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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.

Current VATAP contact information is as follows:

VA Technology Assessment Program (11T)

VA Boston Healthcare System

150 South Huntington Avenue

Boston, MA 02130

Tel: 617.278.4469 Fax: 617.264.6587

vatap@med.va.gov

<http://www.va.gov/vatap> <http://vawww.va.gov/vatap>

Appendix 7

**Systematic Review:
PET as a Diagnostic Test in
Solitary Pulmonary Nodules**

Author: Elizabeth Adams, R.R.T., M.P.H., *Management & Program Analyst,
MDRC Technology Assessment Program*

*Appendix 7***Systematic Review:
PET as a Diagnostic Test in Solitary Pulmonary Nodules**

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 diagnosing solitary pulmonary nodules. 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 discussion in this overview section, unless otherwise noted, is based on information provided by Lillington and Caskey (1993).

B. Description

This report will confine its discussion to those nodules that are solitary. A solitary pulmonary nodule (SPN) is a single spherical lesion within the lung not associated with hilar enlargement or atelectasis (incomplete expansion and/or collapse of lung tissue characterized on x-ray by local opacification), and whose size is generally less than 4.0 cm in diameter. Detection of multiple pulmonary nodules suggests a different group of diagnostic possibilities and a correspondingly different management approach.

C. Epidemiology

SPNs represent approximately 15% of all lung cancer diagnosed; in 1996, it is estimated that there will be 26,550 new cases of malignant SPNs in the United States (Cancer Facts & Figures 1996, American Cancer Society). The differential diagnoses of a SPN include many malignant and benign processes. Approximately 50% of SPNs are benign; infectious granulomas represent 80% of all benign SPNs and are caused predominately by coccidiomycosis, histoplasmosis, and tuberculosis (Midthun, 1993). Less common etiologies include hamartomas, noninfectious granulomas, infectious lesions, and vascular lesions.

The most common forms of malignant SPNs are bronchogenic carcinomas. According to the TNM staging system adopted by the American Joint Committee on End Results Reporting, a malignant SPN represents a clinical stage I lesion, which is potentially curable with resection (Mountain, 1993). Reported prevalence of malignant SPNs, ranging from less than 5% to greater than 70%, varies as a result of referral bias within each reported patient series. Lesions that have metastasized from extrathoracic tumors represent approximately 10-30% of all malignant SPNs (Midthun, 1993).

The following risk factors directly correlate with the probability of cancer in patients with a SPN: 1) patient's age; 2) patient's smoking history; 3) prior history of malignancy; 4) stability of lesion size on chest x-ray for 2 years; 5) presence of occult calcification within the nodule, and; 6) nodule size and characteristics of the nodule's edge as visualized on radiography. Additionally, the baseline prevalence of malignancy in the study population may suggest the likelihood of malignancy of the SPN. Exposure to benign diseases such as tuberculosis or a history of residence in areas endemic for coccidiomycosis or histoplasmosis will suggest a lesser likelihood of, but not rule out, malignancy.

D. Diagnosis

The vast majority of SPNs are incidental findings on a standard chest x-ray. Once the SPN is detected, the goal of clinical management is to choose the diagnostic approach most suited to the patient's clinical risk of malignancy, thus minimizing the number of thoracotomies for

benign disease and expediting surgical resection of malignancies. Figure 1 represents a typical algorithmic approach to the clinical diagnosis and management of SPNs (Karlinsky, 1991).

