for either PET or CT</p> <p>Detecting mediastinal lymph node involvement (24 positive sides, 52 negative sides) PET + CT: Se=83%; Sp=94%; accuracy=91% CT: Se=63%; Sp=73%; accuracy=70%</p> <p>Detecting distant metastases •PET showed evidence of distant metastases in 18 (18%) patients; only 12 patients had histologic or clinical confirmation, with no false positive PET results •authors reported more false positive distant CT findings in 19 patients (19%) than true positive</p> <p>Other findings •mean interval between CT and PET scans=23 days (range 1-51 days) •PET correctly changed the N stage as determined by CT in 18 (24%) staging evaluations; in 16 of 17 discordant cases, PET proved to be correct •false negative PET results attributed to micrometastasis; PET limited by minimal detectable tumor mass •false positive PET results attributed to anthracotic lymph nodes and hyperplasia</p>

Study	Patients/Methods	Results/Comments
<p>Sazon, et al., 1996 (Veterans Affairs Medical Center, West Los Angeles, California)</p>	<p>Purpose to assess the diagnostic accuracy of PET and CT in detecting and staging lung cancer</p> <p>Cases 107 patients with an abnormal chest x-ray: 73 with non-small cell; 5 small cell; 25 various benign chest diseases •of 73 with non-small cell: 32 had mediastinal evaluation (16 malignant, 16 benign) •4 distant metastases</p> <p>Methods •PET and CT read independently •PET results for primary lung lesion and mediastinal involvement determined qualitatively •criteria for positive nodes on CT defined as nodal enlargement > 1 cm in diameter on transaxial images •mediastinal evaluation accomplished by transbronchial needle biopsy, mediastinoscopy, thoracotomy, or at autopsy •PET and CT interpretations blinded to and correlated with biopsy</p> <p>Limitations of study design •number of cases and internal controls not equivalent •influence of PET result on choice of patient cohort for mediastinal evaluation unclear •variations in nodal sampling techniques •independence of test result and determination of final diagnosis unclear</p>	<p>Detecting primary disease (82 malignant cases, 25 benign cases) PET: Se=100%; Sp=52% CT: data not reported</p> <p>Detecting mediastinal lymph node involvement (16 malignant cases, 16 benign cases) PET: Se=100%; CT: Se=81% (95% CI of difference=-13% to 39.3%; p=0.22) PET: Sp=100%; CT: Sp=56% (95% CI of difference= 15.3% to 72.7%; p=0.01)</p> <p>Authors' comments •low Sp of PET in detecting primary disease may be due to broader range of patients chosen for study and to criteria used for PET scan results •authors report the potential of PET in mediastinal staging and distant metastases with whole body imaging requires further confirmation</p>
<p>Scott, et al., 1996 (Creighton University and Omaha VAMC, Omaha, Nebraska)</p>	<p>Purpose to prospectively assess the role of PET and CT versus CT alone in detecting N2 or N3 lymph node metastases</p> <p>Cases •27 patients with CT evidence of known or suspected NSCLC; 75 total lymph node stations analyzed •exclusions included: - patients not appropriate for mediastinoscopy or thoracotomy, or - patients with solitary pulmonary nodules > 2 cm in diameter without evidence on CT of mediastinal lymph node involvement</p> <p>Methods •all patients underwent CT, PET and surgical staging •CT results used to determine location of lung mass or regional metastases on PET •CT and PET scans read by separate radiologists blinded to surgical staging results •ATS lymph node mapping system used to correlate nodes on imaging with biopsy; biopsy procedures included scalene node biopsy, mediastinoscopy, or thoracotomy •both CT and PET images available to surgeon during the operation •CT criteria for positive lymph node was 1.0 cm in short-axis diameter •PET criteria for positive lymph nodes was a SUV > 4.2; for lung masses was > 2.0</p> <p>Limitations of study design •number of cases and internal controls not equivalent •test result and determination of final diagnosis not independent •variations in nodal sampling technique •influence of PET results on choice of patient cohort unclear</p>	<p>Detecting mediastinal lymph node involvement by patient (9 malignant cases, 18 benign cases) PET + CT: Se=100%; Sp=100% CT: Se=67%; Sp=83% •CT had 3 false positive and 3 false negative diagnoses</p> <p>Detecting mediastinal lymph node involvement by node (10 positive nodes, 65 negative nodes) PET + CT: Se=100%; Sp=98% CT: Se=60%; Sp=94% •PET had 1 false positive; CT had 4 false positives and 4 false negatives</p> <p>Other findings •when data were analyzed by patient, there were 6 discrepancies between CT and PET over the presence or absence of positive lymph nodes in the mediastinum (p=0.031) •when data were analyzed by node, there were 9 discrepancies between CT and PET over the presence or absence of positive lymph nodes in the mediastinum (p=0.039)</p> <p>Authors' comments •more data are required to determine the optimal threshold value for mediastinal evaluations</p>

