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POSITRON EMISSION TESTING FOR SIX CANCERS (BRAIN, CERVICAL, SMALL CELL LUNG, OVARIAN, PANCREATIC AND TESTICULAR)

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Table of Contents

1 Introduction 5
1.1. Overview 5
1.2. Request by Centers for Medicare and Medicaid Services..... 8
1.3. Structure of the Evidence Report 14
2 Methods..... 15
2.1. Classification of Diagnostic Studies 15
2.2. Literature Review 22
2.2.1. Literature Identification ……..22
2.2.1.1. Search Strategy Used for Identifying Abstracts ……22
2.2.2. Literature Selection ……...…24
2.2.2.1. General Inclusion/Exclusion Criteria for Identifying Abstracts……24
2.2.2.2. Inclusion Criteria for Identifying Articles for Full Text Review ……24
2.2.3. Data Abstraction and Quality Scores Assigned to Full Text Articles ……26
3 Results 28
3.1. Brain Cancer 28
3.1.1. Background ……28
3.1.2. CMS Statement of Work Questions ……32
3.1.3. Importance of Questions Posed by CMS in Clinical Management ……33
3.1.4. Results ……35
3.1.5. Conclusions ……44
3.1.6. Tables ……...46
3.1.7. Figures ……48
3.2. Cervical Cancer..... 52
3.2.1. Background ……52
3.2.2. CMS Statement of Work Questions ……53
3.2.3. Importance of Questions Posed by CMS in

Clinical Management ……53
3.2.4. Results ……56
3.2.5. Conclusions ……64
3.2.6. Tables ……..66
3.2.7. Figures ……68
3.3. Ovarian Cancer 74
3.3.1. Background ……74
3.3.2. CMS Statement of Work Questions ……74
3.3.3. Importance of Questions Posed by CMS in
Clinical Management ……75
3.3.4. Results ……78
3.3.5. Conclusions ……86
3.3.6. Tables ……...88
3.3.7. Figures ……90
3.4. Pancreatic Cancer..... 92
3.4.1. Background ……92
3.4.2. CMS Statement of Work Questions ……93
3.4.3. Importance of Questions Posed by CMS in
Clinical Management ……94
3.4.4. Results ……96
3.4.5. Conclusions ……...121
3.4.6. Tables ……124
3.4.7. Figures ……...130
3.5. Small Cell Lung Cancer 136
3.5.1. Background ……..136
3.5.2. CMS Statement of Work Questions ……137
3.5.3. Importance of Questions Posed by CMS in
Clinical Management ……..137
3.5.4. Results ……..140
3.5.5. Conclusions ……..148
3.5.6. Tables ……151

3.5.7. Figures ……..153
3.6. Testicular Cancer 159
3.6.1. Background ……..159
3.6.2. CMS Statement of Work Questions ……160
3.6.3. Importance of Questions Posed by CMS in Clinical Management ……..160
3.6.4. Results ……..164
3.6.5. Conclusions ……..178
3.6.6. Tables ……182
3.6.7. Figures ……..186
4 General Limitations of the Literature Reviewed 192
5 Bibliography 193
6 Appendices 204
6.1. Appendix A – Neuroepithelial Tumors of the CNS 204
6.2. Appendix B – Glossary..... 210
6.3. Appendix C – Data Abstraction Form ……213
6.4. Appendix D – Evidence Tables ……221
6.5. Appendix E – References……..302

1. INTRODUCTION

1.1 Overview

Computed tomography (CT) and magnetic resonance (MRI) are anatomic, high-resolution imaging techniques currently used in oncology to detect or confirm the presence of a tumor; to provide information about the size and location of the tumor and whether it has spread; to guide a biopsy; to help plan radiation therapy or surgery; and to determine whether the cancer is responding to treatment. Despite widespread use, concerns remain that use of these imaging techniques may result in false negatives due to their inability to resolve small volumes (diameter < 1cm) of disease and false positives due to their inability to distinguish between viable tumor masses and masses consisting of necrotic or scar tissue.

Functional imaging methods such as positron emission tomography (PET) can establish the metabolic or functional parameters of tissue that may aid in these distinctions. Instead of using anatomical deviations to identify areas of abnormality, PET uses positron-emitting radioactive tracer that accumulates in abnormal tissue. Therefore, it primarily measures metabolism and function as opposed to structure. The process involves release of a

positron from a radioisotope (e.g. 18-fluorine), which subsequently collides with an electron, forming two photons in a process called annihilation. The two photons travel away from each other at 180° angles and are picked up by detectors placed around the body. The source of the photons is then spatially determined. Areas with increased photon activity are areas of radioisotope accumulation. Quantitative measurements can be made when photon attenuation, which occurs during passage through the body, is corrected using a transmission scan. Semi-quantitative measurement is performed using the standardized uptake value (SUV) of a region of interest. The SUV is calculated by measuring the tissue radioactivity concentration (μCi/mL) and dividing by the total injected dose (μCi/kg), normalized to the body weight. Results may be variable depending upon the scanner image resolution (should be small enough to adequately visualize the organ or region of interest), time of image acquisition after radioisotope injection (later images will have higher SUVs as FDG accumulates), the presence of hyperglycemia, method of normalization (use of body surface area or lean body mass) and the method of quantitative measurement.

The most commonly used radioisotope tracer is ^{18}Fluro-deoxy-glucose (FDG), a glucose analog. Like glucose FDG is taken up into cells through glucose transport proteins (GLUT) and then phosphorylated by a hexokinase. At this point glucose is further metabolized while deoxyglucose is not, leaving the ^{18}FDG to accumulate intra-cellularly as ^{18}F-FDG-6-phosphate. Some tissues contain glucose-6-phosphatase, which can dephosphorylate the molecule returning it to its original form as ^{18}FDG. Tumor cells have both an overexpression of GLUT and an under expression of glucose-6-phosphatase, permitting a relatively large localized accumulation of tracer molecules within the tumor cells. In addition, depending on the area or organ under study, baseline glucose metabolism may be low, further establishing the difference between normal background tissue and tumor. Thus, compared to structural imaging techniques, FDG-PET may be a more accurate technique for diagnosis, staging and treatment decisions in oncology.

PET is currently approved for coverage by the Center for Medicaid and Medicare Services (CMS) for use, for certain indications, in non-small cell lung cancer, esophageal cancer, colorectal cancer, lymphoma, melanoma, breast cancer, head and

neck cancers and thyroid cancer (http://www.cms.hhs.gov/coverage/ accessed September 27th, 2003).

1.2. Request by the Centers for Medicare and Medicaid Services

The Centers for Medicare & Medicaid Services (CMS) requested a technology assessment by the Agency for Health Care Research and Quality (AHRQ) to evaluate the performance of FDG-PET when compared to conventional imaging (such as CT and MRI) and when used as an adjunct to conventional imaging for patient management of six different cancers (brain, cervical, ovarian, pancreatic, small cell lung, and testicular). The Duke Evidence-based Practice Center was asked to conduct an assessment of this technology. In particular, the key questions to be addressed were:

1.2.1. Brain Cancer

1. How does the diagnostic test performance of FDG-PET, as an adjunct to conventional imaging (e.g. CT, MRI), compare to conventional imaging alone with respect to the following clinical situations in primary brain tumors (i.e. not tumors metastatic to brain):

a. In performing guided lesion biopsy of recurrent low-grade brain tumors in patients with an indeterminate MRI?
b. In distinguishing high-grade from low-grade tumors and distinguishing tumor from radiation necrosis in recurrent brain lesions?

2. How does the diagnostic test performance of FDG-PET, as an adjunct to biopsy, compare to biopsy alone with respect to the following clinical situation:
    a. In the initial grading of the degrees of malignancy for patients with primary brain tumors when the initial biopsy result was indeterminate grade II/III glioma?

1.2.2. Cervical Cancer

1. How does the diagnostic test performance of FDG-PET compare to conventional imaging (e.g., CT, lymphangiography, chest radiograph, IV pyelography) in the detection of pre-treatment metastases in newly diagnosed cervical cancer?
2. How does the diagnostic test performance of FDG-PET compare to conventional imaging (e.g., CT, MRI) in the following clinical situations:

a. In detection of residual cervical cancer following treatment (surgery, radiation, chemotherapy, or combination)?

b. In detection of recurrent cervical cancer following treatment (surgery, radiation, chemotherapy, or combination)?

1.2.3. Ovarian Cancer

1. How does the diagnostic test performance of FDG-PET as an adjunct to conventional imaging (e.g., CT, MRI) compare to conventional imaging alone in the following clinical situations:

   a. In staging at the time of initial diagnosis?

   b. In detecting recurrent disease following treatment (surgery, radiation, chemotherapy, or combination)?

      As a subset within this indication, does FDG-PET accurately and reliably detect recurrence in a patient with a history of ovarian cancer who has a rising CA-125 titer and a negative CT:

      i. In determining if there has been a recurrence of the tumor?

      ii. In localizing, if present, such recurrence?

iii. In yielding appropriate staging of such recurrence?

c. In monitoring the effect of chemotherapy

1.2.4. Pancreatic Cancer

1. How does the diagnostic test performance of FDG-PET as an adjunct to conventional imaging (e.g., CT, MRI, endoscopic ultrasound) compare to conventional imaging alone in the following clinical situations:
    a. In differentiating benign from malignant pancreatic lesions?
    b. In detecting metastatic pancreatic cancer?
2. If adjunctive use of FDG-PET is superior to conventional imaging alone for detection of metastatic pancreatic cancer, for what subpopulation(s) of patients has this superiority been shown?
3. How does FDG-PET compare to conventional imaging (e.g. MRI, CT) for detection of residual or recurrent disease following treatment of primary pancreatic cancer?

1.2.5. Small Cell Lung Cancer

1. How does the diagnostic test performance of FDG-PET compare to conventional imaging modalities (e.g., CT, MRI) with respect to the following clinical situations:
    b. In staging to determine the true extent of disease at initial diagnosis in patients with small cell lung cancer (SCLC)?
    c. In restaging post treatment to evaluate the response to initial treatment (detect residual or new disease sites) in patients with SCLC?
    d. In diagnosing occult small cell lung cancer in patients with paraneoplastic syndrome(s) commonly associated with this neoplasm?

1.2.6. Testicular Cancer

1. In patients with an established diagnosis of pure seminomas or non-seminomatous germ cell tumors, how does the diagnostic test performance of FDG-PET compare to conventional imaging modalities (e.g., CT, MRI) or histology with respect to the following clinical situations:
    a. For initial staging?

b. In evaluation of residual masses or suspected recurrent disease to reliably distinguish between viable tumor and fibrosis/necrosis?

c. In determining if there has been a recurrence of tumor in patients with rising serum tumor markers and a normal CT?

1.3. Structure of the Evidence Report

Generally, the questions that CMS posed relate to the overall accuracy of conventional imaging compared to FDG-PET for one or more of the following: (1) initial staging, (2) monitoring response to therapy, and (3) detection of recurrence. In order to address these questions and for ease in reading and comprehension, the report is arranged with a general methods section applicable to all the cancers. The remainder of the report is organized by cancer type; each section addressing a particular cancer is organized so that it can be considered a stand-alone report and includes a general review of the cancer in question, the relevance of the questions posed regarding FDG-PET to clinical management of the specific cancer, and a text summary of the results of the identified studies. In addition, to facilitate an overview of the studies, we provided both a table and a figure summarizing the test performance (sensitivity, specificity, with 95% confidence intervals). At the end of the document, we have placed the bibliography and appendices, which include the detailed evidence tables ordered by cancer type (brain, cervical, ovarian, pancreatic, small cell lung and testicular).

2. METHODS

2.1 Classification of Diagnostic Studies

The Medicare Coverage Advisory Committee (MCAC) report on "Recommendations for Evaluating Effectiveness; Executive Committee Working Group Medicare Coverage Policy" (Executive Committee Working Group, 2001) developed recommendations for evaluating evidence. Although the preference is for direct evidence, few studies directly measure the effect of diagnostic tests on health outcomes. Studies of these tests typically focus on technical feasibility or operating characteristics.

Thus, in order to provide a framework for systematically identifying and reviewing relevant studies, we used a classification described by Fryback and Thornbury (Fryback, 1991). For each clinical question, we classified articles into a hierarchy of Categories, from 1 through 6 as described by Fryback et al (1991). According to the MCAC assessment criteria, the studies most useful for assessing FDG-PET are Category 2 or higher, since Category 1 articles relate to technologies that are under development rather than routinely used in clinical practice. After consultation with AHRQ and CMS, it was

decided that only Category 2 or higher articles would be included in the evidence report and reviewed in-depth. Since the majority of studies fell into Category 1 or 2, we used pre-specified criteria for determining which of the two categories was applicable to a particular article.

For studies in Categories 2 to 6, we identified study design features that would ideally address the goal of that category. These study design features were then used to develop a quality score for each article. The elements of the score were based on commonly accepted study design criteria for obtaining unbiased estimates of sensitivity and specificity (Rothman and Greenland, 1998) and were as follows:

1) Use of a prospective design. This type of study is the most flexible since it allows for investigator control over the design of the study and data collection. In particular, the investigator can enroll patients consecutively, develop and implement standard protocols for the collection of study data, including pre-specifying cut points for determining test positive and test negative patients. This type of design would allow for appropriate blinding of

radiologists and pathologists instead of relying on retrospective chart review, which may lead to selection biases in terms of the patients included in the study and limitations in terms of available data for answering the study question.

2) Use of a matched study design, in which FDG PET and the comparator test are both obtained on one patient or use of a randomized controlled trial, in which patients are randomly assigned to receive FDG-PET or the comparator test. These designs reduce the possibility of confounding due to differences in patient characteristics (sex, age, distribution of underlying disease) that may result in biased estimates of test accuracy.

3) Use of a pre-specified cut-point to determine sensitivity and specificity. This was a key criteria for categorizing studies as Category 1 (technical feasibility) or Category 2 (diagnostic accuracy). In order for the results obtained from a given technology to be reproducible across different settings and populations, there needs to be commonly accepted criteria for determining which

patients have a positive or negative test result. Studies that do not pre-specify a cut-point would usually be considered technical feasibility studies rather than diagnostic accuracy studies. These studies form the basis for determining the optimal cut-point. This cut-point can, in turn, be used to standardize test positive and test negative patients across different populations thus ensuring reproducibility of study results.

4) Availability of histology or long-term follow-up information on all patients. In order to determine the true disease status for all patients, an independent gold standard is usually needed. Ideally the results from this gold standard, whether it be pathology or long-term follow-up, should be obtained blinded to all test results. Determining true disease status unblinded to one or more test results may result in a higher estimate of sensitivity for a given test than would be obtained if true disease status was unknown.

The Fryback categories, criteria for distinguishing between Category 1 and 2, and hallmarks of an ideal study design for Category 2 (or higher) articles are summarized in Table 1.

Table 1. Relationship between clinical question, Fryback et al. Category and study design (for Categories 1 and 2 only)

CLINICAL QUESTION	CATEGORY	CATEGORY DESCRIPTION	MEASURES	STUDY DESIGN
Does the test have good technical characteristics that make it appropriate for use in a clinical setting?	1.	Technical feasibility and optimization	Ability to produce consistent spectra	Study presents patient specific data i.e. SUV's but does not categorize the data using pre-specified cut-points
Does the test have good operating characteristics that make it useful for 1) determining the presence of disease? 2) determining the severity of disease? 3) improving the yield of specimens for diagnosing disease?	2.	Diagnostic accuracy	Sensitivity and specificity % yield of abnormal diagnoses	Ideal studies for answering this question 1) are prospective 2) are randomized controlled trials or matched studies that obtain test information on all patients 3) use a pre-specified cut-point to determine % positive or negative 1) obtain histology or long-term follow-up information on all patients to determine true disease status

Table 1. Relationship between clinical question, Fryback et al. Category and study design (for Categories 1 and 2 only (continued)

Does the test influence the clinicians' subjective assessment of disease status?	3.	Diagnostic thinking impact	Difference in clinician's subjectively estimated diagnosis probabilities pre and post-test	
Does the test influence the therapy given to a patient?	4.	Therapeutic choice impact	% of times therapy planned prior to PET changed after PET	
Does the test result in an improvement in life expectancy from the patient viewpoint?	5.	Patient outcome impact	% of patients who improved with PET compared to % without PET Cost per QALY saved with image information	
Does the test result in an improvement in life expectancy at a reasonable cost from the viewpoint of society?	6.	Societal impact	Cost-benefit or cost-effectiveness analysis conducted from a societal viewpoint	

2.2.Literature Review

2.2.1. Literature Identification

An OVID search of the Medline database was conducted on April 18th, 2003. Filters and limitations were used to eliminate inappropriate publications. General inclusion criteria were included to maximize the applicability of the search results to the SOW questions (see below Section 2.2.2.1). The search used applicable MeSH headings and text words with appropriate Boolean operators. After filtering irrelevant publication types, the search resulted in 1058 citations for download and screening. Individual review of the abstracts resulted in 226 citations identified for complete article review.

2.2.1.1. Search Strategy Used for Identifying Abstracts

Ovid Technologies, Inc. Email Service

Search for: 9 and 39
Citations: 1

Database: MEDLINE <1966 to April Week 1 2003>
Search Strategy:
---
1 brain neoplasms/ (49633)
2 exp brain neoplasms/ (71050)
3 exp glioma/ (31687)
4 or/2-3 (81482)

5 testicular neoplasms/ (14494)
6 exp "neoplasms,germ cell and embryonal"/ (175246)
7 or/5-6 (181892)
8 Cervix Neoplasms/ (33177)
9 exp endometrial neoplasms/ (5954)
10 exp lung neoplasms/ (88849)
11 exp paraneoplastic syndromes/ (8184)
12 Carcinoma, Small Cell/ (12646)
13 or/10-12 (97789)
14 exp Pancreatic Neoplasms/ (27054)
15 exp ovarian neoplasms/ (34704)
16 ca-125 antigen/ (1244)
17 ca-125.mp. (2705)
18 or/15-17 (35859)
19 exp *Tomography, Emission-Computed/ (16259)
20 positron emission tomography.mp. (10892)
21 fdg-pet.mp. (1900)
22 or/19-21 (22228)
23 4 and 22 (1024)
24 exp tomography, emission-computed/ (30872)
25 or/20-21,24 (32462)
26 4 and 25 (1369)
27 26 not 23 (345)
28 exp Deoxyglucose/du [Diagnostic Use] (4254)
29 4 and 28 (244)
30 29 not 26 (8)
31 29 not 23 (21)
32 fluorodeoxyglucose.mp. (2079)
33 or/21,28,32 (5157)
34 4 and 33 (327)
35 23 not 24 (77)
36 23 not 34 (723)
37 limit 34 to (human and English language and yr=1990-2003) (237)
38 "fdg pet".mp. (1900)
39 limit 33 to (human and English language and yr=1990-2003) (3661)
40 7 and 39 (302)
41 8 and 39 (26)
42 9 and 39 (5)

43 13 and 39 (388)
44 14 and 39 (65)
45 18 and 39 (38)

2.2.2. Literature Selection

2.2.2.1 General Inclusion/Exclusion Criteria for Identifying Abstracts

Two levels of inclusion criteria were used for accepting studies. The first were general criteria applied during the initial literature search, and were as follows:

- English language articles reporting primary data and published in a peer review journal (not abstracts)
- Studies that include at least 12 human subjects (not animal studies) with one of the conditions of interest and technology of interest (PET)

2.2.2.2. Inclusion Criteria for Identifying Articles for Full Text Review

A second level of inclusion criteria was applied to all articles (n= 226) identified for full text review based on a review of the abstracts. Prior to full text review, these articles were screened to ensure that they answered at least one of the SOW questions. If an article was only a Category 1 article, it was excluded as discussed previously.

For Category 2 or higher articles, inclusion criteria were applied as follows:

Category 2. Diagnostic accuracy efficacy

A reference standard had to be obtained on all patients.

Category 3. Diagnostic thinking impact

No additional criteria

Category 4. Therapeutic choice impact

No additional criteria

Category 5. Patient outcome impact

Limitation to 12 human subjects relaxed if simulation modeling, with hypothetical populations, used to calculate survival/quality-adjusted life expectancy

Category 6. Societal impact

Limitation to 12 human subjects relaxed if simulation modeling, with hypothetical populations, used to calculate cost-effectiveness or cost-benefit ratios

2.2.3. Data Abstraction and Quality Scores Assigned to Full Text Articles

Data on patient population characteristics, PET scanner, conventional imager, criteria for test positivity, results of tests including sensitivity, specificity and prevalence of cancer was abstracted using a data abstraction form (refer to Appendix C for form).

A quality score was assigned to each article identified for full text data abstraction. In addition to the criteria used to describe an ideal study design for determining test accuracy (prospective, matched or randomized assignment of patients receive tests, pre-specified threshold for determining test accuracy, independent confirmation of disease status (gold standard) obtained on all patients), additional criteria for determining the quality of a given study were developed and applied during data abstraction. These criteria were as follows:

1. The study had a representative sample
2. The setting and selection of the population under investigation were clearly described

3. The study design minimized differences between patients who received the tests
4. The scanner model or the type and resolution of the scanner were mentioned
5. Defined criteria were used for test interpretation
6. Histopathological or clinical confirmation of disease were mentioned
7. The test reader and person assigning the reference standard diagnosis were blinded

Quality scores were determined by adding up the points assigned (from 0 to 7) based on an in-depth review of each article. Each article was reviewed by at least two reviewers. Discrepancies between reviewers were resolved by consensus. Articles were ranked using the score from 0 to 7 and are presented in the results section for each cancer, grouped by scores of either 4 through 7 or 0 through 3, to provide the reader with a general impression of the quality of the articles available for answering a specific question.

3. RESULTS

3.1. Brain Cancer

3.1.1. Background

Each year, approximately 17,000 people in the US are diagnosed with primary brain tumors. Overall, 13,100 will die of their disease (American Cancer Society, 2002). Prognosis is highly variable and depends on pathological classification; 5-year survival ranges from 3% to 85%.

Primary brain tumors arise predominantly from the neuroglia (or glial cells), which provide neuronal support. There are four types of glial cells: astrocytes, oligodendrocytes, microglia, and ependyma (ependymocytes). Gliomas – the most common type of brain tumor – arise from glial cells and this wide variety explains the heterogeneity of gliomas. In addition to classification by cell type, brain tumors are characterized by grade, using the widely accepted WHO classification (Kleihues, 1993). The criteria that are utilized to grade brain tumors are: (a) cellular atypia, (b) mitoses, (c) infiltration, (d) necrosis, and (e) vascular changes. Details of this classification and the relationship between cell type and WHO grade are provided in Appendix B.

Grading is relevant in brain tumors since treatment decisions are primarily based on the grade of the tumor. In general, grades I and II are considered “low-grade” malignancies, and treated less aggressively than grade III and IV tumors that are deemed “high-grade”, and therefore treated aggressively.

Individuals with brain masses typically present with neurological symptoms, often insidious, and more rarely are discovered serendipitously on a brain imaging study performed without brain tumor being suspected. Once discovered, the diagnostic imaging issues are primarily ruling out lesions for which biopsy can be avoided, targeting the most promising areas for stereotactic biopsy, and guiding therapy when biopsy is equivocal (e.g., not clearly high or low grade). During the course of therapy, imaging may be used further to evaluate immediate response to therapy, possibly allowing a change of therapy, and for patients who develop new symptoms or equivocal CT or MR results, specialized imaging may be sought to distinguish recurrence from other abnormalities such as tumor necrosis.

Several diagnostic-imaging modalities may be available to help address these management issues. The most generally available

and used are CT, MRI, and 201-Thallium-SPECT. These modalities are standard services in a broad range of hospitals, particularly those institutions that would be faced with evaluation patients with brain lesions.

As with all malignant tumors, brain tumors rapidly consume glucose. Unlike most other tissues, brain tissue uses glucose almost exclusively. This leads to a high background accumulation of FDG, with gray matter having particularly high uptake.

The images obtained from ^{18}FDG-PET scanning are generally examined visually and graded subjectively using one of a variety of descriptive scales (Table 2). This approach takes advantage of the tendency for more malignant brain tumors to take up FDG more intensely (Delbeke, 1995). Low-grade tumors tend to have uptake similar to white matter while high-grade tumor uptake resembles gray matter. Since tumors can become indistinct from adjacent tissue, it is considered essential in many cases to directly compare – perhaps through co-registration – the PET image with CT or MRI results.

Table 2. PET Visual Grading Scale

Visual grade	Description
0	No visible uptake
1	Uptake < adjacent area
2	Uptake ≥ adjacent cortex but < contralateral cortex
3	Uptake ≥ contralateral cortex

3.1.2. CMS Statement of Work Questions

1. How does the diagnostic test performance of FDG-PET, as an adjunct to conventional imaging (e.g. CT, MRI), compare to conventional imaging alone with respect to the following clinical situations in primary brain tumors (i.e. not tumors metastatic to brain):

    a. In performing guided lesion biopsy of recurrent low-grade brain tumors in patients with an indeterminate MRI?

    b. In distinguishing high-grade from low-grade tumors and distinguishing tumor from radiation necrosis in recurrent brain lesions?

2. How does the diagnostic test performance of FDG-PET, as an adjunct to biopsy, compare to biopsy alone with respect to the following clinical situation:

    a. In the initial grading of the degrees of malignancy for patients with primary brain tumors when the initial biopsy result was indeterminate grade II/III glioma?

3.1.3. Importance of Questions Posed by CMS in Clinical Management

The statement of work specified three management questions relevant to the use of ^{18}FDG-PET in the care of patients with primary brain tumor.

Below we briefly review the clinical significance of each question raised by CMS. Note that for brevity we use more compact phrasing for each question in this and subsequent sections.

Ia. Performance in guided lesion biopsy for patients with a recurrent brain tumor and indeterminate MRI, compared with biopsy performed with conventional imaging.

Glial tumors are often heterogeneous. For recurrent tumor, abnormalities may be particularly unevenly distributed since high-grade tumors often originate from malignant degeneration of lower grade tumors. By identifying the tissue with the highest metabolic activity, it may be possible to improve the yield of biopsy, decrease the number of biopsy trajectories required, and increase the likelihood that the specimen will correctly represent the worst histology. This

could improve the appropriateness of therapy and, in turn, may lead to improved patient outcomes.

1b. Performance in distinguishing tumor from radiation necrosis in recurrent brain lesions, compared with conventional imaging.

Radiation treatment may lead to necrosis. Tissue necrosis can be difficult to distinguish from recurrent malignancy using conventional imaging. The distinction between recurrent malignancy and necrosis can be important clinically since uncertainty may lead to biopsy, and because therapy and prognosis are substantially different.

2. Performance in distinguishing high-grade from low-grade gliomas when a new brain tumor is deemed indeterminate by biopsy.

On occasion, a biopsy specimen may not provide sufficient tissue to distinguish a low-grade tumor (WHO class I or II) from a high-grade tumor (WHO class III or IV). This is most likely when the actual tumor class is either II or III. Patients with high-grade tumors are generally treated more aggressively than are patients with low-grade tumors.

3.1.4. Results

The literature search identified 237 abstracts. Review of the abstracts identified 100 potential articles for full-text review. Of these, 13 met the criteria for full text review and are discussed below. Data on the operating characteristics for the tests, including 95% confidence intervals are presented in tables and figures at the end of this section. Detailed evidence tables are available in Appendix D.

1a. Performance in guided lesion biopsy for patients with a recurrent brain tumor and indeterminate MRI, compared with biopsy performed with conventional imaging.

No studies were identified in the literature search that assessed the utility of PET as a guide to biopsy for recurrent brain tumors associated with an indeterminate MRI.

1b. Performance in distinguishing tumor from radiation necrosis in recurrent brain lesions, compared with conventional imaging.

Category 4. Therapeutic choice impact

<u>Quality score 4-7</u>

No studies of therapeutic impact reviewed had a quality score in the range of 4-7.

Quality score 0-3

In the two studies that examined the use of PET on patient management, charts were reviewed retrospectively. In the first study (Oliverio et al., 1995), 39 patients with known or suspected primary brain tumors had PET. Of these, there was concordance between MRI and PET in 30 (77%), implying no added benefit of PET. Of the nine patients with discordant MRI and PET scans, 5 (23%) related to the issue of recurrence vs. necrosis. In 3 of the 5 patients, MRI suggested high-grade glioma while PET indicated radiation necrosis and biopsy confirmed high grade glioma. In the other 2 patients, MRI showed an enhancing lesion with no mass effect while PET indicated radiation necrosis and follow up suggested radiation necrosis. In a second report, Deshmukh et al (1996) performed a similar evaluation of PET in 75 patients. Of the 75% of patients who had PET scans with a reason discernable from the chart, the most common reason (77 studies in 61 patients) was to discriminate tumor recurrence from radiation necrosis. It was not evident from the report how often in this circumstance therapy was changed specifically in response to the PET scan. In this study PET did not appear to have an evident advantage over MRI.

Category 2: Diagnostic accuracy

Quality score 4-7

Janus et al (1992) studied 50 patients with primary brain tumor and subsequent surgery, radiotherapy, or chemotherapy. All patients were reported to have an MR image suggesting possible recurrence. PET was compared to final diagnosis of recurrence vs. necrosis by biopsy (n = 20) or clinical follow-up (n = 30). Of the 20 with biopsy results, 12 (60%) had recurrence demonstrated by histology. PET had a sensitivity of 83% and specificity of 62% for the diagnosis of recurrence. Compared to the prevalence of recurrence of 60% in the biopsied patients, the proportion of patients with recurrence among those with a positive PET was 77% and the proportion of patients with recurrence among those with a negative PET was 29%. Of the 30 with clinical follow up only, six (20%) were deemed to have recurrence by death within 26 weeks. Assuming clinical course is a surrogate for presence or absence of recurrence, PET had a sensitivity of 67% and specificity of 74%. Of the 12 with proven recurrence, 11 had MRIs results reported and 9 of these (82%) were considered diagnostic for recurrence. Compared to the overall prevalence of recurrence of 20% in the patients without biopsy, the proportion of patients with recurrence among those with a positive PET was 40% and the proportion of patients with recurrence among those with a negative PET was 11%. This suggests that PET was not highly discriminative between recurrence and necrosis.

However since the definition of recurrence by clinical course was not precise, it is difficult to give substantial weight to these estimates.

In three studies, FDG PET was compared to SPECT/SPET. Kahn (1994) compared FDG PET and ^{201}Tl-SPECT in distinguishing radiation necrosis from tumor recurrence among 19 patients. Reference diagnosis was based on histology (n=5) and clinical follow up (n=14). For patients diagnosed by clinical follow-up, mean follow up was 12 months (range 0.5-32 months). Sensitivity of PET for the diagnosis of radiation necrosis was 50% with specificity 80%. Equivalently, for the diagnosis of recurrence, sensitivity was 80% and specificity was 50%.[1] Performance of SPECT was similar: for radiation necrosis, sensitivity was 50% and specificity was 75%, for recurrence, sensitivity was 75% and specificity was 50%. In the second study, Stokkel et al (1999) studied 16 patients with PET and ^{201}Tl-SPET on a dual scanner. For recurrence, PET had a sensitivity of 67% and specificity of 100%. For SPET the sensitivity was 100% and specificity was 100%. In the third comparative study performed in Hamburg/Saar, Germany, Bader et al (1999) examined 30 patients chosen because they were suspected of recurrent tumor and had had both PET and IMT SPET. PET and SPET were categorized by blinded qualitative consensus by two radiologists. Based on biopsy specimen, only one patient in the population did not have recurrence. For PET, sensitivity for recurrence vs. non-

[1] For a test with two possible diagnoses, A and B, sensitivity for diagnosis of A is the same as specificity for the diagnosis of B.

recurrence was 76% and specificity (based on one patient) was 100%. For the comparator, IMT SPET the sensitivity was 70% and specificity was (based on one patient) 100%.

Barker et al (1997) evaluated 55 patients who had undergone PET for suspected recurrent glioma following radiotherapy. All patients had an MR image compatible with either tumor progression or necrosis. The PET image was evaluated on a 4-point scale and compared to survival (here taken as a surrogate for likelihood of recurrence). Median survival was significantly associated with qualitative assessment of FDG uptake, with a median survival not reached at two years for patients with no visible lesion on PET to 281 days median survival with tumor activity greater than both adjacent and contralateral cortex. In a Cox regression model, three factors were statistically significant: age, recurrence number, and FDG-PET score. Notably, the study did not provide coefficient estimates for these factors. Therefore it is not possible to assess the extra contribution of PET in predicting survival beyond conventional clinical information or imaging studies.

2. Performance in distinguishing high-grade from low-grade gliomas when a new brain tumor is deemed indeterminate by biopsy.

There were four studies that evaluated the role of FDG-PET in newly identified primary brain tumors in differentiating between grade II and grade III tumors. None of them specifically evaluated patients in whom the histology diagnosis was indeterminate.

Category 2: Diagnostic accuracy

Quality score 4-7

Meyer et al (2001) performed a retrospective study in Aachen, Germany of 47 patients (30 of them had glial lesions). PET was performed in all patients. PET was interpreted qualitatively, using a visual grading scale (VGS), as well as quantitatively. The reference standard for tumor grade was either histology or a clinical follow-up. On this basis, seven of the 30 glial tumors were diagnosed as grade II gliomas and 23 were grade III-IV gliomas. Results were not presented separately for new and recurrent tumors. High-grade gliomas showed a significantly higher FDG uptake than low-grade gliomas by both qualitative and quantitative measures. The criterion used for separating high grade from low grade was the transition between 3a (tumor FDG uptake > white matter and << gray matter uptake) and 3b (tumor uptake >> white matter uptake but < gray matter uptake) on the visual grading scale. Using this cut-off, PET had a sensitivity of 83% and specificity 94% for differentiating between high

and low grade gliomas. The authors conclude that the VGS is at least as accurate as the quantitative scales. The study did not correlate the results of the VGS with survival.

Delbeke et al (1995) retrospectively evaluated the utility of PET, with histology as the reference standard, in a group of 58 patients in Nashville, TN. The study population was comprised of consecutively enrolled patients with histologically proven new brain tumors. Of these 38 were gliomas; 20 of these were high-grade and 18 were low-grade. The authors calculated FDG uptake ratios for tumor/white matter, and tumor/cortex. They determined that differentiation between low-grade and high-grade tumors was best when the cut-off for the FDG uptake ratio was1.5 for tumor/white matter and 0.6 for tumor/cortex. When the cut-off was1.5, PET had a sensitivity of 100% and specificity of 67% in differentiating high and low grade tumors. When a higher cut-off value was chosen for all tumors, the specificity increased but the sensitivity decreased. The authors suggest a standard value that can be used by other investigators. A limitation of this study is that the cut-point was adjusted *a posteriori* and no follow up validation was reported.

Kaschten et al (1998) studied FDG uptake in 54 patients with brain tumors in Liege, Belgium. Patients were studied before any treatment was initiated. FDG-PET was performed on 45 patients, and the diagnoses were confirmed by biopsy or by radiology and clinical follow-up. FDG-PET data

was evaluated qualitatively (visual grades 1-5) and quantitatively. The results of the analysis were correlated with histological grading systems and clinical follow-up. Results were not reported in terms of cut-points for FDG-PET and we inferred that a high-grade tumor diagnosis could have been assigned for scans with a visual grade of 3-5, or 4-5. Using the former cut-point, PET had a sensitivity of 87% and specificity of 62%. Using the more stringent cut-point, the sensitivity was 82% and specificity was 74%.

Sasaki et al (1998) studied 23 patients in Fukuoka, Japan to assess the utility of FDG-PET for evaluating the grade and the extent of newly diagnosed astrocytomas. Seven tumors were astrocytomas (grade II), 10 were anaplastic astrocytomas (grade III), and six were glioblastomas (grade IV). FDG-PET was performed in all 23 patients. The results were compared with results obtained with MRI. The FDG uptake was evaluated by a semi-quantitative analysis using the standardized uptake value. The study did not provide results by cut points. From the data that was provided, we assumed 2.9 as a cut-off between grade II and III/IV tumors for FDG uptake and ++ to +++ (apparent enhancement to marked enhancement exceeding that of choroid plexus) for MRI. When these cut points were used for evaluating the operating characteristics, the sensitivity of FDG-PET in its ability to distinguish low-grade (grade II) from high-grade

(grades III/IV) gliomas was 69% and the specificity was 57%. For MRI the sensitivity and specificity were 69% and 100% respectively.

There were two significant limitations common to all the studies. First, none of them specifically evaluated those grade II/III tumors where biopsy histology was indeterminate. Second, none of the studies were blinded to the reader of the gold standard. In addition, two studies did not provide cut-points for a positive PET.

3.1.5. Conclusions

1a. Performance in guided lesion biopsy for patients with recurrent brain tumor and indeterminate MRI, compared with biopsy performed with conventional imaging.

No studies were identified that directly addressed the issue of how PET may affect biopsy performance specifically for patients with recurrent brain tumor.

1b. Performance in distinguishing tumor from radiation necrosis in recurrent brain lesions, compared with conventional imaging.

It is notable that distinguishing tumor from radiation necrosis appears to be the most common reason for using PET in the context of brain tumor management.(Deshmukh, 1996) With the exception of one study with only one patient without recurrence, the sensitivity of PET in this context appears to be in the range of 76% to 83% with specificity from 50% to 62%. While the specificity may not be sufficient to rule in recurrence (and rule out necrosis), it may be adequate in some cases to rule in radiation necrosis (and rule out recurrence.) For example, if a patient suspected of either recurrence or radiation necrosis has a likelihood of recurrence of 20% (most likely radiation necrosis but recurrence a modest concern), a negative PET would reduce the likelihood of recurrence to approximately

10%, which may be sufficient to proceed with management as though the patient has radiation necrosis.

The conclusion that PET may be a valuable modality is tempered by the results of three studies in which PET had comparable operating characteristics to the more accessible radionuclide studies (SPET/SPECT).

2. Performance in distinguishing high-grade from low-grade gliomas when a new brain tumor is deemed indeterminate by biopsy.

No studies identified in the current review examined the performance of PET in clarifying the grade of tumor for patients with indeterminate (grade II/III) biopsy. However, four studies provided data on patients with definite biopsy grade; these provide estimates of sensitivity for high-grade tumor ranging from 69% to 100%, and specificity from 57% to 100%. What is unclear from these results is the degree to which PET performance for patients with truly indeterminate biopsy results will resemble the reviewed studies.

3.1.6. Tables

Table 3. Estimates of PET and comparator test(s) sensitivity and specificity with 95% confidence intervals for distinguishing tumor from radiation necrosis in primary recurrent brain lesions, compared with conventional imaging.

Study	**Sensitivity**	**95% Confidence Interval**	**Specificity**	**95% Confidence Interval**
Bader 1999 – PET	0.759	0.564-0.897	1.00	0.025-1.00
Janus 1992 – PET	0.833	0.515-0.979	0.625	0.245-0.915
Stokkel 1999 – PET	0.667	0.349-0.901	1.00	0.398-1.00
Kahn 1994 – PET	0.500	0.0676-0.932	0.800	0.519-0.957
Stokkel 1999 – SPET	1.00	0.735-1.00	1.00	0.398-1.00
Kahn 1994 – SPECT	0.500	0.0676-0.932	0.667	0.383-0.882

Table 4. Estimates of PET and comparator test(s) sensitivity and specificity with 95% confidence intervals for distinguishing high-grade from low-grade gliomas when a new brain tumor is deemed indeterminate by biopsy.

Study	**Sensitivity**	**95% Confidence Interval**	**Specificity**	**95% Confidence Interval**
Delbeke 1995 – PET	1.00	0.832-1.00	0.667	0.410-0.867
Sasaki 1998 – PET	0.688	0.413-0.890	0.571	0.184-0.901
Meyer 2000 – PET	0.833	0.653-0.944	0.938	0.698-0.998
Kaschten 1998 – PET (>3VG)	0.867	0.595-0.983	0.615	0.406-0.798
Kaschten 1998 – PET (>=3VG)	0.867	0.595-0.983	0.615	0.406-0.798
Sasaki 1998 – MRI	0.688	0.413-0.890	1.00	0.590-1.00

3.1.7. Figures

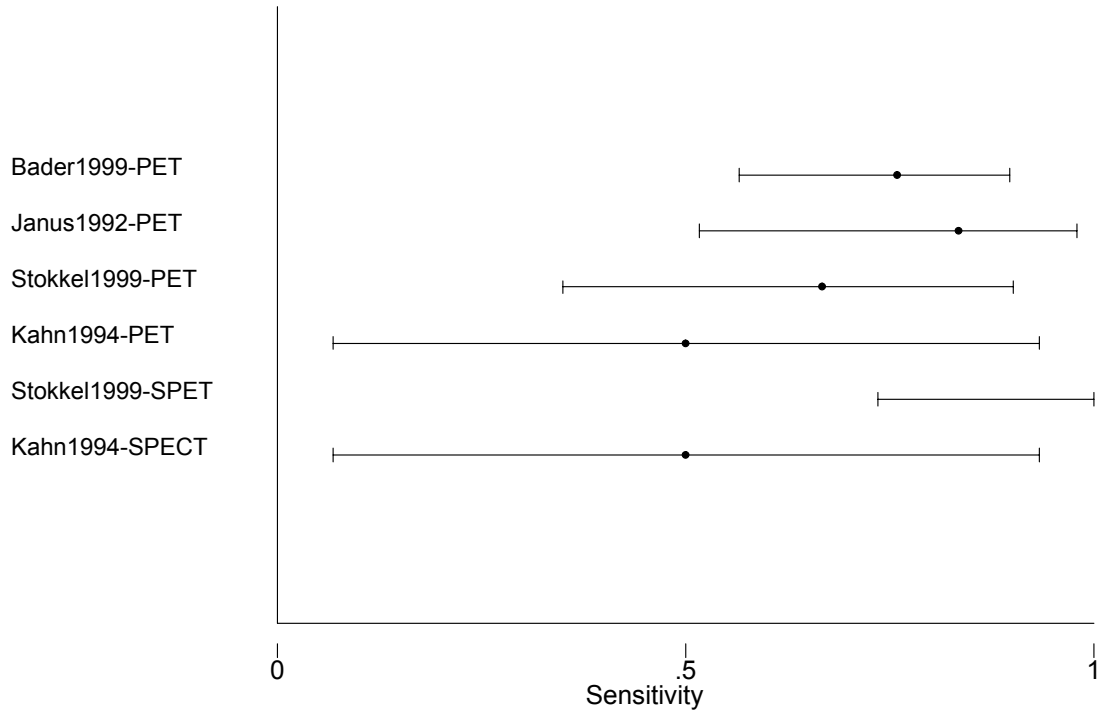

Figure 1.a. Estimates of PET and comparator test(s) sensitivity with 95% confidence intervals for distinguishing tumor from radiation necrosis in primary recurrent brain lesions, compared with conventional imaging.

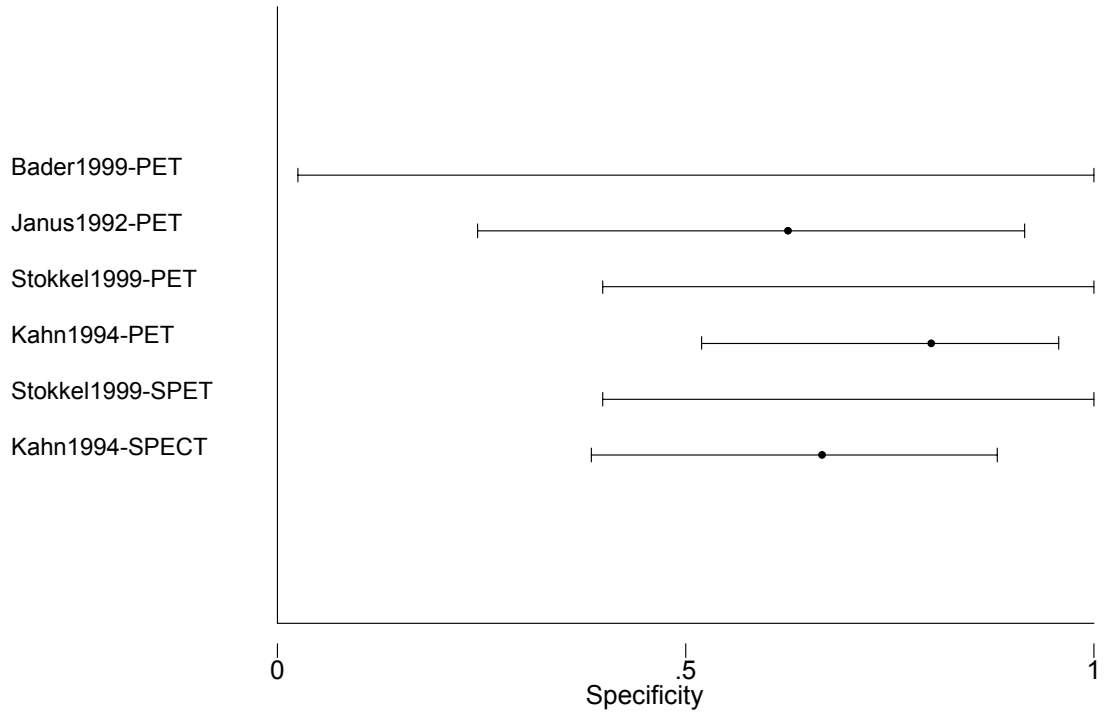

Figure 1.b. Estimates of PET and comparator test(s) specificity with 95% confidence intervals for distinguishing tumor from radiation necrosis in primary, recurrent brain lesions, compared with conventional imaging.

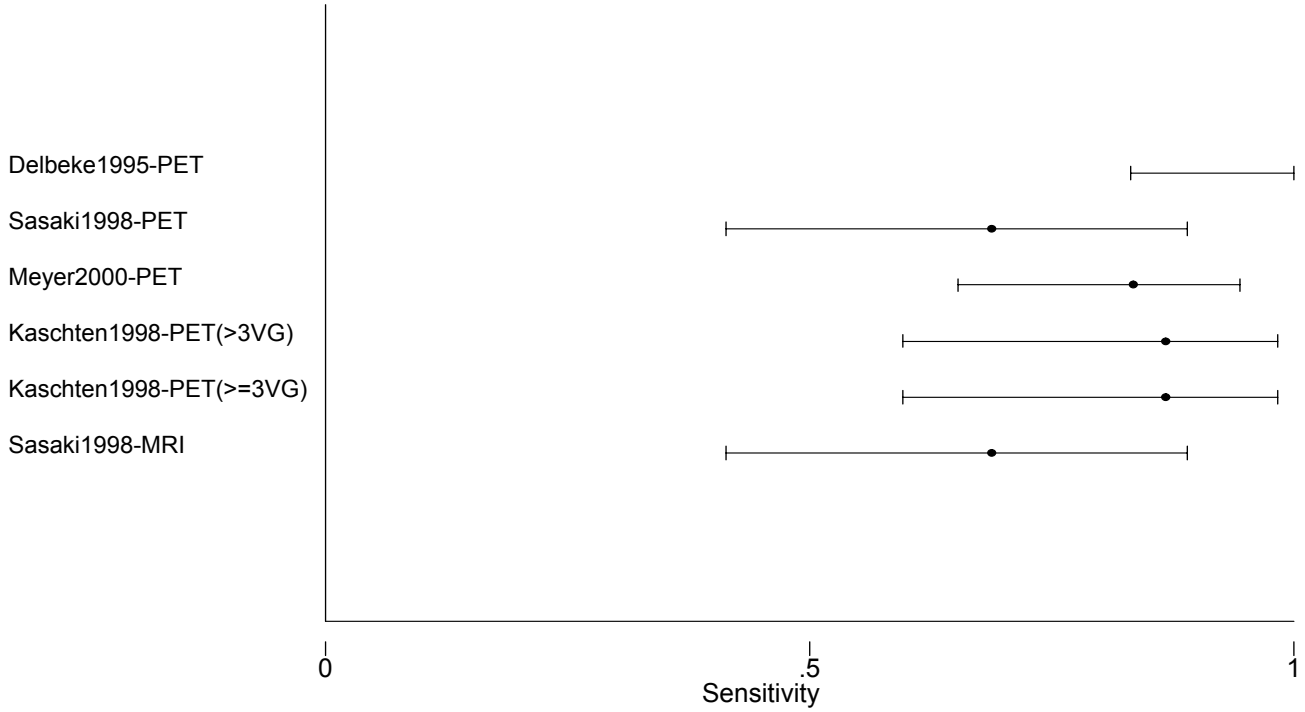

Figure 2a. Estimates of PET and comparator test(s) sensitivity with 95% confidence intervals for distinguishing high-grade from low-grade gliomas when a new brain tumor is deemed indeterminate by biopsy.