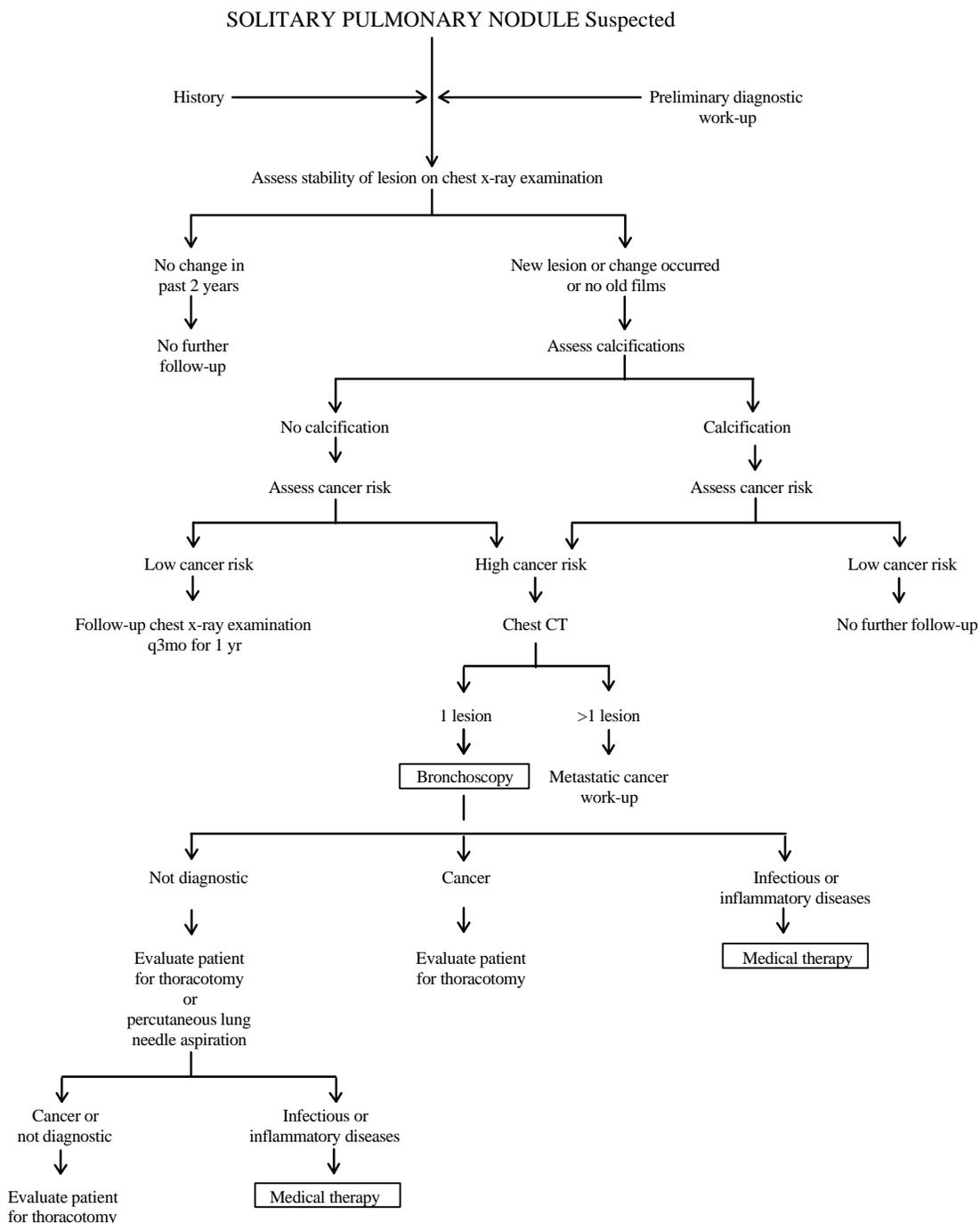


FIGURE 1. Algorithm for the management of solitary pulmonary nodules. (Karlinsky, 1991)

The patient's clinical risk of malignancy is estimated by weighing the patient's risk factors. These clinical data are collected through physical examination, review of the patient's medical history, and radiologic assessment. In a typically older veteran patient, who presents with an extensive smoking history and who is a surgical candidate, the probability of malignancy is often sufficiently high to proceed directly to thoracotomy without prior histologic confirmation. However, confirmation may be required if the patient is a high surgical risk or requests diagnostic confirmation of cancer prior to surgical resection. In the nonveteran population, where the probability of malignancy is likely to be lower, histologic confirmation may be needed to rule out benign disease and avoid an unnecessary thoracotomy.

Tissue may be sampled using several procedures including sputum collection, fiberoptic bronchoscopy, transthoracic needle aspiration biopsy (TTNA), thoracoscopy, and thoracotomy. Their diagnostic yields vary widely and depend on the procedures themselves, operator expertise, as well as size, type, and location of the nodule.

Sputum sampling has shown limited utility in patients with SPNs. Midthun (1993) reported ranges of diagnostic yield for bronchoscopy and TTNA of 20 to 80% and 43 to 97%, respectively. The lower yield of bronchoscopy may be attributed to the peripheral nature of the typical SPN. The wide range of diagnostic yield for TTNA may be attributed in part to the size of the nodule, with nodules larger than 2.0 cm in diameter associated with greater yield. Unlike bronchoscopy TTNA is a higher risk procedure with a reported incidence in pneumothorax of 15-30%, although only a small portion of these pneumothoraces may actually require treatment.

Minimally invasive surgical alternatives to thoracotomy for diagnosing indeterminate SPNs, such as thoracoscopy, are being studied and may contribute to the reduction in thoracotomies performed on patients with benign disease. Thoracotomy remains the definitive means for obtaining the diagnostic gold standard, but is the most invasive and exposes the patient to the risks of surgery.

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

Surgical removal of the malignancy and medical therapy for benign infectious or inflammatory diseases are the treatments of choice for diagnostically confirmed SPNs. For indeterminate SPNs the choices are to proceed with thoracotomy or to observe nodule change through serial chest x-rays (i.e., the "wait and watch strategy"). Observation is considered appropriate for patients with a very low probability of malignancy, although the potential adverse affect of the delay in resection on patient survival is controversial.