Study	Patients/Methods	Results/Comments
<p>Knight, et al., 1996 (Vanderbilt University, Nashville, Tennessee)</p>	<p>Purpose to prospectively assess PET in differentiating benign from malignant primary lung cancer in patients with and without a history of malignancy</p> <p>Cases 48 patients with lesions suspicious for malignancy on chest x-ray and CT: •Group 1- 27 patients with no prior history of malignancy (15 malignant, 12 benign) •Group 2- 19 patients with history of malignancy (17 malignant, 4 benign)</p> <p>Methods •initial chest x-ray and CT interpretations blinded to PET results •all patients fasted before PET •independent PET interpretations blinded to CT and chest x-ray interpretations, but chest x-ray and CT data used to locate lesion on PET •ROIs determined; SUR and L/B ratios calculated; SUR cut-off > 2.5 and L/B cut-off > 5 chosen to define malignant nodules •SURs not obtained due to motion artifact (n=1) and partial volume effect (n=2) for lesions < 1 cm •confirmation by various biopsy procedures (n=30); by pleural cytology (n=2); clinical and radiologic follow-up (n=16) for 6-16 months •radiologic confirmation of malignant disease defined as increase in size on follow-up CT performed between 6-12 months after initial evaluation; size parameter not defined •PET + CT vs. CT compared with biopsy or follow-up, reported by patient</p> <p>Limitations of study design •except in Group 1, number of cases and internal controls not equivalent (high prevalence of malignancy) •PET result and determination of final diagnosis not independent •temporal differences between PET scans and clinical/radiologic follow-up</p>	<p>Semiquantitative analysis of unknown primary (reported as mean ± SD) Group 1 (14 malignant cases, 12 benign cases) SUR: malignant= 8.9 ± 4.9 vs. benign= 3.3 ± 3.2 (p = 0.001) L/B: malignant= 20.6 ± 14.2 vs. benign= 5.2 ± 5.5 (p = 0.0008)</p> <p>Group 2 (15 malignant cases, 4 benign cases) SUR: malignant= 8.9 ± 5.1 vs. benign= 1.3 ± 1.0 (p = 0.00003) L/B: malignant=13.0 ± 8.3 vs. benign= 2.6 ± 3.2 (p = 0.0009)</p> <p>Group 1 + 2 (29 malignant cases, 16 benign cases) SUR: malignant=8.9 ± 5.0 vs. benign= 2.8 ± 2.9 (p = 0.00003) L/B: malignant=16.6 ± 12.0 vs. benign= 4.5 ± 5.0 (p = 0.00001)</p> <p>Corresponding operating characteristics (for lesions > 1 cm) Group 1 (15 malignant, 12 benign) PET + CT: Se=100%; Sp=58%; PPV=75%; NPV=100% CT: Se=33%*; Sp=52%*; PPV=83%*; NPV=52%*</p> <p>Group 2 (17 malignant, 4 benign) PET + CT: Se=100% CT: Se=41%*</p> <p>Group 1 + 2 (32 malignant, 16 benign) PET + CT: Se=100%; Sp=62.5% CT: Se=38%*; Sp=88%*</p> <p>Other findings •findings using SUR correlated with findings using L/B ratio in distinguishing benign from malignant disease •six false-positives due to tuberculosis, granuloma, schwannoma, fibrous mesothelioma with focally increased cellularity, and inflammatory mass with macrophages</p> <p>Authors' comments •study is limited by patient selection bias</p>