<u>Legend</u>

VG – Visual grade

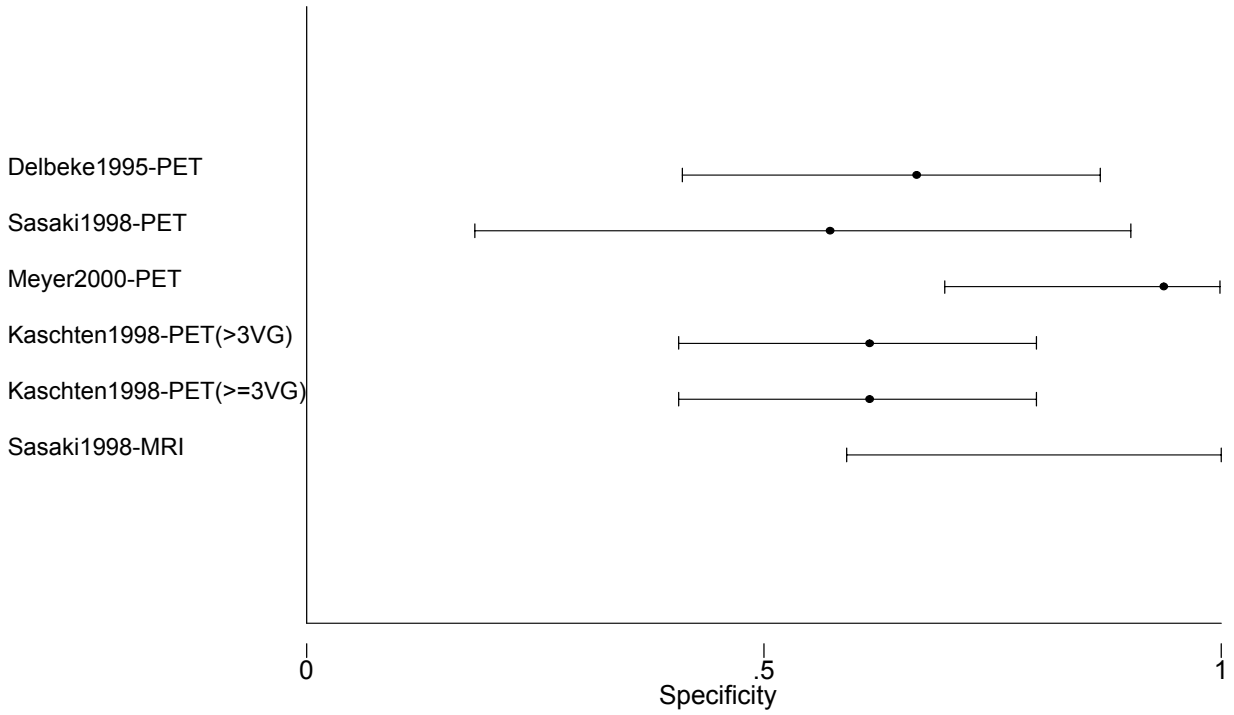

Figure 2b. Estimates of PET and comparator test(s) specificity with 95% confidence intervals for distinguishing high-grade from low-grade gliomas when a new brain tumor is deemed indeterminate by biopsy.

<u>Legend</u>

VG – Visual grade

3.2. Cervical Cancer

3.2.1. Background

Cervical cancer kills 4,100 women each year in the United States with 12,200 new cases diagnosed annually (CA Cancer J Clin 2003; 53:5-26). Although early stage cervical cancer can be treated successfully with surgery or radiation resulting in five-year survival estimates of 80-95%, it may be possible to improve survival by identifying patients with more advanced occult disease (usually in the pelvic or para-aortic lymph nodes) requiring additional treatment. Sensitive and specific radiologic imaging modalities that identify occult lymph node metastasis can facilitate tailored treatment strategies and reduce the morbidity of unnecessary treatment. For example, patients who are managed with surgery will require both adjuvant radiation and chemotherapy if lymph node metastases are subsequently diagnosed. The identification of occult metastases during the initial diagnostic evaluation could lead to avoidance of surgery and its accompanying risk of complications. In addition, the improved early detection of recurrent disease using radiologic imaging may lead to higher salvage and survival rates. Thus, the development of improved imaging modalities directed towards evaluation for retroperitoneal and distant disease has the potential to positively impact the clinical course of cervical cancer.

3.2.2. CMS Statement of Work Questions

1. How does the diagnostic test performance of FDG-PET compare to conventional imaging (e.g., CT, lymphangiography, chest radiograph, IV pyelography) in the detection of pre-treatment metastases in newly diagnosed cervical cancer?
2. How does the diagnostic test performance of FDG-PET compare to conventional imaging (e.g., CT, MRI) in the following clinical situations:
    a. In detection of residual cervical cancer following treatment (surgery, radiation, chemotherapy, or combination)?

In detection of recurrent cervical cancer following treatment (surgery, radiation, chemotherapy, or combination)?

3.2.3. Importance of Questions Posed by CMS in Clinical Management

1. Performance of FDG-PET compared to conventional imaging in the detection of pre-treatment metastases in newly diagnosed cervical cancer.

Unlike other gynecological cancers, FIGO (International Federation of Gynecology and Obstetrics) staging for cervical cancer is based on criteria from clinical examination and basic radiological studies — findings from surgery or advanced radiological imaging studies are not used in assigning stage. The standard evaluation for its staging includes physical examination, chest radiograph, and intravenous pyelogram. Although

patients with early stage disease are often cured by surgery alone, many patients receive primary radiation, often with adjuvant chemotherapy, and therefore never undergo a staging laparotomy. Imaging modalities, which can identify metastatic disease, allow tailored treatment. For example, a patient with suspected aortic nodal metastasis may be treated with extended field radiotherapy. Survival and progression-free survival are expected to continue to improve with such tailored treatments as intensity-modulated radiation therapy, which allows a substantial radiation dose to the lymph nodes with sparing of normal structures (Portelance, 2001). An accurate assessment of the extent of pre-treatment disease is therefore becoming even more critical. CT and MRI rely on size criteria for the detection of retroperitoneal nodal metastasis and are notoriously inaccurate, with sensitivities ranging from zero to 89% in one meta-analysis (Scheidler, 1997). The imaging modality, which proves most accurate for pre-treatment staging of cervical cancer, has the potential to positively impact survival from this disease.

2. Performance of FDG-PET compared to conventional imaging in (a) detection of residual cervical cancer following treatment, and (b) detection of recurrent cervical cancer following treatment.

Early detection of recurrent cervical cancer has the potential to improve survival, since some patients may be salvaged using radiotherapy or radical surgery. Patients with local recurrence of cervical cancer without extension to the pelvic sidewall are sometimes candidates for pelvic exenteration, a radical surgical procedure with a 30 to 50% likelihood of long-term cure. Locally recurrent disease is often difficult to detect on pelvic examination due to thickening of the soft tissue structures following radiation and/or surgery. Detection of recurrent disease in the pelvis using MRI and CT is problematic in this setting because in many instances discrete masses are not present. Rather, the cancer often grows by infiltration of tissues causing only subtle changes in architecture. Cervical cancer recurrences at the pelvic sidewall or in pelvic or aortic nodes are unlikely to be cured, but new treatment modalities such as radical resection in combination with intraoperative high-dose-rate brachytherapy have afforded prolonged local control in preliminary reports (Leitao et al, 2002). As the available treatments for cervical cancer recurrence improve, the improvement of imaging modalities to identify recurrences early becomes more important.

3.2.4. Results

The literature search identified 31 abstracts. Review of the abstracts identified 16 articles for full-text review. Of the 16 articles, 11 met the criteria for full text review and are discussed below. Data on the operating characteristics for the tests, including 95% confidence intervals are presented in tables and figures at the end of this section. Detailed evidence tables are available in Appendix D.

1. Detection of pre-treatment metastases in newly diagnosed cervical cancer

Category 2: Diagnostic accuracy

<u>Quality score 4-7</u>

Rose et al (1999) prospectively performed PET for assessment of aortic nodal metastasis on 32 patients, from Cleveland, OH with stage II-IV cervical cancer and no evidence of extrapelvic disease on CT. All patients underwent aortic lymphadenectomy following radiologic studies. Radiologic results were assessed against histologic diagnosis following surgery. The sensitivity and specificity of PET for detection of aortic nodal metastasis were 75% and 92%, respectively. 17 patients also underwent pelvic lymphadenectomy at the discretion of the surgeon. The sensitivity of PET for detection of pelvic nodal metastasis was 100% compared to 45% for CT.

Reinhardt et al (2001) prospectively compared MRI to PET for lymph node staging in 35 patients from Freiburg, Germany prior to radical hysterectomy and lymphadenectomy. All radiologic findings were confirmed by pathology. The sensitivity and specificity of PET for detection of retroperitoneal nodal metastasis on a per-patient basis were 91% and 100%, compared to 73% and 83% for MRI. Analysis by nodal site yielded PET sensitivity and specificity of 81% and 99%, compared to 67% and 97% for MRI.

Grigsby et al (2003) retrospectively studied pre-treatment lymph node staging using PET and CT in 101 consecutive patients from St. Louis, MO with newly diagnosed stage I-IV cervical cancer prior to primary radiotherapy. The primary outcome studied was progression-free survival. Patients with PET-positive and CT-negative aortic lymph nodes had a 2-year progression-free survival of 18%, compared to 64% for PET-negative and CT-negative aortic nodes and 14% for PET-positive, CT-positive aortic nodes. In multivariate analysis, PET-positive aortic lymph node status was the only significant variable predicting lower progression-free survival ($p=0.025$); lymph node status by CT assessment was not prognostic. A limitation of the study is a lack of defined criteria for PET interpretation. In addition, there was a difference in treatment in the two groups: para-aortic radiation was given to 7 of 7 patients with positive nodes by CT, by only 4 of 14 of those with positive nodes only on PET. However, exposure to

para-aortic external radiation was not included in the survival models, potentially biasing survival estimates due to differences in treatment.

Miller et al (2003) retrospectively analyzed survival among 47 patients from St. Louis, MO who underwent PET prior to primary radiotherapy for stage I-IV cervical cancer. PET results were read in a blinded fashion by 3 radiologists; scoring criteria for PET interpretation were given. Patients with PET-positive lymph nodes had better overall (P=0.04) and progression-free (P=0.03) survival using Kaplan-Meier analysis at 2 ½ years than patients whose lymph nodes were assessed as negative by PET.

Lin et al (2003) prospectively evaluated PET for detection of aortic nodal metastasis in 50 patients with locally advanced cervical cancer and normal abdominal CT findings. Confirmation of diagnosis was by histologic confirmation at aortic lymphadenectomy. The sensitivity and specificity of PET for detection of aortic nodal metastasis were 86% and 94%. The major weakness of this study was the lack of blinding of radiologists to the pathology results.

Yeh et al (2002) prospectively analyzed PET for detection of aortic lymph nodal metastasis in 42 patients, from Taipei, Taiwan with stage IB-IVA cervical cancer prior to aortic lymphadenectomy. All patients had negative findings on abdominal MRI. Confirmation of radiologic findings was by histology. 12/42 (28%) patients had aortic nodal metastasis on final

pathology; the sensitivity and specificity of PET for detection of aortic nodal metastasis were 83% and 97%, respectively.

Belhocine et al (2002) retrospectively studied the results of PET compared with CT or MRI for the pre-treatment staging of 22 patients from Leige, Belgium with newly diagnosed cervical cancer. Imaging results were confirmed by histology (18 patients) or clinical and radiologic follow up of at least 12 months (4 patients). The sensitivity and specificity of PET for lymph node staging were 70% and 98%, respectively, compared to 48% and 97% for conventional imaging modalities. Sensitivity and specificity were calculated on a “per lymph node” as opposed to a “per patient” basis, which may contribute to bias (by allowing patients with positive findings to be counted multiple times).

Sugawara et al (1999) retrospectively compared PET to CT for lymph node evaluation in 17 patients, from Ann Arbor, MI with newly diagnosed cervical cancer. Confirmation of results was by histology or prolonged clinical and radiologic follow up. Results were not confirmed in 4 patients, leaving 13 patients for analysis. The sensitivity and specificity of PET for detection of lymph node metastasis were 86% and 100%, compared to 57% and 100% for CT scan when equivocal results were counted as negative.

A limitation common to all studies in this section is the lack of blinding for the pathologists or “gold standard” readers. In addition, there were no

Category 3 through 6 studies identified in the literature review that addressed this question.

2a. Detection of residual cervical cancer following treatment

Category 2: Diagnostic accuracy

Quality score 4-7

Grigsby et al (2001) retrospectively reviewed 76 patients from St. Louis, MO who underwent a post treatment surveillance PET within 10.4 months of completion of primary radiotherapy for stage I-IV cervical cancer. Two-year progression-free survival was 40% among patients with persistent PET abnormalities following treatment, compared to 86% for patients without abnormalities. In a multivariate analysis, post treatment abnormal PET was a significant predictor of death ($p<0.0001$). A limitation of the study is lack of defined criteria for PET interpretation.

Nakamoto et al (2002) reported 20 patients from Baltimore, MD with stage IB-IVA cervical cancer who underwent PET within 7 months of completion of radiotherapy for cervical cancer (19 newly diagnosed, 1 with recurrent disease). Assessment of accuracy was by histology (4 patients) or clinical follow up (16 patients). The authors reported that the sensitivity and specificity of PET for detection of recurrent or persistent disease were 100% (95% CI: 47.8-1) and 60% (95%C.I.: 32.3-83.7%), respectively. Although the authors interpreted PET results using both a visual score and

a semi quantitative analysis, no clear cutoffs were given for determination of “positive” versus “negative.” A limitation of this study is the lack of data presented in the results section regarding the use of CT as the comparator test. Results on 9 patients are presented in the Discussion section, but not in a manner that allows for construction of a 2 x 2 table.

A limitation common to all studies in this section is the lack of blinding for the pathologists or “gold standard” readers. In addition, there were no Category 3 through 6 studies identified in the literature review that addressed this question.

2b. Detection of recurrent cervical cancer

Category 2: Diagnostic accuracy

Quality score 4-7

Grigsby et al (2003) retrospectively reviewed 76 patients from St. Louis, MO who underwent a post treatment surveillance PET within 10.4 months of completion of primary radiotherapy for cervical cancer. Two-year progression-free survival was 40% among patients with persistent PET abnormalities following treatment, compared to 86% for patients without abnormalities. Patients who developed new abnormalities on PET following treatment had a 0% 2-year survival. In a multivariate analysis, post-treatment abnormal PET was a significant predictor of death (p=.0073). Limitations of the study are lack of data provided on whether

any salvage therapies were differentially given by PET status and lack of defined criteria for PET interpretation.

Belhocine et al (2002) retrospectively studied the results of PET compared with CT or MRI for the post-treatment surveillance of 38 patients from Liege, Belgium with invasive cervical cancer. Radiologists were blinded to clinical outcomes and criteria for PET and MRI interpretation were defined. Confirmation of imaging findings was by histologic evaluation (11 patients) or clinical and radiologic follow up greater than 12 months (27 patients). The sensitivity and specificity of PET for detection of recurrence were 100% and 77%, compared to 48% and 85% for conventional imaging.

Ryu et al (2002) retrospectively studied the results of PET in 249 patients with a history of cervical cancer and no evidence of recurrence by conventional methods. Final diagnosis was by histology or clinical follow up of at least 6 months. The sensitivity and specificity of PET for detection of recurrence were 90% and 76%, respectively, with prevalence of recurrence 12%. This study is strengthened by the large sample size and the fact that radiologists were blinded to clinical data.

Park et al (2000) retrospectively studied 36 patients from Seoul, Korea in whom recurrent cervical cancer was suspected clinically. All patients underwent CT and PET; criteria for interpretation of both were defined quantitatively. Results were confirmed by histology (n=13) or

clinical follow up using radiology and tumor markers (n=23). 50% of patients were found to have recurrent disease. The sensitivity and specificity of PET for detection of cervical cancer recurrence were 100% and 94%, compared to 77% and 83% for CT.

Sun et al (2001) retrospectively studied PET in 20 patients from Taiwan who were clinically suspected to have recurrent cervical cancer. PET findings were evaluated using operative histology or clinical follow up greater than one year. 19/20 (95%) of patients were ultimately diagnosed with recurrence; the overall sensitivity and specificity of PET for detection of recurrence were 100% and 0% (the only patient with no recurrence was called falsely positive by PET). The sensitivity and specificity of PET were 86% and 83% for local recurrence, 100% and 75% for pelvic nodal recurrence, 100% and 100%, for aortic nodal recurrence, and 100% and 100% for distant metastasis. Limitations of the study are lack of defined criteria for test interpretation and a dearth of patients without recurrence, which limits the overall specificity calculation.

A limitation common to all studies in this section is the lack of blinding for the pathologists or “gold standard” readers. In addition, there were no Category 3 through 6 studies identified in the literature review that addressed this question.

3.2.5. Conclusions

1. Detection of pre-treatment metastases in newly diagnosed cervical cancer

There is fair to good evidence that PET is more sensitive than CT or MRI for detection of retroperitoneal nodal metastasis in patients with newly diagnosed cervical cancer. Several prospective studies using pathology report as a gold standard (Rose, 1999; Reinhardt 2001; Yeh, 2002; Lin 2003) find superior sensitivity of PET over conventional imaging in this setting, with comparable specificities; however, the studies are all limited by small sample sizes and resulting large confidence intervals in the estimates of sensitivity and specificity of both modalities. In addition, two retrospective studies (Grigsby, 2001; Miller, 2003) demonstrated that pre-treatment PET findings are predictive of progression-free survival and possibly overall survival; however, potential differences in treatment based on radiology findings were not controlled for the analysis of these patients (both papers were from the same institution).

Given the potential for PET to have a substantial impact on patient outcomes and costs by altering management strategies (e.g., by avoiding surgery in patients with known lymph node metastases), a well-designed study which addressed the issues of sample size and bias discussed above should be a high priority.

2. Detection of (a) residual and (b) recurrent cervical cancer following treatment

Two retrospective studies (Belhocine, 2002; Park, 2000) showed greater sensitivity and comparable specificity of PET compared to conventional imaging for detection of recurrent cervical cancer. A third retrospective study (Grigsby, 2003) demonstrated that abnormalities on post treatment surveillance PET predict lower progression-free survival, while the appearance of new abnormalities on surveillance PET predicts poor overall survival. Taken together these data suggest that PET is more sensitive than conventional imaging and has the potential to improve the early diagnosis of recurrent cervical cancer. Again, these data are limited by small sample sizes. In addition, it is unclear whether improved early diagnosis of extra-pelvic recurrent cervical cancer leads to improved patient outcomes except in the setting of patients who have not previously received radiation.

3.2.6. Tables

Table 5. Estimates of PET and comparator test(s) sensitivity and specificity with 95% confidence intervals for detection of pre-treatment metastases in newly diagnosed cervical cancer.

Study	**Sensitivity**	**95% Confidence Interval**	**Specificity**	**95% Confidence Interval**
Belhocine 2002 – PET	0.704	0.498-0.862	0.984	0.955-0.997
Reinhardt 2001 – PET – Pt	0.909	0.587-0.998	1.00	0.858-1.00
Reinhardt 2001 – PET – Node	0.809	0.581-0.946	0.993	0.974-0.999
Rose 1999 – PET – Node	1.00	0.715-1.00	1.00	0.541-1.00
Sugawara 1999 – PET	0.857	0.421-0.996	1.00	0.692-1.00
Yeh 2002 – PET	0.833	0.516-0.979	0.967	0.828-0.999
Lin 2003 – PET	0.857	0.572-0.982	0.923	0.749-0.991
Belhocine 2002 – CT or MRI	0.481	0.287-0.681	0.968	0.933-0.988
Reinhardt 2001 – MRI – Pt	0.727	0.390-0.940	0.833	0.626-0.952
Reinhardt – MRI – Node	0.667	0.430-0.854	0.970	0.943-0.987
Sugawara 1999 – CT	0.571	0.184-0.901	1.00	0.692-1.00
Rose 1999 – CT – Node	0.455	0.167-0.766	-	-

Table 6. Estimates of PET sensitivity and specificity with 95% confidence intervals for the detection of residual cervical cancer following treatment.

Study	**Sensitivity**	**95% Confidence Interval**	**Specificity**	**95% Confidence Interval**
Nakamoto 2002	1.00	0.478-1.00	0.600	0.323-0.837

Table 7. Estimates of PET and comparator test(s) sensitivity and specificity with 95% confidence intervals for detection of recurrent cervical cancer.

Study	**Sensitivity**	**95% Confidence Interval**	**Specificity**	**95% Confidence Interval**
Belhocine 2002 – PET	1.00	8.63-1.00	0.769	0.462-0.950
Park 2000 – PET	1.00	0.815-1.00	0.944	0.727-0.999
Sun 2001 – PET – local*	0.857	0.572-0.982	0.833	0.359-0.996
Sun 2001 – PET – lymph*	1.00	0.794-1.00	0.750	0.194-0.994
Sun 2001 – PET – para-aortic*	1.00	0.768-1.00	1.00	0.541-1.00
Sun 2001 – PET – distant metastasis*	1.00	0.3980-1.00	1.00	0.794-1.00
Ryu 2003 – PET	0.903	0.742-0.978	0.761	0.699-0.816
Belhocine 2002 – CT or MRI	0.480	0.278-0.687	0.846	0.546-0.981
Park 2000 – CT	0.778	0.524-0.936	0.833	0.586-0.964
Sun 2001 – PET – overall*	1.00	0.8240-1.00	0.00	0.00-0.975

3.2.7. Figures

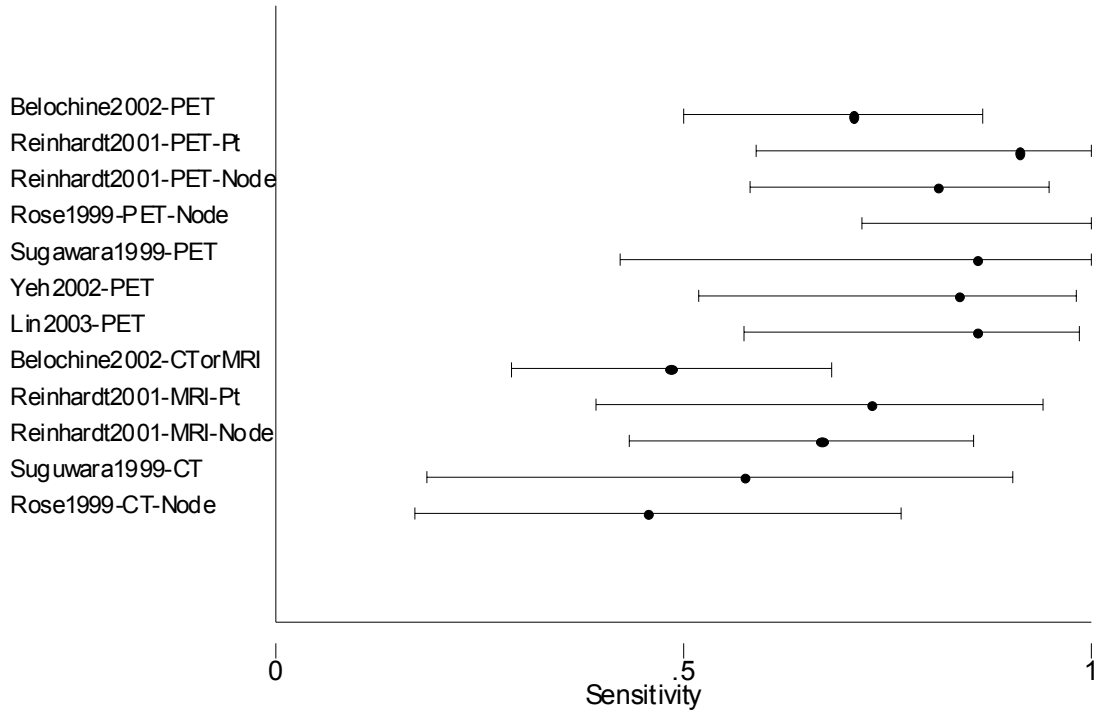

Figure 3a. Estimates of PET and comparator test(s) sensitivity with 95% confidence intervals for detection of pre-treatment metastases in newly diagnosed cervical cancer

<u>Legend</u>

Pt – Sensitivity assessed using patients as the denominator

Node – Sensitivity assessed using nodes as the denominator

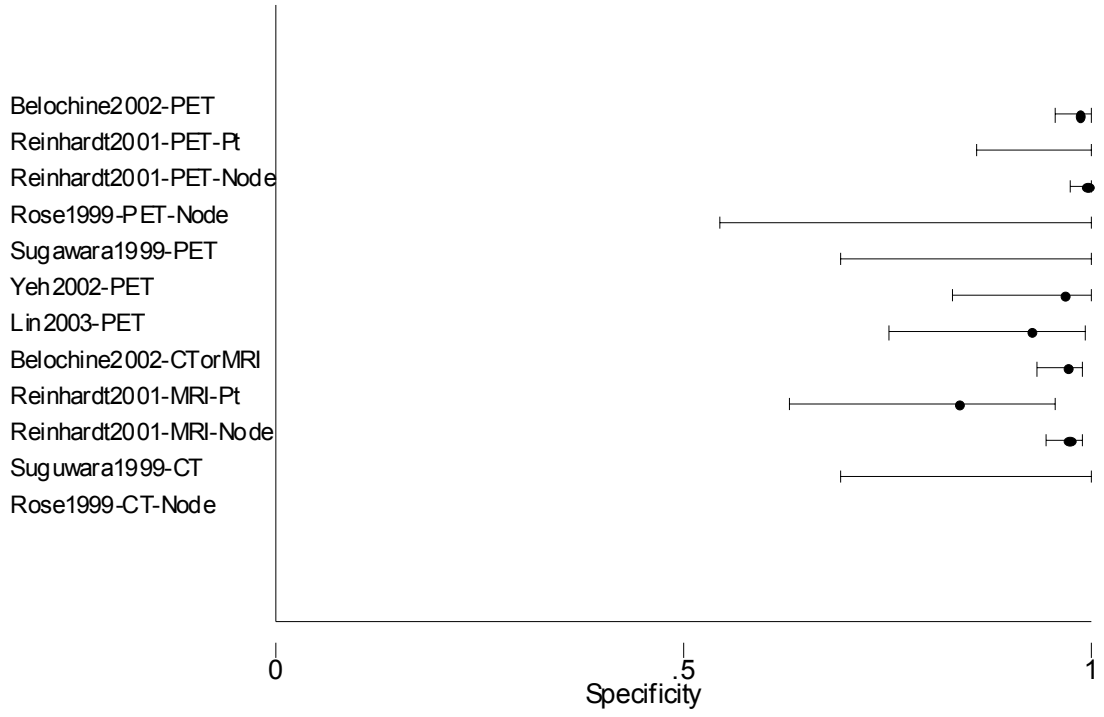

Figure 3b. Estimates of PET and comparator test(s) specificity with 95% confidence intervals for detection of pre-treatment metastases in newly diagnosed cervical cancer

<u>Legend</u>

Pt – Specificity assessed using patients as the denominator

Node – Specificity assessed using nodes as the denominator

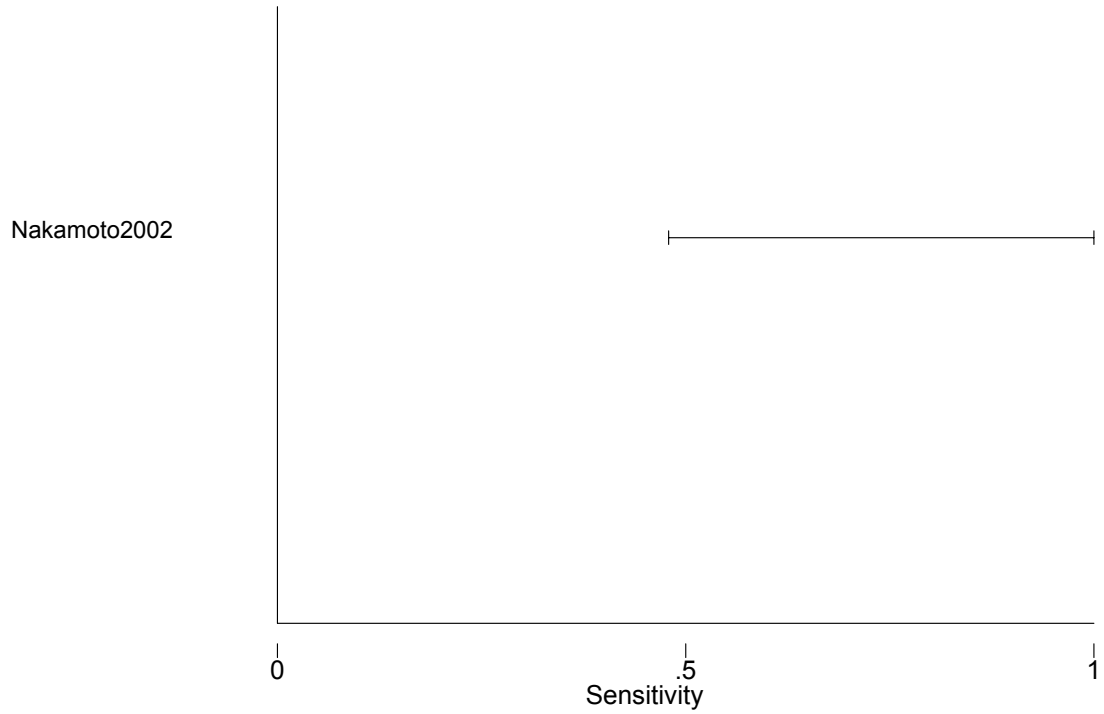

Figure 4a. Estimates of PET sensitivity with 95% confidence intervals for the detection of residual cervical cancer following treatment.

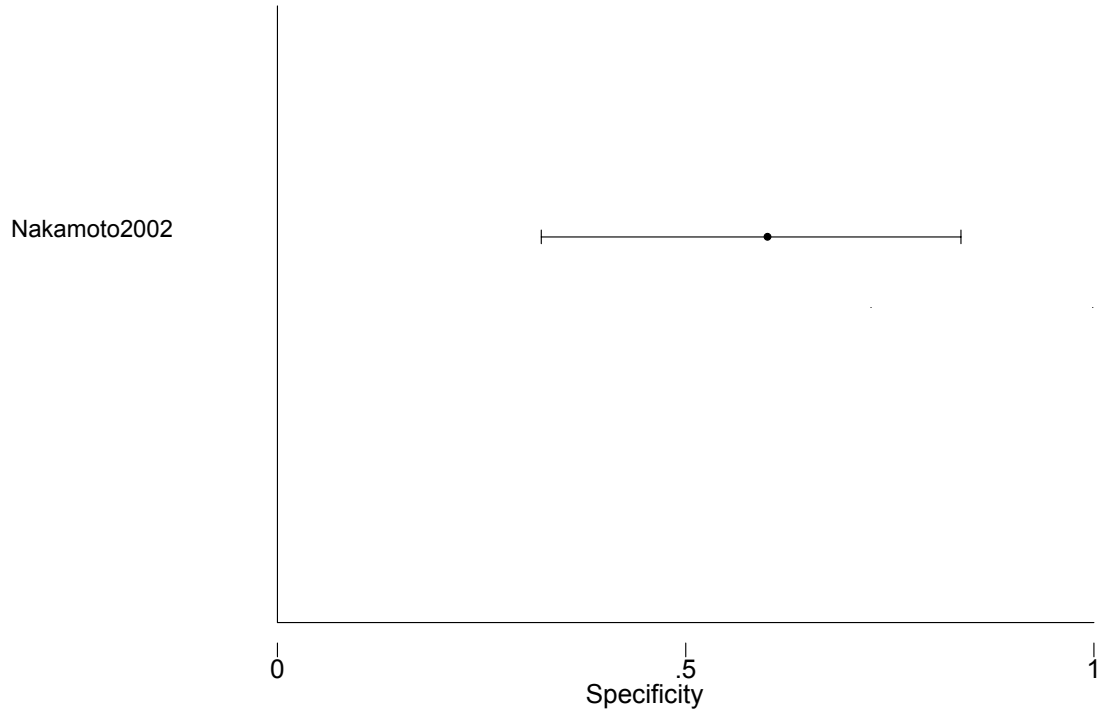

Figure 4b. Estimates of PET specificity with 95% confidence intervals for detection of residual cervical cancer following treatment.

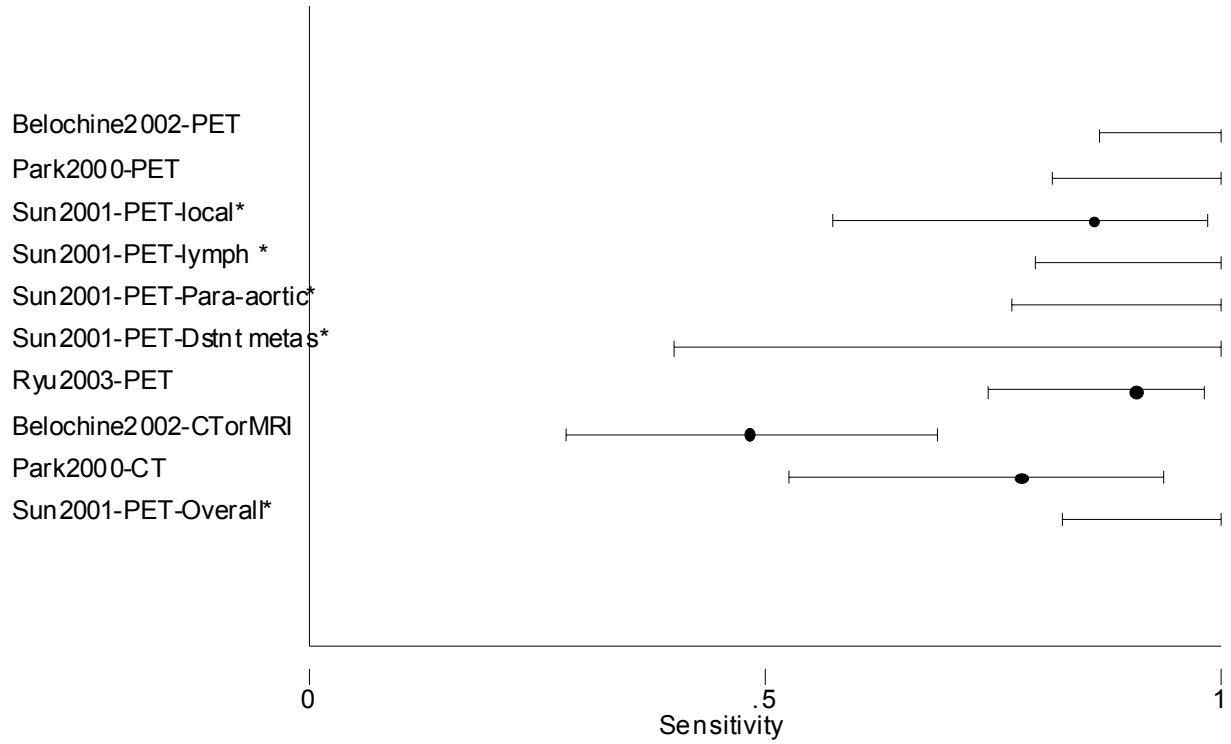

Figure 5a. Estimates of PET and comparator test(s) sensitivity with 95% confidence intervals for detection of recurrent cervical cancer.

<u>Legend</u>

* - site of recurrence (lymph nodes, para-aortic nodes)

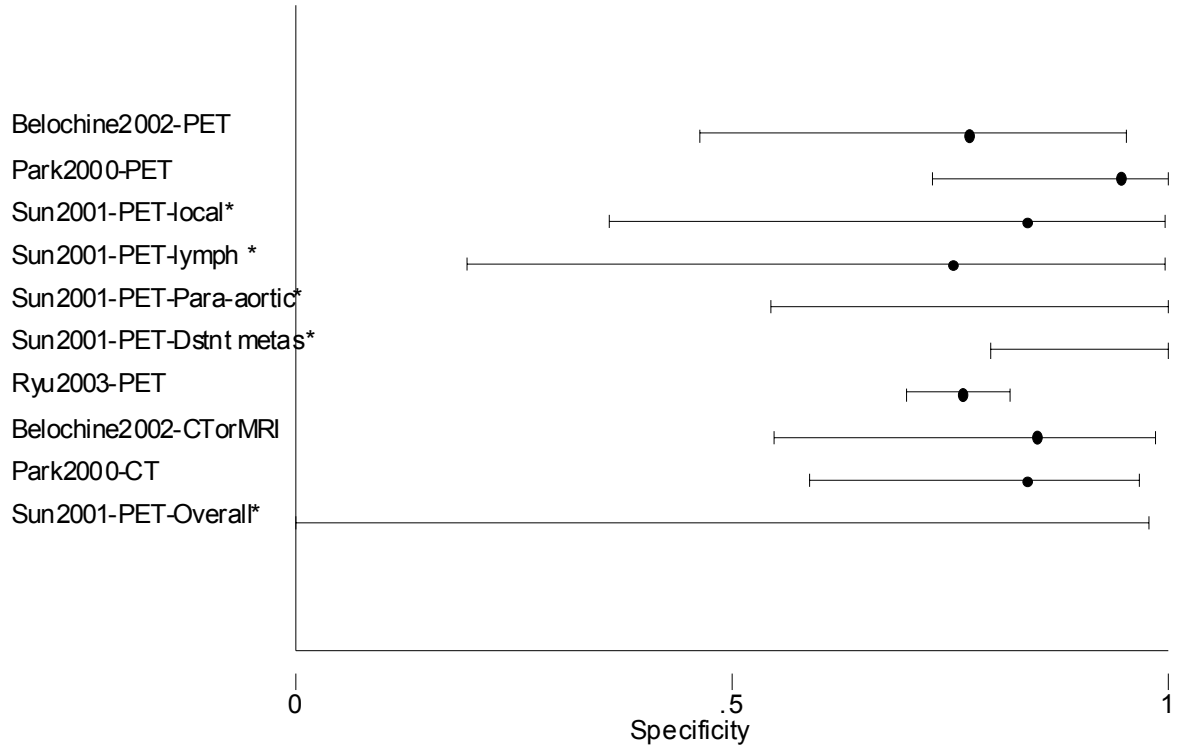

Figure 5b. Estimates of PET and comparator test(s) specificity with 95% confidence intervals for detection of recurrent cervical cancer

<u>Legend</u>

* - site of recurrence (lymph nodes, para-aortic nodes)

3.3. Ovarian Cancer

3.3.1. Background

Epithelial ovarian cancer affects over 25,000 and kills over 14,000 women in the United States yearly (Jemal, 2003). Since there is no accepted screening test for ovarian cancer and early stage disease is usually asymptomatic, the majority of patients are diagnosed at an advanced stage when cure is unlikely. While the 5 year survival for stage I disease is 80 to 90% (Bolis, 1995), patients with stage IV disease have median survivals of 10 to 40 months (Bristow, 1999; Curtin, 1997). The treatment of recurrent ovarian cancer is a challenging problem because it is almost never curable. The majority of patients who initially respond will develop chemotherapy-resistant disease and ultimately die. Thus the primary treatment objectives in the salvage setting are prolonging remission and maintaining quality of life.

3.3.2. CMS Statement of Work Questions

1. How does the diagnostic test performance of FDG-PET as an adjunct to conventional imaging (e.g., CT, MRI) compare to conventional imaging alone in the following clinical situations:
    a. In staging at the time of initial diagnosis?
    b. In detecting recurrent disease following treatment (surgery, radiation, chemotherapy, or combination)?

As a subset within this indication, does FDG-PET accurately and reliably detect recurrence in a patient with a history of ovarian cancer who has a rising CA-125 titer and a negative CT:

i. In determining if there has been a recurrence of the tumor?

ii. In localizing, if present, such recurrence?

iii. In yielding appropriate staging of such recurrence?

iv. In monitoring the effect of chemotherapy

3.3.3. Importance of Questions Posed by CMS in Clinical Management

1a. Performance of FDG-PET as an adjunct to conventional imaging compared to conventional imaging alone in staging at the time of initial diagnosis.

The standard treatment for newly diagnosed epithelial ovarian cancer is surgical staging with assessment for metastatic disease and cytoreduction followed by six to eight courses of platinum-based chemotherapy (McGuire, 1996). The current standard regimen consists of a platinum-based compound and a taxane (Ozols, 1997). Full surgical staging for ovarian cancer consists of hysterectomy, bilateral salpingo-oophorectomy, biopsies of multiple peritoneal sites including paracolic gutters, pelvis, and diaphragms, and pelvic and paraaotic lymph nodes.

Optimal cytoreduction for advanced disease at initial staging is associated with an improved overall survival (Hoskins, 1994). Patients who are known at diagnosis to have widespread metastases or massive ascites are less likely to achieve optimal cytoreduction at surgery. Patients with known advanced disease who are initially deemed medically at risk for surgical complications may benefit from chemotherapy alone or from chemotherapy followed by surgery after a clinical response has been achieved. Imaging studies, which correctly identify sites of metastasis at diagnosis, are potentially useful in determining a treatment plan for patients who are not felt to be good surgical candidates and for those who have been incompletely surgically staged.

1b. Performance of FDG-PET as an adjunct to conventional imaging compare to conventional imaging alone in detecting recurrent disease following treatment. As a subset within this indication, performance of FDG-PET in a patient with a history of ovarian cancer who has a rising CA-125 titer and a negative CT:

i. In determining if there has been a recurrence of the tumor

ii. In localizing, if present, such recurrence

iii. In yielding appropriate staging of such recurrence

Although recurrent ovarian cancer is almost never curable, early detection of recurrence affords a better chance of salvage treatment, which may result in prolonged remission and sustained quality of life. CA125 is a glycoprotein which is elevated in the serum of 85% of patients with epithelial ovarian cancer (Bast, 1983). Serum CA125 levels are often useful in detecting ovarian cancer recurrence (Canney, 1984). However, at least 10% of patients with advanced ovarian cancer do not have an elevation in CA125. In addition, although CA125 elevation is often useful in detecting recurrence, it is not helpful in localizing recurrent disease. Knowledge of the location of recurrence is helpful in tailoring salvage treatment. For example, a patient with a localized pelvic recurrence is a candidate for secondary cytoreductive surgery, while one with miliary peritoneal carcinomatosis would be better served by treatment with salvage chemotherapy. Conventional imaging modalities often give nonspecific results and are suboptimal for the reliable detection of peritoneal recurrence of ovarian cancer (Clarke-Pearson, 1986; Buist, 1994). Any imaging modality which significantly improves upon the accuracy of CT and MRI should have a place in the management of recurrent ovarian cancer.

1c. Performance of FDG-PET as an adjunct to conventional imaging compared to conventional imaging alone in monitoring the effect of chemotherapy.

CA125 is the most commonly used test to monitor responses to treatment for ovarian cancer (Bast, 1993; Hawkins, 1989). However, at least 10% of patients with advanced ovarian cancer do not have an elevation in serum CA125 at diagnosis. Intraperitoneal lesions are often difficult to monitor using conventional imaging modalities. Any imaging modality which improves upon the accuracy of CT and MRI should be useful in managing patients undergoing active treatment for ovarian cancer.

3.3.4. Results

The literature search identified 36 abstracts. Review of the abstracts identified 19 articles for full-text review. Of the 19 articles, 9 met the criteria for full text review and are discussed below. Data on the operating characteristics for the tests, including 95% confidence intervals are presented in tables and figures at the end of this section. Detailed evidence tables are available in Appendix D.

1a. PET for staging at initial diagnosis

There were no studies identified in the literature review that addressed this question.

1b. PET for detecting recurrence following treatment

Category 2: Diagnostic accuracy

<u>Quality Score 4-7</u>

Rose et al. (2001) prospectively studied 22 patients from Cleveland, OH with advanced stage ovarian or peritoneal cancer who had achieved complete clinical remission by radiologic and CA125 criteria following 6 cycles of chemotherapy. All patients underwent PET prior to second look laparotomy. The sensitivity and specificity of PET for detection of recurrence were 18% and 45%, respectively. A limitation of this study is

the lack of a comparator result and lack of defined criteria for determining PET positivity.

Nakamoto et al (2001) prospectively performed PET on 24 women with a history of ovarian cancer in Kyoto, Japan. Twelve patients had evidence of recurrence using either conventional imaging or tumor markers; 12 had no evidence of recurrence prior to PET. PET was classified as positive or negative qualitatively comparing the accumulation of FDG relative to normal tissue. Findings were confirmed by histology (n=11), clinical follow up greater than 6 months (n=12) or less than 6 months (n=1). PET alone had a sensitivity and specificity of 77% and 82% compared to 73% and 75% for conventional imaging by either CT or MRI. Among patients who were clinically disease free, the sensitivity and specificity of PET were 67% and 89%, compared to 80% and 50% when there was clinical suspicion for recurrence. When PET and conventional imaging results were combined, overall sensitivity and specificity improved to 92% and 100%. An important limitation of this study is that PET and CT/MRI were not performed on the same patients, limiting the ability to determine if improvements in PET were due to superior performances or differences in underlying patient characteristics that may be correlated with positive PET outcomes, such as severity of disease.

Karlan et al (1993) performed PET on 13 women with a history of ovarian (n=12) or fallopian tube (n=1) cancer prior to laparotomy in Los

Angeles, CA. Six patients were clinically disease free at the time of PET and 7 were suspected of having recurrence based on elevated tumor markers, conventional imaging, or physical examination. One patient did not have surgery and is excluded from analysis. PET was classified as positive or negative qualitatively by determining whether uptake was higher than the surrounding area. 11/12 (91%) patients were diagnosed with recurrence at laparotomy. The sensitivity and specificity of PET for detection of recurrent disease were 55% and 100%, respectively. PET missed microscopic residual tumor in 5 patients. A limitation of this study is the lack of a comparator test.

Zimny et al (2001) retrospectively reported 106 PET scans performed on 54 patients with a history of ovarian cancer in Aachen, Germany. Disease recurrence was suspected in 58 cases based on tumor markers, conventional imaging, or physical examination. In 48 cases patients were clinically disease free. PET results were classified as positive or negative using a 5-point scale. Assessment of the accuracy of PET was based on histology (n=37), clinical follow up with median follow up at least 12 months (n=66), or concordant positive CA-125 and conventional imaging (n=3). The sensitivity and specificity of PET for detection of recurrent disease were 83% and 83%, respectively. PET was less accurate among patients in whom recurrence was not suspected, (sensitivity 65% and accuracy 71%), than among patients in whom recurrence was suspected (sensitivity

94%, accuracy 93%). However, among clinically disease-free patients who went on to develop recurrent disease, a positive PET result preceded the diagnosis of recurrence by conventional means by a median of 6 months. A limitation of this study is lack of a comparator test.

Yen et al (2001) performed PET on 24 women with suspected ovarian cancer recurrence in Taipei, Taiwan. All patients also underwent either CT or MRI and serum CA125. Findings were verified by histology (n=16) or clinical follow up (n=8). No minimum clinical follow up was specified. The authors reported the sensitivity and specificity for detection of recurrent ovarian cancer by PET, 91% and 92%; by conventional imaging, 91% and 46%; by CA125, 91% and 77%. When patients with no specified clinical follow up are excluded from analysis, sensitivity and specificity are as follows: PET, 90% and 83%; conventional imaging, 90% and 50%; CA125, 90% and 50%. The higher specificity indicates a potential role for PET in confirming suspicious conventional imaging studies or elevated CA-125 therapy prior to initiating therapy or confirmatory surgery. A limitation of this study is the lack of defined criteria for determining PET, CT/MRI and CA-125 test positives and negatives. In addition, length of time for clinical follow-up was not specified.

Torizuka et al (2002) compared PET to conventional imaging and CA125 in 25 patients from Hirakuchi, Japan with suspicion for recurrent ovarian cancer based on elevated CA125 or abnormal findings at

conventional imaging. PET results were determined using increased FDG uptake for foci, relative to background. Diagnostic accuracy was assessed using histology or clinical follow up greater than 6 months. The sensitivity and specificity of PET for detection of recurrence were 80% and 83%, compared to 55% and 83% for conventional imaging and 75% and 100% for CA125. Among 15 patients with true positive CA125 elevation, PET detected recurrence in 86% compared to 53% for conventional imaging. This study suggests that PET may contribute to localization of disease among patients with elevated CA125 and negative or equivocal conventional imaging studies.

Cho et al (2002) retrospectively studied 31 patients who underwent PET prior to second look surgery for ovarian cancer. PET was categorized as positive or negative qualitatively using visual analysis and quantitatively using SUV results. The degree of clinical suspicion for recurrence was not stated in the text. 21 patients also underwent CT prior to surgery. Diagnostic accuracy was based on histology only with biopsies at each of 15 intra-abdominal sites performed if grossly negative. Fifty two percent (11/21) of patients who underwent both PET and CT were diagnosed with recurrence. The sensitivity and specificity of PET for detection of recurrence were 82% and 90%, compared to 100% and 90% for CT alone and 100% and 90% for the combination of PET and CT.

Chang et al (2002) evaluated 28 patients with a history of stage II-IV ovarian cancer who had an elevated CA125 but negative or equivocal conventional imaging studies. Accuracy of PET was evaluated by histology (n=22) or clinical follow up greater than 1 year (n=6). PET had sensitivity and specificity of 95% and 87%, respectively, for detection of recurrence. This study suggests that PET may be helpful in identifying recurrent ovarian cancer when recurrence is suspected based upon CA125. Limitations of the study are lack of defined criteria for determining PET positivity and lack of a comparator test.

Quality Score 0-3

Hubner et al (1993) performed PET on 14 patients with a history of ovarian cancer in Knoxville, TN. The timing of PET in relation to the original diagnosis, as well as the length of follow up, is unclear. PET was performed qualitatively and quantitatively using visual interpretation and SUV calculations. Results were confirmed by histology. The authors reported the sensitivity and specificity of PET to detect recurrence to be 91% and 100%, respectively. Limitations of the study are lack of details regarding the patient population and inclusion criteria, as well as lack of a comparator test.

Jimenez-Bonilla (2001) performed PET in 20 patients with a history of ovarian cancer in whom recurrence was suspected based on elevated

tumor markers. All patients had CT or MRI studies which were negative or equivocal for recurrence. Confirmation of PET findings was available for 14 patients and was by surgical biopsy or clinical observation. The sensitivity and specificity of PET for detection of recurrence were 100% and 50%, respectively. This study was weakened by a failure to designate the length of clinical follow up as well as a lack of blinding of radiologists and failure to define criteria for PET interpretation.

There were no Category 3 through 6 studies identified in the literature review that addressed this question. In addition, none of the articles mentioned blinding of the pathologist or “gold standard” reader.

1c. PET for monitoring effect of chemotherapy

There were no studies identified in the literature review that addressed this question.

3.3.5. Conclusions

1a. PET for staging at initial diagnosis

There were no studies identified which provided evidence for the utility of PET in the initial staging of ovarian cancer.