F. Potential roles for PET

Conventional wisdom supports a prevalence of malignancy of 30-50% among resected indeterminate SPNs based primarily on a report from the U.S. Veterans Administration Armed Forces Cooperative Study (Steele, 1963). Accordingly, there is a need to improve diagnostic accuracy, with the hope of identifying preoperatively a larger number of benign lesions and avoiding unnecessary thoracotomies. The standard radiologic method of choice for evaluating SPNs is computerized tomography (CT) because of its enhanced visibility and morphologic detail.

CT is used in many capacities in the evaluation of SPNs: 1) to determine the number of nodules; 2) to assess nodule size; 3) to determine shape and characteristics of the nodule's edge; 4) to visualize evidence of calcification and; 5) to serve as a guide for biopsy procedures. Iodinated contrast material and high resolution CT densitometry (HRCT) are used to enhance conventional CT. Preliminary studies describing improved detection of malignant SPNs with CT enhanced with iodinated contrast material have been reported (Swensen, 1995).

HRCT employs a reference "phantom" to indirectly demonstrate "occult" calcification, the presence of which shows a strong, but not definitive, likelihood of benignity in approximately 50% of nodules that appear noncalcified by standard imaging techniques. Although HRCT provides exceptional morphologic detail, limitations in its ability to differentiate benign from malignant lesions have been reported. These limitations become more apparent with decreasing nodule size.

MRI has been proposed as a possible adjunct to CT in the clinical work up, but has not demonstrated greater benefit over CT. Consequently, many lesions classified as

indeterminate before CT are still indeterminate afterward and require evaluation using biopsy procedures most appropriately matched to the patient's level of clinical risk.

PET with FDG has recently been proposed as a potential solution for improving the noninvasive determination of benign from malignant SPNs. Current literature suggests that a PET scan would likely follow conventional imaging, specifically CT, in the diagnostic work up. The utility of PET in differentiating benign from malignant pulmonary nodules less than 3 cm, and occasionally, 4 cm in diameter (i.e., those nodules likely to be indeterminate) is being assessed, because nodules greater than 3 cm in diameter have a higher probability of malignancy.

II. RESULTS

Ten 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, 6 (60%) were found to meet the inclusion criteria for assignment to the following levels of the diagnostic efficacy hierarchy (Fryback and Thornbury, 1991; *Appendix 2: Assessing Diagnostic Technologies*): 2 met the definition of technical efficacy (see Reference List; full data abstraction tables for Technocal Efficacy studies are on file with the MDRC Technology Assessment Program); 2 met the criteria of diagnostic accuracy efficacy (Table 4); 2 met the criteria for diagnostic accuracy efficacy and diagnostic thinking efficacy (Table 5). The MDRC Technology Assessment Program was unable to locate any studies which addressed the impact of PET in the clinical management of these patients or on treatment outcomes.

Two studies not included in Tables 4 or 5 provided technical efficacy data that may provide useful information for subsequent diagnostic efficacy studies. Lowe, et al., (1995) assessed the optimal time for emission data acquisition using dynamic PET imaging. Duhaylongsod, et al., (1995a) assessed retrospectively the relationship between glucose metabolism measured by PET and tumor doubling time on radiography.

All studies presented in Tables 4 and 5 reporting diagnostic accuracy for PET in evaluation of SPNs are derived from case series, providing Level V (i.e., the weakest) evidence of any association between the use of a technology and improved patient outcomes. Operating characteristics from these series are based on a disproportionate number of cases to internal controls. The inclusion criteria varied across series with respect to nodule size and definition of indeterminate focal lesions, which may have included ill-defined infiltrates and pulmonary masses. Since there was either a strong or definite likelihood of work-up bias in these studies, none met the strict evidence-based medicine criteria for blinding. However, with the exception of Gupta, et al., (1996) all studies provided some information on blinding of their test readers to the biopsy gold standard.

A. Characterizing indeterminate solitary pulmonary nodules

Two studies presented in Table 4 evaluated the diagnostic accuracy of PET in the work up of SPNs. Dewan, et al., (1995) reported results comparing PET and transthoracic fine needle aspiration biopsy (TTNA) in patients who had undergone both procedures to diagnose peripheral SPNs. Patients with lung masses > 3 cm, hilar lesions, and multiple pulmonary nodules were also included, implying a high index of suspicion for malignancy. That the decision to perform TTNA may have been influenced by the PET results, implying a strong association between the test result and determination of the final diagnosis, was unclear. These authors also reported a significantly higher rate of complications (incidence of pneumothorax and of chest tubes) from TTNA than from PET.