Abbreviations: Se, sensitivity
Sp, specificity
CT, computerized tomography
ROI, region of interest
SUV, standard uptake value
L/B, lesion-to-background ratio
DUR, differential uptake ratio
ATS, American Thoracic Society

*indicated calculated by MDRC TA Program from data supplied in published article

Table 5 Hypothetical Diagnostic Thinking Efficacy of PET in Lung Cancer

Notes The study in this table met most of the evidence-based criteria for diagnostic test evaluations and is a case series (Level V evidence); all of the patients presented with a high index of suspicion for lung cancer. Although internal controls (i.e. those with benign masses) were used, an insufficient number was available to calculate specificity. Calculations using Bayesian analysis are hypothetical and are used for illustrative purposes.

Abbreviations are listed at the end of the table.

Study	Patients/Methods	Results/Comments
<p>Slosman, et al., 1993 (Geneva University Hospital, Switzerland)</p>	<p>Purpose</p> <ul style="list-style-type: none"> to measure the sensitivity of PET in detecting lung cancer to determine prospectively the role of PET scanning in a satellite center as an adjunct to conventional methods using Bayesian analysis <p>Cases</p> <p>36 patients presented to center with suspected lung cancer of various types and stages based on x-ray CT and clinical work-up, and who were scheduled for thoracotomy</p> <ul style="list-style-type: none"> 21 patients with histological proof of cancer at time of the PET scan 15 patients with a pulmonary mass of unknown etiology <p>Methods</p> <ul style="list-style-type: none"> all patients received CT and PET before treatment ROIs calculated; FDG uptake expressed as tumor to non-tumor ratio (TNT) positive PET scan defined prospectively as TNT ratio 1.5 33 patients obtained final diagnosis by thoracotomy; 3 by observation Bayesian analysis performed using Se from this study and Sp from Kubota, et al., 1990 <p>Limitations of study design</p> <ul style="list-style-type: none"> number of cases and internal controls not equivalent (high prevalence of malignancy) independence of test result and determination of final diagnosis unclear 	<p>Defining unknown primary disease (31 malignant cases, 5 benign cases)</p> <ul style="list-style-type: none"> PET: Se=93.5% unable to calculate specificity due to low number of be not reported CT: data not reported <p>Bayesian Analysis (based on Se=93.5% and Sp=75%) (pD+=prevalence of disease in a population)</p> <ul style="list-style-type: none"> pD+=.80, PET scan (-), the post test probability of disease=26% pD+=.80, PET scan (+), the post test probability=97% pD+=.20, PET scan (-), the post test probability of disease=2% pD+=.20, PET scan (+), the post test probability of disease=29% <p>Other findings</p> <ul style="list-style-type: none"> two false positives due to significant inflammation two false negatives due to small tumor size and/or limitations in spatial resolution <p>Authors' comments</p> <ul style="list-style-type: none"> PET has greatest impact in a population with a low prevalence of cancer and in whom a positive test could lead to more aggressive therapy than one would expect otherwise PET appears of little use in avoiding a thoracotomy in a patient with a high prevalence of cancer choice of the appropriate TNT ratio threshold needs further study

Abbreviations: Se=sensitivity
Sp=specificity
CT=computerized tomography
ROI=region of interest

*indicated calculated by MDRC TA Program from data supplied in published article

VI. REFERENCES Background and studies meeting evidence-based medicine criteria for evaluations of diagnostic tests

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VIII. REFERENCES: Excluded studies

Exclusion criteria included:

- number of cases < 12
- duplicated or superseded by subsequent or concurrent study from the same institution
- abstract, not peer reviewed

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