1b. PET for detecting recurrence following treatment

Two studies of patients undergoing second look laparotomy without clinical evidence of recurrence demonstrate that PET is not sensitive for the detection of microscopic residual disease (Rose, 2001; Karlan, 1993). Other retrospective studies (Nakamoto, 2001; Yen, 2001; Cho, 2002; Zimny, 2001) show that PET has similar sensitivity and specificity to conventional imaging in the detection of recurrent ovarian cancer, and that PET is generally more sensitive when there is a clinical suspicion of recurrence. Since increased sensitivity is more useful for ruling out disease, this also suggests that a negative PET is not particularly useful for reassurance in the setting of a low level of clinical suspicion. Two studies (Chang, 2002; Torizuka, 2002) provide some evidence that PET is helpful for detecting recurrence when CA125 is elevated despite negative conventional imaging. Taken together, these studies suggest that PET is not expected to be useful in the routine surveillance of patients with a history of ovarian cancer. However, there is fair evidence to support the use of PET for the detection of recurrent ovarian cancer when the CA125 is

elevated and conventional imaging is negative or equivocal. An adequately powered prospective study to confirm this, ideally with survival as one of the primary outcomes, would be very helpful.

1c. PET for monitoring effect of chemotherapy

There were no studies identified which provided evidence for the utility of PET in monitoring the response to chemotherapy for ovarian cancer.

3.3.6. Tables

Table 8. Estimates of PET and comparator test(s) sensitivity and specificity with 95% confidence intervals for detecting recurrence following treatment for ovarian cancer.

Study	**Sensitivity**	**95% Confidence Interval**	**Specificity**	**95% Confidence Interval**
Chang 2002 – PET	0.950	0.7510-0.999	0.875	0.473-0.997
Cho 2002 – PET	0.818	0.482-0.977	0.900	0.555-0.997
Cho 2002 – PET and CT	1.00	0.715-1.00	0.900	0.555-0.997
Hubner 1993 – 1st PET	0.909	0.587-0. 998	1.00	0.292-1.00
Jiminez-Bonilla 2000 – PET	1.00	0.735-1.00	0.500	0.0126-0.987
Karlan 1993 – PET	0.545	0.234-0.833	1.00	0.0250-1.00
Nakamoto 2001 – PET – Clin. Dx. Free	0.667	0.0943-0.992	0.889	0.518-0.997
Nakamoto 2001 – PET – Clin. Susp.	0.800	0.444-0.975	0.500	0.0126-0.987
Nakamoto 2001 – PET – all	0.769	0.462-0.950	0.818	0.482-0.977
Nakamoto 2001 – PET and CT or MRI	0.923	0.640-0.998	1.00	0.478-1.00
Rose 2001 – PET	0.182	0.0228-0.518	0.455	0.167-0.766
Torizuka 2002 – PET	0.800	0.563-0.943	0.833	0.359-0.996
Yen 2001 – PET	0.909	0.587-0.998	0.923	0.640-0.998

Zimny 2001 – PET	0.830	0.734-0.901	0.833	0.586-0.964
Cho 2002 – CT	1.00	0.715-1.00	0.900	0.555-0.997
Jiminez-Bonilla 2000 – CT	0.00	0.00-0.265	1.00	0.158-1.00
Nakamoto 2001 – CT or MRI	0.727	0.390-0.940	0.750	0.194-0.994
Torizuka 2002 – CT	0.55	0.315-0.769	0.833	0.359-0.996
Yen 2001 – CT or MRI	0.909	0.587-0.998	0.462	0.192-0.749
Torizuka 2002 – CA125	0.750	0.509-0.913	1.00	0.478-1.00
Yen 2001 – CA125	0.909	0.587-0.998	0.769	0.462-0.950

3.3.7. Figures

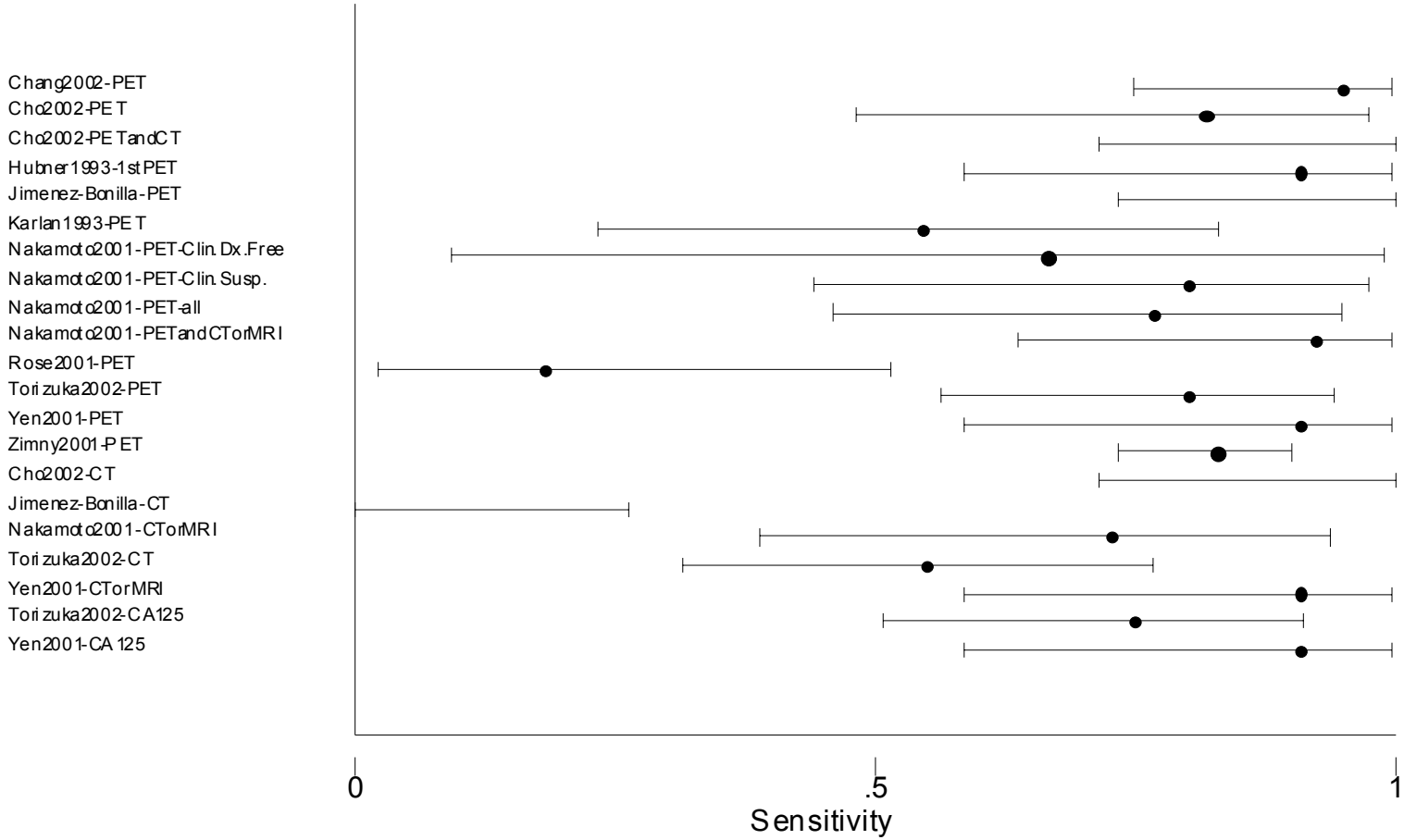

Figure 6a. Estimates of PET and comparator test(s) sensitivity with 95% confidence intervals for detecting recurrence following treatment for ovarian cancer

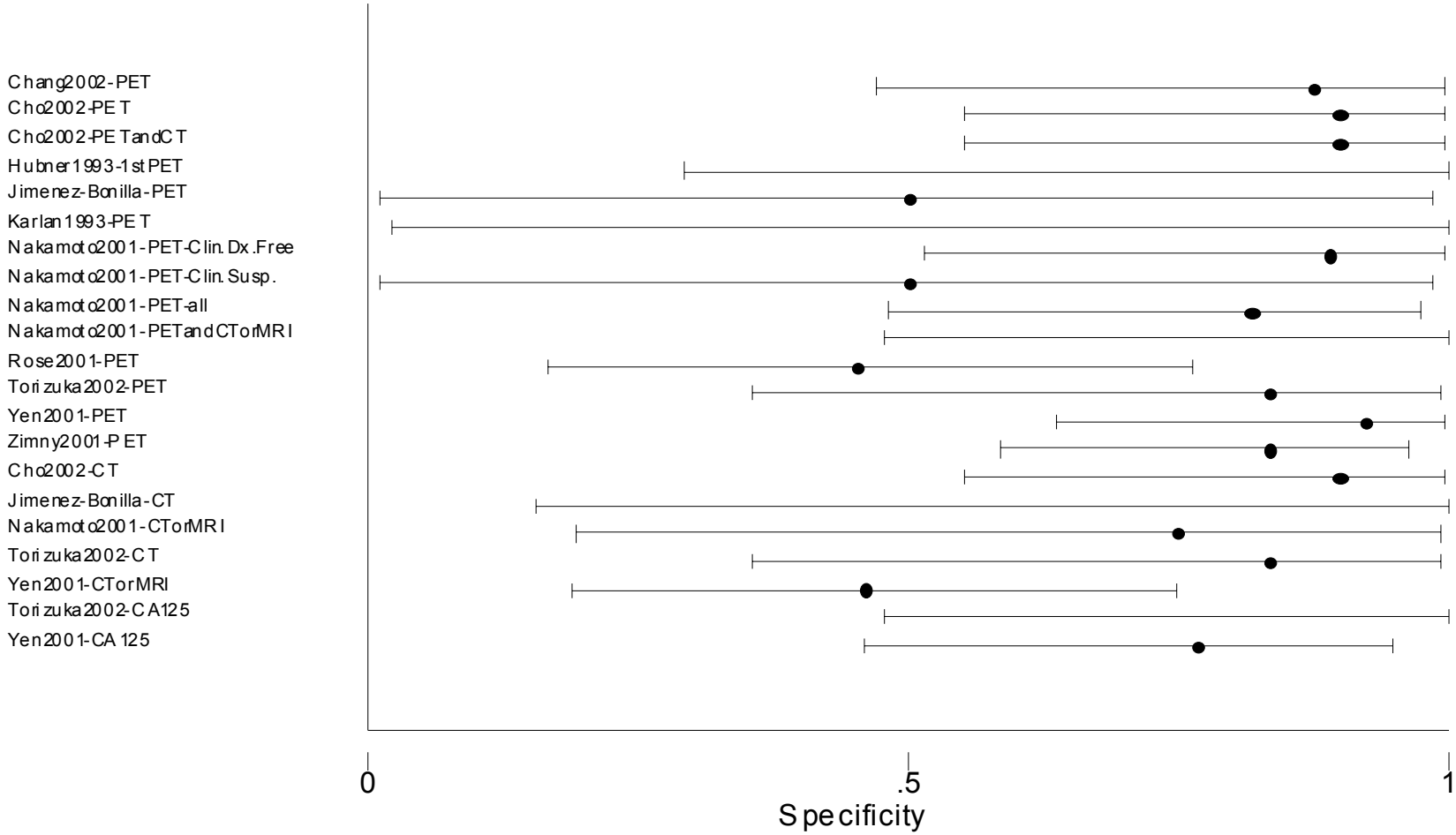

Figure 6b. Estimates of PET and comparator test(s) specificity with 95% confidence intervals for detecting recurrence following treatment for ovarian cancer

3.4. Pancreatic Cancer

3.4.1. Background

Pancreatic cancer, the fourth most common cause of cancer deaths, has a very poor prognosis with a 3% five-year survival rate (Warshaw, 1992) accounting for 30,000 deaths yearly (American Cancer Society, 1995). Most patients, almost 80%, die within one year of diagnosis (Evans, 1997). High mortality rates are related to the highly aggressive nature of the tumor, the nonspecific symptoms leading to late presentations, and the diagnostic limitations of current imaging modalities (Maringini, 1993). Because pancreatic tumors have a good prognosis when detected early, before metastases, imaging studies that can easily detect small isolated lesions would be valuable. The limitations of our current imaging studies include difficulty detecting small lesions in the pancreas and difficulty in differentiating pancreatic carcinoma from mass-forming pancreatitis. The latter is especially troublesome, since chronic pancreatitis is a risk factor for the development of pancreatic carcinoma. In addition, there is room for improvement in tumor staging, as up to 40% of patients with pre-operatively localized disease are found to have inoperable invasive disease at laparotomy (Warshaw, 1992). Five year survival for resectable disease, after pancreaticoduodenectomy, improves to >20% (Trede, 1990). While

the morbidity and mortality of this procedure is high, in carefully selected patients mortality is only 3% (Trede, 1990).

3.4.2. CMS Statement of Work Questions

1. How does the diagnostic test performance of FDG-PET as an adjunct to conventional imaging (e.g., CT, MRI, endoscopic ultrasound) compare to conventional imaging alone in the following clinical situations:
    a. In differentiating benign from malignant pancreatic lesions?
    b. In detecting metastatic pancreatic cancer?
2. If adjunctive use of FDG-PET is superior to conventional imaging alone for detection of metastatic pancreatic cancer, for what subpopulation(s) of patients has this superiority been shown?
3. How does FDG-PET compare to conventional imaging (e.g. MRI, CT) for detection of residual or recurrent disease following treatment of primary pancreatic cancer?

3.4.3. Importance of Questions Posed by CMS in Clinical Management

1. Performance of FDG-PET as an adjunct to conventional imaging compared to conventional imaging alone in the following clinical situations:

    a. In differentiating benign from malignant pancreatic lesions.

Differentiating benign from malignant pancreatic lesions has been particularly difficult as some episodes of pancreatic inflammation take on the shape of a mass. This mass-forming pancreatitis is of particular concern since it is frequently present in the patient population being investigated. While very severe cases of pancreatitis may require surgical management, most cases can be managed without the morbidity associated with pancreatectomy. Therefore, early and accurate differentiation of these two processes can prevent invasive and potentially harmful procedures.

    b. In detecting metastatic pancreatic cancer.

Differentiating localized from metastatic pancreatic tumors has also been particularly difficult, especially identification of regional lymph node or liver involvement. Since these lesions are typically quite small, resolution with conventional imaging (CT, MRI, ultrasound (US)) has been limited (Maringini, 1993). The potential benefit of PET in this situation is a reflection of its unique imaging technique. Metabolic abnormalities are

theoretically not as dependent upon tumor size as anatomical abnormalities and therefore, PET should better detect small lesions than other radiological imaging studies. Pre-operative determination of localized versus metastatic disease is important for both prognosis and treatment. Localized tumors are amenable to cure with resection while metastatic disease has very high fatality and low response rates. Resection in these patients exposes them to a significant surgical morbidity and mortality without much benefit.

2. Subpopulation(s) of patients for which FDG-PET is superior to conventional imaging.

Accurate staging by conventional tests may be affected by the size and location of metastatic lesions. Characterizing PET's performance in these select sub-populations is an important step in the search to avoid unnecessary surgical procedures. Metastatic lesions are often small and difficult to detect, up to 40% of those with pre-operative stage I disease, have metastases detected at laparotomy (Warshaw, 1992). If PET is better than CT at detecting small lesions, it could play a vital role in avoiding surgical procedures when pre-operative conventional imaging tests are negative. Despite, the advantages of tumor metabolism based imaging, there are disadvantages. One of these is poor delineation of anatomical structures. This limitation may prevent PET from adequately differentiating

localized and locally invasive primary tumors. If PET is used in conjunction with anatomical imaging this may not be an issue; however, a comparison of PET alone to CT or MRI would help to clarify its role in this population.

3. FDG-PET compared to conventional imaging for detection of residual or recurrent disease following treatment of primary pancreatic cancer.

Differentiating recurrent or residual tumor after primary pancreatic tumor treatment is very important for prognosis and ultimately therapeutic options. Those with evidence of tumor regression after chemotherapy and radiation may respond well to resection, while those without regression may not. Therefore, surgical options for these patients will rely upon the ability to identify responders. Using PET, smaller incremental changes in tumor size may be detectable as metabolism is hypothesized to be less dependent upon tumor size than anatomical imaging tests; therefore an assessment of PET compared to conventional imaging for identification of treatment responders is important.

3.4.4. Results

The literature search identified 66 abstracts. Review of the abstracts identified 55 articles for full-text review. Of the 54 articles, 24 met the criteria for full text review; however, the populations were unique in only

twenty-one. Rose used the same population as Delbeke but performed a new analysis of residual or recurrent disease after primary therapy. Frolich (1999) and Stollfus (1995) used the same populations as described by Diederichs (1999) and Friess (1995), respectively, without adding new information. These two studies were therefore, excluded from further assessment. Data on the operating characteristics for the tests, including 95% confidence intervals are presented in tables and figures at the end of this section. Detailed evidence tables are available in Appendix D.

1a. Diagnostic test performance as an adjunct to conventional imaging in differentiating benign from malignant pancreatic lesions

Category 4: Therapeutic choice impact.

Quality score 4-7

Sperti (2001) performed a blinded (radiologist and pathologist) prospective study in Padua, Italy. They enrolled 56 patients with suspected cystic pancreatic tumor or intraductal hypersecreting mucinous pancreatic tumor. Further details regarding prior history and imaging studies for these patients were not provided. All patients received PET, CT, and tumor marker (CA 19-9) evaluation. PET was performed with the Siemens ECAT-EXACT 47 60 minutes after injection with 12 mCi of ^{18}FDG. Patients were fasted overnight. Tumor presence was defined qualitatively with visual assessment of focally increased tracer uptake and quantitatively with a

SUV > 2.4. Histology was used as the gold standard in all but one patient who was followed clinically for more than 6 months. PET scans impacted further patient evaluation by avoiding laparotomy (6 patients), or pancreatectomy (18 patients), or splenectomy (9 patients) in those who were asymptomatic and had negative PET scans. Tumor prevalence was 30%.

Quality score 0-3

Kalady (2002) performed a blinded (radiologist only) retrospective study in Durham, NC. They included 54 patients with pancreatic mass by prior imaging study who were evaluated with both an abdominal CT and PET scan. Because patients did not receive PET unless they had a previous abnormal imaging study assessment of PET is really an assessment of PET as an adjunct to CT. Differences between this population and those with suspected pancreatic cancer who were not evaluated with both studies were not mentioned. PET was performed with the GE Advance 60 minutes after injection of 10 mCi of ^{18}FDG. Patients were fasted for 4 hours. Tumor presence was defined qualitatively by visual assessment of focally increased tracer uptake greater than background and quantitatively with SUV on 18 of the patients. No SUV cut-off was suggested. Histology was used as the gold standard for 47 patients and clinical follow-up greater than 6 months for 7. The sensitivity and specificity for visually assessed PET scans were 88% and 92%, respectively. For CT

scan the sensitivity was 90% and the specificity 62%. PET identified one patient with pancreatic cancer that was missed by CT scan although the management did not change. It also identified 4 patients with benign disease that were misclassified by CT as having cancer, thus sparing them unnecessary laparotomy. However, it missed 3 cancers that were picked up on CT. PET provided no additional information for either local extension or nodal metastases over that provided by CT. Tumor prevalence was 76%. A limitation of the study is that no SUV cut-off was presented.

Category 2: Diagnostic accuracy

Quality score 4-7

Sperti (2001) performed a prospective study in Padua, Italy of 56 patients with suspected cystic pancreatic tumor or intraductal hypersecreting mucinous pancreatic tumor. This study was previously described in detail for category 4. Please refer to this discussion for more details. Using an SUV cut-off of 2.4, sensitivity for PET was 94% and the specificity 97%. CT had a sensitivity of 65% and specificity of 87%, while CA 19-9 had a sensitivity of 65% and a specificity of 90%.

Imdahl (1999) performed a prospective blinded (radiologist only) study in Freiberg, Germany. They enrolled 48 consecutive patients, 42 with pancreatic disease (pancreatic mass or pancreatitis) and 6 controls. All patients received both PET and CT and 36 received ERCP. PET was

performed with the Siemens CTI ECAT-EXACT 90 minutes after injection of 350 MBq of ^{18}FDG. No mention of glucose monitoring was made. Tumor presence was defined by an SUV > 4.0 or qualitatively by visual assessment of a focally increased uptake. Histologic diagnosis from biopsy or laparotomy was used as the gold standard. When comparing tumor versus non-tumor (ie both normal and pancreatitis patients considered tumor negative) the sensitivity of CT, ERCP, and PET were 81%, 85%, and 96% respectively. The specificity for each was 95%, 81%, and 100% respectively. Tumor prevalence in the patient population was 56%.

Sendler (2000) performed a prospective blinded (radiologist only) study in Munich, Germany. They enrolled 42 non-consecutive patients referred to a surgical center after identification of a pancreatic mass (imaging study not specified). All patients received PET, CT and US. Because patients did not receive PET unless they had a previous abnormal imaging study, the assessment of PET is really an assessment of PET as an adjunct imaging test. PET was performed with the Siemens ECAT 951R/31 after injection of 270-390 MBq of ^{18}FDG. Time between radiotracer injection and image acquisition was not specified. Patients were fasted overnight. Tumor presence was defined qualitatively by a score > 3 on a 5 point visual scale with 1 being decreased uptake compared to background and 5 being intense focal uptake. SUVs were calculated but no cut-off for tumor diagnosis was suggested. Histology or at least six months

of clinical follow-up were used as the gold standard. The sensitivity of CT, US, and PET were 74%, 54%, and 71% respectively. The specificity for each was 73%, 55%, and 64% respectively. Tumor prevalence in the patient population was 74%. If an SUV cut-off of 2.5 was used then PET sensitivity was 72% and specificity was 71%.

Diederichs (1999) performed a retrospective study on 162 non-consecutive patients referred to the department of surgery in Ulm, Germany for pancreatic resection. All patients received imaging with CT, ERCP, and PET. PET was performed with the Siemens CTI ECAT 931/08/12 60 minutes after injection of 85-448 MBq of ^{18}FDG. Patients were fasted for 12 hours. Tumor presence was defined qualitatively by focally increased tracer uptake. SUVs were calculated but no cut-off suggested. Histology or at least six months of clinical follow-up were used as the gold standard. Sensitivity and specificity were only provided for a subgroup of 123 patients with fasting glucose < 130 and normal c-reactive protein levels. In addition, indeterminate studies were removed from the calculation of sensitivity and specificity. CT had a sensitivity of 88% and specificity of 73% with 20 excluded indeterminate results. ERCP had a sensitivity of 95% and specificity of 91% with 22 excluded indeterminate results. PET had a sensitivity of 88% and 87% with 1 excluded indeterminate result. The sensitivity and specificity of both CT and ERCP would be significantly altered by the inclusion of these indeterminate

studies however insufficient information was provided to re-calculate the results. Tumor prevalence in the sub-group of patients evaluated was 54%.

Friess (1995) performed a prospective blinded study in Berne, Switzerland and Ulm, Germany. They enrolled 80 patients with either histologically proven pancreatitis or pancreatic carcinoma admitted to their hospital for pancreatic surgery and 10 normal controls. All patients received PET and all but 6 received CT. The 6 who did not receive a CT scan all had pancreatic carcinoma. PET was performed with the Siemens CTI ECAT 931/08 45 minutes after injection of 250-350 MBq of ^{18}FDG. Patients were fasted for 6 hours. Tumor presence was defined qualitatively by focally increased tracer uptake. SUVs were calculated but no cut-off suggested. Histologic diagnosis was used as the gold standard. The sensitivity and specificities were calculated for the 80 patients with pancreatic disease but do not include the 10 normal controls. Sensitivity and specificity for CT was 79% and 60% respectively, and for PET was 98% and 88% respectively. Tumor prevalence was 60% for the entire population and 57% in those who received CT. SUVs for pancreatitis and pancreatic carcinoma overlapped although the medians were significantly different at 3.09 (+/- 2.18) and 0.87 (+/- 0.56) respectively. Though described as a “blinded” study this was not defined in the report.

Zimny (1997) performed a retrospective study of 122 patients suspected of having pancreatic carcinoma by clinical, laboratory, or

imaging studies in Aachen, Germany who underwent PET imaging. No further details were provided regarding patient presentation or inclusion criteria. PET was performed with the Siemens ECAT 953/15 40 min after injection of 190 MBq of ^{18}FDG. Patients were fasted for 12 hours. Tumor presence was defined qualitatively by visual assessment of focally increased radiotracer uptake and quantitatively by an SUV > 2.9. Histology or at least 6 months of clinical follow-up were used as the gold standard. Using SUV values the sensitivity and specificity for PET was 89% and 53% respectively. In the sub-population of euglycemic patients sensitivity was 91% and specificity 52% while in the hyperglycemic population sensitivity was 85% and specificity was 71%. Tumor prevalence was 70% for the entire population, 65% for the euglycemic population and 79% for the hyperglycemic population. Limitations of the study are lack of a comparator test and no mention of blinding for the radiologist or pathologist/gold standard reader.

Bares (1994) performed a prospective study in Aachen, Germany. They enrolled 40 patients with either a pancreatic mass on CT or chronic pancreatitis with recurrent abdominal pain and no mass on CT. All patients received CT, US, and PET. PET was performed with the Siemens CTI ECAT 953/15 45 minutes after injection of 150-300 MBq of ^{18}FDG. Patients were fasted for 12 hours. Tumor presence was defined qualitatively by focally increased radiotracer uptake that exceeded the background liver

uptake. Quantitative measurements were taken using the tumor-liver ratio (TLR) = ratio of enhancement in region of interest to enhancement in the liver and the differential uptake ratio (DUR) = enhancement in region of interest (uCi/mL) divided by the total injected dose per body weight (uCi/kg). While the TLR and DUR were calculated and compared no cut-off was suggested for tumor diagnosis. Histology in 37 patients and clinical follow-up in 3 patients were used as the gold standard. Using visual assessment the sensitivity and specificity of each test were: CT 100% and 23%; US 75% and 33%, and PET 92% and 85% respectively. The DUR for malignancy was 6.4 +/- 3.2 and for chronic pancreatitis was 3.2 +/- 0.9. The TLR for malignancy was 2.5 +/- 1.9 and for chronic pancreatitis 1.0 +/- 0.4. Both the DUR and TLR overlapped in benign and malignant disease and when using a ROC curve did not add information to that obtained using visual analysis. There was no correlation between uptake, TLR, or tumor size.

Papos (2001) performed a non-blinded study of 22 patients in Hungary. Patients were included if they presented with clinical symptoms suggestive of pancreatic carcinoma such as abdominal pain and weight loss. They were excluded if they had acute pancreatitis, as diagnosed by an elevated serum amylase. All patients received PET and CT. 21 patients received US, 20 received serum tumor markers (CA 19-9), and 18 received ERCP. The difference in patients who received all the tests and those who

only received some of the tests was not discussed. Pet was performed with the GE 4096 plus 60 minutes after injection of 232-418 MBq of ^{18}FDG. Patients were fasted overnight. Tumor presence was defined as visually increased tracer uptake. Histology or clinical follow-up greater than 6 months were used as the gold standard. The sensitivity and specificity for each study were as follows: CT 100% and 56%, US 100% and 50%, CA 19-9 80% and 73%, ERCP 60% and 92%, and PET 100% and 87.5%. Tumor prevalence was 27% for the full patient population.

Keogan (1998) performed a blinded (radiologist only) prospective study in Durham, NC. They enrolled 37 patients with either known or suspected pancreatic carcinoma. Pancreatic carcinoma was suspected when a prior CT or ERCP suggested the presence of a pancreatic mass or dilated pancreatic duct. Because patients did not receive PET unless they had a previous abnormal imaging study assessment of PET is really an assessment of PET as an adjunct to CT or ERCP. All patients received PET, 36 received CT, and 22 received ERCP. The difference in patients who received all the tests and those who only received some of the tests was not discussed. PET was performed with the GE Advance 60 minutes after injection of 10 mCi of ^{18}FDG. Patients were fasted for 4 hours. Tumor presence was defined qualitatively by visually increased tracer uptake and quantitatively with a standardized uptake ratio (SUR). The SUR is equivalent the SUV and is calculated the same. No cut-off was suggested

for tumor diagnosis using the SUR. Histology was used as the gold standard. The sensitivity and specificity for each study were as follows: CT 75% and 83%, ERCP 86% and 38%, and PET 88% and 83%. The SURs were displayed on a scattergram. The means appeared to be around 1.8 for benign disease and 5.6 for malignancy. The difference in the means was reported to be 3.167 with the 95% CI for malignancy being +/- 4.52. This results in an overlap of values from patients with malignancy and those without malignancy. Tumor prevalence was 68%.

Ho (1996) performed a study of 14 patients in St Louis, MO. Inclusion and exclusion criteria were not described for this patient population; however all patients had received an abdominal CT scan with either an indeterminate mass (12 patients) or typical mass (2 patients) found in the pancreas. Because patients did not receive PET unless they had a previous abnormal imaging study assessment of PET is really an assessment of PET as an adjunct to CT. All patients received PET with either the Super PET-IIB (8 patients) or the Siemens ECAT-EXACT (6 patients). PET was performed 45 minutes after injection of 10 mCi of ^{18}FDG. Patients were fasted for 6 hours. Tumor presence was defined visually by focally increased tracer uptake or by a SUV > 2.4. The gold standard used was histology in 12 patients and clinical follow-up greater than 6 months in 2 patients. PET had a sensitivity of 100% and specificity of 67%. Tumor prevalence was 57%.

Delbeke (1999) performed an unblinded prospective study of 65 patients in Nashville, TN. Consecutive patients with suspected pancreatic carcinoma were enrolled if they had received both PET and CT. Criteria for suspected pancreatic carcinoma were not defined. Differences in the population of all those with suspected pancreatic cancer and the subset who received both PET and CT were not mentioned. PET was performed with the Siemens ECAT-EXACT 933/08/16 60 minutes after injection of 370 MBq of ^{18}FDG. Patients were fasted for 4 hours. Tumor presence was defined qualitatively by visual assessment of focal tracer uptake greater than uptake in the liver and quantitatively by calculation of the SUV. Two cut-offs were compared, an SUV > 1.9 and > 2.9. Histology was used as the gold standard in 56 patients and clinical follow-up greater than 6 months in 9. The sensitivity and specificity for CT with PET using an SUV cut-off of > 1.9 was 100% and 77%, respectively. For CT with PET using an SUV cut-off > 2.9 the sensitivity was 92% and the specificity 85%. CT alone had a sensitivity of 65% and specificity of 62%. Tumor prevalence was 80%.

Koyoma (2001) performed a retrospective blinded (radiologist only) study in Osaka, Japan. They enrolled 86 patients who had a pancreatic mass on CT, US, or MRI. Other details regarding clinical presentation or reason for abdominal imaging were not elucidated. Because patients did not receive PET unless they had a previous abnormal imaging study

assessment of PET is really an assessment of PET as an adjunct imaging test. All patients received a PET and CT scan, while 37 received an MRI as well. PET was performed with the Shimadzu Headtome IV SET1400W-10 40-55 minutes after injection of 180-370 MBq of ^{18}FDG. Patients were fasted for 4 hours. Tumor presence was defined qualitatively by visual assessment with focally increased tracer uptake greater than background and quantitatively with the SUV_{gluc} . Two cut-offs were compared > 2.1 and > 2.2. The SUV_{gluc} is equivalent to the SUV in patients with glucose < 131. If the glucose exceeds 130 the SUV_{gluc} = SUV * (130/fasting blood glucose). Histology was used as the gold standard in 55 patients and follow up greater than 6 months in 31. Using visual assessment the sensitivity of PET was 82% and the specificity 81%. Using an SUV cut-off of > 2.1, sensitivity was 89% and specificity was 76%, while increasing the cut-off to > 2.2 increased sensitivity to 91% without changing specificity (76%). CT had a sensitivity of 91% and specificity of 62%, while MRI had a sensitivity of 78% and specificity of 70%. Of note, not enough data was reported to confirm the author's calculations for sensitivity and specificity. Tumor prevalence was 76%.

Kato (1995) performed an unblinded prospective study in Nagoya, Japan. They enrolled 24 patients with pancreatic masses identified by prior imaging studies (not specified). All patients received a PET scan and histologic tissue examination. Because patients did not receive PET unless

they had a previous abnormal imaging study assessment of PET is really an assessment of PET as an adjunct imaging test. PET was performed with the Shimadzu Headtome IV SET1400W-10 50 minutes after injection with 121-287 MBq of ^{18}FDG. Patients were fasted for an unspecified amount of time. Tumor presence was defined quantitatively by a differential absorption ratio (DAR) > 2.7. The DAR is equivalent to the SUV and calculated using the same formula. Histology was used as the gold standard in 21 patients and clinical follow-up greater than 3 years in 23. The sensitivity and specificity of PET for distinguishing mass-forming pancreatitis from pancreatic carcinoma using a DAR > 2.7 was 93% and 78%, respectively. Tumor prevalence was 63%. In addition to lack of blinding, another limitation of this study is lack of a comparator test.

Nakamoto (2000) performed an unblinded retrospective study in Kyoto, Japan. They enrolled 47 patients with suspected pancreatic carcinoma and performed a PET scan on all of them. Further details on the presentation, prior imaging studies, or reason for suspected pancreatic carcinoma in the patient population were not reported. PET was performed three times per patient with the Hitachi PCT 3600W 1, 2, and 3 hours after injection of 10 mCi of ^{18}FDG. Patients were fasted for 5 hours. Tumor presence was defined using both an SUV and a retention index (RI). The RI = 100 * (SUV_{2hours}-SUV_{1hour})/SUV_{1hour}. Several combined cut-offs were evaluated including SUV_{2hours} > 2.3; SUV_{2hours} > 2.3 with an RI > -14;

SUV_{1hour} > 2.8; and RI > 0.0. Histology was used as the gold standard in 31 patients, and clinical follow-up greater than 6 months in 16. Mean values for the RI were 12 +/- 13.37 for pancreatic carcinoma and -7.05 +/- 17.28 for chronic pancreatitis with individual values overlapping considerably. The sensitivity and specificity for the proposed cut offs were as follows:

SUV_{2hours} > 2.3 sensitivity 100% and specificity 75%

SUV_{2hours} > 2.3 with an RI > -14 sensitivity 100% and specificity 80%

SUV_{1hour} > 2.8 sensitivity 96% and specificity 75%

RI > 0.0 sensitivity 82% and specificity 85%

The SUV provides greater sensitivity while the RI improves specificity when combined with the SUV. Tumor prevalence was 57%. In addition to lack of blinding, another limitation of this study is lack of a comparator test

Inokuma (1995) performed a blinded (radiologist only) prospective study in Kyoto, Japan. They enrolled 46 consecutive patients with suspected pancreatic carcinoma who were scheduled for laparotomy. Carcinoma was suspected based upon clinical findings, tumor markers, and imaging studies with US or CT. All patients received US, CT, and PET, while 40 patients underwent an endoscopic ultrasound (EUS). PET was performed with the Hitachi PCT 3600W 60 minutes after injection of 150 MBq of ^{18}FDG. Patients were fasted overnight. Tumor presence was defined qualitatively by visual assessment of focally increased tracer uptake compared to background tissue. SUVs were calculated but no cut-

off suggested. Histology was used as the gold standard in 41 patients and follow-up for greater than 6 months in 5. Using visual assessment the sensitivity and specificity of PET was 94% and 82%, respectively. CT had a sensitivity of 89% and specificity of 73%, US a sensitivity of 89% and specificity of 45%, and EUS a sensitivity of 97% and specificity of 64%. If an arbitrary SUV cut-off of > 2.4 is proposed then the sensitivity of PET improves to 97% and the specificity improves even more to 91%. Tumor prevalence was 76%.

Mertz (2000) performed a retrospective unblinded study in Nashville, TN. They enrolled 35 patients with a pancreatic mass or dilated pancreatic duct without obvious metastatic lesions. Because patients did not receive PET unless they had a previous abnormal imaging study assessment of PET is really an assessment of PET as an adjunct imaging test. All patients received both a PET and CT and 33 patients received an endoscopic ultrasound (EUS). PET was performed with the Siemens ECAT-EXACT 933/08/16 after injection of 370 MBq of ^{18}FDG. Time between injection and scan initiation was not stated. Patients were fasted for 4 hours. Tumor presence was defined qualitatively by visual assessment of focally increased uptake as compared to the liver and quantitatively with an spontaneous uptake ratio (SUR). The SUR is equivalent to the SUV and is calculated the same way. The SUR cut-off for diagnosis of tumor was > 2.8. Histology was used as the gold standard. Sensitivity and specificity for

PET was 87% and 50% respectively. For CT sensitivity was 52% and specificity was 25%, while for EUS the sensitivity was 95% and specificity was 75%.

Quality Score 0-3

Rajput et al (1998) performed a retrospective study in Cleveland, Oh. The records of 13 patients with suspected pancreatic cancer who had received a PET scan. All of these patients also received a CT scan, 12 received an ERCP, and 7 underwent an endoscopic ultrasound (EUS). Reasons for the clinical suspicion were not clarified in the paper. PET was performed with the Siemens CTI ECAT-EXACT 45 minutes after injection with 407-802 MBq of ^{18}FDG. Patients were fasted overnight. Tumor presence was defined qualitatively by visual assessment of focally increased tracer uptake. Histology was used as the gold standard. The sensitivity and specificity of PET was 82% and 100%, of CT 73% and 0%, of ERCP 60% and 50%, and of EUS 100% and 0%, respectively. Tumor prevalence was 85%. Limitations of the study are lack of adequate descriptions regarding the patient inclusion criteria and lack of criteria for defining the comparator tests as positive or negative.

Bares (1993) performed an unblinded prospective study in Aachen, Germany. They enrolled 15 patients with suspected pancreatic carcinoma who had suggestive pancreatic masses on CT. Because patients did not

receive PET unless they had a previous abnormal imaging study assessment of PET is really an assessment of PET as an adjunct to CT. The patients all underwent PET, CT, and US. PET was performed with the Siemens CTI ECAT-EXACT 953/15 45 minutes after injection of 150-300 MBq of ^{18}FDG. Patients were fasted for 18 hours, except for 3 who were given glucose infusions prior to the scan. Tumor presence was defined qualitatively by visual assessment of focally increased tracer uptake greater than the surrounding background and quantitatively with a differential uptake ratio (DUR). The DUR is the same as the SUV and is calculated using the same formula. No DUR cut-off for the diagnosis of tumor was suggested. Histology was used as the gold standard. Using visual assessment the sensitivity and specificity of PET was 92% and 100%. US had a sensitivity and specificity of 85% and 50%, respectively, while ERCP had a sensitivity of 100% and specificity of 50%. The authors did not provide the data but reported that the DUR did not add information to visual assessment. Tumor prevalence was 87%. Additional limitations of the study were that no DUR cut-off for the diagnosis of tumor was suggested.

No studies in Fryback categories 3, 5, or 6 relevant to this question were identified in the literature search.

1b. Diagnostic test performance as an adjunct to conventional imaging in detecting metastatic pancreatic cancer

Category 4: Therapeutic choice impact

Delbeke, et al in 1999 performed an unblinded prospective study of 65 patients in Nashville, TN. This study was previously discussed under the first statement of work question- differentiating benign from malignant lesions in the pancreas. For details of the study refer to the more detailed discussion earlier. The sensitivity and specificity for PET and CT in staging pancreatic carcinoma were as follows: stage I 100% and 56%, stage II 0% and 36%, stage III 17% and 38%, stage IV 81% and 71%. For CT alone the sensitivity and specificity were as follows: stage I 100% and 56%, stage II 70% and 56%, stage III 8% and 38%, and stage IV 48% and 50%. PET altered management by indicating the need for laparotomy in 30% of patients because CT showed either no malignancy or metastases. PET altered management in 13% by avoiding surgery because they either had no malignancy or had metastases.

Category 2:Diagnostic accuracy

Quality score 4-7

Mertz, et al in 2000 performed a retrospective study of 35 patients in Nashville, TN. This study was previously discussed under the first statement of work question- differentiating benign from malignant lesions in

the pancreas. For details of the study refer to the more detailed discussion earlier. PET was not able to assess vascular invasion by the tumor but CT identified this phenomenon in 32% of patients. The sensitivity of PET for liver metastases was 78% while for CT it was 33%. No information was provided on false positives so specificity could not be calculated for either imaging technique. Prevalence of liver metastases was 26%. PET was not used to assess locally invasive disease, however CT had a sensitivity of 32%. Not enough information was provided to calculate the specificity.

Bares, et al in 1994 performed a prospective study in Aachen, Germany. This study was previously discussed under the first statement of work question- differentiating benign from malignant lesions in the pancreas. For details of the study refer to the more detailed discussion earlier. Seventeen lymph node metastases were present in the 27 patients with malignancy. The sensitivity and specificity for PET in detection of lymph node metastases was 48% and 83%, respectively. For liver metastases it was 57% and 88%, respectively. The sensitivity and specificity of CT in detection of lymph node metastases was 18% and 56%, respectively. For liver metastases it was 28% and 67%, respectively. US has a sensitivity of only 7% for lymph node metastases. Prevalence was 42% for lymph node involvement and 17% for liver.

Nakamoto, et al in 1998 performed a retrospective blinded (radiologist only) study in Hokkaido, Japan. They enrolled 34 patients with

histologically proven pancreatic carcinoma who received PET scans. Of the 34 patients, 28 were evaluated before therapy while 6 were evaluated after primary therapy during follow-up. All patients were evaluated with PET, US and CT. PET was performed with the Hitachi Medico 3600W 55 minutes after injection with 185-370 MBq of ^{18}FDG. Patients were fasted for 5 hours. Tumor presence was defined qualitatively by visual assessment with focally increased radiotracer uptake and quantitatively with an SUV > 3.3. Histology was used as the gold standard in 29 patients and clinical follow up for greater than 6 months in 5. Sensitivity and specificity for detection of liver metastases with PET was 91% and 92%, respectively. Both US and CT had a sensitivity of 67% and specificity of 100%. There were 2 lesions less than 2cm that were missed by PET while there were 7 lesions less than 2cm missed by CT. Prevalence of liver metastases was 57%.

Diederichs, et al in 1999 performed a retrospective study in Ulm, Germany of patients referred for pancreatic resection. This study was previously discussed under the first statement of work question- differentiating benign from malignant lesions in the pancreas. For details of the study refer to the more detailed discussion earlier. The sensitivity and specificity of PET for detecting lymph node metastases was 49% and 62% respectively. For liver metastases sensitivity was 70% and specificity 94%. The 5 false negative liver metastases were all less than 1cm in size. The

prevalence of lymph node metastases was 16%, while liver metastases were present in 26%.

Keogan, et al in 1998 performed a prospective study in Durham, NC. They enrolled 25 patients with a pancreatic mass or dilated pancreatic duct. This study was previously discussed under the first statement of work question- differentiating benign from malignant lesions in the pancreas. For details of the study refer to the more detailed discussion earlier. Sensitivity and specificity for detection of lymph node metastases by PET was 50% and 100%, respectively. For CT it was 75% and 100%, respectively. The authors report that two of the false negative nodes were “small”, but do not report the size. The prevalence of lymph node metastases was 16%.

Zimny, et al in 1997 performed a retrospective study in Aachen, Germany. They enrolled 105 patients with suspected pancreatic carcinoma by clinical, laboratory, or imaging studies. No further details were provided regarding patient presentation or inclusion criteria. This study was previously discussed under the first statement of work question- differentiating benign from malignant lesions in the pancreas. For details of the study refer to the more detailed discussion earlier. PET sensitivity for lymph node metastases was 46% and for liver metastases was 52%. Not enough information was provided to calculate the specificity for PET or the sensitivity and specificity for CT. The prevalence of lymph node lesions was 25% and liver lesions were 29%.

Quality Score 0-3

Bares, et al in 1993 performed a prospective study in Aachen, Germany. They enrolled 15 patients with a pancreatic mass on previous imaging studies. This study was previously discussed under the first statement of work question- differentiating benign from malignant lesions in the pancreas. For details of the study refer to the more detailed discussion earlier. The sensitivity and specificity of PET for lymph node metastases was 89% and 100%, respectively, and for liver metastases was 80% and 100%, respectively. The sensitivity and specificity of CT for lymph node metastases was 22% and 75%, respectively, and for liver metastases was 60% and 80%, respectively. The prevalence of lymph node lesions was 60% and liver lesions were 33%.

Kalady, et al in 2002 performed a retrospective study in Durham, NC. They enrolled 54 patients with a pancreatic mass on previous imaging studies. This study was previously discussed under the first statement of work question- differentiating benign from malignant lesions in the pancreas. For details of the study refer to the more detailed discussion earlier. local extension and nodes. PET provided no additional information beyond what was provided by CT. On distant metastases PET detected one that was missed by CT. In addition, PET avoided 4 unnecessary operations but missed 3 cancers.

2. In metastatic pancreatic carcinoma the subpopulations in which PET has been found useful

None of the studies identified characterized test sensitivity and specificity by patient or disease characteristics.

3. Diagnostic test performance for detection of residual or recurrent disease after primary treatment for pancreatic carcinoma

There is only one article that evaluates the use of PET for detecting residual or recurrent pancreatic carcinoma after primary therapy. The quality score of this article was a 6, and addresses Fryback category 4: therapeutic choice impact.

Rose (1998) performed a prospective blinded study of 82 patients in Nashville, TN. Of the recruited patient population 17 patients were being evaluated after primary treatment for pancreatic carcinoma. These patients received both a PET and CT. Since these 65 patients are the same 65 patients reported by Delbeke in the 1999 study, the design, methods, and results are the same. See the discussion of this article for further details. In the 9 patients who were evaluated before and after chemoradiation PET identified 4 responders, 3 stable lesions, and 2 progressors. CT did not identify any of the responders and only one of the progressors. Clinically, all 4 of the PET responders went on to successful resection. Of the

remainder only one showed histologic evidence of response to chemoradiation. In the 8 patients evaluated for recurrence of tumor after successful resection all 8 had evidence of recurrence on PET. CT was indeterminate for all.

3.4.5. Conclusions

1a. Diagnostic test performance as an adjunct to conventional imaging in differentiating benign from malignant pancreatic lesions

Of the 24 studies of PET in pancreatic cancer reviewed, 18 were both related to differentiating benign from malignant pancreatic disease and included in the analysis. The patients were generally representative of the relevant populations, although details were sparse. When comparator tests were performed, the study designs usually permitted evaluation of PET as an adjunct to conventional imaging, but some studies evaluated it as a substitute. PET sensitivity and specificity were generally slightly better than the comparator alone. One study that examined the clinical impact of PET compared to CT (Kalady, 2002) suggests that the additional impact is mixed – PET occasionally picks up malignant lesions not found on CT but also misses lesions found on CT, although no patients with a normal CT were included in the study. In studies that used both visual assessment and an SUV to define PET positivity there was little additional benefit to using SUVs. When comparing PET to state of the art imaging techniques such as MRI and EUS, PET performed reasonably well. In two of the three studies using EUS, the confidence intervals for EUS were large and PET performed better, but in the third study the confidence intervals were narrower and PET was superior only in reducing false positives. In the one study comparing PET to MRI, PET was more sensitive and specific. No

sub-populations with more or less benefit from PET than the general study population were identified; however insufficient information and the generally homogenous populations limited assessment. For example, only 7 studies even mentioned tumor size, and within those only 8 lesions < 2cm were reported. In addition, sensitivity and specificity were no different for those referred for PET because of pancreatic masses than those referred for other reasons.

1b. Diagnostic test performance as an adjunct to conventional imaging in detecting metastatic pancreatic cancer

In the 9 studies identified, subjects and clinical context were relevant to the question. The studies were generally consistent in demonstrating a trend towards greater sensitivity compared to conventional imaging. Specificity of PET for the detection of metastasis, on the other hand, tended to be a bit lower than the comparators. Future studies will need to be larger in order to provide a more definitive assessment of relative test performance.

2. In metastatic pancreatic carcinoma, the sub-populations in which PET is useful.

It is difficult to identify a subpopulation of patients with metastatic pancreatic cancer that might achieve a substantially greater benefit,

because details regarding the patient populations and tumor characteristics were incompletely reported. As an example, only false negatives were mentioned in the three studies that discussed the size of metastases. PET was compared to CT for local invasion (vascular structures around primary tumor) in only one study. In this study PET failed to provide a benefit beyond that provided by CT.

3. Diagnostic test performance for detection of residual or recurrent disease after primary treatment for pancreatic carcinoma

Only one study was identified related to this question (Rose, 1998). This study indicated greater discrimination between patients using PET compared to CT and the distinctions were clinically meaningful. Specifically, the four patients who responded to treatment identified on PET were not identified on CT and all went on to successful resection while the eight patients with recurrence after resection were correctly identified on PET but they had indeterminate for CT studies.

3.4.6. Tables

Table 9. Estimates of PET and comparator test(s) sensitivity and specificity with 95% confidence intervals for differentiating malignant from benign pancreatic lesions.