Bury, et al., (1996) evaluated the complementary role of PET in characterizing indeterminate SPNs at a point in the work up after radiography. Nodules were noncalcified and ranged from 0.5 cm-4.5 cm in size. Patient selection was limited to those scheduled for biopsy determination, suggesting a high index of suspicion of malignancy. Results from both of these studies should be viewed cautiously, as the degree of bias is significant.

Table 5 presents data abstracted from two studies that assessed the quantitative importance of PET in the diagnostic work up (diagnostic thinking efficacy) of SPNs and diagnostic accuracy. Duhaylongsod, et al., (1995b) reported operating characteristics and likelihood ratios based on a quantitative methodology for patients with an indeterminate nodule 4 cm in diameter. The cut-off value of 2.5 to define malignancy was determined retrospectively from a receiver operating characteristic (ROC) curve. A subgroup analysis for lesions < 3 cm in diameter yielded similar results to those categorized as < 4 cm in diameter.

Likelihood ratios for quantitative standard uptake ratio (SUR) values, which have a continuous distribution, were reported in an attempt to determine the incremental value of PET in the work up of SPNs, and may provide additional information on the relationship between the SUR and severity of disease. SUR values located farther from the cut-off may assist clinical decision making with greater certainty than those values located closer to the cut-off. Diagnostic certainty and subsequent treatment decisions may also vary with the choice of cut-off. The degree to which PET would have changed diagnostic certainty and treatment decisions, particularly with respect to the number of thoracotomies spared, was not systematically assessed in this study, and firm conclusions on the incremental value of PET in this diagnostic process can not be drawn.

These authors presented a hypothetical cost analysis to assess the economic impact of PET in this patient population. Thirteen patients, who were initially excluded from the study because of insufficient follow-up and diagnostic confirmation, were included in these calculations. These authors calculated a reduction in overall costs of \$397,062 when using PET in the work-up. The MDRC Technology Assessment Program revised the potential cost savings to be \$158,934 to reflect only the results of the 87 patients initially included in the study. However, both of these calculations were based on a narrow group of assumptions using hospital charge data that may not accurately reflect true costs and may not be sufficiently generalizable to other patient populations. Variations in case-mix and optimal cut-off value, which may occur across populations, and the hypothetical nature of the cost analysis suggest that these results are preliminary.

Gupta, et al., (1996) assessed the diagnostic accuracy of qualitative PET scans in patients with indeterminate SPNs 3 cm in size and compared methods for computing the probability of malignancy based on PET results, patient's age, and nodule size. This study may not have met evidence-based medicine criteria, because blinding of the PET readers to the diagnostic gold standard was not noted. Limitations in reporting with respect to blinding of the PET readers to other clinical and radiographic data prevented determination of the conditional independence between tests in a sequence, an assumption required of Bayes' Theorem in sequential testing, and the subsequent incremental value of PET in the work up.

In their calculations the authors used a pre-test probability of malignancy of 0.40 based on the overall prevalence of malignancy in the general population. In patients (particularly veterans), who would be referred to a PET center at a point in the diagnostic process after radiologic imaging but before tissue sampling, the prevalence of malignancy is likely to be much higher. This study may not provide valid estimates of the quantitative importance of PET in these patients and should be interpreted cautiously.

III. SUMMARY

Table 3 lists preliminary studies of the accuracy of PET in diagnosing indeterminate solitary pulmonary nodules (i.e., those lesions with equivocal findings on CT) at a point in the diagnostic process after CT but before biopsy procedures. All four studies of diagnostic accuracy were case series with a high proportion of malignant cases reflecting both the study inclusion criteria and, indirectly, the relative accuracy of current modalities used prior to PET in the diagnostic work up to identify benign disease.

Each study varied in its inclusion criteria with respect to maximal lesion size and image characteristics (pulmonary mass, ill-defined infiltrates, focal lesions). No data comparing PET with alternative imaging technologies such as CT were presented, although one study (Dewan, 1995) attempted to assess the complementary role of PET with an invasive needle biopsy procedure (TTNA) to characterize SPNs. Two of these studies (Duhaylongsod, 1995b and Gupta, 1996) also attempted to quantify the importance of PET in the diagnostic work up of SPNs. Limitations in reporting and study design preclude drawing firm conclusions from these series.

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 by the heterogeneity of normal, benign, and malignant 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 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.

Methodologies have been developed to enhance the interpretation of diagnostic information in patients with SPNs. They include the application of probabilistic reasoning methods such as Bayesian analysis and decision analysis, and computer-assisted analytic techniques using neural networks, thresholding, or profile matching.

Bayesian analysis combines radiographic findings, such as location, size, and edge characterization on CT and/or x-ray, with clinical information, such as age and smoking history, to estimate the probability that a nodule in an individual patient is malignant. An estimation of likelihood ratios for various individual radiographic and clinical characteristics on previously evaluated patients with SPNs must first be determined from the literature. The case mix of the sample population will likely affect the derivation of these ratios (Gurney, Part 1., 1993).

The utility of this analysis may be found in its examination of all of the pertinent clinical and radiologic information, rather than reliance on the results of one test. For example, Gurney and associates focused on interpretation of detected nodules, rather than detection itself, by comparing the accuracy of diagnosis of SPNs using Bayesian analysis with the accuracy of independent estimation by expert radiologists (Gurney, Part 2., 1993). This study found that the readers using Bayesian analysis performed better than the expert readers (i.e., fewer misclassifications of the nodules) in reading both individual studies and patients' combined studies. There was better concordance among readers who used Bayesian analysis. Moreover, additional clinical information did not necessarily improve the readers' performance in either group.

Decision analysis has been used to assess the relative value of clinical strategies in the presence of an uncertain diagnosis (Lillington, 1989). The probability of cancer (pCA) in any given case will depend on the clinical factors present in that case. Variations in the magnitude of the calculated values for pCA will affect the utility of each strategy. A high pCA suggests the use of thoracotomy, whereas a low pCA supports the observation strategy. A pCA in the middle range supports the use of advanced needle biopsy procedures followed by thoracotomy, if needed. Lillington (1989) found that patient preferences should be considered when the difference in expected utility between biopsy and surgery tends to be small. With decision analysis, it is also possible to approximate the value for the deleterious effect of delaying the resection of a malignant nodule.

Preliminary work has been performed using digital techniques to assist the radiologist in the diagnosis of SPNs (Lo, 1993 and Gurney, 1995). The specific aim of these techniques is to enhance true positive detection, thereby reducing the number of false positive results, through the use of computer image processing. The results of these studies have not shown greater benefit over conventional methods to date, although their application will likely increase with the increasing use of digital imaging technology.

V. SUGGESTIONS FOR FURTHER PET RESEARCH

The potential benefits of PET in the diagnosis and management of solitary pulmonary nodules (SPNs) have been purported. However, no evidence published to date definitively supports the routine use of PET in these patients. Four studies attempted to define the operating characteristics of PET as a diagnostic test in this area, including two that also attempted to quantify the importance of PET in the diagnostic work up of SPNs. All have methodologic shortcomings, and their results should be interpreted cautiously.

CT has a more established role in the clinical management of solitary pulmonary nodules, is more widely available with associated lower costs, and provides valuable anatomical detail not always available with PET. Conventional wisdom has defined the limitations of CT with respect to characteristics of resected indeterminate nodules based primarily on data that were reported from surgical series comprising a significant proportion of young patients with shorter smoking histories, and that were derived from studies conducted prior to the use of CT or during its early stages of diffusion.

A recent study conducted by Rubins and Rubins (1996) reported an increasing proportion of malignancy in resected indeterminate SPNs over the last fourteen years (from 55% in 1981 to 60% in 1983 and from 90% in 1990 to 100% in 1994) at a single university-affiliated VA Medical Center. They attributed these trends to improvements in the ability to diagnose benign SPNs preoperatively, primarily through the use of CT. In the presence of these trends, a technology such as PET would need to demonstrate significant improvements in patient outcome or reductions in associated costs in order to justify its role in the clinical work up of SPNs.

Less resource-intensive analytical models exist to provide the framework with which to assess the impact of diagnostic imaging in the management of SPNs. Nevertheless, these models require that evidence of both operating characteristics and underlying characteristics of the study population exist prior to implementation.

Contributions from other investigators working with larger and well-defined patient populations and comparing PET to existing modalities will be needed to refine the characteristics of PET as a diagnostic tool in SPNs, specifically as they pertain to the veteran population, and to establish a

base for further research. Any attempt to expand the role of PET into earlier stages in the diagnostic work up would require an evaluation designed accordingly.

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

- 1) establishment of a PET registry, which would provide a range of data on demographic and clinical characteristics of patients in whom PET studies are performed, and on their clinical outcomes in a variety of settings;
- 2) establishment of estimates of a cut-off point to define disease and of subsequent diagnostic accuracy;
- 3) studies designed to assess the role and impact of PET in the diagnostic work-up of SPNs (eg., to avoid unnecessary surgery, to replace needle biopsy, or to replace conventional imaging in detecting disease)

Table 2 Summary of the Literature: Diagnostic accuracy efficacy studies of PET in solitary pulmonary nodules

Notes: All of the studies in the table are case series (Level V evidence) and met most of the evidence-based medicine criteria for diagnostic test evaluations. None of the studies met strict evidence-based medicine criteria for blinding, but all except Gupta, et al., (1996) provided information on the comprehensiveness of blinding of test interpreters to the biopsy gold standard. Blinding of PET interpreters to other clinical and radiologic data varied across studies.