Study	**Sensitivity**	**95% Confidence Interval**	**Specificity**	**95% Confidence Interval**
Bares 1993 – PET	0.923	0.640-0.998	1.00	0.158-1.00
Delbeke 1999 CT and PET (SUV>=3.0)	0.923	0.814-0.979	0.846	0.545-0.980
Diedrichs 1999 – PET	0.882	0.781-0.948	0.870	0.751-0.946
Friess 1995 – PET	0.936	0.828-0.987	0.875	0.710-0.965
Ho 1996 – PET	1.00	0.631-1.00	0.667	0.223-0.957
Imdahl 1999 – PET	0.963	0.810-0.999	1.00	0.782-1.00
Inokuma 1995 – PET	0.971	0.851-0.999	0.909	0.587-0.998
Kalady 1995 – PET	0.878	0.738-0.959	0.923	0.640-0.998
Kato 2002 – PET	0.933	0.681-0.998	0.778	0.400-0.972
Keogan 1998 – PET	0.880	0.688-0.975	0.833	0.516-0.979
Nakamoto 2000 – PET (SUV 2.3-2.4 @2 hrs and RI@-15)	1.00	0.872-1.00	0.800	0.563-0.942
Papos 2001 – PET	1.00	0.541-1.00	0.875	0.617-0.984
Rajput 1998 – PET	0.818	0.482-0.977	1.00	0.158-1.00
Sendler 2000 – Visual PET	0.710	0.520-0.858	0.636	0.308-0.891
Sperti 2001 – PET	0.941	0.713-0.999	0.974	0.865-0.999

Zimny 1997 – PET (all)	0.892	0.798-0.952	0.531	0.347-0.709
Bares 1994 – PET	0.889	0.708-0.976	0.846	0.546-0.981
Koyoma 2001 – PET	0.815	0.700-0.901	0.810	0.581-0.946
Mertz 2000 – PET	0.871	0.702-0.964	0.500	0.0676-0.932
Delbeke 1999 – CT	0.654	0.509-0.780	0.615	0.316-0.861
Diedrichs 1999 – CT	0.881	0.771-0.951	0.727	0.572-0.850
Freiss 1995 – CT	0.786	0.632-0.897	0.688	0.500-0.839
Imdahl 1999 – CT	0.814	0.619-0.937	0.810	0.581-0.946
Inokuma 1995 – CT	0.886	0.733-0.968	0.727	0.390-0.940
Kalady 2002 – CT	0.902	0.767-0.973	0.615	0.316-0.861
Keogan 1998 – CT	0.750	0.533-0.902	0.833	0.516-0.979
Papos 2001 – CT	1.00	0.541-1.00	0.562	0.299-0.802
Rajput 1998 – CT	0.727	0.390-0.940	0.00	0.00-0.842
Sendler 2000 – CT	0.742	0.554-0.881	0.727	0.390-0.940
Sperti 2001 – CT	0.647	0.383-0.858	0.872	0.726-0.957
Bares 1994 – CT	1.00	0.872-1.00	0.231	0.0504-0.538
Koyoma 2001- CT	0.908	0.810-0.965	0.381	0.181-0.616
Mertz 2000 – CT	0.516	0.331-0.698	0.250	0.0063-0.806
Bares 1993 – ERCP	1.00	0.753-1.00	0.500	0.0126-0.987
Diedrichs 1999 – ERCP	0.946	0.851-0.989	0.911	0.788-0.975

Imdahl 1999 – ERCP	0.850	0.621-0.968	0.812	0.544-0.960
Keogan 1998 – ERCP	0.857	0.572-0.982	0.375	0.0852-0.755
Papos 2001 – ERCP	0.600	0.147-0.947	0.923	0.638-0.998
Rajput 1998 – ERCP	0.600	0.262-0.878	0.500	0.0126-0.987
Inokuma 1995 – EUS	0.966	0.822-0.999	0.636	0.308-0.891
Papos 2001 – EUS	1.00	0.541-1.00	0.533	0.266-0.787
Bares 1993 – VIS	0.846	0.546-0.981	0.923	0.640-0.998
Inokuma 1995 – US	0.885	0.732-0.968	0.454	0.167-0.766
Sendler 2000 – US	0.581	0.391-0.755	0.545	0.234-0.833
Papos 2001 – CA19-9	0.800	0.284-0.995	0.733	0.449-0.922
Sperti 2001 – CA19-9	0.647	0.383-0.858	0.897	0.758-0.971
Rajput 1998 – EUS	1.00	0.478-1.00	0.00	0.00-0.842

Table 10. Estimates of PET and comparator test(s) sensitivity and specificity with 95% confidence intervals for detecting metastatic pancreatic cancer.

Study	**Sensitivity**	**95% Confidence Interval**	**Specificity**	**95% Confidence Interval**
Mertz 2000 – PET	0.871	0.702-0.964	0.500	0.0676-0.932
Nakamoto 1998 – PET	0.917	0.615-0.998	0.909	0.709-0.989
Delbeke 1999 – PET and CT – Stage I	1.00	0.541-1.00	0.558	0.399-0.709
Delbeke 1999 – PET and CT – Stage II	0.00	0.00-0.308	0.359	0.212-0.528
Delbeke 1999 – PET and CT – Stage III	0.167	0.0209-0.484	0.378	0.225-0.552
Mertz 2000 – CT	0.516	0.331-0.698	0.250	0.0063-0.806
Nakamoto 1998 – CT	0.667	0.349-0.901	1.00	0.845-1.00
Delbeke 1999 – CT Stage I	1.00	0.541-1.00	0.581	0.421-0.730
Delbeke 1999 – CT Stage II	0.700	0.348-0.933	0.564	0.396-0.722
Delbeke 1999 – CT Stage III	0.0833	0.0021-0.385	0.378	0.225-0.552
Delbeke 1999 – CT Stage IV	0.476	0.257-0.702	0.500	0.306-0.694
Mertz 2000 – EUS	0.931	0.772-0.991	0.750	0.194-0.994

Nakamoto 1998 – US	0.667	0.349-0.901	1.00	0.846-1.00
Bares 1993 – PET – LN	0.889	0.518-0.997	1.00	0.541-1.00
Bares 1993 – CT – LN	0.222	0.0281-0.600	0.750	0.194-0.994
Bares 1993 – PET – Liver	0.800	0.284-0.995	01.00	0.692-1.00
Bares 1993 – CT – Liver	0.600	0.147-0.947	0.800	0.444-0.975
Bares 1994 – PET – LN	0.765	0.501-0.932	0.826	0.612-0.951
Bares 1994 – CT – LN	0.176	0.038-0.434	0.565	0.345-0.768
Bares 1994 – PET – Liver	0.571	0.184-0.901	0.879	0.718-0.966
Bares 1994 – CT – Liver	0.286	0.0367-0.710	0.667	0.482-0.820
Diederichs 1999 – PET – LN	0.489	0.337-0.642	0.625	0.354-0.848
Diederichs 1999 – PET – Liver	0.700	0.457-0.881	0.942	0.858-0.984
Keogan 1998 – PET – LN	0.500	0.0676-0.932	1.00	0.839-1.00
Keogan 1998 – CT – LN	0.760	0.194-0.994	1.00	0.839-1.00
Zimny 1997 – PET – LN	0.462	0.266-0.666	-	-
Zimny 1997 – PET – metastasis	0.516	0.330-0.698	-	-

Table 11. Estimates of PET and comparator test(s) sensitivity and specificity with 95% confidence intervals for detection of residual or recurrent disease after primary treatment for pancreatic carcinoma.

Study	**Sensitivity**	**95% Confidence Interval**	**Specificity**	**95% Confidence Interval**
Rose 1998 – PET	0.923	0.815-0.979	0.846	0.545-0.981
Rose 1998 – CT	0.654	0.509-0.780	0.615	0.316-0.861

3.4.7.Figures

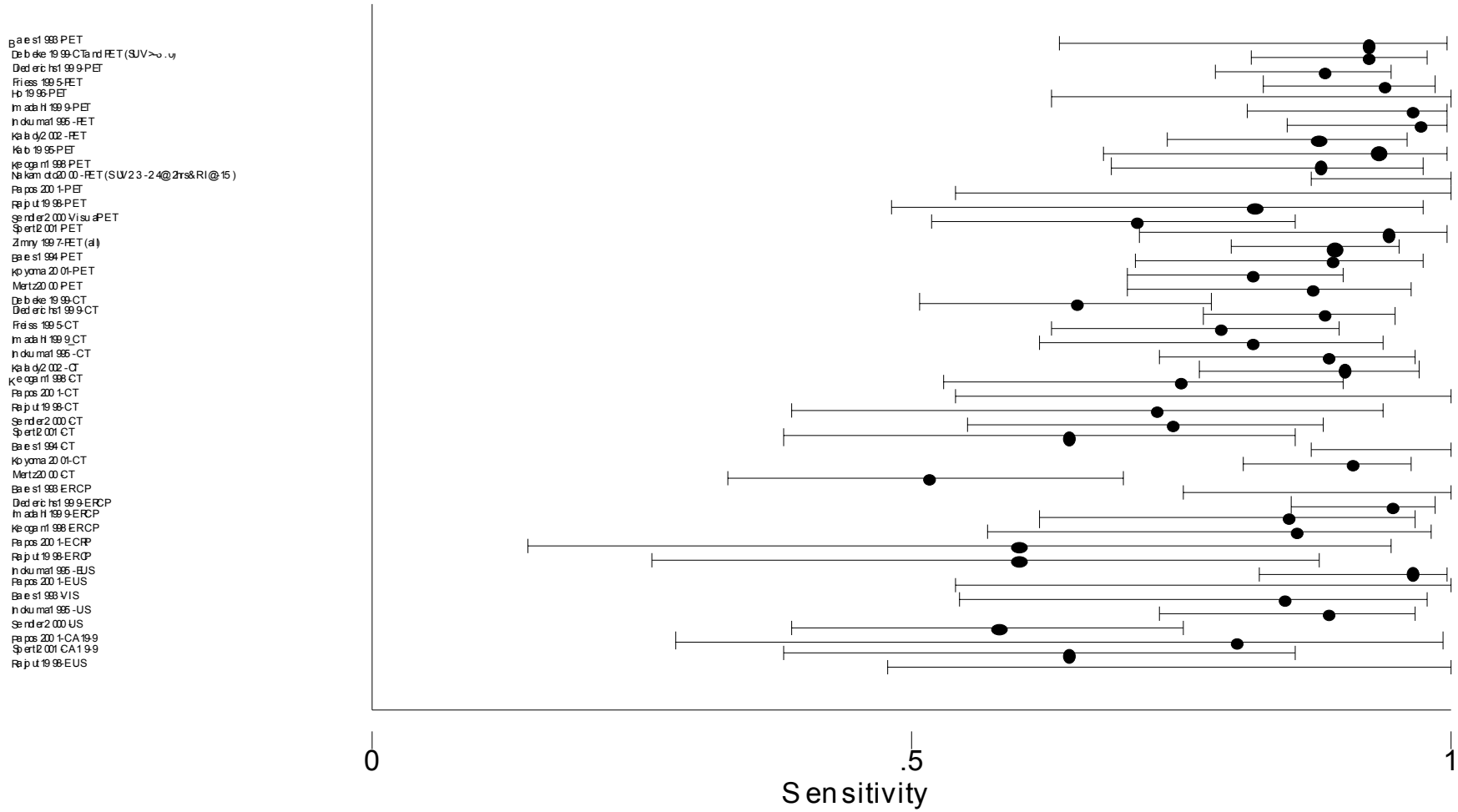

Figure 7.a. Estimates of PET and comparator test(s) sensitivity with 95% confidence intervals for differentiating malignant from benign pancreatic lesions.

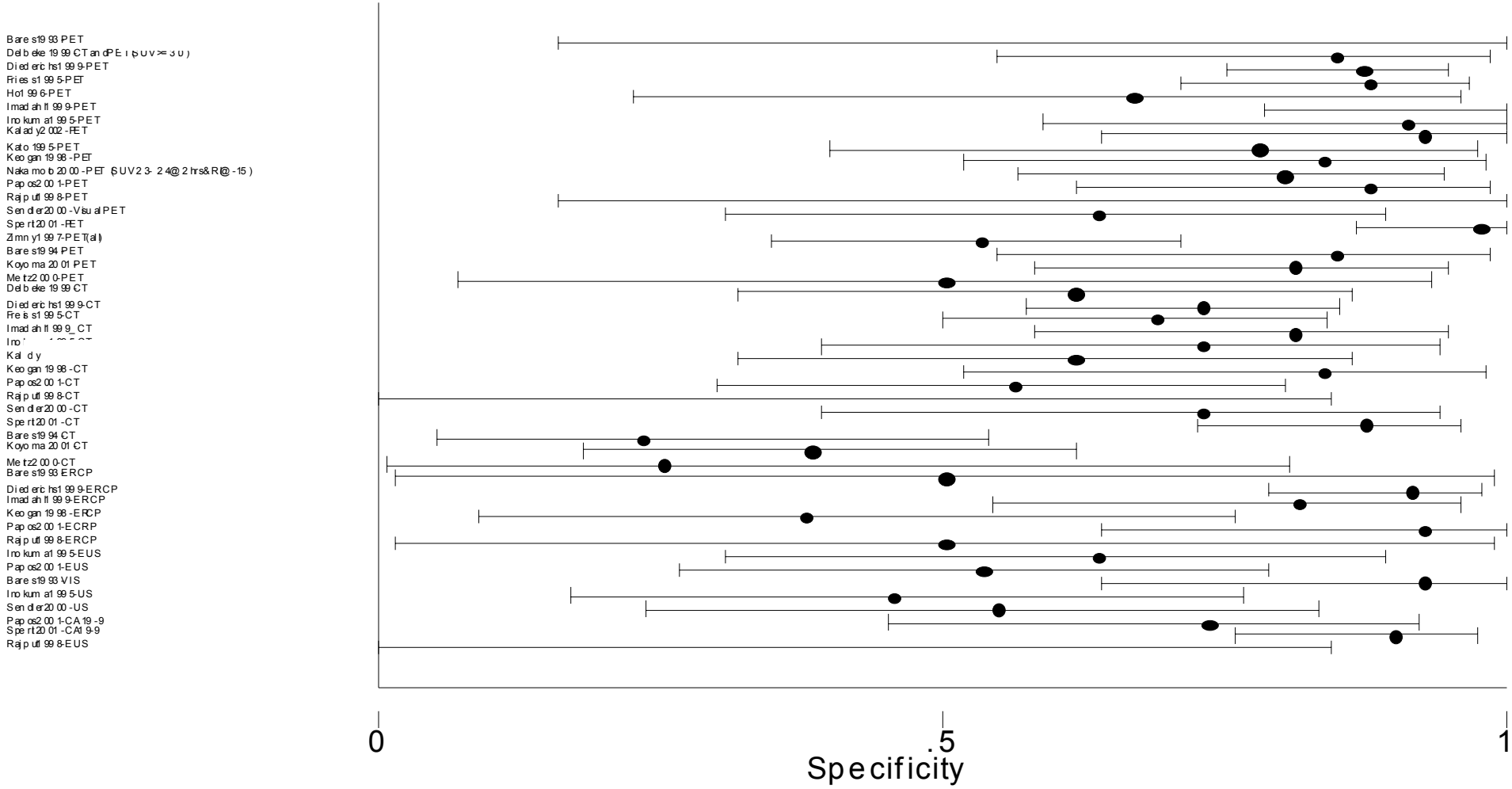

Figure 7.b. Estimates of PET and comparator test(s) specificity with 95% confidence intervals for differentiating malignant from benign pancreatic lesions.

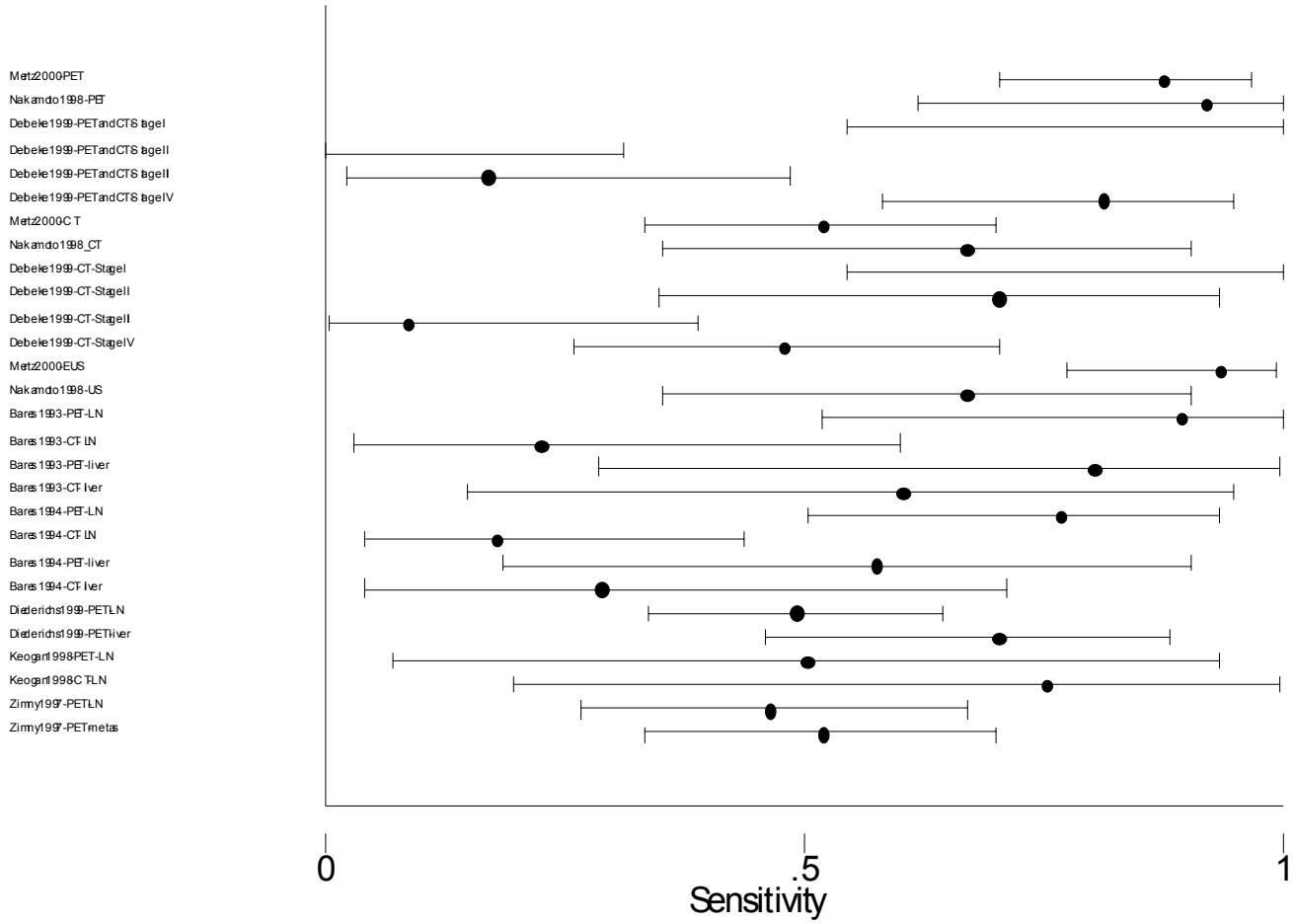

Figure 8.a. Estimates of PET and comparator test(s) sensitivity with 95% confidence intervals for detecting metastatic pancreatic cancer

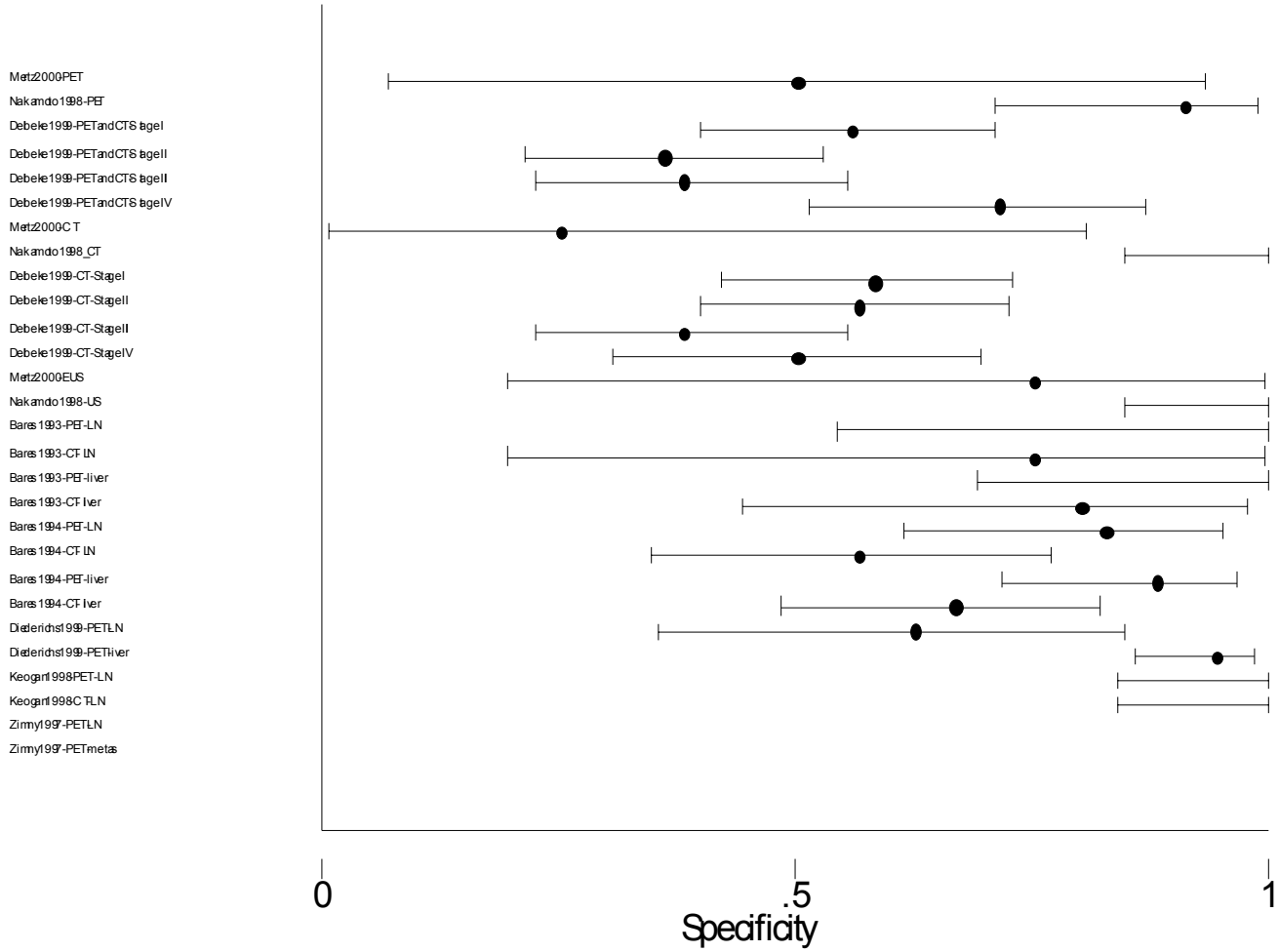

Figure 8.b. Estimates of PET and comparator test(s) specificity with 95% confidence intervals for detecting metastatic pancreatic cancer

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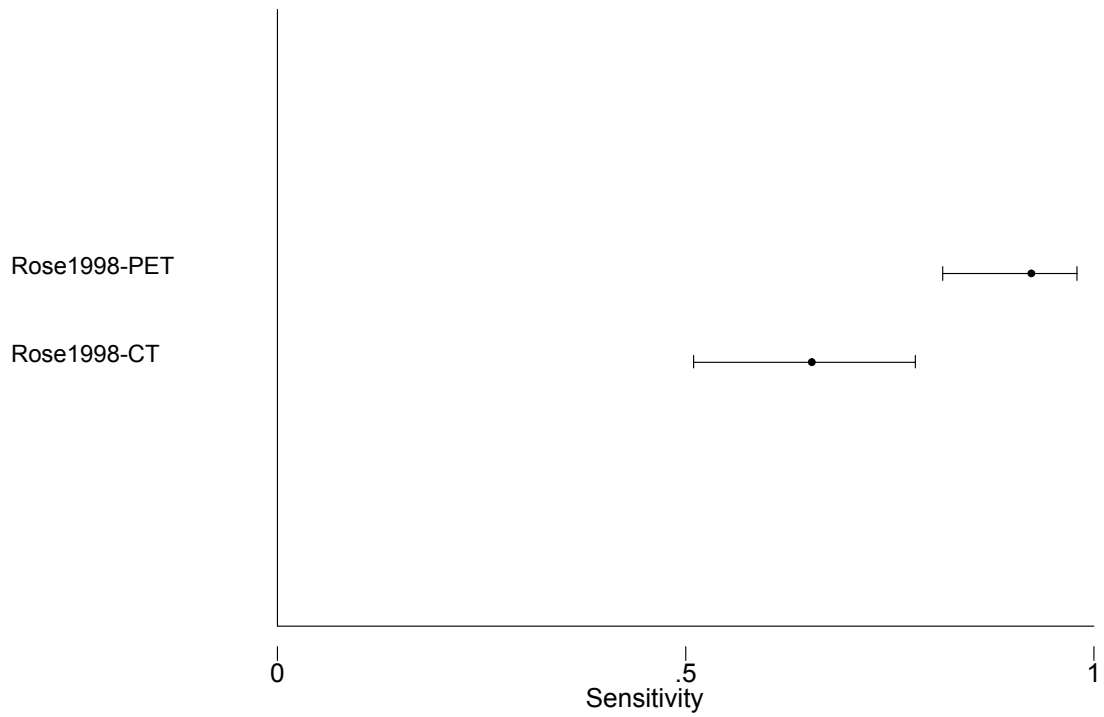

Figure 9.a. Estimates of PET and comparator test(s) sensitivity with 95% confidence intervals for detection of residual or recurrent disease after primary treatment for pancreatic carcinoma.

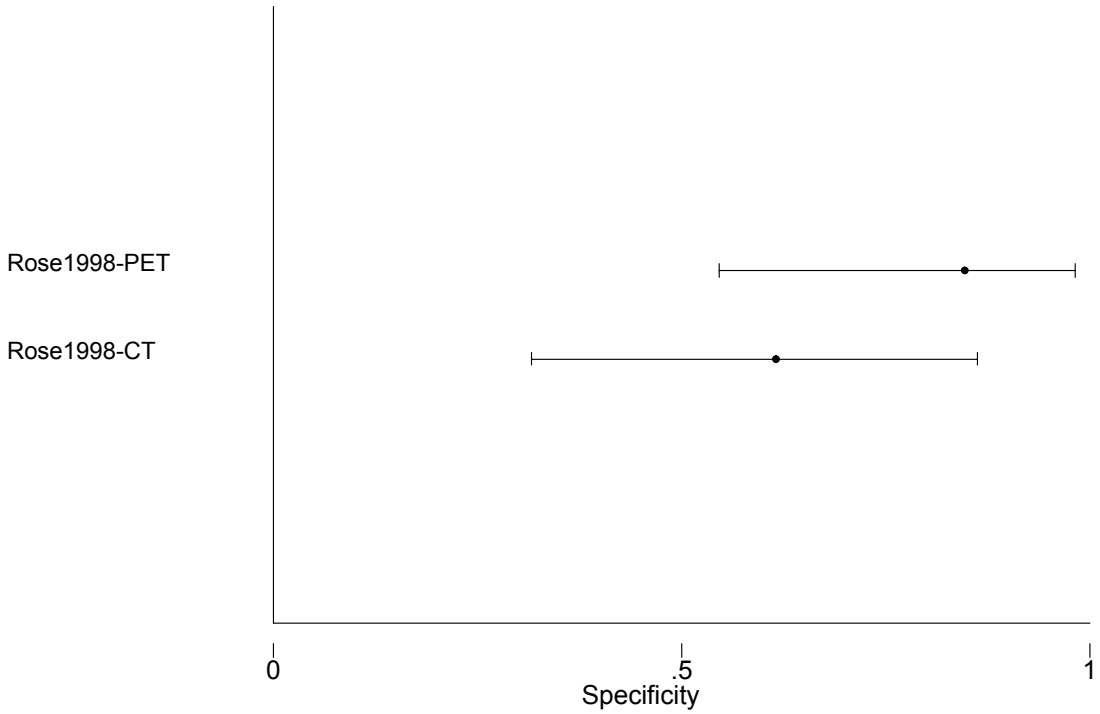

Figure 9.b. Estimates of PET and comparator test(s) specificity with 95% confidence intervals for detection of residual or recurrent

3.5. Small Cell Lung Cancer

3.5. 1. Background

The estimated incidence of new cases of lung cancer in 2001 in the US was 169,500 with an estimated 157,400 cancer deaths (Greenlee, 2001). Small cell lung cancer (SCLC) accounts for approximately 20% of all new cases of lung cancer diagnosed each year (Clark, 1998), of which approximately two thirds are metastatic at the time of presentation. The stage of SCLC is important and impacts treatment decisions. Overall, patients with limited disease survive longer than those with extensive disease, and with a combined treatment approach, up to 20% of patients with limited disease can be cured. (Bunn, 1997). Thus, sensitive and specific radiologic imaging modalities used to stage SCLC can facilitate tailored treatment strategies, reduce the morbidity of unnecessary treatment and potentially improve survival.

Paraneoplastic syndromes are rare, non-metastatic manifestations of cancer, which usually present as neurological or endocrinologic dysfunction. The syndrome usually improves with the successful treatment of the underlying malignancy and does not appear to adversely affect survival. Sensitive and specific radiologic imaging modalities that can detect underlying metastases signaled by a paraneoplastic syndrome can potentially reduce mortality.

3.5.2. CMS Statement of Work Questions

1. How does the diagnostic test performance of FDG-PET compare to conventional imaging modalities (e.g., CT, MRI) with respect to the following clinical situations:
   a. In staging to determine the true extent of disease at initial diagnosis in patients with small cell lung cancer (SCLC)?
   b. In restaging post treatment to evaluate the response to initial treatment (detect residual or new disease sites) in patients with SCLC?
   c. In diagnosing occult small cell lung cancer in patients with paraneoplastic syndrome(s) commonly associated with this neoplasm?

3.5.3. Importance of Questions Posed by CMS in Clinical Management

1a. Performance of FDG-PET for staging to determine the true extent of disease at initial diagnosis in patients with SCLC.

1b. Performance of FDG-PET in restaging post treatment to evaluate the response to initial treatment (detect residual or new disease sites) in patients with SCLC.

The stage of SCLC impacts treatment decisions. Staging and treatment is based on the simplified Veterans Administration (VA) (Clark,

1998) staging method. Limited disease is defined as disease that can be encompassed within a radiation port or confined to one hemithorax, while extensive disease indicates disease that has spread outside the ipsilateral hemithorax (Clark, 1998). Chemotherapy is the primary form of treatment for SCLC with radiation added for patients with limited disease. As stated previously, overall patients with limited disease survive longer than those with extensive disease, and with a combined treatment approach, up to 20% of patients with limited disease can be cured. (Bunn, 1997). The standard approach to staging includes chest and abdominal CT or MRI, bone scan and bone marrow biopsy. PET has been shown to be more sensitive and specific than CT in detecting malignancy and staging mediastinal disease for non-small cell lung cancer (NSCLC) (Chin, 1995;Marom 1999). Whole body PET may also be able to detect extra-thoracic metastases not detected by routine imaging (Marom, 1999; Pieterman, 2000; Saunders, 1999). Thus, PET may provide a more accurate means of determining tumor grade for initial diagnosis, as well as for recurrent disease, than MRI or CT. Hence use of PET may affect prognosis for patients with SCLC.

1c. Performance of FDG-PET in diagnosing occult small cell lung cancer in patients with paraneoplastic syndrome(s) commonly associated with this neoplasm.

Paraneoplastic syndromes usually present as neurological or endocrinologic dysfunction. The most common endocrinologic syndrome is inappropriate secretion of antidiuretic hormone (SIADH), which is clinically apparent in 11% to 45% of SCLC patients (Marchioli 1997; Patel 1993). The syndrome usually improves with successful treatment of the underlying malignancy and does not appear to adversely affect survival. Atrial natriuretic peptide (ANP), which promotes natriuresis and hypotension, may also contribute to hyponatremia in approximately 15% of SCLC patients. Its effects are also ameliorated by cancer treatment (Marchioli, 1997).

In terms of neurologic dysfunction, both the central and peripheral nervous systems, including the neuromuscular junction, may be affected. The neurologic syndromes associated with SCLC include Lambert-Eaton myasthenic syndrome, cerebellar degeneration, encephalomyelitis, sensory neuropathy and a cancer-associated retinopathy. Among patients with suspected PNS, conventional imaging techniques may not be very useful for determining presence of an underlying malignancy, due to the small size of the tumor. PET allows for detection of metabolically active tumor tissue with a resolution of 6 - 8 mm. Thus, it may be more accurate than conventional imaging techniques (CT and MRI) for diagnosing occult small cell lung cancer in patients with PNS.

3.5.4. Results

The literature search identified 388 abstracts. Review of the abstracts identified 112 articles for full-text review. Of the 112 articles, 6 met the criteria for full text review and are discussed below. Data on the operating characteristics for the tests, including 95% confidence intervals are presented in tables and figures at the end of this section. Detailed evidence tables are available in Appendix D.

Question 1.a. In staging to determine the true extent of disease at initial diagnosis in patients with SCLC.

Category 2: Diagnostic accuracy

Quality Score (4-7)

Pandit et al. (2003) retrospectively evaluated 46 patients with histological confirmed SCLC, enrolled consecutively. Eight patients were newly diagnosed; 38 were post-treatment. A positive PET was defined qualitatively as “focal intense uptake.” A negative PET was defined as either no uptake or ill-defined diffuse areas of low-grade uptake. Radiologists were blinded to histology results. Follow-up was performed at 1 year for surviving patients, or until the date of last visit or death in non-surviving patients. Of the 46 patients, eight patients were referred for initial staging of their disease. All 8 (100%) were positive by PET with SUV values that ranged from 5.5 to 17.5. Four showed evidence of limited

disease and four showed extensive disease. Findings were confirmed by conventional methods (not specified). Limitations of the study were lack of a defined comparator, lack of information on whether detected disease in treated individuals was recurrent or residual, and impact of PET on treatment decisions for these patients.

Shen et al. (2002) prospectively examined the use of PET in 25 patients in Taipei, Taiwan. Patients were included in the study if they had histological confirmed SCLC. Patients were excluded if they had any prior radiotherapy or chemotherapy. Ten (40% overall) patients had limited disease, the rest (60%, n=15) had extensive disease. PET results were classified as positive or negative qualitatively based on the agreement of at least two of three experienced specialists. CT was performed on all patients as a comparator test. Criteria for categorizing CT as positive or negative were not presented. A definitive diagnosis was based on findings from thoracotomy/mediastinoscopy, other modalities or follow-up of at least one year. PET identified 15 of 15 (100% sensitivity) patients with extensive disease and 10 of 10 patients (100% specificity) with limited disease. In contrast, CT had a sensitivity of 93% (14 of 15 patients with disease) for detecting extensive disease and a 90% (9 of 10 patients) specificity for limited disease.

<u>Quality score 0-3</u>

Chin et al. (2002) prospectively studied 18 patients with histologically confirmed SCLC seen consecutively in Winston Salem, NC. PET results were categorized as positive or negative based on the interpretation of two radiologists who were not blinded to histology results. The comparator was a combination of CT, MRI, bone scan and bone biopsy results. Criteria for defining PET and comparator results as positive and negative were not stated. A definitive diagnosis was based on long-term survival data, with patients followed from 13 to 1087 days. Results for the PET and conventional imaging/bone biopsy were concordant in 15 of 18 patients. Among patients with either positive conventional image or biopsy findings, PET was falsely negative in one patient (sensitivity of 88.9%; specificity not available) who was positive by conventional imaging, and, among patients who were negative by conventional imaging, PET was positive in 2 patients who had disease confirmed using pathology (sensitivity=100%, specificity=100%). Limitations of the study were lack of defined criteria for categorizing PET and CT results as positive or negative, small numbers of patients, no mention of blinding for either the radiologist or pathologist, and lack of a description regarding the study setting and patient population.

Zhao et al. (2002) retrospectively examined the use of PET in 15 patients, with histologically confirmed SCLC, from the Bronx, NY. Patients had a mean age of 68 years, with a range from 50 to 81 years; 8 were men.

Three patients had an initial diagnosis of SCLC, 12 had previous diagnosis of SCLC. The 12 patients with previous disease had received chemotherapy, radiotherapy or both. PET and CT were performed on all patients. Criteria for determining a positive result were not presented. A definitive diagnosis was based on surgery and clinical follow-up. Among patients with an initial diagnosis of SCLC, PET had a sensitivity of 100%. Results for patients post-treatment are presented below. Limitations of the study include lack of information regarding blinding of the radiologist and pathologist, lack of defined criteria for interpreting PET and CT results as positive or negative, and small sample size. In addition, data were not presented in a manner that allowed for presentation of CT results by patient type (initially diagnosed or post-treatment).

Schumacher et al. (2001) examined the role of PET in staging 30 patients with histologically confirmed SCLC, in Frieburg, Germany. PET results were categorized as malignant based on focally increased tracer uptake exceeding normal limits of regional FDG uptake, location of the lesion at a metastatic site, or an SUV>4. CT and MRI scans were performed as the comparator tests; criteria for classifying patients as positive or negative were not specified. A definitive diagnosis was based on follow-up of patients with histologic confirmation for those with suspected disease. Staging was based on follow-up and additional tests. The radiologist was blinded to the results of other tests and histology. PET

identified 20 of 20 (100% sensitivity) patients with extensive disease and 6 of 6 patients (100% specificity) with limited disease. In contrast, use of CT and/or MRI identified 13 of 20 patients with extensive disease (sensitivity of 65%), and identified 6 of 6 patients without disease, representing a specificity of 100%. Limitations of the study include collapsing of results for CT/MRI as the comparator, lack of details regarding use of standard criteria for interpreting CT/MRI as well as no report of blinding for histologic confirmation of disease.

There were no Category 3 through 6 studies identified as pertinent to this question.

Question 1.b. In restaging post treatment to evaluate the response to initial treatment (detect residual or new disease sites) in patients with SCLC.

Category 2: Diagnostic accuracy

Quality score 4-7

Pandit et al. (2003) [summarized in the previous section] also examined the accuracy of PET in determining presence or absence of recurrent disease in patients with SCLC. Thirty-eight patients had PET scans performed for detection of residual or recurrent disease after treatment that included chemotherapy (14 patients), radiation (1 patient) or

both (23 patients). Of these, 27 (73%) had positive PET scans, suggesting residual or recurrent disease, while 10 (27%) had negative scans. Survival data indicated 4 of 27 patients with positive PET scans were alive at 1 year, compared to 9 of 10 patients with negative PET scans. Using survival as the outcome, PET had a sensitivity of 95.8% and a specificity of 69.2% for detection of residual or recurrent disease. Data for one patient was not reported. Limitations of the study were lack of a defined comparator and how impact of PET on treatment decisions for these patients.

Quality Score 0-3

Zhao et al. (2002) [details presented previously] also examined the role of PET in detecting recurrent/residual disease. Among the 12 patients, 7 of 7 (100%), with recurrent disease had a positive PET result. Among patients with no recurrence or residual disease, PET correctly identified 4 of 5 patients for a specificity of 80%. Comparable data on CT were not presented; however, collapsed across disease status (newly diagnosed or post-treatment), PET had higher sensitivity for detection of SCLC (10/10; 100%) and specificity (4/5; 80%) than CT (9/10; 90% sensitivity and 2/5; 40% specificity respectively.

There were no Category 3-6 studies that were pertinent to this question. A problem with both studies presented is the lack of information

on blinding of the pathologist; in addition, the study by Zhao et al. (2002) makes no mention of blinding for the radiologist.

Question 1.c. In diagnosing occult small cell lung cancer in patients with paraneoplastic syndrome(s) commonly associated with this neoplasm.

Category 2: Diagnostic accuracy

Quality score 4-7

Only one study was identified that addressed this question. Rees et al. (2001) conducted a retrospective review of the use of PET in 43 patients with suspected paraneoplastic syndrome (PNS), who had negative conventional imaging (CT scanning, ultrasound, mammography and bronchoscopy), and were seen in London, England. Twenty four of the patients were men; 15 presented with cerebellar syndrome; 6 with motor neuropathy, 8 with sensory neuropathy, 3 with myelo(radiculo)pathy, 2 with respiratory failure and 3 with Lambert-Eaton myasthenic syndrome. Six patients had other indications for PNS that were not specified. Criteria for defining patients as positive or negative by PET were not specified. A definitive diagnosis was based on a combination of CT, follow-up and surgery. Radiologists were blinded to clinical results. PET identified 9 of 10 patients (sensitivity of 90%) diagnosed with cancer, including 3 patients with small cell lung cancer. Specificity was 90%: 26 of 29 patients without cancer had negative PET scans, including 2 patients with paraneoplastic

sensory neuropathy. An important limitation of this study was lack of defined criteria for categorizing PET as positive or negative. In addition, since only 5 patients had either SCLC (n=3) or paraneoplastic syndrome (n=2), these results should be considered preliminary.

There were no Category 3-6 studies that were pertinent to this question. Blinding of the pathologist was not mentioned in this study.

3.5.5. Conclusions

1. Performance of FDG-PET compared to conventional imaging in staging to determine the true extent of disease at initial diagnosis in patients with SCLC.

There were five studies identified that addressed this question. However, three either lacked information on a comparator test (Pandit, 2003), or presented information in a manner that prevented data on test accuracy for the comparator test being calculated (Chin, 2002; Zhao 2002), limiting the ability to comment on the comparative test accuracy performance of PET. In one study, (Chin, 2002) data stratified by CT result (positive or negative) suggest that PET was more likely to classify patients as falsely negative or falsely positive. Given the small number of patients (n=18), the significance of this misclassification is unclear. Two studies presented data that allowed for test accuracy data to be calculated for both PET compared to CT or CT and MRI (Shen 2002; Schumacher 2001). While one study (Schumacher, 2001) showed PET to have higher sensitivity (100% versus 65%) than CT or MRI, the other (Shen, 2002) found similar high sensitivity (93% versus 100%) for PET and CT. Specificity ranged from 94% (CT – Shen, 2002) to 100% and were statistically indistinguishable due to small samples sizes and, therefore, wide confidence intervals.

1b. Performance of FDG-PET compared to conventional imaging in restaging post treatment to evaluate the response to initial treatment (detect residual or new disease sites) in patients with SCLC.

Two studies were identified that addressed this question (Pandit 2003; Zhao 2003). Pandit et al. did not include information on a comparator test. Results from long-term followup suggest that PET has high sensitivity (>90%) but moderate specificity (<70%) for predicting survival beyond 1 year, in patients post-treatment. Zhao et al. (2003) also do not present data on restaging post-treatment for CT, although CT results were obtained. PET identified all patients with recurrent disease (7 of 7) and 4 of 5 patients without recurrence. These data suggest a role for PET in restaging post-treatment, but cannot be considered definitive due to lack of comparative data on CT/MRI performance.

1c. Performance of FDG-PET compared to conventional imaging in diagnosing occult small cell lung cancer in patients with paraneoplastic syndrome(s) commonly associated with this neoplasm.

Only one study was identified that addressed this question (Rees, 2001). The study examined the use of PET among patients with suspected PNS, who had negative conventional imaging test results. PET had a sensitivity of 90% for detecting cancer (including 3 patients with SCLC) and a specificity of 90%. Given the extremely small number of patients with

SCLC, lack of a comparator test and lack of defined criteria for categorizing PET results as positive or negative, this study suggests a role for PET in diagnosing occult small cell lung, but one that remains to be confirmed using a larger sample size as well as a comparator test.

3.5.6. Tables

Table 12. Estimates of PET and comparator test(s) sensitivity and specificity with 95% confidence intervals for staging to determine the true extent of disease at initial diagnosis in patients with SCLC**.**

Study	**Sensitivity**	**95% Confidence Interval**	**Specificity**	**95% Confidence Interval**
Chin 2002 – PET – CT-	1.00	0.158-1.00	1.00	0.590-1.00
Schumacher 2001 – PET	1.00	0.832-1.00	1.00	0.541-1.00
Shen 2002 – PET	1.00	0.782-1.00	1.00	0.692-1.00
Zhao 2002 – PET	0.429	0.0989-0.816	1.00	0.478-1.00
Schumacher 2001 – CT	0.650	0.408-0.846	1.00	0.541-1.00
Shen 2002 – CT	0.933	0.681-0.998	0.900	0.555-0.997
Chin 2002 – PET – CT+	0.889	0.517-0.997	-	-
Pandit 2003 – PET	1.00	0.631-1.00	-	-

Table 13. Estimates of PET and comparator test(s) sensitivity and specificity with 95% confidence intervals for restaging post treatment to evaluate the response to initial treatment (detect residual or new disease sites) in patients with SCLC.

Study	**Sensitivity**	**95% Confidence Interval**	**Specificity**	**95% Confidence Interval**
Pandit 2002 – PET	0.958	0.789-0.999	0.409	0.207-0.636
Zhao 2002 – PET	1.00	0.590-1.00	0.800	0.284-0.995

Table 14. Estimates of PET and comparator test(s) sensitivity and specificity with 95% confidence intervals for diagnosing occult small cell lung cancer in patients with paraneoplastic syndrome(s) commonly associated with this neoplasm.

Study	**Sensitivity**	**95% Confidence Interval**	**Specificity**	**95% Confidence Interval**
Rees 2001	0.900	0.555-0.997	0.897	0.726-0.978

3.5.7. Figures

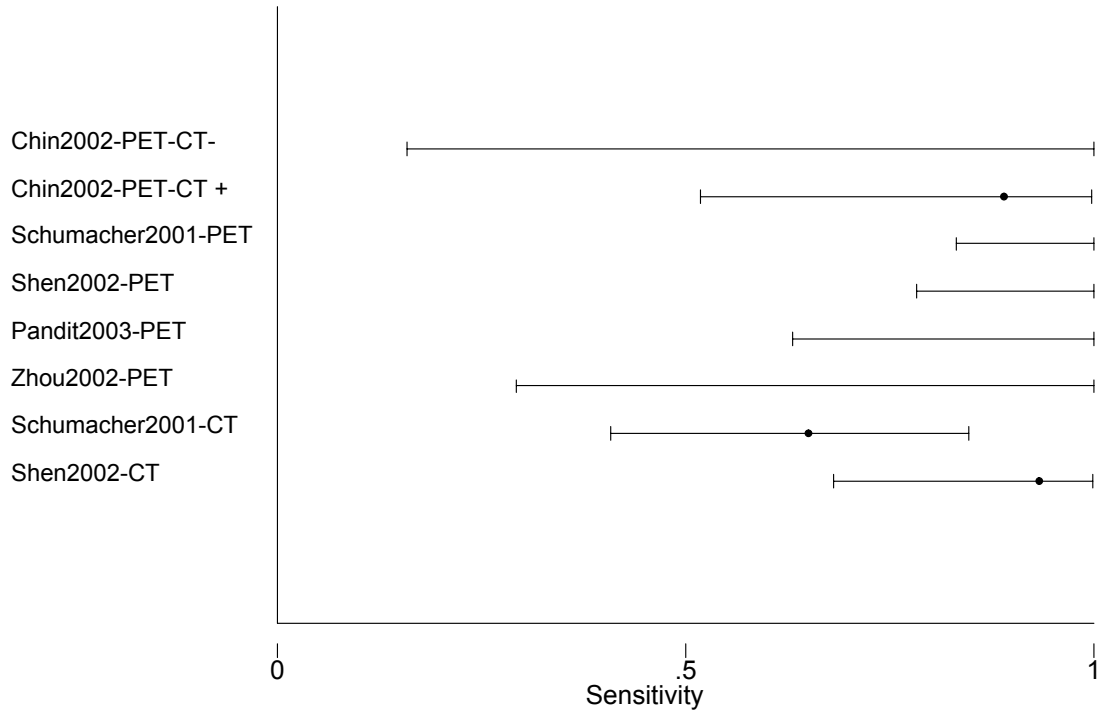

Figure 10a. Estimates of PET and comparator test(s) sensitivity with 95% confidence intervals for staging to determine the true extent of disease at initial diagnosis in patients with SCLC**.**

<u>Legend</u>

CT+ - CT positive test result

CT- CT negative test result

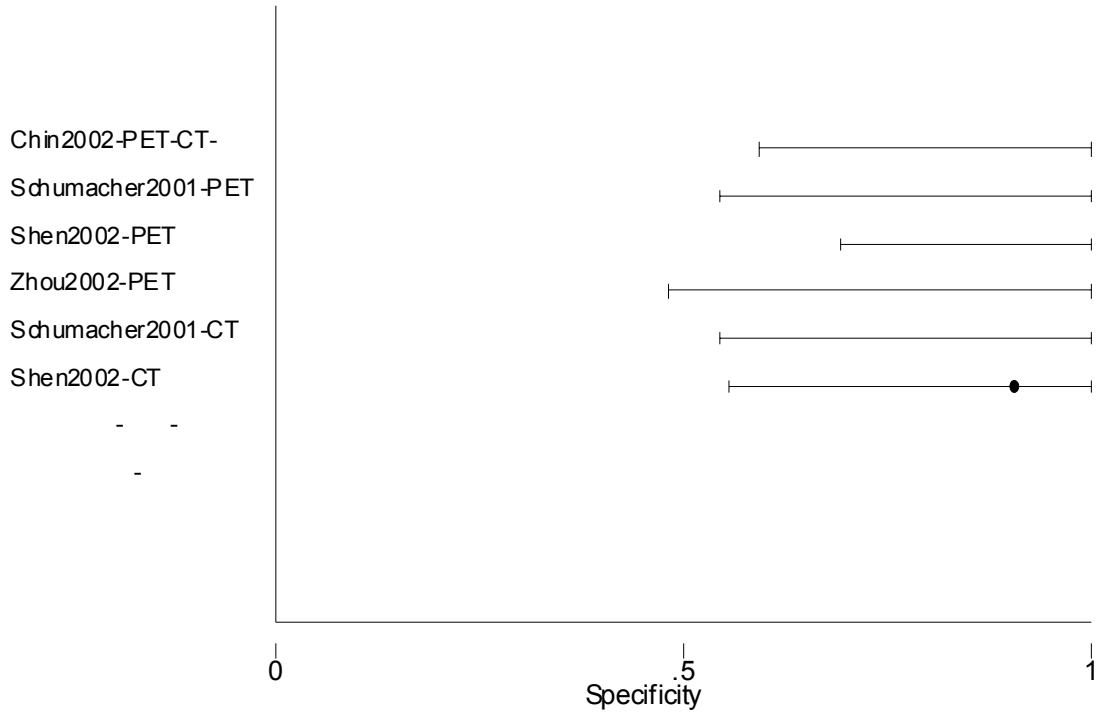

Figure 10b. Estimates of PET and comparator test(s) specificity with 95% confidence intervals for staging to determine the true extent of disease at initial diagnosis in patients with SCLC.