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. The pre-test probability of disease in these study populations was very high, and predictive values were not reported. Each study varied in inclusion criteria with respect to maximal lesion size and image characteristics (pulmonary masses, ill-defined infiltrates, focal lesions). Operating characteristics from these studies should be interpreted with caution.

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. While data from Dewan, et al., (1995) and Gupta, et al., (1996) are likely derived from the same patient population, these studies addressed different purposes, and inclusion of both was felt to be warranted. Studies reviewed but not included are listed under "References".

Abbreviations are listed at the end of the table.

Role	Study	N	Operating Characteristics*			Evidence-Based Medicine Criteria**			Methodologic Quality Grade***
			PET	TTNA	other	comparison group	histologic gold standard	blinding	
Defining unknown SPN	Dewan, et al., 1995	26 malignant lesions 9 benign lesions	Se=100% Sp=78% accuracy=94%	Se=81% Sp=100% accuracy=86%		+ internal	+	partial	D
	Bury, et al., 1996	33 malignant cases 17 benign cases	Se=100% Sp=88%			+ internal	+	+	C
	Duhaylongsod, et al., 1995b	59 malignant cases 28 benign cases	for lesions < 4 cm Se=97% Sp=81% accuracy=92%			+ internal	+	+	C
	Gupta, et al., 1996	45 malignant cases 16 benign cases	Se=93% Sp=88% accuracy=92%			+ internal	+	unclear	C

Se, sensitivity
Sp, specificity
TTNA, transthoracic needle aspiration biopsy

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

Table 3 Diagnostic efficacy of FDG PET in diagnosing solitary pulmonary nodules

Notes: The studies in this table are case series and met all or most of the evidence-based criteria for diagnostic test evaluations. Internal controls (i.e. those with benign masses) were used, and it was possible to calculate sensitivity and specificity for PET. There was a high ratio of malignant to benign cases; therefore, predictive values were not reported. Each study varied in inclusion criteria with respect to maximal lesion size and image characteristics (pulmonary masses, ill-defined infiltrates, focal lesions). Blinding of PET interpreters to other clinical or radiologic findings was not explicit, and the incremental value of PET could not be determined. Operating characteristics should be interpreted cautiously.

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 this table.

Study	Patients/Methods	Results/Comments
Dewan, et al., 1995 <i>(Creighton University and Veterans Affairs Medical Center, Omaha, Nebraska)</i>	<p>Purpose a retrospective analysis to compare PET to transthoracic fine-needle aspiration biopsy (TTNA) in diagnosing peripheral solitary pulmonary lesions</p> <p>Cases 33 patients with 35 lung lesions who had undergone both PET and TTNA (26 malignant, 9 benign) <ul style="list-style-type: none"> • 22 SPNs (< 3 cm); 4 hilar lesions; 8 lung masses (> 3 cm); 1 with multiple pulmonary nodules </p> <p>Methods</p> <ul style="list-style-type: none"> • all patients had chest x-ray and CT • decision to perform TTNA made by primary physician aware of PET results • qualitative PET performed • both PET interpreters blinded to biopsy • TTNA performed under CT guidance • PET and TTNA compared to biopsy results <p>Limitations of study design</p> <ul style="list-style-type: none"> • retrospective analysis • number of cases and internal controls not equivalent • blinding of PET interpreters to clinical or radiologic data not noted • test result and determination of final diagnosis not independent 	<p>Defining SPN lesion (26 malignant lesions, 9 benign lesions)</p> <ul style="list-style-type: none"> • PET: Se=100%; Sp=78%; accuracy=94% • TTNA: Se=81%; Sp=100%; accuracy=86% • no statistically significant differences reported between two techniques <p>Complications</p> <ul style="list-style-type: none"> • pneumothorax: PET=0/35 (0%) TTNA=16/35 (46%) p=0.0001 • chest tube: PET=0/35 (0%) TTNA=9/35 (26%) p=0.0039 <p>Discussion</p> <ul style="list-style-type: none"> • authors report study size limitation; a highly select group may affect generalizability of results • authors report interobserver agreement, but not measured

Study	Patients/Methods	Results/Comments
<p>Bury, et al., 1996 (CHU, Liège, Belgium)</p>	<p>Purpose to prospectively assess the diagnostic accuracy of FDG PET in diagnosing solitary pulmonary nodules (SPN)</p> <p>Cases 50 patients with indeterminate SPNs after chest x-ray and CT, ranging from 0.5 cm to 4.5 cm in size (33 malignant, 17 benign)</p> <p>Methods</p> <ul style="list-style-type: none"> • all patients fasted for six hours prior to PET • PET interpreted visually and classified as no uptake, moderate or intense • independent interpretation by two groups of nuclear medicine physicians reached by consensus and who had knowledge of chest x-ray but not CT, and blinded to biopsy results • PET results compared to biopsy results <p>Limitations in study design</p> <ul style="list-style-type: none"> • number of cases and internal controls not equivalent (high prevalence of malignancy) • patient selection limited to those scheduled for invasive procedure (biased toward those with a high index of suspicion for malignancy) • partial blinding of PET readers to other clinical data • independence of test result and determination of disease unclear 	<p>Defining SPN lesion (33 malignant cases, 17 benign cases)</p> <ul style="list-style-type: none"> • PET: Se=100%; Sp=88% • CT: no data reported • two false positive results due to tuberculosis and chronic nonspecific inflammation • mean size (range) of nodules: malignant=3 cm (1.5 cm- 4.5 cm) benign= 1.8 cm (0.5 cm- 3.5 cm) <p>Authors' comments no difference in FDG uptake across histopathologic types was observed; quantitative analysis may be needed for clarification</p>

Abbreviations: Se, sensitivity
Sp, specificity
CT, computerized tomography

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

Table 4 Diagnostic thinking efficacy of FDG PET in solitary pulmonary nodules

Notes: Both studies are case series (Level V evidence) with internal controls (i.e. those with benign masses), and it was possible to calculate sensitivity and specificity for PET. 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. The study by Gupta, et al., (1996) may not have met the evidence-based medicine criteria for blinding. Each study varied in inclusion criteria with respect to maximal lesion size and image characteristics (pulmonary masses, ill-defined infiltrates, focal lesions). Operating characteristics and likelihood ratios should be interpreted with caution.

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 this table.

Study	Patients/Methods	Results/Comments
Duhaylongsod, et al., 1995b <i>(Duke University, Durham North Carolina)</i>	<p>Purposes to evaluate the diagnostic accuracy of FDG PET in differentiating benign from malignant focal pulmonary lesions, suspected primary lesions or recurrent cancer</p> <p>Cases 87 patients with indeterminate focal pulmonary lesions by chest x-ray and CT (13 patients had been excluded lacking firm pathologic diagnosis and < 2 years follow up)</p> <ul style="list-style-type: none"> • 59 malignant; 28 benign • 79 SPNs (defined as focal abnormalities 4 cm diameter); 11 pulmonary masses; 10 ill-defined infiltrates • included 16 patients evaluated for recurrent disease <p>Methods</p> <ul style="list-style-type: none"> • two PET cameras used in study • ROIs chosen; SURs calculated by one nuclear medicine physician blinded to patient history, physical exam, and labs, including biopsy results • biopsy (n=84) and follow up > 2 years (n=3) confirmation obtained • SURs compared; mean ± SD reported • Se, Sp, accuracy, and likelihood ratios calculated • cost analysis performed to assess economic impact of two strategies, immediate thoracotomy and PET, on diagnosis and management of focal pulmonary lesions with following assumptions, using hospital charge data: <ul style="list-style-type: none"> - SUR 2.5 lead to thoracotomy, SUR < 2.5 warranted observation - all indeterminate SPNs < 3 cm diameter - pretest probability of malignancy=50% - PET Se=97%; Sp=82% - thoracotomy complication rate=zero - total hospital stay for thoracotomy=5 days <p>Limitations of study design</p> <ul style="list-style-type: none"> • choice of SUR cutoff determined retrospectively • number of cases and internal controls not equivalent (high pre-test probability of disease) • study included subjects with disease other than SPNs • independence of test result and determination of final diagnosis unclear 	<p>Defining unknown focal disease (59 malignant cases, 28 benign cases) overall SUR: malignant=6.6 ± 3.1 vs. benign= 2.0 ± 1.6 (p = 0.0001) based on cut-off SUR 2.5 chosen for malignancy determined from ROC curve Se=97%; Sp=82%; accuracy=92%</p> <p>Defining unknown SPNs (45 carcinomas, 22 benign) SUR: malignant=5.5 ± 2.1 vs. benign= 1.7 ± 1.1</p> <p>Defining unknown pulmonary masses (10 malignant, 1 benign) SUR: malignant=8.7 ± 3.8 vs. benign= 1.3</p> <p>Defining unknown pulmonary infiltrates (4 malignant, 5 benign) SUR: malignant=5.1 ± 2.0 vs. benign= 2.8 ± 2.1</p> <p>Defining unknown SPNs < 3 cm diameter (31 malignant, 16 benign) based on cut-off SUR 2.5 chosen for malignancy determined from ROC curve PET: Se=100%; Sp=81%; accuracy=94%</p> <p>Likelihood ratios (LR) for five levels of SUR computed from FDG PET (malignant/benign cases) Se and Sp data used for calculations was not noted SUR 6.0 LR= 16.136 (34/1) SUR 4.0-5.9 LR:= 3.085 (13/2) SUR 2.5-3.9 LR:= 1.582 (10/3) SUR 1.5-2.49 LR= 0.095 (2/10) SUR < 1.5 LR:= 0.000 (0/12)</p> <p>Cost analysis</p> <ul style="list-style-type: none"> • strategy using PET resulted in 41 fewer nontherapeutic operations and reduced overall costs by 24.8% (= \$397, 062) based on all 87 patients + 13 patsxcluded from the study • cost savings calculated by MDRC Technology Assessment Program based on 87 patients included in the study= \$158,934 • conservative cost estimates did not account for extended length of stay, intensive care management, other discomfort, lost wages, or expenses from other procedures <p>Other findings</p> <ul style="list-style-type: none"> • false positives attributed to active infections • one false negative attributed to small lesion size (4 mm) • in patients evaluated for recurrent disease, all benign cases (n=10) had SURs < 2.5 • authors stress need to establish cost-effectiveness before widespread application