<u>Legend</u>

CT+ - CT positive test result

CT- CT negative test result

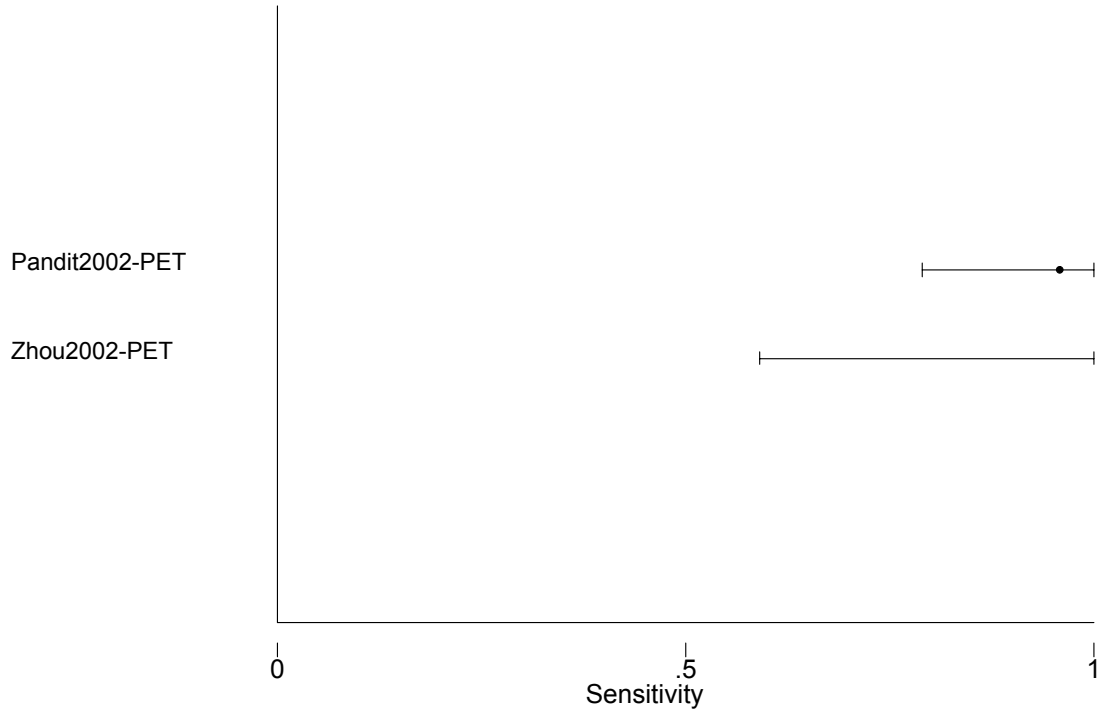

Figure 11a. Estimates of PET and comparator test(s) sensitivity with 95% confidence intervals for restaging post treatment to evaluate the response to initial treatment (detect residual or new disease sites) in patients with SCLC.

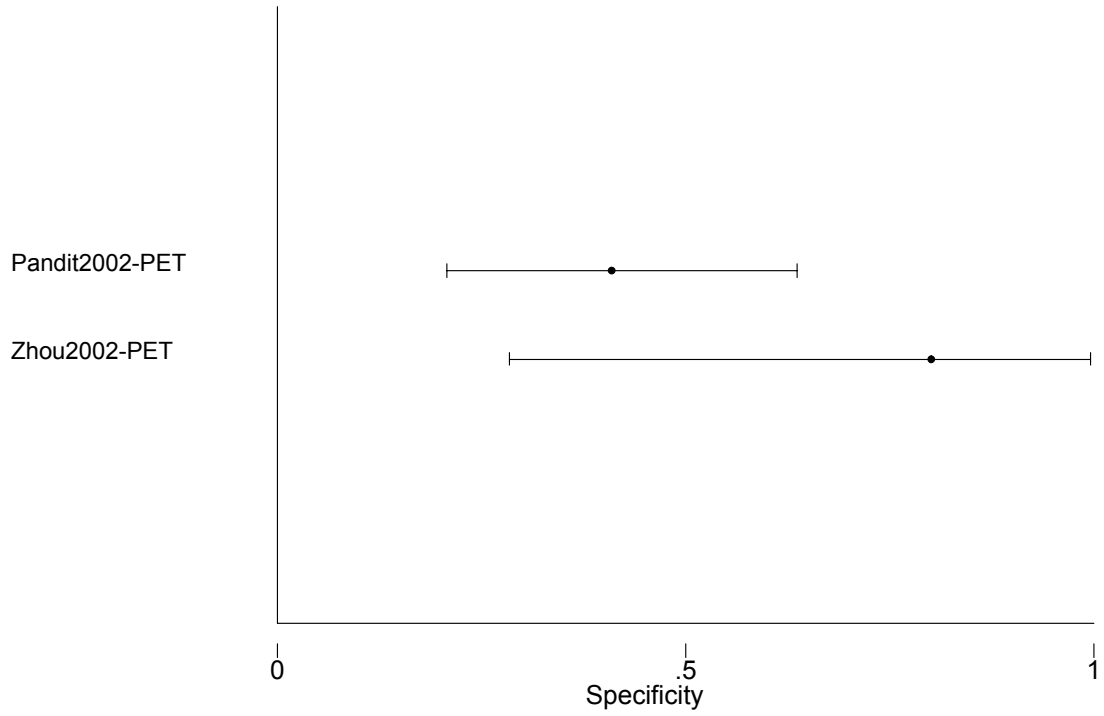

Figure 11b. Estimates of PET and comparator test(s) specificity with 95% confidence intervals for restaging post treatment to evaluate the response to initial treatment (detect residual or new disease sites) in patients with SCLC.

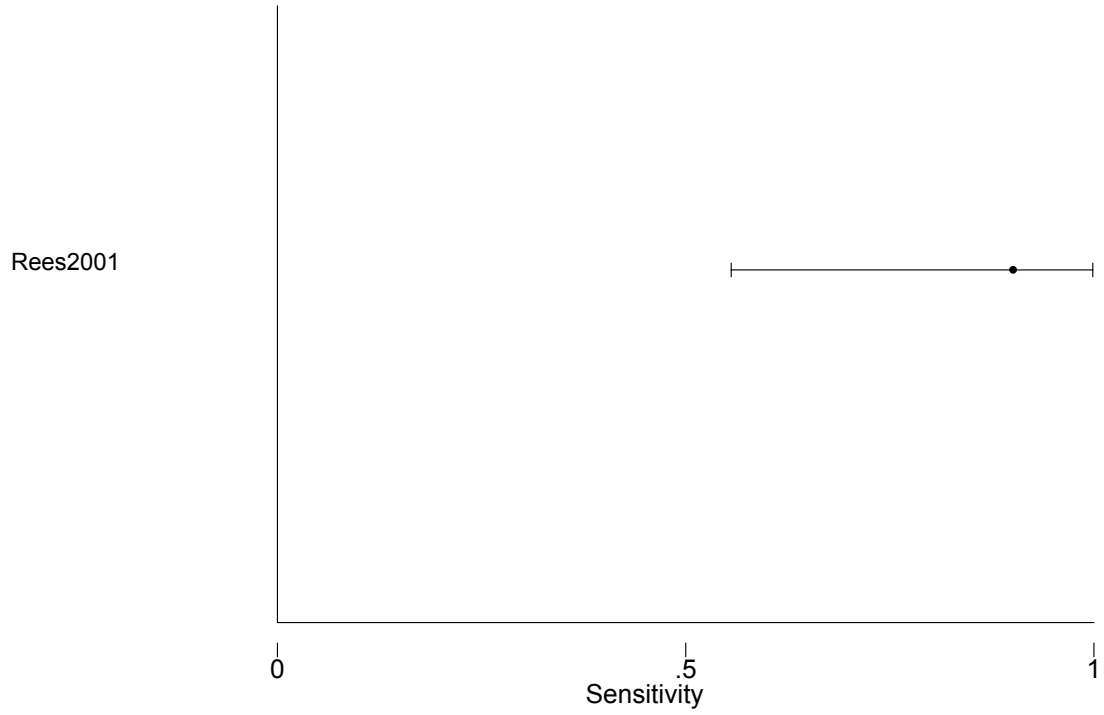

Figure 12a. Estimates of PET and comparator test(s) sensitivity with 95% confidence intervals for diagnosing occult small cell lung cancer in patients with paraneoplastic syndrome(s) commonly associated with this neoplasm.

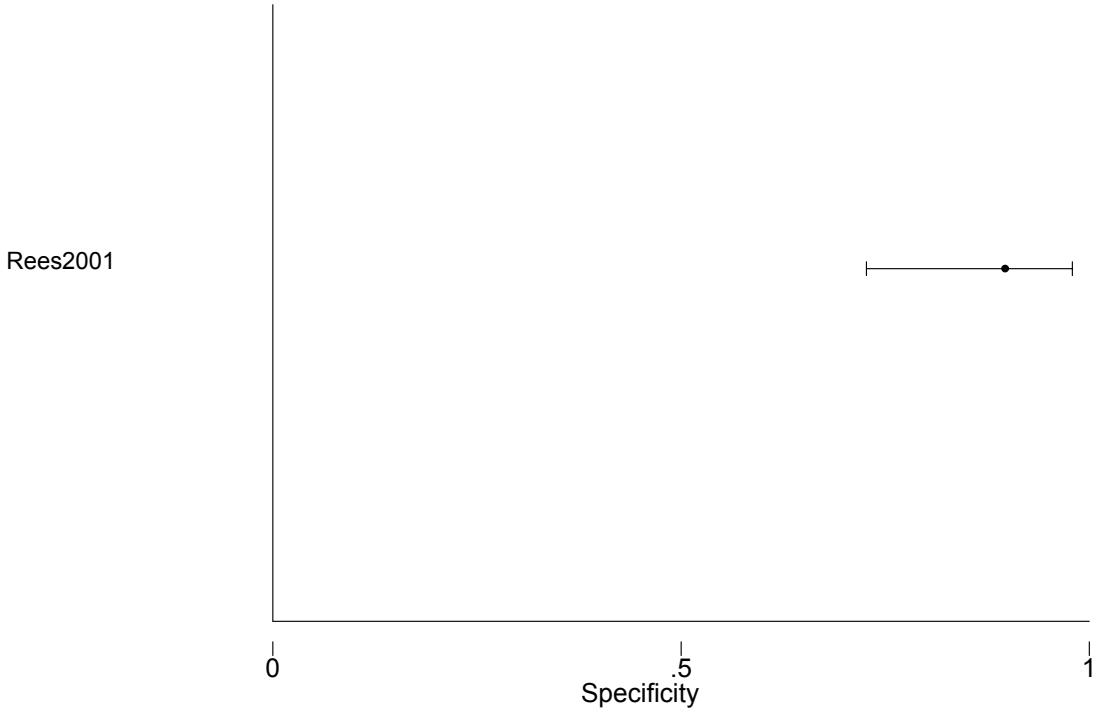

Figure 12b. Estimates of PET and comparator test(s) specificity with 95% confidence intervals for diagnosing occult small cell lung cancer in patients with paraneoplastic syndrome(s) commonly associated with this neoplasm.

3.6. Testicular Cancer

3.6.1. Background

Testicular cancer accounts for approximately 1 percent of all cancers in men. About 7,500 men in the United States are diagnosed with testicular cancer each year. Testicular cancer occurs most often in men between the ages of 15 and 39, and is the most common form of cancer in men between the ages of 20 and 34. Testicular cancers are germ cell tumors (GCTs) that can be broadly classified into two general types: seminomas and nonseminomas. Seminomas make up about 30 percent of all testicular cancers. Nonseminomas are a group of cancers that include choriocarcinoma, embryonal carcinoma, teratoma, and yolk sac tumors. Testicular tumors may contain both seminoma and nonseminoma cells. Diagnosis, staging and monitoring of response to therapy in patients with testicular cancer is currently accomplished using structural imaging techniques such as CT or MRI. However, a concern with these techniques is that they may result in false negatives due to their inability to resolve small volumes (diameter < 1 cm) of disease and can also lead to false positives due to their inability to distinguish between viable tumor masses and masses consisting of necrotic tissue or scar tissue. By relying on the differential uptake of glucose in malignant versus benign tissue, FDG-PET

may provide an alternative imaging technique with improved accuracy for patients with testicular GCTs.

3.6.2. CMS Statement of Work Questions

1. In patients with an established diagnosis of pure seminomas or non-seminomatous germ cell tumors, how does the diagnostic test performance of FDG-PET compare to conventional imaging modalities (e.g., CT, MRI) or histology with respect to the following clinical situations:
    a. For initial staging?
    b. In evaluation of residual masses or suspected recurrent disease to reliably distinguish between viable tumor and fibrosis/necrosis?
    c. In determining if there has been a recurrence of tumor in patients with rising serum tumor markers and a normal CT?

3.6.3. Importance of Questions Posed by CMS in Clinical Management

1. In patients with an established diagnosis of pure seminomas or non-seminomatous (NS) GCTs, performance of FDG-PET compared to conventional imaging modalities or histology:

a. For initial staging?

Following pathologic staging by retroperitoneal lymph node dissection (RPLND) 30% of patients with clinical stage I NSGCT are upstaged to pathologic stage II. (Fernandez, 1994; Albers, 1996.) The flip side of the equation is that 70% of patients with clinical stage I NSCGT will undergo an unnecessary RPLND, thereby risking the complications of that procedure with no long-term benefit. Similarly, patients with clinical stage I seminoma are upstaged 20% of the time by RPLND (Horwich, 1992). Current management options for patients with clinical stage I seminoma are 1) close observation with frequent (every 3-6 months) CT scans of the abdomen and pelvis, 2) adjuvant para-aortic nodal radiation or 3) diagnostic RPLND. A 20% rate of occult para-aortic nodal disease implies that 20% of observed patients will eventually fail and require salvage therapy and that 80% of patients undergoing radiation or RPLND will do so unnecessarily. More accurate radiographic staging would help ensure that those who have “occult” (by current imaging methods) retroperitoneal nodal metastases receive radiation and that those who do not have occult disease are managed by observation.

b. In evaluation of residual masses or suspected recurrent disease to reliably distinguish between viable tumor and fibrosis/necrosis?

The evaluation of residual masses after radiotherapy or chemotherapy in patients with stage II-IV testicular GCT has important prognostic and therapeutic implications. Following CT for NSGCT, the majority of residual masses are identified in the retroperitoneum. Accurate classification of these masses has important prognostic and therapeutic implications. There are three possibilities: 1) these masses may represent necrosis/fibrosis in which case prognosis is excellent, 2) they may consist of mature or immature teratoma in which case prognosis is still excellent but surgical excision is required to prevent “growing teratoma syndrome” in which slow growth of the teratoma compromises vital organ function, or 3) a residual mass may indicate residual viable tumor in which case prognosis is poorer and additional chemotherapy is indicated. Because conventional imaging techniques fail to reliably distinguish between these three possible scenarios, the present standard of care is to perform retroperitoneal lymph node dissections in patients with residual masses after chemotherapy if serum tumor markers are not elevated. In fact, at laparotomy, 40-50% of residual masses are found to consist of necrosis/fibrosis, 30-40% are mature or immature teratoma, and 15-20% are residual NSGCT. If residual masses after chemotherapy could be identified accurately by radiographic imaging, appropriate treatment and prognosis could be established without surgery.

c. In determining if there has been a recurrence of tumor in patients with rising serum tumor markers and a normal CT?

For most solid tumors, there is no survival advantage conferred by early detection of distant disease because metastatic disease remains incurable regardless of tumor burden. Because testicular cancer is uniquely sensitive to chemotherapy, early detection of distant disease may indeed confer a survival advantage. At present, surveillance following treatment for testicular cancer consists of periodic morphological imaging (typically CT) and periodic evaluation of serum tumor markers (in patients who present with abnormal elevation of alpha fetoprotein (AFP), beta human chorionic gonado tropin (HCG), or lactate dehyrogenase (LDH)). Although extremely sensitive for detection of recurrent disease, the utility of serum tumor markers is limited to patients who had elevated markers at presentation. CT scan is potentially valuable in all patients but the sensitivity of surveillance by CT is limited to detection of recurrent lesions that are greater than 1 cm in size.

3.6.4. Results

The literature search identified 301 abstracts. Review of the abstracts identified 28 potential articles for full-text review. Of these, 11 met the criteria for full text review and are discussed below. Data on the operating characteristics for the tests, including 95% confidence intervals are presented in tables and figures at the end of this section. Detailed evidence tables are available in Appendix D.

1a. Studies examining the role of FDG-PET in initial staging of patients

Category 2: Diagnostic accuracy

Quality score 4-7

Albers et al. (1999) compared FDG-PET and CT for the initial staging of patients with clinical stage (CS) I and II testicular germ cell tumors. A total of 37 patients with newly diagnosed testicular cancer were consecutively enrolled in this prospective study conducted in Bonn, Germany. Twenty-five patients had CS I disease by conventional staging procedures and 12 patients had CS II disease. Twenty-four patients had NSGCT and 13 had seminoma. CT and PET were obtained on all patients. CT scans were interpreted by blinded radiologists. A solitary nodule $\geq$ 1cm or a group of $\geq$ five sub-centimeter nodules was considered positive. PET scans were interpreted qualitatively and quantitatively by blinded

radiologists. An SUV of > 2.0 was considered positive (quantitative analysis). The reference standard for this study was based on histology for the 24 patients with NSGCT and on prolonged clinical FU (median 24 months) for the 13 patients with seminoma. The sensitivity and specificity of CT scan for the detection of retroperitoneal lymph node metastases were 40% and 93%. The sensitivity and specificity of PET was 70% and 100%. The main limitations of this study were as follows: 1) the methodology of qualitative analysis was not explicitly stated although most studies use simple “visual analysis” in which regions of FDG uptake that are greater than background or greater than seen in a paired contra-lateral structure and scored as “positive” and 2) the means of resolving any discrepancies in interpretation between qualitative and quantitative analysis was not described.

Cremerius et al. (1999) compared FDG-PET with CT and serum tumor markers for the initial staging of patients with CS I-III testicular cancer. A total of 50 patients from the University Hospital in Aachen, Germany were enrolled. 37 patients were CS I, 9 were CS II, and 5 were CS III. Thirty patients had seminoma and 20 patients had non-seminoma. PET and CT scans were interpreted by blinded radiologists. Findings were verified by histology or prolonged clinical follow-up. The sensitivity and specificity was 87% and 94% for PET, 73% and 94% for CT, and 67% and 100% for tumor markers. However, PET scans failed to detected

retroperitoneal node involvement in 3/10 patients with NSGCT (these three patients had teratocarcinomas). This study received a near perfect quality score. The only methodologic flaw identified was a lack of blinding of the gold standard (histology) reader. However, nearly ever study reviewed suffered from this flaw.

Hain et al. (2000a) compared FDG-PET with CT for the initial staging of patients with testicular cancer. They conducted a retrospective review of 31 patients with testicular cancer who were staged at diagnosis with PET scanning in addition to conventional staging with tumor markers and CT scans. Eighteen patients had NSGCT and 13 had seminoma. The reference standard for this study was based on histology or prolonged clinical follow-up. The sensitivity and specificity of PET was 67% and 100%, respectively, compared to 87% and 56% for CT. The limitations of this study were as follows: 1) the type of CT scanner used in this study and the positivity criterion were not stated, 2) the authors do not state if CT scans were read blindly, and 3) PET scans were read blindly but the positivity criteria were not stated.

Tsatalpas et al. (2002) compared FDG-PET with CT for initial staging and to assess response to therapy in patients with testicular cancer. Their findings with regard to assessment of response to therapy are discussed below (refer to section on role of PET in assessing response to therapy section). A total of 23 patients from Dresden, Germany with testicular

cancer were studied. Twelve patients had CS I disease by conventional staging and 11 had CS II-III disease. Ten patients had seminoma and 12 had NSGCT. A total of 32 PET scans were done in these 23 patients; 21 were done for initial staging and 11 were done to assess response to chemotherapy (CS II-III patients only). CT scans were interpreted qualitatively and quantitatively by blinded radiologists. Lymph nodes larger than 1.5 cm and areas of abnormal enhancement on contrast images were considered positive. PET scans were interpreted qualitatively using visual analysis and quantitatively using calculated SUV by blinded radiologists. Scans were scored as positive on visual analysis if an area of abnormal FDG accumulation was seen. The reference standard for this study was based on histology (n=7) or clinical followup of 6-11 months after the last PET study (n=16). The sensitivity and specificity of CT scan for the detection of metastatic disease was 60% and 100% respectively. The sensitivity and specificity of PET was 90% and 100% respectively. The main limitations of this study were as follows: 1) the cutoff value for positivity by SUV analysis was not stated, and 2) the lack of details regarding the test performance of PET in relevant subsets of patients (seminoma vs. NSCGT, CS I vs. II. vs. III).

There were no Category 3 through 6 studies identified in the literature review that addressed this question.

1b. Studies examining the role of FDG-PET for evaluation of residual masses after chemotherapy

Category 2: Diagnostic accuracy

Quality score 4-7

Tsatalpas et al. (2002) compared FDG-PET and CT for the evaluation of residual masses after chemotherapy. The characteristics of the patients enrolled in this study and the methods employed by the investigators were described in the previous section. The sensitivity and specificity of CT were 100% and 60% respectively. The sensitivity and specificity of PET were also 100% and 60% respectively. Although the test characteristics of CT and PET were identical the test results were not. Four patients with false positive CT scans after chemotherapy were correctly identified as not having any residual viable tumor by PET scan. The false positive CT scans were attributed to scar tissue. Conversely, four patients with false positive PET scans after chemotherapy were correctly identified as having no residual tumor by CT scan. The false positive PET scans were attributed to inflammation. Because all four false positive PET scans after chemotherapy occurred in supradiaphragmatic locations and were correctly identified as true negative by CT scan, the authors chose to perform an additional analysis in which the test characteristics of PET and CT for the evaluation of supra- and infradiaphragmatic lesions were examined

separately. For supradiaphragmatic lesions, the specificity of CT was shown to be higher than that of PET. The main limitation of the study is a lack of details provided on the patient population.

Sugawara et al. (1999) investigated the utility of FDG-PET in classifying residual masses after chemotherapy in germ cell tumor patients as viable tumor, mature teratoma, or necrotic tissue. A total of 21 patients treated at the University of Michigan were studied, 15 of whom presented with metastases from testicular primaries and 6 of whom had primary tumors in the retroperitoneum or mediastinum. PET scans were interpreted by unblinded radiologists qualitatively (3 point scale: intense uptake, equivocal uptake, no uptake) and quantitatively (SUV). The reference standard for this study was based on histology in 21 lesions (number of patients not stated) and by clinical data in 5 lesions (number of patients not stated). The authors did not report the sensitivity and specificity of their qualitative analysis. If PET scans scored as “equivocal” on visual analysis were considered “positive,” the sensitivity and specificity of PET would be 67% and 89%. If equivocal readings are scored as “negative,” the sensitivity and specificity of PET would be was 67% and 100%. Although PET was able to identify viable malignant tumor and necrotic masses accurately, PET was unable to correctly identify mature teratomas. All false negatives in this study were histologically proven to be mature teratomas. If “equivocal” readings were scored as “positive”, then 4

teratomas were misclassified as “negative” by PET. If “equivocal” readings were scored as “negative”, then 6 teratomas were misclassified as “negative” by PET. In contrast, viable tumor after chemotherapy was correctly identified in 6/6 cases and necrosis was correctly identified in 8/9 cases. Overall this was a high quality study. The main methodologic limitation that the radiologists were not blinded. Furthermore, the blinding status of the gold standard reader was not stated explicitly.

Nuutinen et al. (1997) evaluated the ability of PET to characterize correctly residual masses after chemotherapy in 15 patients with testicular cancer in Turku, Finland. Four patients had seminoma and 11 had non-seminoma. PET scans were interpreted qualitatively and quantitatively using calculated SUV. A 2 x 2 table was generated from the qualitative results but could not be generated from the quantitative results as the authors did not explicitly state a cutoff SUV for interpreting a scan as positive or negative. Using a reference standard of histology or prolonged follow-up, the sensitivity and specificity of PET was 75% and 78%. The 2 false positive readings were due to inflammation, whereas the 1 false negative diagnosis was due to teratoma. A main limitation of this study is the lack of a comparator test.

Kollmannsberger et al. (2002) compared FDG-PET, CT/MRI, and combined CT/MRI/Tumor Marker testing for the evaluation 85 residual lesions after chemotherapy in 45 patients with metastatic NSGCT. The

patients were consecutively enrolled in one of two German multicenter high-dose chemotherapy trials. PET scans were interpreted using semiquantitative analysis with SUV $\geq$ 2 considered positive. On CT scan lesions that progressed in size, lesions with a reduction in size of > 50%, and lesions with persistent/increased contrast medium uptake were considered viable. The criteria for positivity on MRI was not explicitly stated. In addition, the exact criteria for positivity by tumor markers was also not specified. Compared to a reference standard based on histology or prolonged follow-up, the specificity of PET was 92%, combined CT/MRI/Tumor Markers was 92% and CT/MRI was 86% while the sensitivity of PET was 59%, combined CT/MRI/Tumor Markers was 78% and CT/MRI was 55%. There were 3 false positive PET findings, two of which were due to inflammation and 1 of which was found to be a necrotic mass. There were 20 false negative PET findings. Two were due to mature teratoma (proven by biopsy); the etiology of the remaining 18 false negative results was unclear (lesions progressed within 6 months but no biopsy done). The primary limitations of this study were as follows: 1) the criteria for positivity on MRI was not explicitly stated, and 2) the exact criteria for positivity by tumor markers was also not specified.

Desantis et al. (2001) compared FDG-PET and CT scan for the evaluation of patients with bulky seminoma following chemotherapy. Thirty-scans were obtained in 33 patients with bulky seminoma who were

consecutively enrolled on a prospective multicenter trial conducted at 5 centers in Austria and 1 in Germany. The initial stage was not stated. Twenty-eight patients were scanned after undergoing first line chemotherapy, 5 after conventional dose salvage chemotherapy, and 4 after high-dose salvage chemotherapy with peripheral stem cell support. CT scans were considered positive if a lesion $\geq$ 3 cm in size was seen. PET scans were interpreted visually. Scans were classified as positive or negative based on the "localization, shape, and intensity of the increased [PET] uptake." SUVs were recorded but quantitative interpretation was apparently not performed. Compared to a reference standard based on histology (n=9) or prolonged clinical follow-up (n=28), PET had a sensitivity of 89% and specificity of 100%. For CT, sensitivity was 78% and specificity was 75%. There were no false positive PET scans and only 1 false negative PET that occurred in a patient with two small (largest 1.9cm) masses in the retroperitoneum and mediastinum after chemotherapy. The results of this trial contradict the results of the trial reported by Ganjoo et al. (see below). The primary limitation of this study is that the authors do not clearly state whether the radiologists or the gold standard readers were blinded.

Ganjoo et al. (1999) prospectively studied the utility of PET scan in the evaluation of postchemotherapy masses in 29 patients with seminoma in Indiana. Nineteen patients were evaluated after primary chemotherapy

(Group A) and 10 patients were studied after salvage chemotherapy (Group B). The authors do not state if PET or CT scans were read blindly. Confirmation of radiologic findings was by prolonged follow up or histology. Masses with an SUV $\geq$ 4 were considered positive by PET. Masses $\geq$ 3 cm in size were considered positive by CT. The sensitivity for PET and CT for viable tumor in Group A could not be calculated because no patient had viable tumor. The specificity of PET was 89% compared with 26% for CT. In patients treated with salvage chemotherapy (Group B), PET was unable to detect residual viable tumor, which was present in 5 of 10 patients. In Group B patients the sensitivity of PET was 0% compared with 50% for CT while the specificity of PET was 80% compared with 100%. For the two groups combined the sensitivity and specificity was 0% and 96% for PET and 50% and 42% for CT. The authors conclude that PET scanning is "not beneficial in distinguishing necrosis from viable seminoma" and they did "not recommend the routine use of PET scans in the evaluation of residual postchemotherapy masses in seminoma." The main limitation of the study (in the salvage chemotherapy setting) was the small number of patients. Findins in the first-line chemotherapy setting were limited by the fact that no patient treated with first line chemotherapy had residual viable GCT or teratoma (therefore the sensitivity of PET was indeterminate). An additional limitation of this study is the lack of detail on the PET scanner used including model description.

Stephens et al. (1996) assessed the ability of PET to differentiate residual radiographic abnormalities following chemotherapy in 30 nonseminomatous germ cell tumor patients. The same investigators later reported their experience with seminoma patients (refer to Ganjoo, 1999). All patients had normal tumor marker (AFP, beta HCG) levels. Twenty-two patients had received first line chemotherapy and 8 had been treated with salvage chemotherapy. PET scans were evaluated by quantitative analysis, using an SUV cutoff of 5.0. Radiographic results were verified by either histology or prolonged follow-up. Viable GCT (median SUV 8.82) was distinguished from necrosis/fibrosis (median SUV 2.86) but teratoma (median SUV 3.07) was not. As a result, all 15 teratomas resulted in false negative readings. While the specificity of PET was 91%, the sensitivity of PET was only 16%. Because all patients included in this study had CT abnormalities, by definition the sensitivity of CT was 100% and the specificity was 0%. The main limitation of this study was that the authors did not specify if PET scan readers were blinded to the results of the CT scans.

Cremerius et al (1998) compared FDG-PET and CT for evaluation of residual postchemotherapy masses in patients with germ cell tumors. Thirteen scans were done less than 2 weeks after patients had finished chemotherapy and 29 scans were done more than 2 weeks after

chemotherapy. For patients scanned within 2 weeks after chemotherapy the sensitivity and specificity of PET were 44% and 100%, compared with 78% and 50% for CT. For patients scanned more than 2 weeks after chemotherapy the sensitivity of PET increased to 78% while the SP remained high at 90%. By comparison, sensitivity and specificity of CT were relatively unchanged at 67% and 55%. The authors speculate that performing PET scans within 2 weeks of chemotherapy results in a large number of FN results because chemotherapy leads to a transient suppression of metabolic activity in germ cell tumors regardless of their final response to therapy. The authors therefore conclude that PET scans should not be performed for at least 2 weeks after chemotherapy is finished. The main limitation of this study was that the radiologists were not blinded.

There were no Category 3 through 6 identified in the literature that addressed this question.

1c. Studies examining the role of FDG-PET in detecting recurrent tumor in patients with rising serum tumor markers but a normal CT

Category 2: Diagnostic accuracy

<u>Quality Score 4-7</u>

Hain et al (2000b) performed a retrospective review to determine the test performance of FDG-PET in 55 patients with germ cell tumors consecutively evaluated from 1994-1998. A total of 70 PET scans were done; 47 in patients with residual masses after chemotherapy and 41 in patients with elevated tumor markers after chemotherapy. (Eighteen scans were performed in patients with both residual masses and raised tumor markers.) The reference standard was based on histology or prolonged clinical follow-up. For patients with residual masses after chemotherapy the sensitivities of PET, CT, and tumor markers were 89%, 100%, and 62%, respectively while corresponding specificities were 95%, 0%, and 95%. For patients with elevated tumor markers the sensitivities of PET, CT, and tumor markers were 82%, 55%, and 100%, respectively while the corresponding specificities were 88%, 0%, and 0%. For the entire group of 70 scans the sensitivity of PET and tumor markers was 81% vs. 76%, while the specificity was 92% vs. 70%. Among patients with elevated serum tumor markers but a normal CT, PET was found to have sensitivity of 73% and a specificity of 88% for the diagnosis of recurrent germ cell tumor. The main limitations of this study were as follows: 1) the interpretation criteria for PET and CT were not explicitly stated, 2) the authors did not mention whether the radiologist or the gold standard (pathology or clinical follow-up) readers were blinded.

Category 3: Diagnostic Thinking Impact

Category 4: Therapeutic Choice Impact

Quality Score 4-7

In the study by Hain et al (2000b), the authors calculated that 57% (27/47) of patients had a change in management based on PET findings compared with the plan of care based on CT findings alone. The impact of PET on patient outcomes (Category 5) and on society (Category 6) was not discussed.

3.6.5. Conclusions

1a. Performance of FDG-PET compared to conventional imaging modalities or histology with respect to initial staging in patients with germ cell tumors.

Because of the rarity of germ cell tumors and the relatively recent introduction of PET scanners into widespread clinical use, only a few small studies have evaluated the utility of FDG-PET imaging in patients with this malignancy. Five studies evaluating PET in the initial staging of patients with GCTs met criteria for inclusion in this review. Although all are limited by small sample size, these five studies provide direct and fairly consistent evidence that the sensitivity and specificity of FDG-PET is higher than CT for the initial staging of patients with germ cell tumors. One prospective study (Albers, 1999) and 3 retrospective studies (Cremerius, 1999; Hain, 2000a; Tsatalpas, 2002) showed improved sensitivity and specificity for PET compared with CT. A fourth retrospective study (Cremerius, 1998) showed no difference in sensitivity and specificity between PET and CT. However, the clinical relevance of most of these studies is hampered by: 1) failure to report results for seminoma and non-seminoma patients separately and 2) failure to report results separately by clinical stage. (Upstaging or downstaging by an improved radiographic test would have important implications for therapy, which would differ by stage.)

1b. Diagnostic performance of FDG-PET compared with conventional imaging in the evaluation of residual masses or suspected recurrent disease to reliably distinguish between viable tumor and necrosis/fibrosis.

Our review did not identify any studies, which evaluated the role of FDG-PET in detecting recurrent disease following initial treatment for germ cell tumors.

Eight studies assessing the ability of FDG-PET to characterize residual post chemotherapy masses as either viable tumor or necrosis/fibrosis met criteria for inclusion within this review. Several features of these studies make it difficult to draw firm conclusions regarding the test characteristics of PET and CT in this setting: 1) Most of these studies focus primarily on evaluating the test characteristics of PET scan, rather than directly comparing PET with CT. 2) Several of these studies do not explicitly state a positivity criterion for CT. (For the purpose of this analysis, if no positivity criterion for CT was stated, a size cutoff of 1cm was assumed in calculations of sensitivity and specificity.) 3) The relative sensitivity of PET and CT for the detection of viable tumor after chemotherapy is highly dependent on the positivity criterion used for CT. If any residual mass seen on CT is defined as a “positive” CT, then by definition CT has a sensitivity of 100%. Alternatively, if a “positive” CT is defined as one which shows an unchanged or growing mass or a mass greater than a certain size (e.g. 3 cm), then the sensitivity of CT is reduced.

4) The results may differ in patients with seminoma versus non-seminoma. Residual masses in seminoma patients are either viable tumor or necrosis/fibrosis. In patients with non-seminoma a third possibility exists: the residual mass may be a teratoma.

For the reasons described above, estimates of the sensitivity of PET to detect viable tumor varied widely in the literature included for review. Four studies showed a relatively high sensitivity in the range of 75-100% and 4 studies showed relatively low sensitivity in the range of 16-67%. The low sensitivity of PET in these 4 studies was largely due to the inability of PET to distinguish between teratoma and necrosis/fibrosis. Although teratomas are benign, most authorities consider them a “true positive” in the sense that surgical resection is required to prevent complications secondary to benign teratoma syndrome and to prevent malignant transformation. To improve the sensitivity of PET scan, some authors advocate avoiding its use in patients with a high probability of having residual teratoma (i.e. patients with teratomatous elements in the primary tumor). Similarly, the sensitivity of CT scan varied widely from 55% to 100% and was highly dependent on the positivity criterion used.

On the other hand, the specificity of PET was consistently higher than that of CT in this context. Seven out of eight studies showed markedly higher specificity for PET (range: 78-100%) compared with CT (range: 0-86%). The eighth study found that PET and CT had an equal specificity of

60%. From a clinical standpoint, a high specificity would mean that a positive PET scan indicates a high probability of residual viable tumor while a low sensitivity means that a negative PET scan does not provide complete assurance that the patient does not have a mass, which requires surgical resection, especially in patients with non-seminomatous germ cell tumors.

1c. The diagnostic performance of FDG-PET compared with conventional imaging in determining if there has been a recurrence of tumor in patients with rising serum tumor markers and a normal CT?

Our review identified only one study addressing this question. In the study by Hain et al (2000b), PET was found to have sensitivity of 73% and a specificity of 88% for the diagnosis of recurrent germ cell tumor in patients with rising tumor markers but a normal CT.

3.6.6. Tables

Table 15. Estimates of PET and comparator test(s) sensitivity and specificity with 95% confidence intervals for initial staging of patients with testicular cancer.

Study	**Sensitivity**	**95% Confidence Interval**	**Specificity**	**95% Confidence Interval**
Albers 1999 – PET	0.700	0.348-0.933	1.00	0.872-1.00
Cremerius 1999 – PET	0.867	0.595-0.983	0.943	0.808-0.993
Hain 2000a – PET	0.667	0.384-0.882	1.00	0.795-1.00
Tsatalpas 2002 – PET	0.900	0.555-0.997	1.00	0.715-1.00
Albers 1999 – CT	0.400	0.122-0.738	0.926	0.757-0.991
Cremerius 1999 – CT	0.733	0.449-0.922	0.943	0.808-0.993
Hain 2000a – CT	0.867	0.595-0.983	0.562	0.299-0.802
Tsatalpas 2002 – CT	0.600	0.262-0.878	1.00	0.715-1.00
Cremerius 1999 – Tumor markers	0.667	0.384-0.882	1.00	0.900-1.00

Table 16. Estimates of PET and comparator test(s) sensitivity and specificity with 95% confidence intervals for evaluation of residual masses after chemotherapy in patients with testicular cancer.

Study	**Sensitivity**	**95% Confidence Interval**	**Specificity**	**95% Confidence Interval**
DeSantis 2001 – PET	0.889	0.517-0.997	1.00	0.876-1.00
Kollmansberger 2002 – PET	0.592	0.442-0.730	0.917	0.775-0.982
Nuutinen 1997 – PET	0.75	0.194-0.994	0.778	0.400-0.972
Sugawara 1999 – PET(equiv.=+)	0.667	0.349-0.901	0.889	0.517-0.997
Sugawara 1999 – PET(equiv.=-)	0.667	0.383-0.882	1.00	0.715-1.00
Tsatalpas 2002 – PET	1.00	0.025-1.00	0.600	0.262-0.878
Ganjoo 1999 0 PET	0.00	0.00-0.522	0.958	0.789-0.999
Stephens 1996 – PET	0.158	0.034-0.396	0.909	0.587-0.998
DeSantis 2001 – CT	0.778	0.400-0.972	0.750	0.551-0.893
Tsatalpas 2002 – CT	1.00	0.025-1.00	0.600	0.262-0.878
Ganjoo 1999 – CT	0.500	0.068-0.932	0.417	0.221-0.633
Stephens 1996 – CT	0.480	0.278-0.687	0.00	0.00-0.841
Kollmansberger 2002 – CT or MRI	0.551	0.402-0.693	0.861	0.705-0.953
Kollmansberger 2002 – CT or MRI or Serum	0.776	0.634-0.882	0.917	0.775-0.982
Cremerius 1998 – PET < 2 weeks	0.444	0.137-0.788	1.00	0.398-1.00

Cremerius 1998 – CT < 2 weeks	0.778	0.400-0.972	0.500	0.068-0.932
Cremerius 1998 – PET > 2 weeks	0.778	0.400-0.972	0.900	0.683-0.988
Cremerius 1998 – CT > 2 weeks	0.667	0.299-0.925	0.550	0.315-0.769

Table 17. Estimates of PET sensitivity and specificity with 95% confidence intervals for evaluation of residual masses after chemotherapy with increased tumor markers and normal CT in patients with testicular cancer.

Study	**Sensitivity**	**95% Confidence Interval**	**Specificity**	**95% Confidence Interval**
Hain 2000b – PET (1)	0.733	0.445-0.922	0.875	0.473-0.997
Hain 2000b – PET (2)	0.893	0.718-0.977	0.947	0.738-0.999

Key

1- Elevated markers- normal CT

2- Residual masses, post chemotherapy

3.6.7. Figures

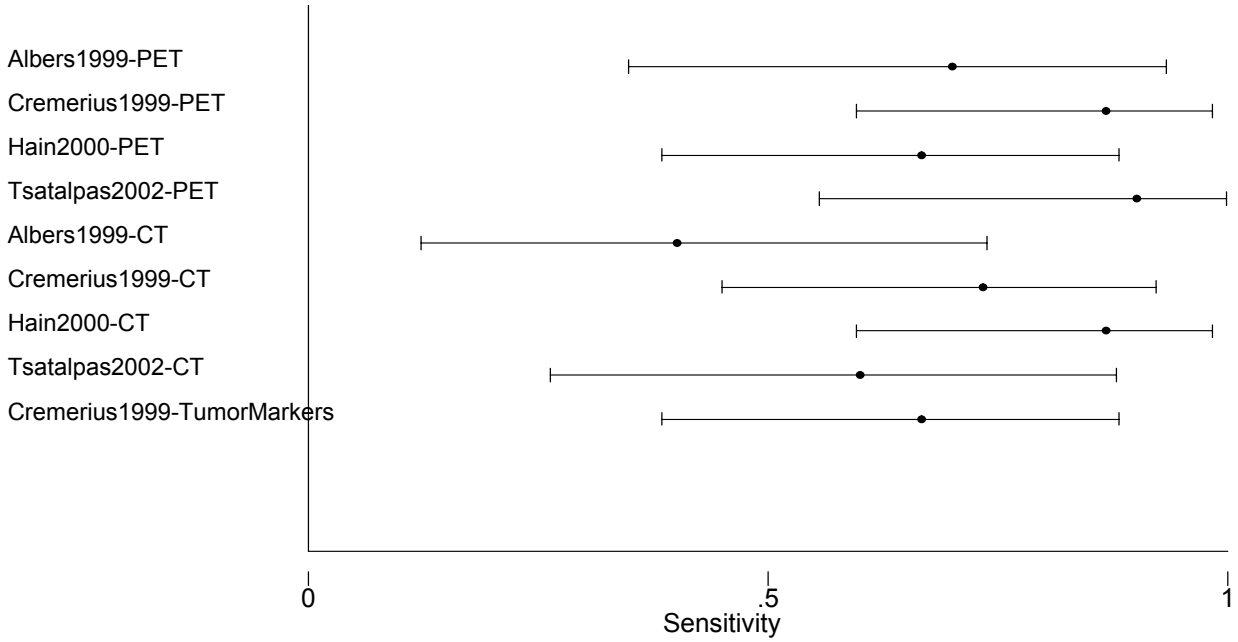

Figure 13.a. Estimates of PET and comparator test(s) sensitivity with 95% confidence intervals for initial staging of patients with testicular cancer

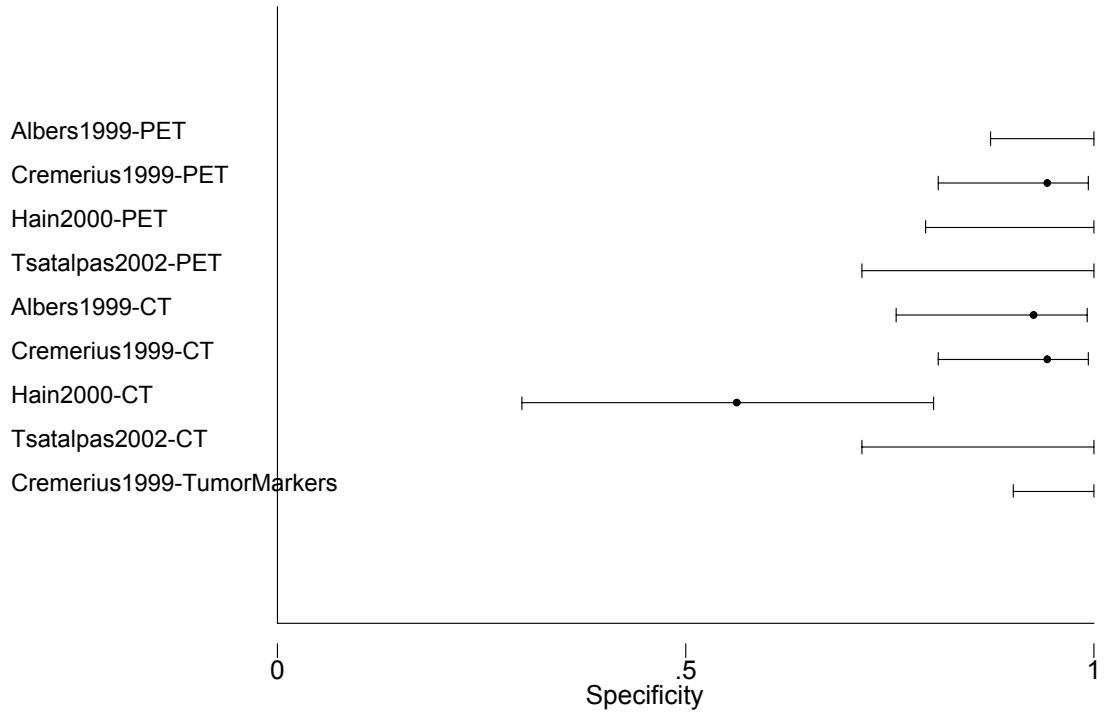

Figure 13.b. Estimates of PET and comparator test(s) specificity with 95% confidence intervals for initial staging of patients with testicular cancer

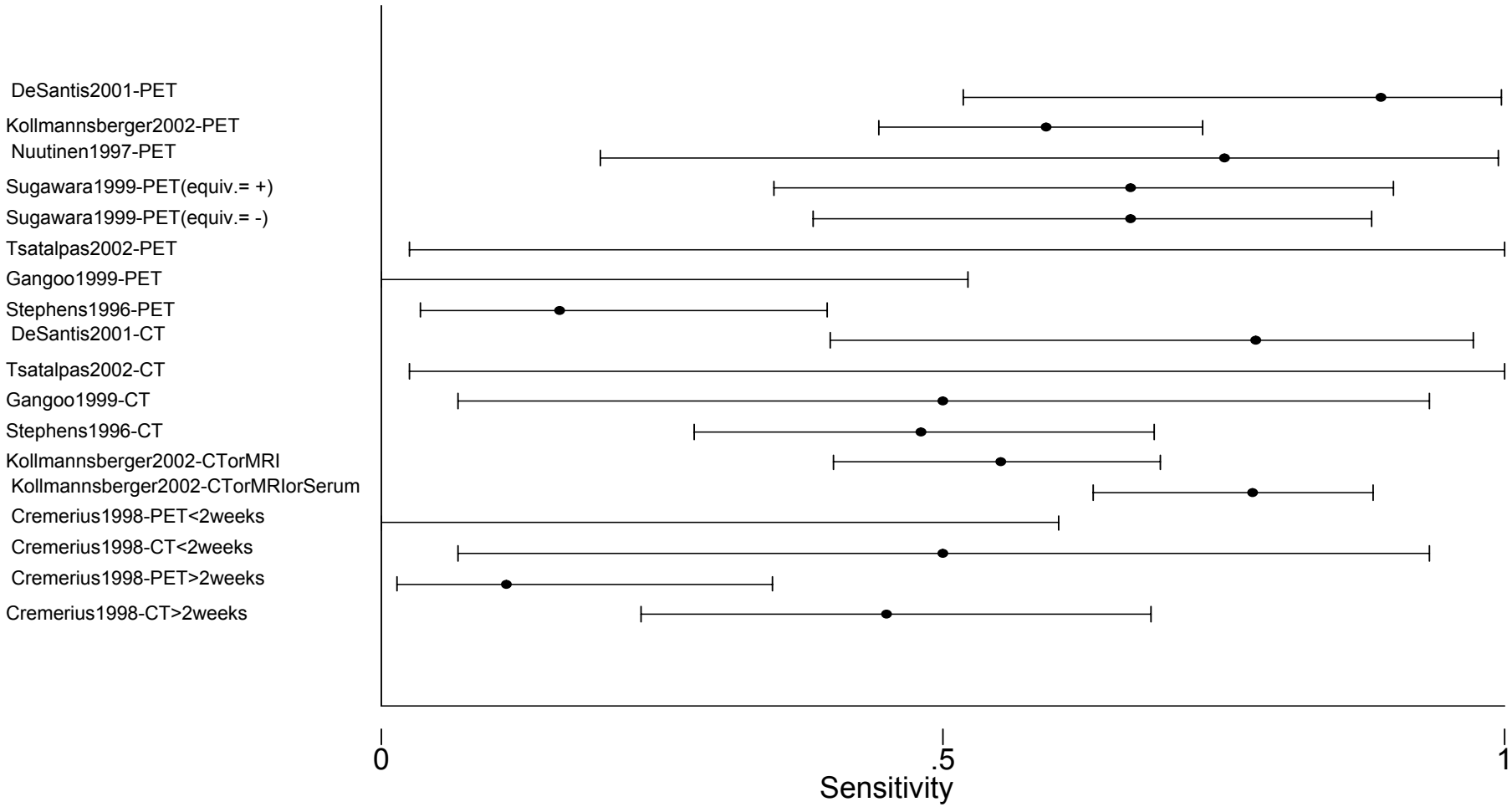

Figure 14.a. Estimates of PET and comparator test(s) sensitivity with 95% confidence intervals for evaluation of residual masses after chemotherapy in patients with testicular cancer