Study	Patients/Methods	Results/Comments
<p>Gupta, et al., 1996 (West Virginia University, Morgantown, West Virginia) (data collected at Creighton University and Omaha VAMC, Nebraska)</p>	<p>Purpose</p> <ul style="list-style-type: none"> to assess the diagnostic accuracy of PET in the evaluation of solitary pulmonary nodules (SPNs) to compare methods for computing the probability of malignancy in SPNs based on PET versus several risk factors <p>Cases</p> <p>61 patients with indeterminate nodules (0.6 cm-3 cm in size) based on chest x-ray and CT (45 malignant cases, 16 benign cases)</p> <p>Methods</p> <ul style="list-style-type: none"> all patients had chest x-ray and CT interpreted independently prior to PET patients fasted for 4 hours before PET scans PET analyzed qualitatively by two observers DURs calculated for semiquantitative analysis for patients in whom no nodule could be detected on PET, ROI was extrapolated from radiographic imaging PET results compared to histology; one patient followed-up for 2 years <p>Limitations of study design</p> <ul style="list-style-type: none"> blinding of PET to other clinical or radiographic data, or to biopsy results, not reported number of cases and internal controls not equivalent (high pre-test probability of disease) pre-test probability of disease used by authors (0.40) did not take into account the clinical data obtained prior to PET 	<p>Defining unknown SPN (45 malignant cases, 16 benign cases)</p> <p>PET: Se=93%; Sp=88%; accuracy=92%</p> <ul style="list-style-type: none"> 3 false negatives due to adenocarcinoma; 2 false-positive findings due to granuloma with histoplasmosis <p>Detecting hilar/mediastinal lymph adenopathy</p> <p>12 patients had confirmed hilar/mediastinal lymphadenopathy; in 5 patients nodal involvement was not suspected prior to PET, but PET accurately identified all abnormalities</p> <p>Likelihood ratios based on PET results (45 malignant cases, 16 benign cases) assuming pre-test probability of disease=0.40; Se=93%; Sp=88%</p> <p>LR=7.464; probability of malignant nodule, given a positive PET scan=0.833 LR=0.075; probability of malignant nodule, given a negative PET scan=0.047</p> <p>Likelihood ratios based on age</p> <p>LR=0.405; probability of malignant nodule, given age < 60 years=0.213 LR=0.915; probability of malignant nodule, given age between 60-69 years=0.380 LR=3.376; probability of malignant nodule, given age between 70-89 years=0.693</p> <p>Likelihood ratios based on nodule size</p> <p>LR=0.400; probability of malignant nodule, given nodule size 1.0 cm=0.211 LR=0.828; probability of malignant nodule, given nodule size between 1.1-1.9 cm=0.356 LR=2.064; probability of malignant nodule, given nodule size 2.0 cm=0.580</p> <p>Authors' comments</p> <ul style="list-style-type: none"> authors reported interobserver variability < 5%, but no supporting data presented all benign nodules < 2.5 cm in size; 14/16 < 2 cm in size 11/45 malignant nodules < 2 cm in size both nodules < 1 cm in size were accurately detected with PET no correlation between DUR indices and histologic type the probability of malignancy increases with nodule size, patient's age, and a positive PET scan simultaneous pre-operative staging for hilar/mediastinal lymph nodes is an additional advantage of PET in patients with malignancies

Abbreviations: CT, computerized tomography
ROC, receiver operating characteristic
ROI, region of interest
DUR, differential uptake ratio
SUR, standard uptake ratio
Se, sensitivity
Sp, specificity

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
- insufficient information to judge comparability of case and control groups, details of imaging protocol, whether visual or quantitative analysis of PET data used, or type of PET data analysis used
- abstract, not peer reviewed

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