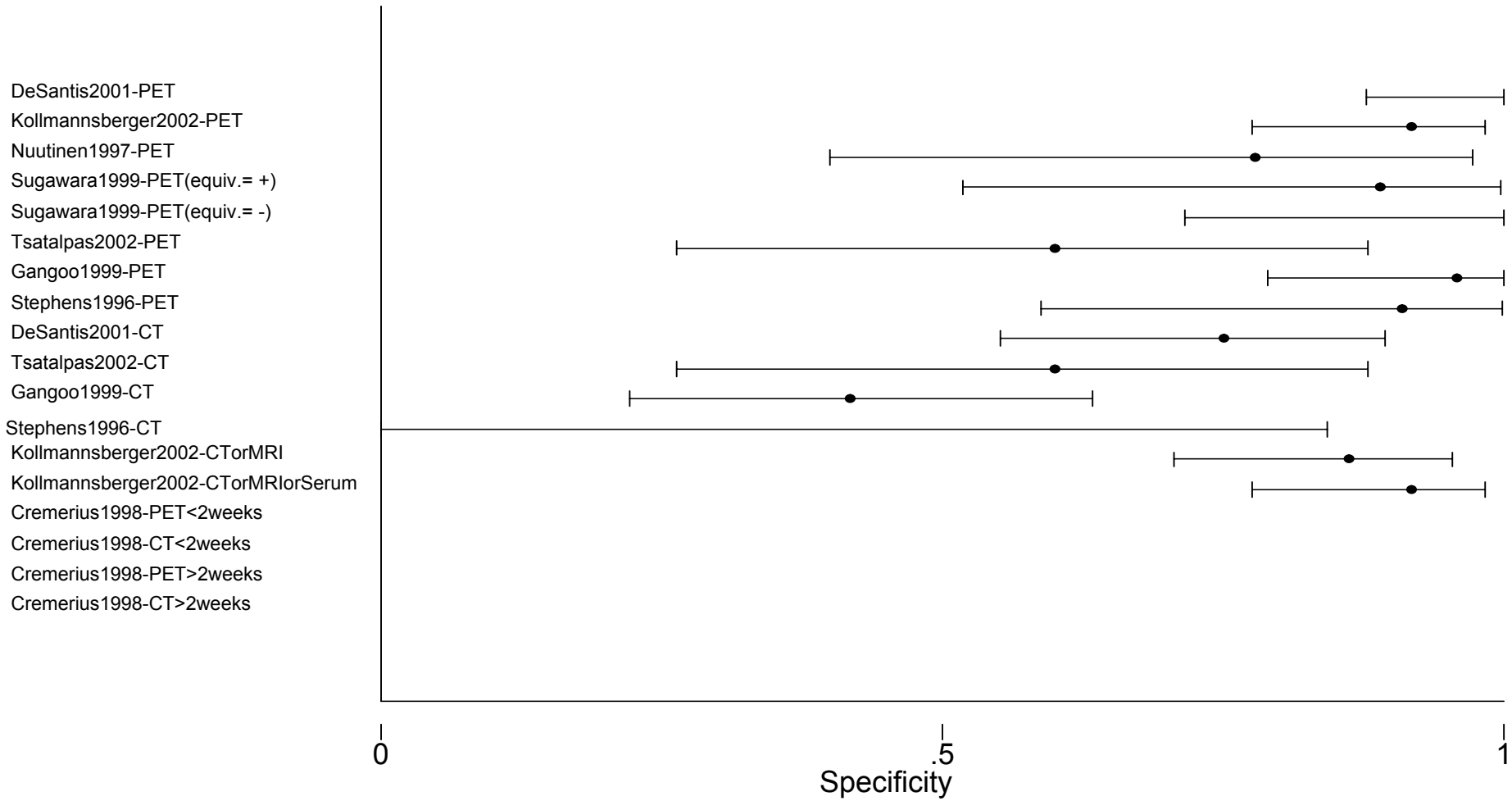

Figure 14.b. Estimates of PET and comparator test(s) specificity with 95% confidence intervals for evaluation of residual masses after chemotherapy in patients with testicular cancer

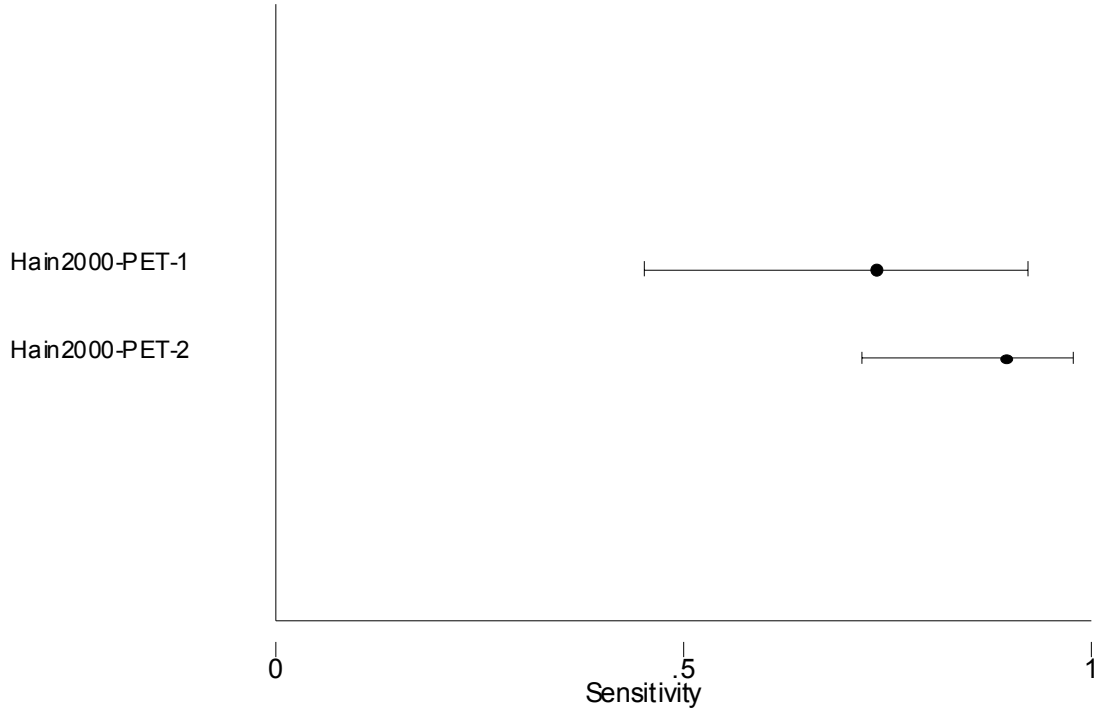

Figure 15.a. Estimates of PET sensitivity with 95% confidence intervals for evaluation of residual masses after chemotherapy with increased tumor markers and normal CT in patients with testicular cancer

Key

1- Elevated markers- normal CT

2- Residual masses, post chemotherapy

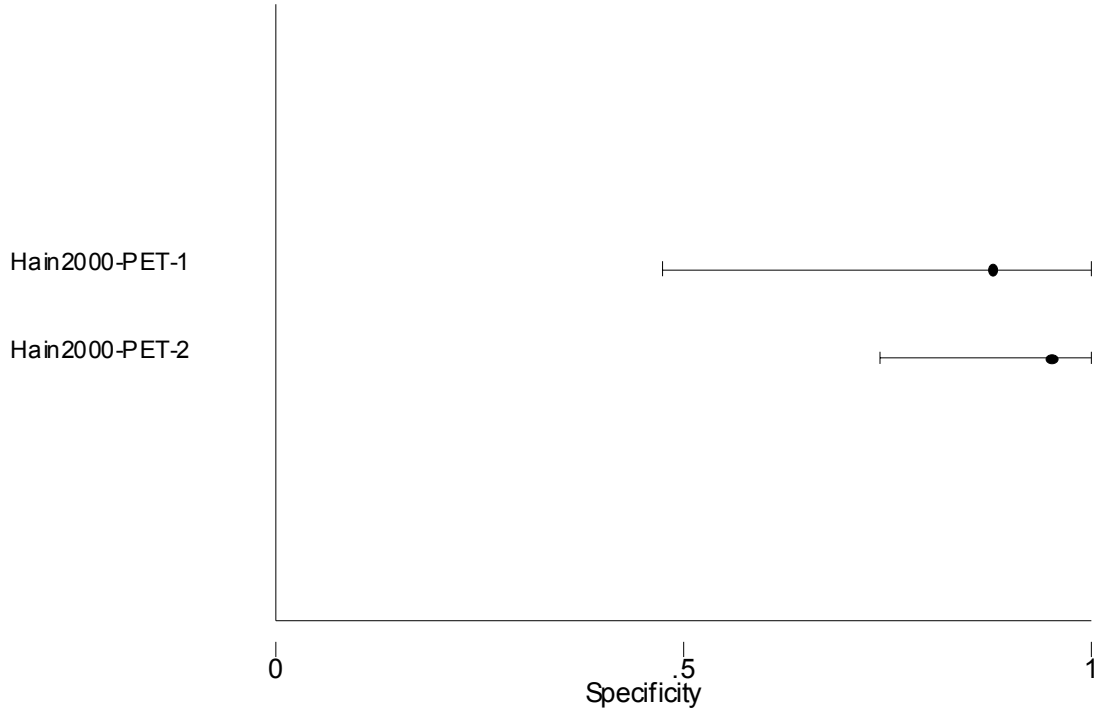

Figure 15.b. Estimates of PET specificity with 95% confidence intervals for evaluation of residual masses after chemotherapy with increased tumor markers and normal CT in patients with testicular cancer

<u>Key</u>

1- Elevated markers- normal CT

2- Residual masses, post chemotherapy

4. General Limitations of the Literature Reviewed

A variety of limitations of the literature can affect the interpretation of evidence related to the use of PET. First, PET is a rapidly evolving technology and, as such, information from a somewhat older generation of equipment may not always be applicable to the newest generation. This limitation may be particularly salient to PET in which there have been advances in the hardware used to acquire the raw data (e.g. the advent of hybrid PET/CT scanners) and the software used to generate an image based on that raw data (e.g. attenuation-correction). Second, the literature regarding PET often does not directly address a focused clinical question, such as those posed by CMS. For example, a common limitation was the inclusion of a heterogeneous population of patients without presentation of results by clinically relevant subgroups. Another common limitation was the absence of data that would allow the reader to infer the information contributed by PET beyond what was available from conventional studies. In some cases the data is presented in a way that only permits an estimate of the operating characteristics of PET versus other technologies; in other cases no comparator was considered at all.

Despite these limitations, there is, for the most part, a meaningful body of evidence that serves to inform the deliberations by CMS regarding the use of FDG-PET in specific cancers.

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6. Appendices

6.1. APPENDIX A – Neuroepithelial Tumors of the CNS (Kleihues,1993)

1. Astrocytic tumors [glial tumors--categories I-V, below--may also be subclassified as invasive or non-invasive, although this is not formally part of the WHO system, the non-invasive tumor types are indicated below. Categories in italics are also not recognized by the new WHO classification system, but are in common use.]
    1. Astrocytoma (WHO grade II)
        1. variants: protoplasmic, gemistocytic, fibrillary, mixed
    2. Anaplastic (malignant) astrocytoma (WHO grade III)
        1. *hemispheric*
        2. *diencephalic*
        3. *optic*
        4. *brain stem*
        5. *cerebellar*
    3. Glioblastoma multiforme (WHO grade IV)
        1. variants: giant cell glioblastoma, gliosarcoma
    4. Pilocytic astrocytoma [non-invasive, WHO grade I]
        1. *hemispheric*
        2. *diencephalic*
        3. *optic*
        4. *brain stem*
        5. *cerebellar*
    5. Subependymal giant cell astrocytoma [non-invasive, WHO grade I]
    6. Pleomorphic xanthoastrocytoma [non-invasive, WHO grade I]

2. Oligodendroglial tumors
    1. Oligodendroglioma (WHO grade II)
    2. Anaplastic (malignant) oligodendroglioma (WHO grade III)
3. Ependymal cell tumors
    1. Ependymoma (WHO grade II)
        1. variants: cellular, papillary, epithelial, clear cell, mixed
    2. Anaplastic ependymoma (WHO grade III)
    3. Myxopapillary ependymoma
    4. Subependymoma (WHO grade I)
4. Mixed gliomas
    1. Mixed oligoastrocytoma (WHO grade II)
    2. Anaplastic (malignant) oligoastrocytoma (WHO grade III)
    3. Others (*e.g.* ependymo-astrocytomas)
5. Neuroepithelial tumors of uncertain origin
    1. Polar spongioblastoma (WHO grade IV)
    2. Astroblastoma (WHO grade IV)
    3. Gliomatosis cerebri (WHO grade IV)
6. Tumors of the choroid plexus
    1. Choroid plexus papilloma
    2. Choroid plexus carcinoma (anaplastic choroid plexus papilloma)
7. Neuronal and mixed neuronal-glial tumors
    1. Gangliocytoma
    2. Dysplastic gangliocytoma of cerebellum (Lhermitte-Duclos)
    3. Ganglioglioma
    4. Anaplastic (malignant) ganglioglioma
    5. Desmoplastic infantile ganglioglioma

        1. *desmoplastic infantile astrocytoma*
    6. Central neurocytoma
    7. Dysembryoplastic neuroepithelial tumor
    8. Olfactory neuroblastoma (esthesioneuroblastoma)
        1. variant: olfactory neuroepithelioma
8. Pineal Parenchyma Tumors
    1. Pineocytoma
    2. Pineoblastoma
    3. Mixed pineocytoma/pineoblastoma
9. Tumors with neuroblastic or glioblastic elements (embryonal tumors)
    1. Medulloepithelioma
    2. Primitive neuroectodermal tumors with multipotent differentiation
        1. medulloblastoma
            1. variants: medullomyoblastoma, melanocytic medulloblastoma, desmoplastic medulloblastoma
        2. cerebral primitive neuroectodermal tumor
    3. Neuroblastoma
        1. variant: ganglioneuroblastoma
    4. Retinoblastoma
    5. Ependymoblastoma

<u>Other CNS Neoplasms</u>

1. Tumors of the Sellar Region
    1. Pituitary adenoma
    2. Pituitary carcinoma
    3. Craniopharyngioma

2. Hematopoietic tumors
    1. Primary malignant lymphomas
    2. Plasmacytoma
    3. Granulocytic sarcoma
    4. Others
3. Germ Cell Tumors
    1. Germinoma
    2. Embryonal carcinoma
    3. Yolk sac tumor (endodermal sinus tumor)
    4. Choriocarcinoma
    5. Teratoma
    6. Mixed germ cell tumors
4. Tumors of the Meninges
    1. Meningioma
        1. variants: meningothelial, fibrous (fibroblastic), transitional (mixed), psammomatous, angiomatous, microcystic, secretory, clear cell, chordoid, lymphoplasmacyte-rich, and metaplastic subtypes
    2. Atypical meningioma
    3. Anaplastic (malignant) meningioma
5. Non-menigothelial tumors of the meninges
    1. Benign Mesenchymal
        1. osteocartilaginous tumors
        2. lipoma
        3. fibrous histiocytoma
        4. others
    2. Malignant Mesenchymal
        1. chondrosarcoma
        2. hemangiopericytoma

        3. rhabdomyosarcoma
        4. meningeal sarcomatosis
        5. others
    3. Primary Melanocytic Lesions
        1. diffuse melanosis
        2. melanocytoma
        3. maliganant melanoma
            1. variant meningeal melanomatosis
    4. Hemopoietic Neoplasms
        1. malignant lymphoma
        2. plasmactoma
        3. granulocytic sarcoma
    5. Tumors of Uncertain Histogenesis
        1. hemangioblastoma (capillary hemangioblastoma)
6. Tumors of Cranial and Spinal Nerves
    1. Schwannoma (neurinoma, neurilemoma)
        1. cellular, plexiform, and melanotic subtypes
    2. Neurofibroma
        1. circumscribed (solitary) neurofibroma
        2. plexiform neurofibroma
    3. Malignant peripheral nerve sheath tumor (Malignant schwannoma)
        1. epithelioid
        2. divergent mesenchymal or epithelial differentiation
        3. melanotic
7. Local Extensions from Regional Tumors
    1. Paraganglioma (chemodectoma)
    2. Chordoma
    3. Chodroma

    4. Chondrosarcoma
    5. Carcinoma
8. Metastatic tumours
9. Unclassified Tumors
10. Cysts and Tumor-like Lesions
    1. Rathke cleft cyst
    2. Epidermoid
    3. Dermoid
    4. Colloid cyst of the third ventricle
    5. Enterogenous cyst
    6. Neuroglial cyst
    7. Granular cell tumor (choristoma, pituicytoma)
    8. hypothalamic neuronal hamartoma

10. Cysts and Tumor-like Lesions (cont)

    9. nasal glial herterotopia
    10. plasma cell granuloma

6.2. Appendix B – Glossary

Abbreviations Used in the Text

AFP	Alpha fetoprotein
AHRQ	Agency for Healthcare Research and Quality
ANP	Atrial natriuretic peptide
beta HCG	beta subunit of human chorionic gonadotropin
CI	Confidence interval
cm	Centimeter(s)
CMS	Centers for Medicare and Medicaid Services
CNS	Central nervous system
CS	Clinical stage
CT	Computed Tomography
DAR	Differential absorption ratio
DUR	Differential uptake ratio
ERCP	Endoscopic retrograde cystopancreatogram
EUS	Endoscopic ultrasound
FDG	2-Fluro 2-deoxy D-glucose
^{18}FDG	18-Fluro-deoxy-glucose
g	Gram(s)
FIGO	International Federation of Gynecology and Obstetrics

FN	False Negative
FP	False Positive
GCT	Germ cell tumor
GLUT	Glucose transport proteins
kg	Kilogram(s)
LDH	Lactose dehydrogenase
MCAC	Medicare Coverage Advisory Committee
MBq	MegaBaquerels
µCi	Microcuries
µg	Microgram(s)
mg	Milligram
mL	Milliliter(s)
MRI	Magnetic Resonance Imaging
NSGCT	Non-seminomatous germ cell tumor
NSCLC	Non-small cell lung cancer
PET	Positron emission tomography
PNS	Peripheral nervous system
PS	Pathologic stage
RCT	Randomized control trials
RI	Retention Index
RPLND	Retroperitoneal lymph node dissection
SCLC	Small cell lung cancer

SIADH	Inappropriate secretion of antidiuretic hormone
SN	Sensitivity
SOW	Statement of work
SP	Specificity
SUR	Standardized uptake ratio
SUV	Standardized uptake value
Thallium-SPECT	Thallium Single photon emission tomography
US	Ultrasound
VA	Veterans Administration
vs.	Versus
WHO	World Health Organization
%	percent

6.3. Appendix C – Data Abstraction Form

FDG-PET SCANNING FOR CANCER

DATA ABSTRACTION FORM

Reviewer: _____ First Author & Year: _____ _____ ProCite # _____

1. ABSTRACT/FULL TEXT INITIAL REVIEW FOR INCLUSION

GENERAL INCLUSION CRITERIA
English: ____

Cancer Type:_____

SOW Analytic Question Addressed:
Yes – Circle all that apply →
No question addressed – Exclude article

Fryback et al. Level 1 Only:_____**[Exclude Article]**

Fryback et al. Level 2-6:_____

___ **≥12 Human Subjects [Level 2-4 Only]:**
___ **<12 [Exclude Article]**

For review articles:
___ **Include for bibliography**
___ **Not relevant [Exclude]**

CATEGORY SPECIFIC INCLUSION/EXCLUSION CRITERIA

Category 2. Diagnostic Accuracy/Yield
Was a reference standard obtained on all patients?
___ Yes
___ No – Exclude Article

Category 3. Diagnostic thinking impact. No General Exclusion Criteria

Category 4. Therapeutic Choice Impact. No General Exclusion Criteria

Category 5. Patient Outcome Impact. No General Exclusion Criteria

Category 6. Societal Impact. No General Exclusion Criteria

Brain (Primary Tumors):
1. FDG-PET as an adjunct to conventional imaging COMPARED to conventional imaging alone
1a – pts. w/indeterminate MRI – guided lesion biopsy of recurrent low-grade dx.
1b – pts. w/recurrent brain lesions – distinguish high from low grade OR tumor from necrosis
2 – FDG PET as an adjunct to biopsy, compared to biopsy alone
2a –pts. w/indeterminate grade II/III glioma – initial grading of the degree of malignancy
Testicular (pure seminomas or non-semonomatous germ cell tumors):
1. FDG PET compared to either conventional imaging or histology
1a. For initial staging
1b. Residual masses OR suspected recurrent disease to distinguish b/n viable tumor and fibrosis/necrosis
Cervical:
1. FDG PET compared to conventional imaging in the detection of pre-treatment metastses
2. FDG PET compared to conventional imaging
2a. Post treatment – detection of residual disease
2b. Post treatment – detection of recurrent cervical cancer
Small Cell Lung:
1. FDG PET compared to conventional imaging
1a pts. with an initial diagnosis – use for staging
1b pts. post treatment – restaging to detect residual or new dx.
1c pts. with paraneoplastic syndrome – diagnose occult small cell lung cancer
Pancreatic:
1. FDG PET as an adjunct to conventional imaging compared to conventional imaging alone
1a. Differentiating benign from malignant pancreatic lesions
1b. Detecting metastatic pancreatic cancer
2 . See Results Section**.**
3. Pts. post treatment for primary disease - FDG PET versus conventional imaging for detection of residual or recurrent disease
Ovarian:
1. FDG PET as an adjunct to conventional imaging compared to conventional imaging alone
1a. Staging during initial diagnosis
1b. Detection of recurrent disease following treatment. Among patients with a history of ovarian CA who have a rising CA 125 titer and a negative CT
1bi - determining if there is a recurrence of tumor
1bii localizing the presence of the recurrence
1biii staging of the recurrence (increased yield)
1c. Monitoring the effect of chemotherapy

IF ARTICLE DOES NOT MEET CRITERIA DEFINED ABOVE IT IS NOT ELIGIBLE FOR FULL TEXT REVIEW. Please Check References and Inform Ayn Huntington or Shalini Kulasingam if an article needs to be pulled for review

1. FULL TEXT REVIEW

NOTE: If study falls into category 3 through 6, summarize study in form provided at the end of this document

STUDY LOGISTICS:
Inclusive dates of data collection (specify month and year):

From _____ to _____

Geographic Location (in US give city and state; outside of US give city and country):
_____

PATIENT POPULATION:

N = _____ Clarify as needed:

Enrolled consecutively? Yes_____/No_____/Information not provided____

Study Setting**:** (check all that apply)
_____ **Inpatient**
_____ **General outpatient clinics/ physician office**
_____ Academic/Research setting
_____ **Other Describe:**
_____ Not specified or unable to determine

Inclusion/Exclusion Criteria (briefly describe):
Note any characteristics of the population that may affect how representative they are of all patients as defined by the SOW question(s) that this study is defined to answer.

STUDY DESIGN

Type of criterion for patient inclusion (check one):
____ **Clinical presentation (not including PET or comparator test)**
____ **Comparator test result***
____ **PET result**
____ **Reference standard result**

For the type of inclusion criterion above, what result led to patient inclusion (check one)?:
____ **Abnormal results only**
____ **Normal and abnormal results**

Comparisons done:
____ Matched study – PET and all comparator tests performed on all patients
____ PET and comparator test(s) done on different patients – patients randomly selected
____ PET and comparator test(s) done on different patients – patients not randomly selected
____ No comparator test(s) done

Use of reference standard:
____ The reference standard was based on histology
____ The reference standard was based on prolonged (> 6 mo) follow up
____ Neither [exclude study]
**** - a test (e.g., CT) that led to inclusion is not a "comparator test" if a later CT was used to compare to PET. Such a test should be considered part of the "clinical presentation."***

PET TECHNICAL CHARACTERISTICS:

(A) Scanner Model–

Name:_____ Not Stated (**NS**)

(B) Resolution Specified–

Intrinsic Resolution:_____ (mm) / NS Image Res.:_____ (mm) / NS

(C) Acquisition Mode–
2-D / 3-D / NS

(D) Acquisition Time per Field of View (FOV) [sometimes stated "per bed position"]–

Emission Scan acquisition time per FOV:_____(min) / NS

Transmission Scan acquisition time per FOV:_____(min) / NS

(E) Method and Amount of FDG Dosing–

Fixed Dose _____(mCi or MBq) NS

Dose Range_____(mCi or MBq)

Weight-Based Dose _____(mCi or MBq/kg)

(F) Time Between Injection of FDG and Performance of Scan–

_____(min) / NS

(G) Reconstruction Algorithm Used–
Filtered Backposition / Iterative / NS

(H) Glucose Monitoring–

Fasting / Nonfasting / NS Duration of fast:_____(hours) / NS

Glucose Measured: Yes / No / NS Max. Gluc Permitted_____(g/dL) / NS

CRITERIA USED FOR ABNORMALITY BY PET OR COMPARATOR TEST

PET done -
Qualitatively (describe below)/ Quantitatively (describe below)/ Not Mentioned

Criteria used for diagnosis:

None Specified

Specified – Please Describe

Comparator Test done (may or may not include PET depending on SOW question) - _____

Qualitatively (describe below)/ Quantitatively (describe below)/ Not Mentioned

Criteria used for diagnosis:

None Specified

Specified – Please Describe

Comparator Test done (if more than one)- _____

Qualitatively (describe below)/ Quantitatively (describe below)/ Not Mentioned

Criteria used for diagnosis:

None Specified

Specified – Please Describe

CRITERIA USED FOR REFERENCE (GOLD) STANDARD

Qualitatively (describe below)/ Quantitatively (describe below)/ Not Mentioned

None Specified [STOP - Article should be excluded]

Specified – Please Describe

ASSESSMENT :

Radiologist: Done blindly / not done blindly / not mentioned
Gold standard reader: Done blindly / not done blindly / not mentioned

SUBJECT CHARACTERISTICS:

1) Specify outcomes or populations examined
2) Use "NR" to indicate "Not reported"

Age:				
Mean				
SD				
Median				
Range				
Race: White	n = / %	n = / %	n = / %	n = / %
Black	n = / %	n = / %	n = / %	n = / %
Hispanic	n = / %	n = / %	n = / %	n = / %
Other	n = / %	n = / %	n = / %	n = / %
Gender: Male	n = / %	n = / %	n = / %	n = / %
Female	n = / %	n = / %	n = / %	n = / %
No.:*				
	n = / %	n = / %	n = / %	n = / %
	n = / %	n = / %	n = / %	n = / %
	n = / %	n = / %	n = / %	n = / %
	n = / %	n = / %	n = / %	n = / %
	n = / %	n = / %	n = / %	n = / %

*Please describe using relevant description i.e. Stage I, II, III, IV, recurrent, necrosis

RESULTS
[if additional copies of the table are necessary please use copies provided and attach to this form]

Results Summary Table			

Use the above table to provide 2 x n cell information (PET positive/negative, cancer present/absent/stage) if study provides information on sensitivity/specificity OR percent identified as necrosis/tumor/grade of tumor for yield/staging studies. For sensitivity and specificity – fill in gold standard results using columns (disease or do disease) and rows for PET (positive or negative), CT (positive or negative) etc. **Provide separate info. if sensitivity/specificity calculated at lesion level or at person level.**

Sensitivity (# positive by PET or comparator ÷ population with disease):
PET
Comparator Test

Specificity – **(# negative by PET or comparator÷population without disease):**

PET
Comparator Test

Prevalence – (# with disease/population studied – use reference standard):

NOTE: For articles that use SURVIVAL as a specified outcome

1) **Please provide a description of study**
2) **Please provide a categorization of the study (Level 3 through 6) and reason behind assignment i.e. PET result impacted treatment decision.** NOTE: If study falls into category 3 through 6, summarize study in forms provided at the end of this document
3) **Provide/calculate OR or RR if possible, (note whether univariate or multivariate analysis conducted– if latter provide list of covariates used)**

SCORE FOR PAPER:

(Please assign a score of 0 if the paper did not adequately meet the criterion, or if the data was inadequate to determine the criterion, and assign a score of 1 if the paper met the criterion.)

1. The study had a representative sample of patients
   0 / 1
2. The setting and selection of the population under investigation was clearly described.
   0 / 1
3. The study design minimizes differences between patients who receive the tests (Either RCT or matched design)
   0 / 1
4. The scanner model (pg. 2, A) or the type and the resolution of the scanner (pg. 2, B and C) were mentioned.
   0 / 1
5. Criteria defined for test interpretation
   0 / 1
6. Histopathological or clinical confirmation defined
   0 / 1
7. The test reader and the person assigning reference standard diagnosis were blinded
   0 / 1

Total score =

Page nos. from the article used to develop table data –

Notes – Please include any design issues that may impact quality of study or interpretation of results.

PLEASE DESCRIBE STUDY IN THE SPACE PROVIDED BELOW (USE BACK OF FORM IF NECESSARY) AND REASONS/RESULTS FOR CLASSIFYING STUDY AS INDICATED:

Category 3. Diagnostic thinking impact

Definition – Studies that examine the following:

1. Number of cases in a series in which image judged "helpful" to making a diagnosis
2. Difference in clinicians' subjectively estimated diagnosis probabilities pre- versus post test

Category 4. Therapeutic choice impact

Definition – Studies that examine the following:

1. Number (percentage) of times image judged helpful in planning management of patient in case series.
2. Percentage of times therapy planned pretest changed after the image information was obtained
3. Number or percentage of times clinicians' prospectively stated therapeutic choices changed after test information

Category 5. Patient outcome impact

Definition – Studies that examine the following:

1. Percentage of patients improved with test compared to improvement without test
2. Morbidity (or procedures) avoided after having image information
3. Change in quality-adjusted life expectancy
4. QALYs
5. Cost per QALY saved with image information

Category 6. Societal impact

Definition – Studies that examine the following:

1. A cost-effectiveness or cost-benefit analysis conducted from the societal perspective

6.4. Appendix D – Evidence Tables

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Bader **1999** **PROCITE#** 920 **Cancer Type:** Brain **SOW Question(s) Addressed:** 1b **Fryback et al. Level:** 2	**Dates of data collection:** Unspecified, "over 30 months" **Geographic Location:** Hamburg/Saar, Germany **Prospective/ Retrospective Study:** NS **Enrolled Consecutively:** No (of a "larger" consecutive group, 30 had SPET and PET) **Study Setting:** Academic/ Research **Patient Incl Crit:** • PET result **Result led to incl:** • Abnorm and norm **Comparisons:** • Matched **Use of ref stand:** • Histology	***Patients:*** **N =** 30 **Mean(Median) Age:** 50.6 years **Gender:** 73% Male **High-grade recurrence: Mean Age:** 54.4 years **Gender:** 87% Male **Low-grade recurrence: Mean Age:** 46.7 years **Gender:** 60% Male **Inclusion criteria:** Subset of group of larger patients consecutively referred for routine IMT-SPET and FDG-PET for suspected recurrent tumor or for determination of upgrading after primary therapy **Exclusion Criteria:** NS	**Scanner Model:** ECAT ART (Siemens/CTI) **Resolution:** • **Spatial:** 6.4 mm in plane, 8.2 mm between planes **Acquisition Mode:** 3-D **Acquisition time per FOV:** • **Emission Scan:** NS • **Transmission Scan:** NS **Dose of FDG:** 200 MBq **Time between injection and performance:** NS **Reconstruction Algorithm used:** Filtered back-projection **Glucose Monitoring:** Fasting – 12 hours	**PET done:** Quantitatively and Qualitatively **Criteria used for diagnosis:** Qualitative: positive or negative for tumor tissue by agreement of 2; Quantitative: ROI ratios of tumor to mean brain activity. **Comparator Test done:** SPET **Criteria used for diagnosis:** Qualitative: Positive or negative for the presence of tumor by agreement of 2; Quantitative: ROI ratio of tumor to mean brain activity. **Gold Standard test done:** Qualitatively **Criteria used for diagnosis:** WHO classification and Daumas-Duport scheme – included grade III. Stereotaxic biopsy by CT – progression assessed by comparing previous biopsy result with current histopathologic sample. **Blinding:** **Radiologist:** Yes **Gold Standard reader:** NS	**Clinical diagnosis and PET results** Upgrade PET | | + | - | | + | 7 | 16 | | - | 0 | 5 | Sensitivity = 100% Specificity = 24% Recurrence PET | | + | - | | + | 22 | 0 | | - | 7 | 1 | Sensitivity = 76% Specificity = 100% **Clinical diagnosis and SPET results** Upgrade IMT-SPET | | + | - | | + | 7 | 18 | | - | 0 | 3 | Sensitivity = 100% Specificity = 14% Recurrence IMT-SPET | | + | - | | + | 24 | 0 | | 5 | 1 | 187 | Sensitivity = 70% Specificity = 98%	***Quality Score:*** **Rep.sample: 0** **Setting selection: 0** **Design minimizes diffs: 1** **Scanner: 1** **Interpretation criteria defined: 1** **Hist or clin confirmation: 1** **Blinded: 0** **Total Score = 4** **Notes:**

<table>
<tr><th>Study, Year/ General Inclusion Criteria</th><th>Study Design</th><th>Patients/ Subject Characteristics</th><th>PET Technical Characteristics</th><th>Criteria for Abnormality</th><th>Results/ Notes</th><th>Quality Score/Notes</th></tr>
<tr>
<td>
Barker

1997

PROCITE# 1370

Cancer Type: Brain

SOW Question(s) Addressed: 1b

Fryback et al. Level: 2
</td>
<td>
Dates of data collection: 9/92 – 1/94

Geographic Location: San Francisco, CA

Prospective/ Retrospective Study: NS

Enrolled Consecutively:

Study Setting: Academic/ Research

Patient Incl Crit:
• Clin Pres
• Comp test result – MRI

Result led to incl:
• Grade III or IV tumors

Comparisons:
• No comp

Use of ref stand:
• Histology
• Prolonged follow-up – survival
</td>
<td>
Patients:

N = 55

Median Age: 45 years
Age Range: 11-65 years

Gender: 51% Male

Staging:
Grade IV: n=40
Grade III: n=15

Inclusion criteria: All patients who underwent PET for suspected recurrent glioma;
All patients who underwent external beam radiotherapy; MR image showed new enhancement compatible with tumor progression or radiation necrosis

Exclusion Criteria: NS
</td>
<td>
Scanner Model: Siemens ECAT EXACT 921/47

Resolution:
• Intrinsic: 5.4 mm
• Image: NS

Acquisition Mode: NS

Acquisition time per FOV:
• Emission Scan: 20 min
• Transmission Scan: NS

Dose of FDG: 0.143 mCi/kg
Average dose = 10 mCi

Time between injection and performance: 30 min

Reconstruction Algorithm used: Parzen Filter

Glucose Monitoring: Fasting – 4 hours
</td>
<td>
PET done: Qualitatively
Criteria used for diagnosis: Assessment made of abnormality at site of MR image enhancement.
Grade:
0 – no visability;
1 – activity < adjacent area;
2 – activity ≥ adjacent cortex but < contralateral cortex;
3 – activity ≥ contralateral cortex

Gold Standard test done: Clinical follow-up
Criteria used for diagnosis: NS – criteria for diagnosis of necrosis or recurrent brain tumor not stated

Blinding:
Radiologist: NS
Gold Standard reader: NS
</td>
<td>
Survival is the outcome of interest.

All patients with suspected recurrence of a glioma based on an abnormal MRI were studied, N=55, retrospectively.

Clinical treatment was based on the results of all available studies and information.

Survival was analyzed using Kaplan Meier and multivariate analysis.

In Kaplan Meier analysis, a higher PET score was significantly correlated with worse survival.

In Cox multivariate analysis, PET score, number of recurrence, and age all significantly predicted survival.

<table>
<tr><th></th><th></th><th>Survival*</th></tr>
<tr><td></td><td>Median</td><td>80%</td></tr>
<tr><td rowspan="4">PET Score</td><td>3</td><td>280.6 (23)</td><td>158.6 (13)</td></tr>
<tr><td>2</td><td>305 (25)</td><td>195.2 (16)</td></tr>
<tr><td>1</td><td>341.6 (28)</td><td>195.2 (16)</td></tr>
<tr><td>0</td><td>NR</td><td>280.6 (23)</td></tr>
</table>

*Survival reported in days (mm), with 1 mm = 1/30 year = 12.2 days.

PET score 2 or 3 – median survival = 299.7 days
PET score 1 or 2 – median survival = 586.6 days
</td>
<td>
Quality Score:

Rep.sample: 1

Setting selection: 1

Design minimizes diffs: 0

Scanner: 1

Interpretation criteria defined: 1

Hist or clin confirmation: 1

Blinded: 0

Total Score = 5

Notes:
</td>
</tr>
</table>

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
De Witte **2000** **PROCITE#** 540 **Cancer Type:** Brain **SOW Question(s) Addressed:** 2a **Fryback et al. Level:** 2	**Dates of data collection:** 1991 – 1996 **Geographic Location:** Brussels, Belgium **Prospective/ Retrospective Study:** NS **Enrolled Consecutively:** NS **Study Setting:** Academic/ Research **Patient Incl Crit:** • Ref stand result **Result led to incl:** • Abnormal only **Comparisons:** • No comp **Use of ref stand:** • Histology	***Patients:*** **N =** 91 Grade III – n=30 Grade IV – n=61 **Mean(Median) Age:** Grade III – 46.33 yrs Grade IV – 61.62 yrs **Gender:** NS **Inclusion criteria:** NS **Exclusion Criteria:** NS	**Scanner Model:** CTI-Siemens 933/08-12 **Resolution:** • **Spatial:** 5 mm **Acquisition Mode:** NS **Acquisition time per FOV:** • **Emission Scan:** 20 min • **Transmission Scan:** NS **Dose of FDG:** Approximately 260 MBq **Time between injection and performance:** 40 min **Reconstruction Algorithm used:** NS **Glucose Monitoring:** NS	**PET done:** Qualitatively **Criteria used for diagnosis: Metabolic g**rading scale: 1 – Uptake less than contralateral white matter; 2 – Between levels of uptake in contralateral white and gray matters; 3 – Uptake equal or greater than in contralateral matter. **Gold Standard test done:** Histology **Criteria used for diagnosis:** WHO classification **Blinding:** **Radiologist:** NS **Gold Standard reader:** NS	**Grade vs. t_{50} (50% survival time)** **All Patients** [illegible] **Glioblastoma (n=61)** [illegible]	***Quality Score:*** **Rep.sample: 0** **Setting selection: 0** **Design minimizes diffs: 0** **Scanner: 1** **Interpretation criteria defined: 1** **Hist or clin confirmation: 1** **Blinded: 0** **Total Score = 3** **Notes:**

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Delbeke **1995** **PROCITE#** 1650 **Cancer Type:** Brain **SOW Question(s) Addressed:** 2a **Fryback et al. Level:** 2	**Dates of data collection:** NS **Geographic Location:** Nashville, TN **Retrospective Study** **Enrolled Consecutively:** No – retrospective **Study Setting:** Academic/ Research **Patient Incl Crit:** • Clin Pres • Ref stand result – Histology **Result led to incl:** • Abnormal only – known brain tumor histologically proven **Comparisons:** • No comp **Use of ref stand:** • Histology	***Patients:*** **N =** 59 tumors in the brain, N=38 gliomas **Staging (all tumors):** N=18 High Grade Glioma N=8 High Grade "other" N=20 Low Grade Glioma N=12 High Grade "other" **Mean Age:** 38±25 years **Gender:** 71.2% Male **Inclusion criteria:** Histologically proven brain tumors; CT or MR shows lesion > 1 cm **Exclusion Criteria:** Prior surgery, radiation or chemotherapy; N=1 patient who had seizures during PET scan, and was therefore excluded	**Scanner Model:** Siemens ECAT 933/08/16 (Iselin, NJ) **Resolution:** • **Intrinsic:** 4.8 mm • **Reconstructed:** 6.5 mm **Acquisition Mode:** NS **Acquisition time per FOV:** • **Emission Scan:** 15 min • **Transmission Scan:** 15 min **Dose of FDG:** 370 MBq (10 mCi) **Time between injection and performance:** 35 min **Reconstruction Algorithm used:** NS **Glucose Monitoring:** Fasting – 4 hours; Glucose measured, maximum amount permitted not specified	**PET done:** Semi-Qualitatively **Criteria used for diagnosis:** 1. FDG uptake in white matter and cortex contralateral to lesion used as reference; 2. ROI identified visually, ratios of tumor uptake to tumor and white matter uptake were made (T/WM and T/C, T=tumor and C=cortex); 3. Optimal cut-off rates for predicting grade were estimated. **Gold Standard test done**: **Qualitatively** **Criteria used for diagnosis:** Histology – type of tumor (grade high or low) **Blinding:** **Radiologist:** NS **Gold Standard reader:** NS	**Results for Gliomas** Sensitivity of their cutoff to predict High Grade vs. Low Grade. Grade T/WM ratio High / Low > 1.5: 20 / 6 < 1.5: 0 / 12 Sensitivity = 100% Specificity = 67% Difference between T/WM and T/C uptake ratios for high-grade and low-grade tumors was significant (p=0.0001).	***Quality Score:*** **Rep.sample: 0** **Setting selection: 1** **Design minimizes diffs: 0** **Scanner: 1** **Interpretation criteria defined: 1** **Hist or clin confirmation: 1** **Blinded: 0** **Total Score = 4** **Notes:** Overestimates OC: Multiple look problem – adjusted cutpoint to derive a derivative OC estimate *a posterini.* Original data only provided as a Figure.

<table>
<tr><th>Study, Year/ General Inclusion Criteria</th><th>Study Design</th><th>Patients/ Subject Characteristics</th><th>PET Technical Characteristics</th><th>Criteria for Abnormality</th><th>Results</th><th>Quality Score/Notes</th></tr>
<tr>
<td>
Deshmukh

1996

PROCITE# 1410

Cancer Type: Brain

SOW Question(s) Addressed: 1b, 2a

Fryback et al. Level: 3, 4
</td>
<td>
Dates of data collection: 9/90 – 6/92

Geographic Location: Boston, MA

Retrospective Study

Enrolled Consecutively: No – retrospective series

Study Setting: Academic/ Research

Patient Incl Crit:
• Clin Pres
• PET result

Result led to incl:
• Abnormal only
• Abnorm and norm

Comparisons:
• No comp

Use of ref stand:
• Histology
</td>
<td>
Patients:

N = 75 patients (89 scans)

Mean(Median) Age: NS

Gender: NS

Inclusion criteria:
1. Patient had a PET scan – primary glioma;
2. Known histological grade;
3. Good history present in records;
4. Records give the data on which clinical decisions were based

Exclusion Criteria: Of 159 patients with primary brain tumors, 106 had glioma. Of these, 31 excluded because record did not show clinical question to be addressed by PET, or did not contain “explicit enumeration of the data on which clinical decisions were based.”
</td>
<td>
Scanner Model: NS

Resolution:
• Intrinsic: NS
• Image: NS

Acquisition Mode: NS

Acquisition time per FOV:
• Emission Scan: NS
• Transmission Scan: NS

Dose of FDG: Approximately 10 mCi

Time between injection and performance: > 45 min

Reconstruction Algorithm used: NS

Glucose Monitoring: NS
</td>
<td>
PET done: NS

Criteria used for diagnosis: Visual inspection of static images

Gold Standard test done: NS

Criteria used for diagnosis: NS

Blinding:
Radiologist: No
Gold Standard reader: NS
</td>
<td>
I. Reasons for PET (overall N=125 because study reports all reasons for all PET scans)
<table>
<tr><th>Reasons</th><th>N</th><th>%</th></tr>
<tr><td>No reason given and/or no statement in record about how PET related to decision making</td><td>31</td><td>25</td></tr>
<tr><td>Radiation necrosis compared with recurrent tumor</td><td>77</td><td>62</td></tr>
<tr><td>Substitute for biopsy</td><td>10</td><td>8</td></tr>
<tr><td>Localization of hypermetabolic regions to aid biopsy or surgery</td><td>2</td><td>2</td></tr>
<tr><td>Localization of hypermetabolic regions to aid radiotherapy</td><td>2</td><td>2</td></tr>
<tr><td>Post-surgical evaluation for residual</td><td>2</td><td>2</td></tr>
<tr><td>Established baseline tumor metabolism prior to therapy</td><td>1</td><td>1</td></tr>
</table>
II. Proportion of PETs done for a stated reason that played a “valuable clinical role”: 86/89 = 96.6%

III. PET findings led to consideration of a new therapy in 31% of cases.

IV. Therapeutic decision made on basis of PET alone in 28% of cases.

V. In 72% of cases the therapeutic decision was supported by information from other sources such as CT, MRI or clinical findings.
</td>
<td>
Quality Score:

Rep.sample: 0

Setting selection: 0

Design minimizes diffs: 0

Scanner: 0

Interpretation criteria defined: 0

Hist or clin confirmation: 0

Blinded: 0

Total Score = 0

Notes:
</td>
</tr>
</table>

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Janus **1993** **PROCITE#** 2010 **Cancer Type:** Brain **SOW Question(s) Addressed:** 1b **Fryback et al. Level:** 2	**Dates of data collection:** NS **Geographic Location:** Houston, TX **Prospective/ Retrospective Study:** NS **Enrolled Consecutively:** Yes **Study Setting:** Academic/ Research **Patient Incl Crit:** • Clin Pres **Result led to incl:** • Abnormal only • Abnorm and norm **Comparisons:** • Matched • PET and comp – random • PET and comp – not random • No comp **Use of ref stand:** • Histology • Prolonged follow-up	***Patients:*** Overall: **N =** 50 **Age Range:** 15-66 years **Gender:** 64% Male **Surgery after PET:** **N =** 20 **Age Range:** 15-64 years **Gender:** 65% Male **Clinical follow-up after PET:** **N =** 30 **Age Range:** 15-66 years **Gender:** 63% Male **Inclusion criteria:** Primary brain tumor; Prior surgery, radiotherapy and chemotherapy; Abnormal MRI suggesting possible recurrence **Exclusion Criteria:** NS	**Scanner Model:** Posicam 6.5 (Positron Co.) **Resolution:** • **Radial:** 5.5 mm • **Axial:** 11.9 mm **Acquisition Mode:** NS **Acquisition time per FOV:** • **Emission Scan:** NS • **Transmission Scan:** 20 min per set (3 sets) **Dose of FDG:** 5-10 mCi **Time between injection and performance:** NS **Reconstruction Algorithm used:** NS **Glucose Monitoring:** NS	**PET done:** Qualitatively **Criteria used for diagnosis:** Increased activity relative to the contralateral hemisphere or adjacent area suggestive of tumor progression; Decreased activity suggestive of radionecrosis **Comparator Test:** MR **Done:** Qualitatively **Criteria used for diagnosis:** Visual inspection **Gold Standard test:** Histology and clinical follow-up **Done:** Qualitatively **Criteria used for diagnosis:** Histology: n=20; Clinical follow-up: n=30. Survival less than 26 weeks considered tumor recurrence. Survival more than 26 weeks considered no tumor recurrence. **Blinding:** **Radiologist:** Yes **Gold Standard reader:** NS	**Biopsy Done:** PET Recurrence | | + | - | | + | 10 | 3 | | - | 2 | 5 | Sensitivity = 83% Specificity = 62% MRI Recurrence | | + | - | | + | 9 | 8 | | - | 2 | 0 | Sensitivity = 82% Specificity = 0% **Clinical follow-up only:** PET Survival | | + | - | | + | 4 | 6 | | - | 2 | 17 | Sensitivity = 67% Specificity = 74% Notes: Best data is the histology criteria data (n=20) which shows SN = 83% and SP = 62%. Clinical criteria for recurrence are weak. For example, if a patient died of their cancer at 27 weeks, they were considered not to have recurred because of the cut-off point of 26 weeks. Reviewer would exclude the 30 patients with “clinical data only” because of this.	***Quality Score:*** **Rep.sample: 0** **Setting selection: 1** **Design minimizes diffs: 1** **Scanner: 1** **Interpretation criteria defined: 1** **Hist or clin confirmation: 1** **Blinded: 0** **Total Score = 5** **Notes:**

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Kahn **1994** **PROCITE#** 1760 **Cancer Type:** Brain **SOW Question(s) Addressed:** 1b **Frybeck et al. Level:**	**Dates of data collection:** NS **Geographic Location:** Iowa City, IA **Enrolled Consecutively:** Yes **Prospective/ Retrospective Study:** NS **Study Setting:** Academic/ Research **Patient Incl Crit:** • Clin Pres **Result led to incl:** • Abnormal only – CT or MRI interpreted as compatible with tumor **Comparisons:** • Matched **Use of ref stand:** • Histology • Prolonged follow-up – no	***Patients:*** **N =** 19 (21 studies in 19 patients) N=17 Astrocytomas N=2 non-brain tumors (excluded) **Mean Age:** 40 years **Age Range:** 26-58 years **Gender:** **53% Male** **Grade:** I: n=1 II: n=4 III: n=7 IV: n=5 Other: n=2 **Inclusion criteria:** Suspected recurrent tumor vs. radiation necrosis based on suspicious CT/MR or deteriorating clinical response; CT or MR compatible with tumor	**Scanner Model:** GE 4096 Plus PET (GEMS) **Resolution:** 5.5 mm in 3 directions **Acquisition Mode:** 3-D **Acquisition time per FOV:** • **Emission Scan:** NS • **Transmission Scan:** NS **Dose of FDG:** 10 mCi **Time between injection and performance:** 45 min **Reconstruction Algorithm used:** Butterworth filter **Glucose Monitoring:** Fasting – 4 hours	**PET done:** Qualitatively **Criteria used for diagnosis:** Markedly reduced uptake in the confines of the tumor region compatible with radiation necrosis; Visual 5 point scale: 1=no FDG uptake 3=equivocal uptake 5=markedly increased uptake **Comparator Test:** SPECT **Done:** Qualitatively and Quantitatively **Criteria used for diagnosis:** Visual inspection by radiologists judgment, looking at 3 reference regions. Considered malignant if tumor region with hottest activity was > than activity in: 1. Tissue immediately adjacent to the tumor 2. homologous contralateral region 3. contralateral scalp region **Quantitative assessment:** ROI uptake vs. contralateral healthy tissue ratio; For transverse slices, the ^{201}Ti index = highest ratio slice **Gold Standard test done:** Histology (n=5) and clinical follow-up (n=14) **Criteria used for diagnosis:** NS **Blinding:**	**Tumor (T) vs. Radiation Necrosis (RN):** PET Diagnosis RN / T RN: 2, 3 T: 2, 12 Sensitivity = 50% Specificity = 80% SPECT Diagnosis RN / T RN: 2, 5 T: 2, 10 Sensitivity = 50% Specificity = 67%	***Quality Score:*** **Rep.sample: 0** **Setting selection: 1** **Design minimizes diffs: 1** **Scanner: 1** **Interpretation criteria defined: 1** **Hist or clin confirmation: 1** **Blinded: 0** **Total Score = 5** **Notes:** No minimum follow-up was given for the 15 patients who did not have a biopsy diagnosis of recurrence. Authors conclude that PET has only 40% specificity for detecting recurrence. SPET had notably

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
	minimum follow-up given	**Exclusion Criteria:** NS		**Radiologist:** Yes **Gold Standard reader:** No		higher reliability than PET.

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Kaschten **1998** **PROCITE#** 1080 **Cancer Type:** Brain **SOW Question(s) Addressed:** 2a **Frybeck et al. Level:** 2	**Dates of data collection:** NS **Geographic Location:** Liege, Belgium **Prospective/ Retrospective Study:** NS **Enrolled Consecutively:** NS **Study Setting:** Academic/ Research **Patient Incl Crit:** • Ref stand result **Result led to incl:** • Abnorm and norm – various grades **Comparisons:**	***Patients:*** **N =** 45 patients with PET (54 patients in all) **Mean Age:** 50±17 years **Age Range:** 12.8-74.9 years **Tumor Grade:** I: N = 1 II: N = 23 III: N = 10 IV: N = 20 **Gender:** 51.8% Male **Inclusion criteria:** Suspected brain gliomas **Exclusion Criteria:** NS	**Scanner Model:** NeuroEcat (EG&G, ORTEC) (N=16) or Siemens ECAT 951/31R (CTI PET Systems) (N=38) **Resolution:** • **NeuroEcat:** 8 mm FWHM • **Siemens ECAT:** 6 mm FWHM **Acquisition Mode:** NS **Acquisition time per FOV:** • **Emission Scan:** 20 min • **Transmission Scan:** NS **Dose of FDG:** 222-370 MBq **Time between injection and performance:** > 30 min **Reconstruction**	**PET done:** Qualitatively and Quantitatively **Criteria used for diagnosis:** **Qualitative:** 2 methods: 1. Comparison with surrounding parenchyma – hypermetabolic (hot) areas considered positive; 2. Visual analysis (Schifter et. al) Grades I-V: I = tumor< white matter II = tumor = white matter **III = WM < tumor < cortex** IV = tumor = cortex V = tumor > cortex **Quantitative:** Tracer uptake ratios – tumor compared to: CTX (contralateral cortex in front of tumor) CCR (same contralateral corresponding region) MCU (mean cortical uptake of 7 ROI's) WM (two ROI's in centrum ovale) W*C (mean uptake of WM and temporal cortex) **Gold Standard test done:** Qualitatively	PET Histological Grade III/IV: VG > 3: 13; VG ≤ 3: 2 III: VG > 3: 10; VG ≤ 3: 16 Sensitivity = 87% Specificity = 62% SPECT Histological Grade III/IV: VG ≥ 3: 13; VG < 3: 2 III: VG ≥ 3: 10; VG < 3: 16 Sensitivity = 87% Specificity = 62%	***Quality Score:*** **Rep.sample: 0** **Setting selection: 0** **Design minimizes diffs: 0** **Scanner: 1** **Interpretation criteria defined: 1** **Hist or clin confirmation: 1** **Blinded: 0** **Total Score = 3** **Notes:**

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
	• No comp **Use of ref stand:** • Histology • Prolonged follow-up		**Algorithm used:** NS **Glucose Monitoring:** Fasting – 4 hours	**Criteria used for diagnosis:** WHO and Mayo-Sainte Anne classifications **Blinding:** **Radiologist:** No **Gold Standard reader:** NS		

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Meyer **2001** **PROCITE#** 500 **Cancer Type:** Brain **SOW Question(s) Addressed:** 2a **Frybeck et al. Level:** 2	**Dates of data collection:** 6/97 – 12/99 **Geographic Location:** Aachen, Germany **Retrospective Study** **Enrolled Consecutively:** Yes **Study Setting:** Academic/ Research **Patient Incl Crit:** • Clin Pres **Result led to incl:** • Abnormal only **Comparisons:** • No comp **Use of ref stand:** • Histology	***Patients:*** **N =** 47 total Staging: Glioma II: N=7 Glioma III: N=10 **MeanAge:** 48.4±14.9 years **Gender:** 51% Male **Inclusion criteria:** All patients with supratentorial brain tumors – Imaging tests not specified and presentation not specified **Exclusion Criteria:**	**Scanner Model:** Siemens – CTI ECAT EXACT 922 **Resolution:** • **Spatial:** 5 mm **Acquisition Mode:** 2-D, n=39 patients 3-D, n=8 patients **Acquisition time per FOV:** • **Emission Scan:** NS • **Transmission Scan:** NS **Dose of FDG:** 2-D scans: 188±56 MBq 3-D scans: 141±17 MBq **Time between injection and performance:** 30 min **Reconstruction Algorithm used:** Filtered Backposition **Glucose Monitoring: NS**	**PET done:** Qualitatively and Quantitatively **Criteria used for diagnosis:** Manual placement of ROIs under MRI guidance. Mean pixel counts of: 1. Tumor ROI of maximal FDG uptake (Tu); 2. Symmetric ROI within normal tissue of the contralateral hemisphere (TIS); 3. Gray matter ROI (GM); 4. White matter ROI (WM). Calculated Tu/TIS, Tu/GM, Tu/WM. Qualitative: FDG uptake assessed by visual grading scale (3 blinded observers) which used comparison to gray and white matter uptakes, and is categorized into grades. **Gold Standard test done:** Histology **Criteria used for diagnosis:** WHO classification based on histology after tumor resection **Blinding:** **Radiologist:** Yes **Gold Standard reader:** NS	Tu/Ti Grade (Glioma Grade): II: Low 6, Not Low 1 Not II: Low 3, Not Low 20 Sensitivity = 86% Specificity = 87% ROI cut-off = .78 Tu/GM Grade (Glioma Grade): II: Low 5, Not Low 2 Not II: Low 4, Not Low 19 Sensitivity = 71% Specificity = 83% ROI cut-off = .7 Tu/WM Grade (Glioma Grade): II: Low 4, Not Low 3 Not II: Low 2, Not Low 21 Sensitivity = 57% Specificity = 91% ROI cut-off = 1.26 VGS Grade (Glioma Grade): Not II: ≥3b 25, ≤3a 5 II: ≥3b 1, ≤3a 15 Sensitivity = 83% Specificity = 94% Note: "Low Grade" = Grade I or II **Prevalence:** Grade II = 23% Grade III = 33%	***Quality Score:*** **Rep.sample: 1** **Setting selection: 0** **Design minimizes diffs: 1** **Scanner: 1** **Interpretation criteria defined: 1** **Hist or clin confirmation: 1** **Blinded: 0** **Total Score = 5** **Notes:**

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Olivero **1995** **PROCITE#** 1660 **Cancer Type:** Brain **SOW Question(s) Addressed:** 1b **Fryback et al. Level:** 3, 4	**Dates of data collection:** 6/91 – 12/92 **Geographic Location:** Peoria, IL **Retrospective Study** **Enrolled Consecutively:** NS – retrospective chart review **Study Setting:** Academic/ Research **Patient Incl Crit:** • PET result **Result led to incl:** • Abnorm and norm **Comparisons:** • Matched **Use of ref stand:** • Histology • Prolonged follow-up	***Patients:*** **N =** 39 (35 known primary tumors, 4 newly suspected tumors) **Mean Age:** NS **Gender:** NS **Inclusion criteria:** NS **Exclusion Criteria:** NS	**Scanner Model:** Siemens 951-31 **Resolution:** • **Intrinsic:** 4 mm • **Image:** NS **Acquisition Mode:** NS **Acquisition time per FOV:** • **Emission Scan:** NS • **Transmission Scan:** 20 min **Dose of FDG:** NS **Time between injection and performance:** NS **Reconstruction Algorithm used:** NS **Glucose Monitoring:** NS	**PET done:** NS **Criteria used for diagnosis:** NS **Comparator Test done:** MRI – gadolinium-enhanced **Criteria used for diagnosis:** NS **Gold Standard test done:** Histology and/or Clinical Follow-up **Criteria used for diagnosis:** NS **Blinding:** **Radiologist:** NS **Gold Standard reader:** NS	In 2 out of 39 patients, PET influenced workup/treatment. In 5 out of 39 cases, PET was helpful in distinguishing tumor from other disease processes.	***Quality Score:*** **Rep.sample: 0** **Setting selection: 0** **Design minimizes diffs: 1** **Scanner: 1** **Interpretation criteria defined: 0** **Hist or clin confirmation: 0** **Blinded: 0** **Total Score = 2** **Notes:** Retrospective chart review.

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Sasaki **1998** **PROCITE#** 1010 **Cancer Type:** Brain **SOW Question(s) Addressed:** 2a **Frybeck et al. Level:** 2	**Dates of data collection:** 7/93 – 5/97 **Geographic Location:** Kyushu, Japan **Prospective/ Retrospective Study:** NS **Enrolled Consecutively:** NS **Study Setting:** Academic/ Research **Patient Incl Crit:** • Ref stand result **Result led to incl:** • Abnormal only **Comparisons:** • Matched **Use of ref stand:** • Histology	***Patients:*** **N =** 23 Grade: II: N = 7 III: N = 10 IV: N = 6 **Mean Age:** 49.4±16.5 years **Age Range:** 16-73 years **Gender:** 56.5% Male **Inclusion criteria:** All patients had undergone surgery; No patients had received any previous therapy for brain tumors. **Exclusion Criteria:** NS	**Scanner Model:** Headtome III (Shimadzu Corp.) **Resolution:** • **Spatial:** 8.2 mm • **Image:** NS **Acquisition Mode:** 2-D **Acquisition time per FOV:** • **Emission Scan:** NS • **Transmission Scan:** 15 min **Dose of FDG:** 140-370 MBq **Time between injection and performance:** 20 min **Reconstruction Algorithm used:** NS **Glucose Monitoring:** NS	**PET done:** Qualitatively and Semi-Quantitatively **Criteria used for diagnosis:** Qualitative: Visual evaluation of tracer uptake: negative, clearly lower positive, almost equal intensity positive, clearly higher. Semi-quantitative: visually identified ROIs, SUV equaling the average of radioactivity in tumor divided by the injected radioactivity normalized to body weight. **Comparator Test:** Gd enhancement **Done:** Qualitatively **Criteria used for diagnosis:** NS **Gold Standard test done:** Histology **Criteria used for diagnosis:** NS **Blinding:** **Radiologist:** NS **Gold Standard reader:** NS	Visual Grade III / IV / III FDG + / 11 / 3 FDG - / 5 / 4 Sensitivity = 69% Specificity = 57% Grade III/ IV / III MRI + / 11 / 0 MRI - / 5 / 7 Sensitivity = 69% Specificity = 100%	***Quality Score:*** **Rep.sample: 0** **Setting selection: 0** **Design minimizes diffs: 1** **Scanner: 1** **Interpretation criteria defined: 1** **Hist or clin confirmation: 0** **Blinded: 0** **Total Score = 3** **Notes:**

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Stokkel **1999** **PROCITE#** 790 **Cancer Type:** Brain **SOW Question(s) Addressed:** 1b **Fryback et al. Level:** 2	**Dates of data collection:** Over an unspecified 10 month period **Geographic Location:** Utrecht, The Netherlands **Prospective/ Retrospective Study:** NS **Enrolled Consecutively:** Yes **Study Setting:** Academic/ Research **Patient Incl Crit:** • Clin Pres **Result led to incl:** • Abnormal only **Comparisons:** • Matched **Use of ref stand:** • Histology • Prolonged follow-up	***Patients:*** **N =** 16 **Overall:** **Mean Age:** 39.5 years **Gender:** 62% Male **FDG+ (n=8):** **Mean Age:** 39.7 years **Gender:** **75**% Male **Recurrence (n=4):** **Mean Age:** 40.5 years **Gender:** 25% Male **Necrosis (n=12):** **Mean Age:** 39 years **Gender:** 82% Male **Inclusion criteria:** Nondiabetic patients with suspected recurrent glioma after external focal radiotherapy. Suspicion included deteriorating clinical course or suspicious change on CT/MRI. **Exclusion Criteria:** NS	**Scanner Model:** ADAC; Vertex-MCD (Dual SPET/PET) **Resolution:** • **Spatial:** 5 mm **Acquisition Mode:** NS **Acquisition time per FOV:** • **Emission Scan:** NS • **Transmission Scan:** NS **Dose of FDG:** 185 MBq **Time between injection and performance:** 60 min **Reconstruction Algorithm used:** Filtered Backprojection **Glucose Monitoring:** Fasting - overnight	**PET done:** Qualitatively **Criteria used for diagnosis:** Increased uptake relative to adjacent tissue considered tumor; FDG Index using counts from ROI divided by counts from adjacent tissue (cut-off value not stated); Uptake graded on scale of 1-5: 1 = no uptake 3 = same uptake as adjacent tissue 5 = markedly increased uptake; FDG Index was highest ratio generated from any slices analysed **Comparator Test Done:** Thallium SPET **Criteria used for diagnosis:** Uptake increased compared to adjacent tissue AND greater than homologous contralateral region AND greater than contralateral scalp considered tumor; Ti Index – ROI counts divided by tissue counts (cut-off value not stated) **Gold Standard test done:** Clinical follow-up 12 months **Criteria used for diagnosis:** NS **Blinding:** **Radiologist:** NS **Gold Standard reader:** NS	PET Recurrence | | + | - | | + | 8 | 0 | | - | 4 | 4 | Sensitivity = 66% Specificity = 100% Ti-SPET Recurrence | | + | - | | + | 12 | 0 | | - | 0 | 4 | Sensitivity = 100% Specificity = 100% Prevalence: 12/16 = 75% **Subject disease characteristics:** N=1 Astrocytoma (II) N=6 Astrocytoma (III) N=1 Astrocytoma/ODG (II) N=4 Astrocytoma (IV) N=1 Astrocytoma/ODG (III) N=1 Glioma (IV) N=1 ODG (B) N=1 ODG (C)	***Quality Score:*** **Rep.sample: 1** **Setting selection: 1** **Design minimizes diffs: 1** **Scanner: 1** **Interpretation criteria defined: 0** **Hist or clin confirmation: 0** **Blinded: 0** **Total Score = 4** **Notes:**

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Belhocine **2002** **PROCITE#** 2430 **Cancer Type:** Cervical **SOW Question(s) Addressed:** 1, 2b **Fryback et al. Level:** 2, 4	**Dates of data collection:** 9/97 – 6/01 **Geographic Location:** Liege, Belgium **Retrospective Study** **Enrolled Consecutively: Yes** **Study Setting:** Academic/ Research **Patient Incl Crit:** • Clin Pres **Result led to incl:** • Abnormal only- invasive cancer referred for PET **Comparisons:** • PET and comp – not random. Some had MRI, some had CT. **Use of ref stand:** • Histology • Prolonged follow-up	***Patients:*** **N =** 60 (all) N=22: PET for pre-therapy staging N=25: suspected recurrence – PET N=13: surveillance – PET **Mean(Median) Age:** 52±14 years **Inclusion criteria:** Histologically proven cervical cancer; Referred for PET; Technical quality of PET is OK; Confirmation of all positive PET results; Minimum follow-up 12 months for negative PET results. **Exclusion Criteria:** Poor technical quality of PET; Inadequate confirmation of positive PET result; Less than 12 month follow-up of negative PET result.	**Scanner Model:** PENN PET 240H / CPET-ADAC **Resolution:** • Intrinsic: NS • Image: NS **Acquisition Mode:** NS **Acquisition time per FOV:** • **Emission Scan:** NS • **Transmission Scan:** NS **Dose of FDG:** 6.3 mCi (average) **Time between injection and performance:** 64 min (average) **Reconstruction Algorithm used:** Iterative **Glucose Monitoring:** Fasting – 4-6 hrs	**PET done:** Qualitatively **Criteria used for diagnosis:** FDG uptake higher than background and noted on ≥ 2 consecutive slides. **Comparator Test:** MRI **Criteria used for diagnosis:** Nodes > 10 mm = pathologic **Comparator Test:** CT **Criteria used for diagnosis:** Nodes > 10 mm = pathologic **Gold Standard test done:** Histology and Clinical **Criteria used for diagnosis:** *Pre-treatment staging (n=22):* Histology: 18 had surgery, histology available Clinical: 4 "clinical and radiological outcomes" *Post-treatment assessment (n=38):* Histology: 11 histology available Clinical: 27 "clinical and radiological outcomes" **Blinding:** **Radiologist:** Yes **Gold Standard reader:** NS	**Pre-treatment Nodal Evaluation** Pathology (nodes) PET | | + | - | | + | 19 | 3 | | - | 8 | 187 | Sensitivity = 70% Specificity = 98% Pathology (nodes) CT/ MRI | | + | - | | + | 13 | 6 | | - | 14 | 184 | Sensitivity = 48% Specificity = 97% Prevalence = 12.4% **Post-treatment Evaluation** Recurrence PET | | + | - | | + | 25 | 3 | | - | 0 | 10 | Sensitivity = 100% Specificity = 77% Recurrence CT/ MRI | | + | - | | + | 12 | 2 | | - | 13 | 11 | Sensitivity = 48% Specificity = 85% Prevalence = 65.8% Pre-diagnosis: 4/22 had initial diagnosis changed by PET result. Post-diagnosis: PET finding influenced diagnosis of 13/25 patients (52%). Comparator tests had equivocal results.	***Quality Score:*** **Rep.sample: 1** **Setting selection: 1** **Design minimizes diffs: 0** **Scanner: 1** **Interpretation criteria defined: 1** **Hist or clin confirmation: 1** **Blinded: 0** **Total Score = 5** **Notes:**

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
					Note: Major design flaw. In this study each individual lymph node is an “n” and allegedly validated by histology. There is no way to assess individual nodes by PET. They should have defined each “n” as one patient – then if any lymph node was histologically positive and the PET was read as “positive lymph nodes”, it would count as one true positive. The authors may be counting this one patient as multiple true positives, thus magnifying results. It is impossible to re-calculate the SN and SP based on the data given.	

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Grigsby **2003** **PROCITE#** 2380 **Cancer Type:** Cervical **SOW Question(s) Addressed:** 2a, 2b **Fryback et al. Level:** 2, 5	**Dates of data collection:** 3/98 – 8/01 **Geographic Location:** St. Louis, MO **Retrospective Study** **Enrolled Consecutively:** No **Study Setting:** General outpatient clinics/ physician office; Academic/ Research **Patient Incl Crit:** • Clin Pres **Result led to incl:** • Abnorm and norm **Comparisons:** • No comp **Use of ref stand:** • Prolonged follow-up – survival was analyzed – did abnormal PET predict survival.	***Patients:*** **N =** 76 (retrospective) **Mean(Median) Age:** 50 years **Age Range:** 23-88 years **Inclusion criteria:** Patients who presented with invasive cervical cancer for definitive radiation therapy and who had a pre- and post-treatment PET scan (routine). **Exclusion Criteria:** Patients with suspected recurrent disease.	**Scanner Model:** ECAT Exact – Siemens CTI **Resolution:** • Intrinsic: 10 mm • Image: NS **Acquisition Mode:** NS **Acquisition time per FOV:** • **Emission Scan:** NS • **Transmission Scan:** NS **Dose of FDG:** 10-15 mCi **Time between injection and performance:** 40 min **Reconstruction Algorithm used:** Filtered Backposition **Glucose Monitoring:** Fasting – 4 hours. Glucose measured with NS maximum amount permitted.	**PET done:** NS **Criteria used for diagnosis:** NS **Gold Standard test:** Survival **Done:** Quantitatively **Criteria used for diagnosis:** Progression free survival and overall survival (Kaplan Meier and Cox) **Blinding:** Radiologist: NS Gold Standard reader: NS	1. Persistent abnormal PET after treatment significantly predicts lower survival (KM & Cox) 2. New areas of uptake on PET after treatment significantly predicts lower survival (KM & Cox)	***Quality Score:*** **Rep.sample: 1** **Setting selection: 1** **Design minimizes diffs: 0** **Scanner: 1** **Interpretation criteria defined: 0** **Hist or clin confirmation: 1** **Blinded: 0** **Total Score = 4** **Notes:** Main issue is no criteria given for how PET was interpreted.

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Grigsby **2001** **PROCITE#** 2500 **Cancer Type:** Cervical **SOW Question(s) Addressed:** 1 **Fryback et al. Level:** 2, 5	**Dates of data collection:** 2/98 – 6/00 **Geographic Location:** St. Louis, MO **Retrospective Study** **Enrolled Consecutively:** Yes **Study Setting:** General outpatient clinics/ Physician office; Academic/ Research **Patient Incl Crit:** • Clin Pres **Result led to incl:** • Abnormal only – must have known cervical cancer **Comparisons:** • Matched **Use of ref stand:** • Prolonged - survival	***Patients:*** **N =** 101 **Mean Age:** 53 years **Age Range:** 26-88 years **Inclusion criteria:** 101 consecutive patients presenting with invasive cervical cancer for primary radiation therapy **Stage:** 1a: N = 2 $1b_1$: N= 8 $1b_2$: N = 18 IIb: N = 39 III: N = 29 Iva: N = 1 Ivb: N = 4	**Scanner Model:** ECAT Exact (Siemens) **Resolution:** • **Intrinsic:** 10 mm • **Image:** NS **Acquisition Mode:** NS **Acquisition time per FOV:** • **Emission Scan:** NS • **Transmission Scan:** NS **Dose of FDG:** 10-15 mCi **Time between injection and performance:** 40 min **Reconstruction Algorithm used:** Filtered Backprojection/ Iterative **Glucose Monitoring:** Fasting – 4 hrs. Glucose measured, maximum amount of glucose permitted not specified.	**PET done:** Qualitatively **Criteria used for diagnosis:** NS – "routine clinical" **Comparator Test:** CT Scan **Done:** Quantitatively **Criteria used for diagnosis:** Lymph nodes > 10 mm diameter are considered abnormal **Gold Standard test:** Progression-free survival **Criteria used for diagnosis:** Kaplan Meier and Cox multivariate **Blinding**: **Radiologist:** No **Gold Standard reader:** No	PET Primary Tumor | | + | - | | + | 100 | 0 | | - | 1 | 0 | Sensitivity = 99% CT Primary Tumor | | + | - | | + | 77 | 0 | | - | 24 | 0 | Sensitivity = 76% Survival used as outcome. Patients followed, stratified by node status by CT or PET. 1. Patients with PET positive lymph nodes had significantly worse progression-free survival than those with PET negative lymph nodes. 2. In multivariate analysis, positive aortic nodes on PET significantly predicted lower progression-free survival, whereas nodal involvement by CT scan did <u>not</u> predict survival.	***Quality Score:*** **Rep.sample: 1** **Setting selection: 1** **Design minimizes diffs: 1** **Scanner: 1** **Interpretation criteria defined: 0** **Hist or clin confirmation: 1** **Blinded: 0** **Total Score = 5** **Notes:**

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Lin **2003** **PROCITE#** 10520 **Cancer Type:** Cervical **SOW Question(s) Addressed:** 1 **Frybeck et al. Level:** 2	**Dates of data collection:** NS **Geographic Location:** Taipei, Taiwan **Prospective Study** **Enrolled Consecutively:** NS **Study Setting:** Academic/ Research Setting Patient Incl Crit: • Clin pres – negative CT **Result led to incl:** • Abnorm and norm **Comparisons:** • No comp **Use of ref stand:** • Histology	***Patients:*** **N =** 50 Stage IIB-IVA **Mean Age:** NS **Inclusion criteria:** Advanced cervical cancer confined to pelvis; Negative abdominal CT findings; At least 18 years of age; Medically fit to undergo surgical para-aortic staging lymphadenectomy **Exclusion Criteria:** Diabetic, lactating and pregnant women	**Scanner Model:** GE Nxi PET **Resolution:** • **Nominal:** 4.8 mm • **Axial:** 4.0 mm **Acquisition Mode:** 2-D **Acquisition time per FOV:** • **Emission Scan:** NS • **Transmission Scan:** 3 min **Dose of FDG:** 370 MBq (10 mCi) **Time between injection and performance:** 60 min **Reconstruction Algorithm used:** NS **Glucose Monitoring:** Fasting – 4 hours	**PET done:** Qualitatively **Criteria used for diagnosis:** Visual interpretation by 2 of 3 nuclear medicine physicians, not blinded to pathological results **Gold Standard test done:** Qualitatively **Criteria used for diagnosis:** Histology of surgical specimen from para-aortic lymphadenectomy **Blinding:** **Radiologist:** No **Gold Standard reader:** NS	Histology (Nodes) PET | | + | - | |---|---|---| | + | 12 | 2 | | - | 2 | 34 | Sensitivity = 85.7% Specificity = 94.4% Prevalence: 14/50 = 28%	***Quality Score:*** **Rep.sample: 1** **Setting selection: 1** **Design minimizes diffs: 1** **Scanner: 1** **Interpretation criteria defined: 0** **Hist or clin confirmation: 1** **Blinded: 0** **Total Score = 5** **Notes:**

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Miller **2003** **PROCITE#** 2400 **Cancer Type:** Cervical **SOW Question(s) Addressed:** 1 **Fryback et al. Level:** 2, 5	**Dates of data collection:** 1/98 – 9/99 **Geographic Location:** St. Louis, MO **Retrospective Study** **Enrolled Consecutively:** No (retrospective) **Study Setting:** General outpatient clinics/ physician office; Academic/ Research **Patient Incl Crit:** • Clin Pres **Result led to incl:** • Abnormal only – cervical cancer on biopsy **Comparisons:** • No comp **Use of ref stand:** • Prolonged follow-up – survival	***Patients:*** **N =** 47 **Stage:** I: N=11 II: N=23 III: N=12 IV: N=1 **Mean Age:** 48 years **Age Range:** 24-87 years **Inclusion criteria:** 1. Invasive cervical cancer; 2. Referred for primary treatment with radiotherapy; 3. Had PET before treatment began. **Exclusion Criteria:** NS	**Scanner Model:** Siemens ECAT/ EXACT **Resolution:** • **Reconstructed Spatial Resolution:** 8 mm **Acquisition Mode:** NS **Acquisition time per FOV:** • **Emission Scan:** 10 min • **Transmission Scan:** 2 min **Dose of FDG:** 10-15 mCi **Time between injection and performance:** 40-90 min **Reconstruction Algorithm used:** Ordered subsets expectation maximization algorithm **Glucose Monitoring:** Fasting – 4 hrs	**PET done:** Quantitatively **Criteria used for diagnosis:** Score for lymph nodes: 0 – None 1 – Pelvic 2 – Para-aortic 3 - Distant Validated and tested in same group of patients. **Note:** Per the SOW criteria, only analysis of lymph node involvement is mentioned, not visual assessment of primary tumor. **Gold Standard test:** Survival **Done:** Quantitatively **Criteria used for diagnosis:** Survival analysis by Kaplan-Meier analysis, broken down into groups based on PET assessment of lymph nodes. No multivariate analysis. **Blinding:** **Radiologist:** Yes **Gold Standard reader:** NS	There was a significant difference in overall (p=0.03) and progression-free (p=0.04) survival between patients felt to have positive nodes on PET and those felt to have negative nodes.	***Quality Score:*** **Rep.sample: 1** **Setting selection: 1** **Design minimizes diffs: 1** **Scanner: 1** **Interpretation criteria defined: 1** **Hist or clin confirmation: 1** **Blinded: 0** **Total Score = 6** **Notes:**

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results/Notes	Quality Score
Nakamoto **2002** **PROCITE#** 2470 **Cancer Type:** Cervical **SOW Question(s) Addressed:** 2a **Fryback et al. Level:** 2	**Dates of data collection:** 8/94 – 8/99 **Geographic Location:** Baltimore, MD **Prospective/ Retrospective Study:** NS **Enrolled Consecutively:** No **Study Setting:** General outpatient clinics/ Physician office; Academic/ Research **Patient Incl Crit:** • Clin Pres **Result led to incl:** • Abnormal only – invasive cancer **Comparisons:** • CT **Use of ref stand:** • Histology • Prolonged follow-up	***Patients:*** **N =** 20 (19 newly diagnosed cancers – PET pre- and post- radiation treatment. 1 recurrent cancer – PET pre- and post-radiation treatment.) **Age Range:** 26-82 years **Inclusion criteria:** Histologically proven cervical cancer. Radiation treatment planned. **Exclusion Criteria:** NS	**Scanner Model:** Model 921 EXACT/ Siemens **Resolution:** • Intrinsic: 12mm • Image: NS **Acquisition Mode:** NS **Acquisition time per FOV:** • **Emission Scan:** 10 min • **Transmission Scan:** 10 min **Dose of FDG:** 370 MBq **Time between injection and performance:** NS **Reconstruction Algorithm used:** NS **Glucose Monitoring:** Fasting ≥ 4 hrs	**PET done:** Quantitatively and Qualitatively **Criteria used for diagnosis:** Qualitatively, visual scale: 0 – normal 1 – prob. normal 2 – equivocal 3 – prob. abnormal 4 – definitely abnormal Quantitatively: SUV-L standardized uptake value corrected for lean body mass. **Comparator test:** CT **Done:** NS **Criteria used for diagnosis:** NS **Gold Standard test done:** Qualitatively: Histology (n=4), Clinical follow-up ≥ 6 months (n=16) **Blinding:** **Radiologist:** Yes **Gold Standard reader:** NS	**Detection of Recurrence** Recurrence PET | | + | - | |---|---|---| | + | 5 | 6 | | - | 0 | 9 | Sensitivity = 100% Specificity = 60% **Notes:** 1. 19 patients were being evaluated for persistent disease after primary radiation. 1 patient was being evaluated after a prior recurrence – they should not have been grouped together because it can not be determined in the results which patient has already had a recurrence. 2. It is unclear what the author's cutoff was for classifying patients' PET as + or -. Quantitative or "visual scale." 3. CT results presented in discussion for 9 patients. Four true negative CT and PET were the same. Five true positive – PET was positive in all 5, CT positive in 2.	***Quality Score:*** **Rep.sample: 1** **Setting selection: 1** **Design minimizes diffs: 0** **Scanner: 1** **Interpretation criteria defined: 1** **Hist or clin confirmation: 1** **Blinded: 0** **Total Score = 5**

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Park **2000** **PROCITE#** 2540 **Cancer Type:** Cervical **SOW Question(s) Addressed:** 2b **Fryback et al. Level:** 2	**Dates of data collection:** 10/97 – 5/98 **Geographic Location:** Seoul, Korea **Retrospective Study** **Enrolled Consecutively:** NS **Study Setting:** Inpatient; Academic/ Research **Patient Incl Crit:** • Clin Pres **Result led to incl:** • Abnormal only **Comparisons:** • Matched **Use of ref stand:** • Histology • Prolonged follow-up	***Patients:*** **N =** 36 **Mean(Median) Age:** NS **Inclusion criteria:** Suspicion of recurrence **Exclusion Criteria:** NS **Initial Treatment:** N=13 surgery only; N=14 radiation therapy only; N=9 surgery and postoperative radiation therapy	**Scanner Model:** GE Advance **Resolution:** • **Intrinsic:** NS • **Image:** NS **Acquisition Mode:** NS **Acquisition time per FOV:** • **Emission Scan:** NS • **Transmission Scan:** NS **Dose of FDG:** 10 mCi **Time between injection and performance:** NS **Reconstruction Algorithm used:** NS **Glucose Monitoring:** Fasting – 6 hours	**PET done:** Quantitatively **Criteria used for diagnosis:** SUV > 2.5 ml/Kg **Comparator Test:** CT **Done:** Qualitatively **Criteria used for diagnosis:** Mass > 1 cm **Gold Standard test done:** Qualitatively **Criteria used for diagnosis:** Considered positive recurrence if: 1. Positive histology; Increased tumor marker; 2. Increased size of masses or lymph nodes on CT; 3. Decreased size of masses and lymph nodes after chemotherapy and radiation therapy **Blinding:** **Radiologist:** NS **Gold Standard reader:** NS	PET Recurrence | | + | - | | + | 18 | 1 | | - | 0 | 17 | Sensitivity = 100% Specificity = 94.4% CT Recurrence | | + | - | | + | 14 | 3 | | - | 4 | 15 | Sensitivity = 77.8% Specificity = 83.3% Prevalence: 18/36 = 50%	***Quality Score:*** **Rep.sample: 1** **Setting selection: 1** **Design minimizes diffs: 1** **Scanner: 1** **Interpretation criteria defined: 1** **Hist or clin confirmation: 1** **Blinded: 0** **Total Score = 6** **Notes:**

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Reinhardt **2001** **PROCITE#** 2520 **Cancer Type:** Cervical **SOW Question(s) Addressed:** 1 **Fryback et al. Level:** 2	**Dates of data collection:** 1995 – 1998 **Geographic Location:** Freiberg, Germany **Prospective Study** **Enrolled Consecutively:** Yes **Study Setting:** Inpatient; Academic/ Research **Patient Incl Crit:** • Clin Pres **Result led to incl:** • Abnormal only **Comparisons:** • Matched **Use of ref stand:** • Histology	***Patients:*** **N =** 35 **Stage:** IB N=21 (60%) II N=14 (40%) **Age Range:** 26-70 years **Inclusion criteria:** 1. Cervical cancer; 2. Candidate for surgical treatment **Exclusion Criteria:** NS	**Scanner Model:** Siemens ECAT EXACT 921 **Resolution:** • **Intrinsic:** NS • **Image:** NS **Acquisition Mode:** 2-D **Acquisition time per FOV:** • **Emission Scan:** 9 min • **Transmission Scan:** 3-8 min **Dose of FDG:** 5 MBq/kg **Dose Range:** 300-500 MBq **Time between injection and performance:** 100±20 min **Reconstruction Algorithm used:** Iterative **Glucose Monitoring:** Fasting overnight; Maximum glucose permitted: 130 mg/dL	**PET done:** Qualitatively **Criteria used for diagnosis:** Consensus of 3 investigators focal increased FDG uptake **Comparator Test:** MRI **Done:** Quantitatively **Criteria used for diagnosis:** Node diameter ≥ 1 cm **Gold Standard test done:** Qualitatively **Criteria used for diagnosis:** Histology after lymph node sampling **Blinding:** **Radiologist:** Yes **Gold Standard reader:** No	**By Patient:** PET Pathology (nodes) | | + | - | |---|---|---| | + | 10 | 0 | | - | 1 | 24 | Sensitivity = 91% Specificity = 100% MRI Pathology (nodes) | | + | - | |---|---|---| | + | 8 | 4 | | - | 3 | 20 | Sensitivity = 73% Specificity = 83% Prevalence: 18/35 = 51.4% **By Node Site:** PET Pathology (nodes) | | + | - | |---|---|---| | + | 17 | 2 | | - | 4 | 269 | Sensitivity = 81% Specificity = 99% MRI Pathology (nodes) | | + | - | |---|---|---| | + | 14 | 8 | | - | 7 | 263 | Sensitivity = 67% Specificity = 97%	***Quality Score:*** **Rep.sample: 1** **Setting selection: 1** **Design minimizes diffs: 1** **Scanner: 1** **Interpretation criteria defined: 1** **Hist or clin confirmation: 1** **Blinded: 0** **Total Score = 6** **Notes:**

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Rose **1999** **PROCITE#** 2580 **Cancer Type:** Cervical **SOW Question(s) Addressed:** 1 **Fryback et al. Level:** 2	**Dates of data collection:** 5/94 – 4/98 **Geographic Location:** Cleveland, OH **Prospective Study** **Enrolled Consecutively:** Yes **Study Setting:** Academic/ Research **Patient Incl Crit:** • Clin Pres **Result led to incl:** • Abnorm and norm **Comparisons:** • No comp **Use of ref stand:** • Histology	***Patients:*** **N =** 32 **Staging:** IIB: n=6 (18%) IIIB: n=24 (75%) IVA: n=2 (6%) **Mean(Median) Age:** NS **Inclusion criteria:** 1. Previously untreated cervical cancer stages IIB-IVA; 2. No extrapelvic diseas on CT or CXR; 3. Medically fit for surgery **Exclusion Criteria:** 1. Known extrapelvic disease; 2. Pregnant/ lactating; 3. Weight >350 lbs	**Scanner Model:** Siemens ECAT EXACT **Resolution:** • **Axial:** 5.4 mm • **Image:** NS **Acquisition Mode:** NS **Acquisition time per FOV:** • **Emission Scan:** NS • **Transmission Scan:** NS **Dose of FDG:** 20 mCi **Time between injection and performance:** 60 min **Reconstruction Algorithm used:** NS **Glucose Monitoring:** Fasting – 4 hours	**PET done:** Qualitatively **Criteria used for diagnosis:** NS **Gold Standard test done:** Histology **Criteria used for diagnosis:** Histology results of nodes removed at surgery **Blinding:** **Radiologist:** NS **Gold Standard reader:** NS	PET for pelvic nodes: Pathology (nodes) PET | | + | - | |---|---|---| | + | 11 | 0 | | - | 0 | 6 | Sensitivity = 100% Specificity = 100% CT for pelvic nodes: Pathology (nodes) CT | | + | - | |---|---|---| | + | 5 | - | | - | 6 | - | Sensitivity = 45% Specificity = N/A	***Quality Score:*** **Rep.sample: 1** **Setting selection: 1** **Design minimizes diffs: 0** **Scanner: 1** **Interpretation criteria defined: 1** **Hist or clin confirmation: 1** **Blinded: 0** **Total Score = 5** **Notes:**

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Ryu **2003** **PROCITE#** 10530 **Cancer Type:** Cervical **SOW Question(s) Addressed:** 2b **Frybeck et al. Level:** 2	**Dates of data collection:** 9/97 – 3/00 **Geographic Location:** Seoul, Korea **Retrospective Study** **Enrolled Consecutively:** Yes, if considered high-risk disease **Study Setting:** Academic/ Research **Patient Incl Crit:** • Clin Pres **Result led to incl:** • Normal only – no evidence of disease after treatment **Comparisons:** • No comp **Use of ref stand:** • Histology • Prolonged follow-up	***Patients:*** **N =** 249 **Mean Age:** 57 years **Age Range:** 31-78 years **Disease:** 59.7% Stages Ib and Iia; 90.7% Squamous **Median duration since completion of treatment by stage (range):** Ib: 30 mo (7-129) IIa: 35 mo(7-108) IIb: 31 mo (6-282) III/IV: 16 mo (6-165) **Median duration of PET from last CT or MRI:** 6 mo (3-12) **Inclusion criteria:** History of histologically-proven cervical cancer,; No evidence of disease after treatment **Exclusion Criteria:** NS	**Scanner Model:** GE Advance HR+ **Resolution:** • **Intrinsic:** NS • **Image:** NS **Acquisition Mode:** 2-D **Acquisition time per FOV:** • **Emission Scan:** 8 min • **Transmission Scan:** 3-5 min **Dose of FDG:** 370-555 MBq (10-15 mCi) **Time between injection and performance:** 50 min **Reconstruction Algorithm used:** Ordered-subset expectation maximization **Glucose Monitoring:** Fasting – 8 hours	**PET done:** Quantitatively and Qualitatively **Criteria used for diagnosis:** SUV and any focal uptake considered not to be physiologic **Gold Standard test done:** Fine needle aspiration **Criteria used for diagnosis:** Histology showing no change in size if lesion after follow-up for 1 year **Blinding:** **Radiologist:** Yes **Gold Standard reader:** Yes	Recurrence PET | | + | - | |---|---|---| | + | 28 | 52 | | - | 3 | 166 | Sensitivity = 90.3% Specificity = 76.1% Prevalence: 31/249 = 12.4%	***Quality Score:*** **Rep.sample: 1** **Setting selection: 1** **Design minimizes diffs: 0** **Scanner: 1** **Interpretation criteria defined: 1** **Hist or clin confirmation: 1** **Blinded: 1** **Total Score = 6** **Notes:**

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Sugawara **1999** **PROCITE#** 2590 **Cancer Type:** Cervical **SOW Question(s) Addressed:** 1, 2b **Fryback et al. Level:** 2	**Dates of data collection:** 5/93 – 5/97 **Geographic Location:** Ann Arbor, MI **Retrospective Study** **Enrolled Consecutively:** NS **Study Setting:** Inpatient; Academic/ Research **Patient Incl Crit:** • Clin Pres **Result led to incl:** • Abnormal only **Comparisons:** • Matched **Use of ref stand:** • Histology • Prolonged follow-up	***Patients:*** **N =** 21 **Mean Age:** 45 years **Age Range:** 26-82 years **Stage:** IB: N = 4 (19%) IIB: N = 9 (43%) IIIB: N = 7 (33%) IVA: N = 1 (5%) **Inclusion criteria:** Histologically proven cervical cancer **Exclusion Criteria:** NS	**Scanner Model:** Siemens 921 EXACT **Resolution:** • **Intrinsic:** NS • **Image:** NS **Acquisition Mode:** NS **Acquisition time per FOV:** • **Emission Scan:** 10 min • **Transmission Scan:** 10 min **Dose of FDG:** 370 MBq **Time between injection and performance:** NS **Reconstruction Algorithm used:** NS **Glucose Monitoring:** Fasting – 4 hours	**PET done:** Qualitatively **Criteria used for diagnosis:** SUV – calculated by not reported **Comparator Test:** CT **Done:** Quantitatively **Criteria used for diagnosis:** Positive if > 1 cm; Equivocal if = 1 cm; Negative if < 1 cm **Gold Standard test done:** Quantitatively **Criteria used for diagnosis:** Histology, prolonged follow-up and additional imaging studies **Blinding:** **Radiologist:** Blinded to other radiology findings, not blinded to clinical findings **Gold Standard reader:** NS	PET Pathology (nodes) | | + | - | | + | 6 | 0 | | - | 1 | 10 | Sensitivity = 86% Specificity = 100% CT (equiv +) Pathology (nodes) | | + | - | | + | 6 | 0 | | - | 1 | 10 | Sensitivity = 86% Specificity = 100% CT (equiv -) Pathology (nodes) | | + | - | | + | 4 | 0 | | - | 3 | 10 | Sensitivity = 57% Specificity = 100% Prevalence: 7/7* = 100% * 4 patients not confirmed, not included in report	***Quality Score:*** **Rep.sample: 1** **Setting selection: 1** **Design minimizes diffs: 1** **Scanner: 1** **Interpretation criteria defined: 1** **Hist or clin confirmation: 1** **Blinded: 0** **Total Score = 6** **Notes:**

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Sun **2001** **PROCITE#** 2490 **Cancer Type:** Cervical **SOW Question(s) Addressed:** 2b **Fryback et al. Level:** 2	**Dates of data collection:** NS **Geographic Location:** Taichung, Taiwan **Retrospective Study** **Enrolled Consecutively:** No (retrospective) **Study Setting:** General outpatient clinics/ Physician office; Academic/ Research **Patient Incl Crit:** • Clin Pres **Result led to incl:** • See inclusion criteria **Comparisons:** • No comp test results presented (CT done) **Use of ref stand:** • Histology • ≥ 1 year follow-up	***Patients:*** **N = 20** Stage I – 5 Stage II – 9 Stage III – 5 Stage IV – 1 **Age Range:** 45-65 years **Inclusion criteria:** History of cervical cancer, suspicion of recurrence **Exclusion criteria:** History of diabetes	**Scanner Model:** Siemens ECAT-EXHACT 47 or HR+ **Resolution:** • **Nominal:** 5 mm • **Axial:** 4 mm **Acquisition Mode:** 2-D **Acquisition time per FOV:** • **Emission Scan:** 7 min • **Transmission Scan:** 3 min **Dose of FDG:** 10 mCi **Time between injection and performance:** 30 min **Reconstruction Algorithm used:** NS **Glucose Monitoring:** Fasting ≥ 4hrs	**PET done:** Qualitatively **Criteria used for diagnosis:** NS **Gold Standard test done:** Quantitatively **Criteria used for diagnosis:** Operative histology or clinical follow-up ≥ 1 year **Blinding:** Radiologist: NS Gold Standard reader: NS	**Overall Recurrence** Recurrence PET: + 19, 1; - 0, 0 Sensitivity = 100% Specificity = 0% **Local Recurrence** Local Recurrence PET: + 12, 1; - 2, 5 Sensitivity = 86% Specificity = 83% **Pelvic Lymph Nodes** Pelvic Nodes PET: + 16, 1; - 0, 3 Sensitivity = 100% Specificity = 75% **Para Aortic Nodes** PA Nodes PET: + 14, 0; - 0, 6 Sensitivity = 100% Specificity = 100% **Distant Metastasis** Distant Metastasis PET: + 4, 0; - 0, 16 Sensitivity = 100% Specificity = 100%	***Quality Score:*** **Rep.sample: 1** **Setting selection: 1** **Design minimizes diffs: 0** **Scanner: 1** **Interpretation criteria defined: 0** **Hist or clin confirmation: 1** **Blinded: 0** **Total Score = 4** **Notes:** Author's calculations for sensitivity and specificity do not match reviewer's calculations. Tables reflect reviewer's calculations.

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Yeh **2002** **PROCITE#** 2390 **Cancer Type:** Cervical **SOW Question(s) Addressed:** 1 **Fryback et al. Level:** 2	**Dates of data collection:** NS **Geographic Location:** Taipei, Taiwan **Prospective Study** **Enrolled Consecutively:** NS (prospective) **Study Setting:** Inpatient; General outpatient clinics/ physician office. **Patient Incl Crit:** • Clin Pres – negative MRI and diagnosis of cervical cancer **Result led to incl:** • Abnormal only – known cancer • Abnorm and norm – normal abdominal MRI **Comparisons:** • No comp **Use of ref stand:** • Histology – surgery and lymph node pathology	***Patients:*** **N =** 42 **Mean(Median) Age:** NS **Inclusion criteria:** Advanced stage IIB – IVA cervical cancer or stage IB – IIA with tumor > 5 cm or positive pelvic LN; Negative abdominal MRI (PA node < 10 mm). **Exclusion Criteria:** <18yrs; Diabetic; Pregnant/ nursing; Medically unfit for surgery.	**Scanner Model:** Siemens ECAT/ EXACT **Resolution:** • Intrinsic: 5 mm • Image: NS **Acquisition Mode:** 2-D **Acquisition time per FOV:** • **Emission Scan:** NS • **Transmission Scan:** 3 min **Dose of FDG:** 10 mCi **Time between injection and performance:** 60 min **Reconstruction Algorithm used:** NS **Glucose Monitoring:** Fasting – 4 hrs	**PET done:** Qualitatively **Criteria used for diagnosis:** Visual agreement of at least 2 of 3 nuclear medicine physicians, not blinded to pathological results **Gold Standard test:** Histology **Done:** Qualitatively **Criteria used for diagnosis:** Positive or negative metastasis in lymph nodes removed surgically after PET scan. **Blinding:** **Radiologist:** No **Gold Standard reader:** NS	**Pathology** Pathology Nodes PET Nodes | | + | - | |---|---|---| | + | 10 | 1 | | - | 2 | 29 | Sensitivity = 83% Specificity = 97% Prevalence: 12/42 = 29%	***Quality Score:*** **Rep.sample: 1** **Setting selection: 1** **Design minimizes diffs: 0** **Scanner: 1** **Interpretation criteria defined: 0** **Hist or clin confirmation: 1** **Blinded: 0** **Total Score = 4** **Notes:**

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Chang **2002** **PROCITE#** 6570 **Cancer Type:** Ovarian **SOW Question(s) Addressed:** 1b, 1bi **Fryback et al. Level:** 2	**Dates of data collection:** NS **Geographic Location:** Taipei, Taiwan **Prospective/ Retrospective Study:** NS **Enrolled Consecutively:** No **Study Setting:** Academic/ Research **Patient Incl Crit:** • Clin Pres **Result led to incl:** • Abnorm and norm – abnormal CA125, normal imaging other than PET **Comparisons:** • No comp **Use of ref stand:** • Histology • Prolonged follow-up	***Patients:*** **N =** 28 **Stage:** IIa: N=4 IIb: N=3 IIc: N=5 IIIa: N=5 IIIb: N=3 IIIc: N=4 IV: N=4 **Age Range:** 44 – 76 years **Inclusion criteria:** 1. History of ovarian cancer; 2. Prior surgery and chemotherapy; 3. Elevated CA125; 4. Negative or equivocal CT or MRI, or other imaging modality **Exclusion Criteria:** NS	**Scanner Model:** Siemens ECAT EXACT 47 or HR+ **Resolution:** • **Nominal:** 5 mm • **Axial:** 4 mm **Acquisition Mode:** 2-D **Acquisition time per FOV:** • **Emission Scan:** 7 min • **Transmission Scan:** 3 min **Dose of FDG:** 10 mCi **Time between injection and performance:** 30 min **Reconstruction Algorithm used:** NS **Glucose Monitoring:** Fasting – 4 hours	**PET done:** Qualitatively **Criteria used for diagnosis:** NS **Gold Standard test done:** Histology or follow-up **Criteria used for diagnosis:** Histology (biopsy or surgery) or clinical follow-up of greater than one year **Blinding:** **Radiologist:** No **Gold Standard reader:** No	Recurrence PET | | + | - | |---|---|---| | + | 19 | 1 | | - | 1 | 7 | Sensitivity = 95% Specificity = 87.5% Prevalence: 20/28 = 71.4% Note: • 6/28 patients did not have 2nd look surgery • 4/6 patients no recurrence, 2/4 had recurrence • Diagnosis not specified	***Quality Score:*** **Rep.sample: 1** **Setting selection: 1** **Design minimizes diffs: 0** **Scanner: 1** **Interpretation criteria defined: 0** **Hist or clin confirmation: 1** **Blinded: 0** **Total Score = 4** **Notes:**

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Cho **2002** **PROCITE#** 6660 **Cancer Type:** Ovarian **SOW Question(s) Addressed:** 1b **Fryback et al. Level:** 2	**Dates of data collection:** 1/96 – 3/00 **Geographic Location:** Seoul, South Korea **Retrospective Study** **Enrolled Consecutively:** No **Study Setting:** Academic/ Research **Patient Incl Crit:** • Clin Pres **Result led to incl:** • Abnormal only **Comparisons:** • PET and comp – not random **Use of ref stand:** • Histology	***Patients:*** **N =** 31 **Mean(Median) Age:** 46 years **Inclusion criteria:** 1. Pathologically proven epithelial ovarian cancer; 2. Planned second look surgery within 1 month **Exclusion Criteria:** Imaging performed > 1 month before the second look surgery	**Scanner Model:** ECAT EXACT 47 (Siemens) **Resolution:** • **Intrinsic:** NS • **Image:** NS **Acquisition Mode:** NS **Acquisition time per FOV:** • **Emission Scan:** 30 min • **Transmission Scan:** 20 min **Dose of FDG:** 370 MBq **Time between injection and performance:** 45 min **Reconstruction Algorithm used:** Filtered Backposition **Glucose Monitoring:** Fasting – 12 hours	**PET done:** Qualitatively and Quantitatively **Criteria used for diagnosis:** Quantitatively: Correlation with CT was used. If nodules were > 2 cm diameter SUV was measured. Qualitatively: If nodules were < 2 cm, visual analysis was used in image interpretation. **Confidence Scoring:** 0 = absent 1 = visual suspicion only 2 = SUV > 3 was positive for tumor recurrence. Scores 1 and two considered positive for final analysis. **Comparator Test done:** CT **Criteria used for diagnosis:** NS **Gold Standard test done:** Histology **Criteria used for diagnosis:** At surgery, the presence or absence of tumor at 15 specific sites was recorded **Blinding:** **Radiologist:** Yes **Gold Standard reader:** NS Blinded biopsies done at each site if no gross mass was seen	**Patient-based analysis *:** PET alone Recurrence | | + | - | | + | 9 | 1 | | - | 2 | 9 | Sensitivity = 82% Specificity = 90% CT alone Recurrence | | + | - | | + | 11 | 1 | | - | 0 | 9 | Sensitivity = 100% Specificity = 90% PET and CT Recurrence | | + | - | | + | 11 | 1 | | - | 0 | 9 | Sensitivity = 100% Specificity = 90% * Authors did lesion- and patient-based analysis. Lesion-based analysis can not be very accurate for PET and the specific locations of the lesions because the results are not given. Therefore, only patient-based results are shown here.	***Quality Score:*** **Rep.sample:1** **Setting selection: 1** **Design minimizes diffs: 0** **Scanner: 1** **Interpretation criteria defined: 1** **Hist or clin confirmation: 1** **Blinded: 0** **Total Score = 5** **Notes:** Authors' conclusion was that PET does not add much to conventional imaging for detection of recurrent ovarian cancer.

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Hubner **1993** **PROCITE#** 6900 **Cancer Type:** Ovarian **SOW Question(s) Addressed:** 1b **Fryback et al. Level:** 2	**Dates of data collection:** 1/92 – 4/93 **Geographic Location:** Knoxville, TN **Prospective/ Retrospective Study:** NS **Enrolled Consecutively:** NS **Study Setting:** Inpatient; Academic/ Research **Patient Incl Crit:** • Clin Pres **Result led to incl:** • Abnorm and norm **Comparisons:** • No comp **Use of ref stand:** • Histology • Prolonged follow-up	***Patients:*** **N =** 14 patients followed for recurrence – 57 total patients in study, but mostly with diagnostic information **Mean(Median) Age:** NS **Inclusion criteria:** NS **Exclusion Criteria:** NS	**Scanner Model:** Siemens ECAT 931; Siemens ECAT EXACT **Resolution:** • **Intrinsic:** 6 mm • **Image:** 5 mm **Acquisition Mode:** NS **Acquisition time per FOV:** • **Emission Scan:** NS • **Transmission Scan:** NS **Dose of FDG:** 185-370 MBq **Time between injection and performance:** NS **Reconstruction Algorithm used:** NS **Glucose Monitoring:** NS	**PET done:** Qualitatively and Quantitatively **Criteria used for diagnosis:** Visual interpretation; SUV calculated. **Gold Standard test done:** Qualitatively and Quantitatively **Criteria used for diagnosis:** Histology of repeat surgery or biopsy, or survival **Blinding:** **Radiologist:** NS **Gold Standard reader:** NS	1st PET Recurrence | | + | - | | + | 10 | 0 | | - | 1 | 3 | Sensitivity = 91% Specificity = 100% 2nd PET Recurrence | | + | - | | + | 7 | 0 | | - | 0 | 7 | Sensitivity = 100% Specificity = 100% Note: Timing of PET in relation to diagnosis, as well as the length of follow-up are unclear, therefore results are of questionable usefulness.	***Quality Score:*** **Rep.sample: 0** **Setting selection: 0** **Design minimizes diffs: 0** **Scanner: 1** **Interpretation criteria defined: 1** **Hist or clin confirmation: 1** **Blinded: 0** **Total Score = 3** **Notes:**

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Jimenez-Bonilla **2000** **PROCITE#** **Cancer Type:** Ovarian **SOW Question(s) Addressed:** 1bi, 1bii **Frybeck et al. Level:** 2, 4	**Dates of data collection:** NS **Geographic Location:** Madrid and Grenada, Spain **Prospective/ Retrospective Study:** NS **Enrolled Consecutively:** No **Study Setting:** Academic/ Research **Patient Incl Crit:** • Clin Pres **Result led to incl:** • Abnorm and norm **Comparisons:** • No comp – normal/equivocal CT/MRI inclusion criteria **Use of ref stand:** • Histology (in 7 patients) • Prolonged follow-up (in 7 patients)	***Patients:*** **N =** 20 **Mean Age:** 51 years **Inclusion criteria:** Suspected recurrent ovarian carcinoma; Rising tumor markers; Normal or equivocal CT or MRI **Exclusion Criteria:** NS	**Scanner Model:** Siemens/CTI ECAT Exact 47 **Resolution:** • **Intrinsic:** NS • **Image:** NS **Acquisition Mode:** NS **Acquisition time per FOV:** • **Emission Scan:** NS • **Transmission Scan:** NS **Dose of FDG:** 1.5 MBq/kg **Time between injection and performance:** 45 min **Reconstruction Algorithm used:** NS **Glucose Monitoring:** Fasting – 6 hours; Mean glycemia: 78 mg/dl, maximum permitted not stated	**PET done:** Qualitatively **Criteria used for diagnosis:** Abnormal increased FDG uptake **Gold Standard test done:** Qualitatively **Criteria used for diagnosis:** Histology or resolution of increased serum markers **Blinding:** **Radiologist:** Yes **Gold Standard reader:** NS	Recurrence PET | | + | - | |+| 12 | 1 | |-| 0 | 1 | Sensitivity = 100% Specificity = 50% Prevalence: 12/14 = 85.7%	***Quality Score:*** **Rep.sample: 0** **Setting selection: 1** **Design minimizes diffs: 1** **Scanner: 1** **Interpretation criteria defined: 0** **Hist or clin confirmation: 0** **Blinded: 0** **Total Score = 3** **Notes:** Confirmation of results provided for only 14 of 20 subjects; No minimum time for clinical follow-up was given; Therapeutic option was altered in 10 of 14 cases or 71% of patients who had PET results confirmed.

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Karlan **1993** **PROCITE#** 6910 **Cancer Type:** Ovarian **SOW Question(s) Addressed:** 1b **Fryback et al. Level:** 2	**Dates of data collection:** NS **Geographic Location:** Los Angeles, CA **Prospective/ Retrospective Study:** NS **Enrolled Consecutively:** No **Study Setting:** Inpatient; Academic/ Research **Patient Incl Crit:** • Clin Pres **Result led to incl:** • Abnormal only • Abnorm and norm **Comparisons:** • No comp **Use of ref stand:** • Histology for n=12, 1 patient did not have surgery	***Patients:*** **N =** 13 (12 Ovarian Cancer, 1 Fallopian Tube Cancer) **Mean (Median) Age:** 51 years **Inclusion criteria:** Patients with history of documented ovarian or tubal cancer **Exclusion Criteria:** NS	**Scanner Model:** Siemens 931/ 08-12 **Resolution:** • **Intrinsic:** NS • **Image:** NS **Acquisition Mode:** NS **Acquisition time per FOV:** • **Emission Scan:** NS • **Transmission Scan:** NS **Dose of FDG:** 10 mCi **Time between injection and performance:** 30 min **Reconstruction Algorithm used:** NS **Glucose Monitoring:** Fasting – 6 hours	**PET done:** Qualitatively **Criteria used for diagnosis:** Uptake higher than surrounding tissues **Gold Standard test done:** Histology at surgery **Criteria used for diagnosis:** Histological results **Blinding:** **Radiologist:** Yes **Gold Standard reader:** NS	Recurrent Disease PET | | + | - | |---|---|---| | + | 6 | 0 | | - | 5 | 1 | Sensitivity = 55% Specificity = 100%	***Quality Score:*** **Rep.sample: 1** **Setting selection: 0** **Design minimizes diffs: 0** **Scanner: 1** **Interpretation criteria defined: 1** **Hist or clin confirmation: 1** **Blinded: 0** **Total Score = 4** **Notes:** One patient did not have histology and her follow up period was not defined and therefore should have been excluded. One patient had fallopian tube cancer which is very similar clinically to ovarian cancer, so this is not a major drawback.

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Nakamoto **2001** **PROCITE#** 6770 **Cancer Type:** Ovarian **SOW Question(s) Addressed:** 1b **Fryback et al. Level:** 2, 4	**Dates of data collection:** NS **Geographic Location:** Kyoto, Japan **Prospective Study** **Enrolled Consecutively:** No **Study Setting:** Inpatient; General outpatient clinics/ physician office; Academic/ Research **Patient Incl Crit:** • Clin Pres **Result led to incl:** • Some with suspected recurrence, some not **Comparisons:** • PET and comp on different patients – not random **Use of ref stand:** • Histology • Prolonged follow-up	***Patients:*** **N =** 24 (N=12 suspected recurrence N=12 thought to be disease free) **Mean(Median) Age:** 51.8 years **Inclusion criteria:** Positive history of ovarian cancer **Exclusion Criteria:** NS	***Set 1 = 6/24 patients*** **Scanner Model:** PCT 3600W **Resolution:** • **Intrinsic:** 7 mm • **Image:** NS **Acquisition Mode:** NS **Acquisition time per FOV:** • **Emission:** 10 min • **Transmission:** 10 min **Dose of FDG:** 370 MBq **Time between injection and performance:** 60 min **Reconstruction Algorithm used:** NS **Glucose Monitoring:** NS ***Set 2 = 18/24 patients*** **Scanner Model:** Advance/ 9E **Resolution:** • **Axial:** 4.2 mm • **Image:** NS **Acquisition Mode:** NS **Acquisition time per FOV:** • **Emission:** NS • **Transmission:** NS **Dose of FDG:** 370 MBq **Time between injection and performance:** 60 min **Reconstruction Algorithm used:** NS **Glucose Monitoring:** NS	**PET done:** Qualitatively **Criteria used for diagnosis:** Abnormal – accumulation of FDG moderately to markedly increased relative to normal structures **Comparator Test done:** CT – not done on all patients **Criteria used for diagnosis:** NS **Comparator Test done:** MR – not done on all patients **Criteria used for diagnosis:** NS **Gold Standard test done:** **Histology or follow-up** **Criteria used for diagnosis:** Histology n=11; At least 6 months for follow-up n=12; One patient did not have at least 6 month follow-up **Blinding:** **Radiologist:** No **Gold Standard reader:** No	**All:** Recurrence PET: + 10, 2; - 3, 9 Sensitivity = 77% Specificity = 82% **Clinically suspicious:** Recurrence PET: + 8, 1; - 2, 1 Sensitivity = 80% Specificity = 50% **Clinically disease free:** Recurrence PET: + 2, 1; - 1, 8 Sensitivity = 67% Specificity = 89% **CT/MRI alone*:** Recurrence CT/MRI: + 8, 1; - 3, 3 Sensitivity = 73% Specificity = 75% **PET plus CT/MRI*:** Recurrence PET plus CT/MRI: + 12, 0; - 1, 5 Sensitivity = 92% Specificity = 100% * Conventional imaging done on only 18 patients, with 3 having inconclusive results.	***Quality Score:*** **Rep.sample: 1** **Setting selection: 1** **Design minimizes diffs: 0** **Scanner: 1** **Interpretation criteria defined: 1** **Hist or clin confirmation: 1** **Blinded: 0** **Total Score = 5** **Notes:** When assessing SN and SP for the combination of PET and conventional imaging, the authors do not give enough information about findings in each case to decide whether to judge overall constellation of radiographic findings as + or -. Therefore Table 2 questionable. "PET alone" calculations not given by author. Overall calculated to be: SN=77%, SP=82%.

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Rose **2001** **PROCITE#** 6760 **Cancer Type:** Ovarian **SOW Question(s) Addressed:** 1b, 1c **Fryback et al. Level:** 2	**Dates of data collection:** 6/94 – 5/96 **Geographic Location:** Cleveland, OH **Prospective Study** **Enrolled Consecutively:** Yes **Study Setting:** Academic/ Research **Patient Incl Crit:** • Clin Pres **Result led to incl:** • Abnorm and norm **Comparisons:** • No comp **Use of ref stand:** • Histology	***Patients:*** **N =** 22 **Staging:** IIIA – 3 (14%) IIIB – 4 (18%) IIIC – 12 (55%) IV – 3 (14%) **Mean Age:** 50 years **Age Range:** 24-67 years **Race:** 91% White 9% Black **Inclusion criteria:** 1. Stage III or IV ovarian or peritoneal cancer; 2. Complete clinical response after chemotherapy; 3. Medically fit for second look surgery **Exclusion Criteria:** **1.** Can't undergo CT; 2. Abnormal CA125; 3. Definitive diagnosis of	**Scanner Model:** Siemens ECAT EXACT **Resolution:** • **Axial:** 5.4 mm **Acquisition Mode:** NS **Acquisition time per FOV:** • **Emission Scan:** NS • **Transmission Scan:** NS **Dose of FDG:** 20 mCi **Time between injection and performance:** 60 min **Reconstruction Algorithm used:** NS **Glucose Monitoring:** Fasting – 4 hours	**PET done:** NS **Criteria used for diagnosis:** NS **Comparative test:** CT **Done:** NS **Criteria used for diagnosis:** NS **Gold Standard test done:** Histology **Criteria used for diagnosis:** Histology at second look surgery: 1. Negative; 2. Macroscopically positive; 3. Microscopically positive **Blinding:** **Radiologist:** NS **Gold Standard reader:** NS	Pathology PET | | + | - | |---|---|---| | + | 2 | 6 | | - | 9 | 5 | Sensitivity = 18% Specificity = 45%	***Quality Score:*** **Rep.sample: 1** **Setting selection: 1** **Design minimizes diffs: 0** **Scanner: 1** **Interpretation criteria defined: 0** **Hist or clin confirmation: 1** **Blinded: 0** **Total Score = 4** **Notes:** Well designed. Conclusion is that the sensitivity of PET for small-volume disease is low in ovarian cancer.

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
		persistent disease is known				

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Torizuka **2002** **PROCITE#** 6600 **Cancer Type:** Ovarian **SOW Question(s) Addressed:** 1b **Fryback et al. Level:** 2	**Dates of data collection:** NS **Geographic Location:** Hirakuchi, Japan **Prospective/ Retrospective Study:** NS **Enrolled Consecutively:** No **Study Setting:** Academic/ Research **Patient Incl Crit:** • Clin Pres **Result led to incl:** • Abnorm and norm **Comparisons:** • Matched **Use of ref stand:** • Histology • Prolonged follow-up	***Patients:*** **N =** 25 **Mean(Median) Age:** 55 years **Stage:** I: N=6 II: N=1 III: N=16 IV: N=2 **Inclusion criteria:** **1.** Ovarian cancer; 2. Have had initial surgery and chemotherapy; 3. Suspected recurrence based on CA125, conventional imaging or symptoms **Exclusion Criteria:** NS	**Scanner Model:** SHR 22000 (Hamamatsu) **Resolution:** • **Spatial:** 3-4 mm **Acquisition Mode:** NS **Acquisition time per FOV:** • **Emission Scan:** NS • **Transmission Scan:** NS **Dose of FDG:** 300-400 MBq **Time between injection and performance:** 60 min **Reconstruction Algorithm used:** NS **Glucose Monitoring:** Fasting – 5 hours	**PET done:** NS **Criteria used for diagnosis:** Any foci of FDG uptake that were increased relative to the background **Comparator Test done:** CT **Criteria used for diagnosis:** NS **Comparator Test done:** MRI **Criteria used for diagnosis:** NS **Comparator Test done:** Ca 125 **Criteria used for diagnosis:** ≥ 35 U/mL **Gold Standard test done:** Histology or follow-up **Criteria used for diagnosis:** Positive histology or > 6 months clinical follow-up	PET Recurrent Disease | | + | - | | + | 16 | 1* | | - | 4 | 5 | Sensitivity = 80% Specificity = 83% Conv. Image Recurrent Disease | | + | - | | + | 11 | 1** | | - | 9 | 5 | Sensitivity = 55% Specificity = 83 % CA125 Recurrent Disease | | + | - | | + | 15 | 0 | | - | 5 | 5 | Sensitivity = 75% Specificity = 100% * One patient with both FN and FP findings is included in the FN category ** One patient with both TP and FP findings is included in the TP category	***Quality Score:*** **Rep.sample: 1** **Setting selection: 1** **Design minimizes diffs: 1** **Scanner: 1** **Interpretation criteria defined: 1** **Hist or clin confirmation: 1** **Blinded: 0** **Total Score = 6** **Notes:**

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
				Blinding: **Radiologist:** No **Gold Standard reader:** NS		

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Yen **2001** **PROCITE#** 6700 **Cancer Type:** Ovarian **SOW Question(s) Addressed:** 1b **Fryback et al. Level:** 2	**Dates of data collection:** NS **Geographic Location:** Taipei, Taiwan **Prospective/ Retrospective Study:** NS **Enrolled Consecutively:** NS **Study Setting:** Inpatient; Academic/ Research **Patient Incl Crit:** • Clin Pres **Result led to incl:** • Abnormal only **Comparisons:** • Matched **Use of ref stand:** • Histology	***Patients:*** **N =** 24 **Age Range:** 41-66 years **Inclusion criteria:** 1. Suspected recurrent ovarian cancer; 2. Prior surgery and chemotherapy **Exclusion Criteria:** NS	**Scanner Model:** Siemens ECAT/ EXACT 47 or HR+ **Resolution:** • **Intrinsic:** NS • **Image:** NS **Acquisition Mode:** 2-D **Acquisition time per FOV:** • **Emission Scan:** 7 min • **Transmission Scan:** 3 min **Dose of FDG:** 10 mCi **Time between injection and performance:** 45 min **Reconstruction Algorithm used:** Filtered Backposition	**PET done:** Qualitatively **Criteria used for diagnosis:** NS **Comparator Test done:** CT **Criteria used for diagnosis:** NS **Comparator Test done:** MRI **Criteria used for diagnosis:** NS **Comparator Test done:** CA125 **Criteria used for diagnosis:** NS **Gold Standard test done:** Histology or clinical follow-up Histology: n=16 Follow-up: n=8 **Criteria used for**	**Patients with Histology as reference standard (n=16):** PET Diagnosis | | + | - | |---|---|---| | + | 10 | 1 | | - | 1 | 12 | Sensitivity = 91% Specificity = 92.3% CT/ MRI Diagnosis | | + | - | |---|---|---| | + | 10 | 7 | | - | 1 | 6 | Sensitivity = 91% Specificity = 46% CA 125 Diagnosis | | + | - | |---|---|---| | + | 10 | 3 | | - | 1 | 10 | Sensitivity = 91% Specificity = 77%	***Quality Score:*** **Rep.sample: 1** **Setting selection: 1** **Design minimizes diffs: 1** **Scanner: 1** **Interpretation criteria defined: 0** **Hist or clin confirmation: 0** **Blinded: 0** **Total Score = 4** **Notes:** No minimum clinical follow-up given (clinical follow-up was gold standard in 8 cases).

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
			Glucose Monitoring: Fasting – 6 hours	**diagnosis:** Clinical results **Blinding:** **Radiologist:** Yes **Gold Standard reader:** NS		Results SN/SP calculations based on cases that had histology as gold standard (n=16).

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Zimny **2001** **PROCITE#** 6750 **Cancer Type:** Ovarian **SOW Question(s) Addressed:** 1b	**Dates of data collection:** 4/96 – 12/00 **Geographic Location:** Aachen, Germany **Retrospective Study** **Enrolled Consecutively:** NS **Study Setting:** Inpatient; Academic/ Research **Patient Incl Crit:** • Clin Pres **Result led to incl:** • Abnorm and norm	***Patients:*** **N =** 54 (106 PET scans in 54 patients) **Mean(Median) Age:** 55±14 yrs **Inclusion criteria:** 1. History of ovarian cancer; 2. Either suspected recurrence <u>or</u> clinically disease free **Exclusion Criteria:** NS	**Scanner Model:** ECAT 953/15 (CTI) **Resolution:** • **Intrinsic:** NS • **Image:** NS **Acquisition Mode:** NS **Acquisition time per FOV:** • **Emission Scan:** NS • **Transmission Scan:** NS **Dose of FDG:** 228±53 MBq **Time between injection and performance:** 45-60 min	**PET done:** Quantitatively **Criteria used for diagnosis:** 5 point scale ranging from definitely normal to definitely abnormal **Gold Standard test done:** Histology and/or clinical follow-up **Criteria used for diagnosis:** Histology: n=37; Follow-up: n=66; Median follow-up was 12-22 months	**PET scans performed (n=106):** Recurrence PET | | + | - | |---|---|---| | + | 73 | 3 | | - | 15 | 15 | Sensitivity = 83% Specificity = 83% PET was more accurate in patients with suspected recurrence with a diagnosis accuracy of 93% and sensitivity of 94%.	***Quality Score:*** **Rep.sample: 1** **Setting selection: 1** **Design minimizes diffs: 0** **Scanner: 1** **Interpretation criteria defined: 1** **Hist or clin confirmation: 1** **Blinded: 0** **Total Score = 5** **Notes:** No minimum clinical follow-up was

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Fryback et al. Level: 2	**Comparisons:** • No comp **Use of ref stand:** • Histology • Prolonged follow-up		**Reconstruction Algorithm used:** NS **Glucose Monitoring:** Fasting – 4 hours; Maximum glucose permitted: 7.5 mmol/L	**Blinding:** **Radiologist:** Yes **Gold Standard reader:** NS		stipulated but the median follow-up was given.

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Bares **1994** **PROCITE#** 7570 **Cancer Type:** Pancreatic	**Dates of data collection:** NS **Geographic Location:** Aachen, Germany **Prospective Study** **Enrolled Consecutively:** NS **Study Setting:** Academic/ Research	***Patients:*** **N =** 40 **Final Diagnosis:** N = 27 malignant N = 13 benign **Mean Age:** 59 years **Gender:** 62.5% Male **Inclusion criteria:** Either: 1. Previously obtained CT scan revealing a pancreatic mass suggestive of	**Scanner Model:** CTI ECAT 953/15 (Siemens) **Resolution:** • **Intrinsic:** NS • **Image:** NS **Acquisition Mode:** NS **Acquisition time per FOV:** • **Emission Scan:** 15 min per bed position (3-4 bed positions) • **Transmission Scan:** NS	**PET done:** Qualitatively and Quantitatively **Criteria used for diagnosis:** Focal accumulation is the ROI; Tumor to liver ratio (TLR); Differential uptake ratio (DUR) = $\frac{\text{Tissue radioactivity}}{\text{Injected dose / body weight}}$ **Comparator Test done:** CT **Criteria used for diagnosis:** NS	**Question 1a:** PET Histology + / - +: 24, 2 -: 3, 11 Sensitivity = 92% Specificity = 85% CT Histology + / - +: 27, 10 -: 0, 3 Sensitivity = 100% Specificity = 23% **US:** Sensitivity: 75% Specificity: 33%	***Quality Score:*** **Rep.sample: 1** **Setting selection: 1** **Design minimizes diffs: 1** **Scanner: 1** **Interpretation criteria defined: 1** **Hist or clin confirmation: 1** **Blinded: 0** **Total Score = 6**

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
SOW Question(s) Addressed: 1a, 1b **Frybeck et al. Level:** 2	**Patient Incl Crit:** • Clin Pres **Result led to incl:** • Abnormal only **Comparisons:** • Matched **Use of ref stand:** • Histology	malignancy, or 2. Recurrent abdominal and lumbar pain in patients with chronic pancreatitis without morphologic signs of cancer **Exclusion Criteria:** Evidence of enopathy or solitary liver metastasis for highly advanced disease only (life expectancy < 3 months)	**Dose of FDG:** 150-300 MBq **Time between injection and performance:** 45 min **Reconstruction Algorithm used:** Iterative **Glucose Monitoring:** Fasting – 12 hours	**Comparator Test done:** US **Criteria used for diagnosis:** NS **Gold Standard test done:** Histology **Criteria used for diagnosis:** NS **Blinding:** **Radiologist:** NS **Gold Standard reader:** NS	Prevalence: 67% Quantitation with FDG uptake did not improve results. **17 lymph node metastasis:** 76% detected by PET 18% detected by CT 7% detected by US **Question 1b:** LN PET Histology + | - + | 27 | 10 - | 0 | 3 Sensitivity = 100% Specificity = 23% CT Histology + | - + | 3 | 10 - | 14 | 13 Sensitivity = 17.6% Specificity = 56.5% Prevalence = 42%	**Notes:** Lack of FDG accumulation in diabetic patients. Close relationship between visual classification and quantification of FDG uptake or TLRs. No correlation between uptake or TLR and tumor size.

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
					Liver PET Histology | + | - | |---|---|---| | + | 4 | 4 | | - | 3 | 29 | Sensitivity = 57.1% Specificity = 87.9% CT Histology | + | - | |---|---|---| | + | 2 | 11 | | - | 5 | 22 | Sensitivity = 28.6% Specificity = 66.7% Prevalence = 17%	

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Bares **1993** **PROCITE#** 7580 **Cancer Type:**	**Dates of data collection:** NS **Geographic Location:** Aachen, Germany **Prospective Study** **Enrolled Consecutively:** NS **Study Setting:** NS Patient Incl Crit: • Comp test result **Result led to incl:**	***Patients:*** **N =** 15 11 pancreatic cancer 2 carcinoma of ampulla vater **Mean(Median) Age:** 61.5 yrs **Gender:** **73% Male** **Inclusion criteria:** Pancreatic masses on CT	**Scanner Model:** CTI – Siemens ECAT 953/15 **Resolution:** • Intrinsic: 3.4 mm • Image: 9 mm **Acquisition Mode:** 3-D **Acquisition time per FOV:** • **Emission Scan:** NS • **Transmission Scan:** 15 min **Dose of FDG:** 150-300 MBq	**PET done:** *Qualitatively:* Compared image contrast between lesion and surrounding background (+ / ++) *Quantitatively:* Calculated differential uptake ratio **Criteria used for diagnosis:** No values were given as to what was considered positive and what was considered negative. **Comparator Test done:** Ultrasound **Criteria used for**	**Question 1a** PET Histology | + | - | |---|---|---| | + | 12 | 0 | | - | 1 | 2 | Sensitivity = 92% Specificity = 100% VIS Histology | + | - | |---|---|---| | + | 11 | 1 | | - | 2 | 12 | Sensitivity = 85% Specificity = 92% ERCP Histology | + | - | |---|---|---| | + | 13 | 1 | Sensitivity = 100% Specificity = 50%	***Quality Score:*** **Rep.sample: 1** **Setting selection: 0** **Design minimizes diffs: 1** **Scanner: 1** **Interpretation criteria defined: 0** **Hist or clin confirmation: 0** **Blinded: 0** **Total Score = 3**

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Pancreatic **SOW Question(s) Addressed:** 1a, 1b **Frybeck et al. Level:** 2	• Abnormal only **Comparisons:** • Matched **Use of ref stand:** • Histology	suggestive of Pancreatic Cancer. **Exclusion Criteria:** NS	**Time between injection and performance:** 45 min **Reconstruction Algorithm used:** Iterative **Glucose Monitoring:** 12 patients fasted ≥ 18 hrs; 3 patients given 500 ml 40% glucose before scan.	**diagnosis:** NS **Comparator Test done:** ERCP **Criteria used for diagnosis:** NS **Gold Standard test done:** Histology **Criteria used for diagnosis:** NS **Blinding:** **Radiologist:** NS **Gold Standard reader:** NS	- 0 1 Overall prevalence: 87% **Question 1b** LN PET Histology + - + 8 0 - 1 6 Sensitivity = 89% Specificity = 100% CT Histology + - + 2 1 - 7 3 Sensitivity = 22.2% Specificity = 75% Prevalence = 60% Liver PET Histology + - + 4 0 - 1 10 Sensitivity = 80% Specificity = 100% CT Histology + - + 3 2 - 2 8 Sensitivity = 60% Specificity = 80% Prevalence = 33%	**Notes:**

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Delbeke **1999** **PROCITE#** 7340 **Cancer Type:** Pancreatic **SOW Question(s) Addressed:** 1a, 1b **Fryback et al. Level:** 2, 4	**Dates of data collection:** NS **Geographic Location:** Nashville, TN **Prospective Study** **Enrolled Consecutively:** Yes **Study Setting:** NS **Patient Incl Crit:** • Clin Pres **Result led to incl:** • NS **Comparisons:** • Matched **Use of ref stand:** • Histology • Prolonged follow-up	***Patients:*** **N =** 65 **Mean Age:** 60±20 years **Age Range:** 36-80 years **Gender:** 51% Male **Inclusion criteria:** Patients with suspected pancreatic carcinoma who underwent both FDG PET and CT **Exclusion Criteria:** NS	**Scanner Model:** ECAT 933/08/16 (Siemens) **Resolution:** **Intrinsic:** 8 mm • **Image:** 8 mm **Acquisition Mode:** NS **Acquisition time per FOV:** • **Emission Scan:** 15 min • **Transmission Scan:** 10 min **Dose of FDG:** 370 MBq **Time between injection and performance:** 60 min **Reconstruction Algorithm used:** Filtered backprojection **Glucose Monitoring:** Fasting – 4 hours	**PET done:** Qualitatively and Quantitatively **Criteria used for diagnosis:** Background liver uptake used as reference for normal uptake; SUV used and ROC curve generated using two cutoffs for malignancy – SUV ≥ 2.0 and ≥ 3.0; SUV_{gluc} is SUV corrected for glucose. **Comparator Test:** CT **Done:** Qualitatively **Criteria used for diagnosis:** Discrete low attenuation lesions in pancreas or diffuse enlargement of pancreatic head/uncinate process when distant metastases were suspected considered positive for cancer **Gold Standard test done:** Histology **Criteria used for diagnosis:** NS **Blinding:** **Radiologist:** No **Gold Standard reader:** NS	CT and PET (SUV≥ 2.0) Cancer | | + | - | | + | 52 | 3 | | - | 0 | 10 | Sensitivity = 100% Specificity = 77% CT and PET (SUV≥ 3.0) Cancer | | + | - | | + | 48 | 2 | | - | 4 | 11 | Sensitivity = 92% Specificity = 85% CT Cancer | | + | - | | + | 34 | 5 | | - | 18 | 8 | Sensitivity = 65% Specificity = 62% CT Stage | | I | II | III | IV | | + | 6 | 7 | 1 | 10 | | - | 0 | 3 | 11 | 11 | PET and CT Stage | | I | II | III | IV | | + | 6 | 0 | 2 | 17 | | - | 0 | 10 | 10 | 4 |	***Quality Score:*** **Rep.sample: 1** **Setting selection: 1** **Design minimizes diffs: 1** **Scanner: 1** **Interpretation criteria defined: 1** **Hist or clin confirmation: 1** **Blinded: 0** **Total Score = 4** **Notes:** Unclear how population was selected.

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes

		I	II	III	IV
PET/ CT	SN	100%	0%	17%	81%
	SP	56%	36%	38%	50%
CT	SN	100%	70%	8%	48%
	SP	58%	56%	38%	50%

Therapeutic impact:

30% of patients who would not have had surgery if using CT results because either 1) no malignancy or 2) probable metastasis present – had surgery due to PET results.

13% avoided surgery because PET identified presence of metastasis or found pancreatic lesions to be benign.

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Diederichs **2000** **PROCITE#** 7220 **Cancer Type:** Pancreatic **SOW Question(s) Addressed:** 1a, 1b **Fryback et al. Level:** 2	**Dates of data collection:** 4/92 – 8/95 **Geographic Location:** NS **Retrospective Study** **Enrolled Consecutively:** NS **Study Setting:** Academic/ Research **Patient Incl Crit:** • Clin Pres **Result led to incl:** • Abnormal only **Comparisons:** • Matched **Use of ref stand:** • Histology: N = 120 • Prolonged follow-up: = 39 N	***Patients:*** **Group I (all patients):** **N =** 159 **MeanAge:** 56±13 years **Gender:** NS **Group II (Glucose not ≥130, not elevated CRP):** **N =** 123 **MeanAge:** 56±13 years **Gender:** NS **Group III(all not in group II):** **N =** 36 **MeanAge:** 58±13 years **Gender:** NS **Inclusion criteria:** NS **Exclusion Criteria:** NS	**Scanner Model:** CTI ECAT 931/08/12 (Siemens) **Resolution:** • **Intrinsic:** NS • **Image:** NS **Acquisition Mode:** NS **Acquisition time per FOV:** • **Emission Scan:** NS • **Transmission Scan:** 10 min per bed position **Dose of FDG: 85-448 MBq** **Time between injection and performance:** 60 min **Reconstruction Algorithm used:** Iterative **Glucose Monitoring:** Fasting – 12 hours	**PET done:** Qualitatively and Quantitatively **Criteria used for diagnosis:** ROI used to calculate SUV; Visual analysis – focally increased FDG uptake considered positive **Comparator Test:** ERCP **Done:** Qualitatively **Criteria used for diagnosis:** Visual grading: 1 = no sign malignant 2 = probably no malignancy 3 = indecisive or technically unsuccessful 4 = probably malignant 5 = definite malignant 4 and 5 considered positive. **Comparator Test:** CT **Done:** Qualitatively **Criteria used for diagnosis:** Visual grading, same as for ERCP – 1-2 considered negative 3 considered indeterminate 4-5 considered positive **Gold Standard test done:** Quantitatively **Criteria used for diagnosis:** Histology or Clinical follow-up **Blinding:** **Radiologist:** NS **Gold Standard reader:** NS	**Question 1a** Cancer PET | | + | - | | + | 60 | 7 | | - | 8 | 47 | Sensitivity = 88% Specificity = 87% * Note: 1 indeterminate study excluded Cancer ERCP | | + | - | | + | 53 | 4 | | - | 3 | 41 | Sensitivity = 95% Specificity = 91% * Note: 22 indeterminate studies excluded Cancer CT | | + | - | | + | 52 | 12 | | - | 7 | 32 | Sensitivity = 88% Specificity = 73% * Note: 20 indeterminate studies excluded Prevalence: 66/123 = 54% Question 1b LN Cancer PET | | + | - | | + | 22 | 6 | | - | 23 | 10 | Sensitivity = 49% Specificity = 62.5% Prevalence: 22%	***Quality Score:*** **Rep.sample: 1** **Setting selection: 1** **Design minimizes diffs: 1** **Scanner: 1** **Interpretation criteria defined: 1** **Hist or clin confirmation: 1** **Blinded: 0** **Total Score = 6** **Notes:**

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
					Liver Cancer CT | | + | - | |---|---|---| | + | 14 | 4 | | - | 6 | 65 | Sensitivity = 70% Specificity = 94% Prevalence: 22%	

<table>
<tr><th>Study, Year/ General Inclusion Criteria</th><th>Study Design</th><th>Patients/ Subject Characteristics</th><th>PET Technical Characteristics</th><th>Criteria for Abnormality</th><th>Results</th><th>Quality Score/Notes</th></tr>
<tr>
<td>
Friess

1995

PROCITE# 7500

Cancer Type: Pancreatic

SOW Question(s) Addressed: 1a

Fryback et al. Level: 2
</td>
<td>
Dates of data collection: 2/92 – 11/93

Geographic Location: Berne, Switzerland and Ulm, Germany

Retrospective Study

Enrolled Consecutively: Yes

Study Setting: Academic/ Research

Patient Incl Crit:
• Clin Pres

Result led to incl:
• Abnormal only

Comparisons:
• Matched

Use of ref stand:
• Histology
</td>
<td>
Patients:

N = 80

Median Age: see results

Gender: see results

Inclusion criteria: NS

Exclusion Criteria: NS
</td>
<td>
Scanner Model: ECAT 931-08 (Siemens/CTI)

Resolution:
• Actual: 7 mm FWHM

Acquisition Mode: NS

Acquisition time per FOV:
• Emission Scan: 10 min
• Transmission Scan: 10 min

Dose of FDG: 250-350 MBq

Time between injection and performance: 45 min

Reconstruction Algorithm used: Iterative

Glucose Monitoring: Fasting – 6 hours; Glucose measured, maximum amount permitted not specified.
</td>
<td>
PET done: Qualitatively

Criteria used for diagnosis: Visual analysis – focally increased FDG uptake considered positive

Comparator Test: CT
Done: Qualitatively
Criteria used for diagnosis: Suspicious tumor mass with direct or indirect signs of malignancy considered positive

Gold Standard test done: Quantiatively

Criteria used for diagnosis: Histology

Blinding:
Radiologist: NS
Gold Standard reader: NS
* Designed as “blind” study
</td>
<td>
PET
<table>
<tr><td></td><td>Cancer +</td><td>Cancer -</td></tr>
<tr><td>+</td><td>45</td><td>4</td></tr>
<tr><td>-</td><td>3</td><td>28</td></tr>
</table>
Sensitivity = 94%
Specificity = 88%

CT
<table>
<tr><td></td><td>Cancer +</td><td>Cancer -</td></tr>
<tr><td>+</td><td>33</td><td>10</td></tr>
<tr><td>-</td><td>9</td><td>22</td></tr>
</table>
Sensitivity = 79%
Specificity = 69%

Prevalence:
PET: 48/80 = 60%
CT: 42/74 = 57%

Patient groups:
<table>
<tr><td></td><td>I</td><td>II</td><td>III</td><td>Control</td></tr>
<tr><td>N</td><td>42</td><td>6</td><td>32</td><td>10</td></tr>
<tr><td>Median Age</td><td>60.5</td><td>58.5</td><td>50</td><td>51.5</td></tr>
<tr><td>Age Range</td><td>36-79</td><td>42-76</td><td>25-74</td><td>29-71</td></tr>
<tr><td>Gender</td><td>71.4</td><td>50.0</td><td>84.3</td><td>60.0</td></tr>
<tr><td>Stage II</td><td>6</td><td>N/A</td><td>N/A</td><td>N/A</td></tr>
<tr><td>Stage III</td><td>19</td><td>N/A</td><td>N/A</td><td>N/A</td></tr>
<tr><td>Stage IV</td><td>17</td><td>N/A</td><td>N/A</td><td>N/A</td></tr>
</table>
Group I: Pancreatic ductal cancer
Group II: Periampullary cancer
Group III: Chronic pancreatitis
Control: Normal controls
</td>
<td>
Quality Score:

Rep.sample: 1

Setting selection: 1

Design minimizes diffs: 1

Scanner: 1

Interpretation criteria defined: 1

Hist or clin confirmation: 1

Blinded: 1

Total Score = 7

Notes:
</td>
</tr>
</table>

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Ho **1996** **PROCITE#** 7470 **Cancer Type:** Pancreatic **SOW Question(s) Addressed:** 1a **Frybeck et al. Level:** 2	**Dates of data collection:** NS **Geographic Location:** St. Louis, MO **Retrospective/ Prospective Study:** NS **Enrolled Consecutively:** NS **Study Setting:** NS Patient Incl Crit: • Comp test result – CT **Result led to incl:** • Abnormal only **Comparisons:** • Matched **Use of ref stand:** • Histology – 12 patients • Prolonged follow-up – 2 patients	***Patients:*** **N =** 14 12 indeterminate masses by CT; 2 typical cancer by CT **Mean(Median) Age:** NS **Gender:** NS **Inclusion criteria:** Abnormal or indeterminate CT result **Exclusion Criteria:** NS	**Scanner Model:** Super PET-IIB (8 patients) and Siemens ECAT-EXACT (6 patients) **Resolution:** • **Intrinsic:** NS • **Image:** 10 mm **Acquisition Mode:** NS **Acquisition time per FOV:** • **Emission Scan:** NS • **Transmission Scan:** 10-15 min **Dose of FDG:** 10 mCi **Time between injection and performance:** 45 min **Reconstruction Algorithm used:** NS **Glucose Monitoring:** Fasting – 6 hrs; Glucose measured, maximum amount permitted not specified.	**PET done:** Qualitatively **Criteria used for diagnosis:** Focal areas of increased uptake; Modified SUV ≥ 2.5 **Comparator Test done:** CT **Criteria used for diagnosis:** NS **Gold Standard test:** Histology and Clinical follow-up **Done:** Qualitatively and Quantitatively **Criteria used for diagnosis:** Histology – 12 patients. Clinical follow-up for 12 months – 2 patients. **Blinding:** **Radiologist:** NS **Gold Standard reader:** NS	Cancer PET | | + | - | | + | 8 | 2 | | - | 0 | 4 | Sensitivity = 100% Specificity = 67% Prevalence = 57% CT used as inclusion criteria, therefore comparator tests could not be done.	***Quality Score:*** **Rep.sample: 1** **Setting selection: 0** **Design minimizes diffs: 1** **Scanner: 1** **Interpretation criteria defined: 1** **Hist or clin confirmation: 1** **Blinded: 0** **Total Score = 5** **Notes:** CT indeterminate for cancer used as inclusion criteria. Article attempts to compare CT alone vs. PET and CT for indeterminate lesions but can't generate table.

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Imdahl **1999** **PROCITE#** 7320 **Cancer Type:** Pancreatic **SOW Question(s) Addressed:** 1a **Fryback et al. Level:** 2	**Dates of data collection:** 7/95 – 7/97 **Geographic Location:** Freiburg, Germany **Prospective Study** **Enrolled Consecutively:** Yes **Study Setting:** NS **Patient Incl Crit:** • Clin Pres **Result led to incl:** • Abnorm and norm **Comparisons:** • Matched **Use of ref stand:** • Histology	***Patients:*** **N =** 48 42 patients with pancreatic disease; 6 controls **Mean(Median) Age:** 58 **Gender: 60% Male** **Inclusion criteria: NS** **Exclusion Criteria:** NS	**Scanner Model:** Siemens/ CTI ECAT-EXACT 921/31 **Resolution:** • **Intrinsic:** 6 mm • **Image:** NS **Acquisition Mode:** NS **Acquisition time per FOV:** • **Emission Scan:** NS • **Transmission Scan:** 10 min **Dose of FDG:** 350 ± 50 MBq **Time between injection and performance:** 90 min **Reconstruction Algorithm used:** NS **Glucose Monitoring:** NS	**PET done:** Quantitatively **Criteria used for diagnosis:** SUV corrected for body weight > 4.0 was a positive test. Focal increased uptake > normal ("normal" not explained) was also a positive test. **Comparator Test done:** ERCP **Criteria used for diagnosis:** NS **Comparator Test done:** CT **Criteria used for diagnosis:** NS **Gold Standard test done:** Histology **Criteria used for diagnosis:** Histologic diagnosis at biopsy or laparotomy except for controls. **Blinding:** **Radiologist:** Yes **Gold Standard reader:** NS	PET (Cancer) | | + | - | Control | | + | 26 | 0 | 0 | | - | 1 | 15 | 6 | Sensitivity = 96% Specificity = 100% n = 48 CT (Cancer) | | + | - | | + | 22 | 4 | | - | 5 | 17 | Sensitivity = 81% Specificity = 81% n = 48 ERCP (Cancer) | | + | - | | + | 17 | 3 | | - | 3 | 13 | Sensitivity = 85% Specificity = 81% n = 36 * * ERCP not done on all patients. Prevalence = 56% **Note:** Because results were broken down into cancer and pancreatitis there is not enough information to actually identify the appropriate number of patients in "Cancer Negative" column for CT. Calculated numbers show all non-cancer patients (i.e. both pancreatitis and normal) as "Cancer Negative."	***Quality Score:*** **Rep.sample: 1** **Setting selection: 0** **Design minimizes diffs: 1** **Scanner: 1** **Interpretation criteria defined: 1** **Hist or clin confirmation: 1** **Blinded: 0** **Total Score = 5** **Notes:**

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Inokuma **1995** **PROCITE#** 7520 **Cancer Type:** Pancreas **SOW Question(s) Addressed:** 1a **Frybeck et al. Level:** 2	**Dates of data collection:** 6/92 – 10/94 **Geographic Location:** Kyoto, Japan **Prospective Study** **Enrolled Consecutively:** Yes **Study Setting:** Academic/ Research **Patient Incl Crit:** • Clin Pres **Result led to incl:** • Abnormal only **Comparisons:** • Matched **Use of ref stand:** • Histology: n=41 • Prolonged follow-up: n=5	***Patients:*** **N =** 46 **Mean Age:** 62 years **Age Range:** 37-79 years **Gender:** 54.3% Male **Inclusion criteria:** Clinical findings suggestive of suspected pancreatic tumor and scheduled to undergo surgery **Exclusion Criteria:** NS	**Scanner Model:** PCT 3600W (Hitachi Medico) **Resolution:** • **Intrinsic:** 4.6 mm FWHM • **Axial:** 7 mm FWHM **Acquisition Mode:** NS **Acquisition time per FOV:** • **Emission Scan:** 15 min • **Transmission Scan:** 20 min **Dose of FDG:** 150 MBq **Time between injection and performance:** 60 min **Reconstruction Algorithm used:** NS **Glucose Monitoring:** Fasting – overnight	**PET done:** Qualitatively and Quantitatively **Criteria used for diagnosis:** SUV calculated; Any obvious foci within the pancreatic area that had greater FDG uptake than the surrounding background were regarded as suggestive of malignancy. **Comparator Test done:** US – endoscopic and transabdominal **Criteria used for diagnosis:** Presence of mass, presence of vascular and/or lymph nodes imaging classification as diagnostic (positive or negative for malignancy) **Comparator Test done:** CT **Criteria used for diagnosis:** NS **Gold Standard test done:** Histology or clinical follow-up **Criteria used for diagnosis:** NS **Blinding:** **Radiologist:** Yes **Gold Standard reader:** NS	**Histologic diagnosis:** N = 26 Ductal Adenocarcinoma N = 7 Chronic Pancreatitis N = 4 Cystadenocarcinoma N = 3 Islet-cell Tumor N = 3 Cystadenoma N = 1 Ampullary Carcinoma N = 1 Inflammatory Pseudocyst N = 1 Metastasis from renal cell cancer PET Cancer | | + | - | | + | 34 | 1 | | - | 1 | 10 | Sensitivity = 97% Specificity = 91% US Cancer | | + | - | | + | 31 | 6 | | - | 4 | 5 | Sensitivity = 89% Specificity = 45% CT Cancer | | + | - | | + | 31 | 3 | | - | 4 | 8 | Sensitivity = 89% Specificity = 73% EUS (n=40) Cancer | | + | - | | + | 28 | 4 | | - | 1 | 7 | Sensitivity = 97% Specificity = 64%	***Quality Score:*** **Rep.sample: 1** **Setting selection: 1** **Design minimizes diffs: 1** **Scanner: 1** **Interpretation criteria defined: 1** **Hist or clin confirmation: 0** **Blinded: 0** **Total Score = 5** **Notes:** Focus of increased FDG uptake is highly suggestive of malignancy. False-negative tumors are very small.

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Kalady **2002** **PROCITE#** 6960 **Cancer Type:** Pancreatic **SOW Question(s) Addressed:** 1a **Fryback et al. Level:** 4	**Dates of data collection:** 1/94 – 7/01 **Geographic Location:** Durham, NC **Retrospective Study** **Enrolled Consecutively:** No **Study Setting:** Academic/ Research **Patient Incl Crit:** • Clin Pres **Result led to incl:** • Abnorm and norm **Comparisons:** • Matched **Use of ref stand:** • Histology (n=47) • Prolonged follow-up (n=7)	***Patients:*** **N =** 54 **Mean Age:** NS **Gender:** NS **Final Diagnosis:** N=6 benign N=41 malignant **Inclusion criteria:** Suspected primary pancreatic cancer; Patients evaluated by both CT and FDG-PET **Exclusion Criteria:** NS	**Scanner Model:** GE Advance **Resolution:** • **Intrinsic:** 5 mm • **Image:** NS **Acquisition Mode:** 2-D **Acquisition time per FOV:** • **Emission Scan:** 10 min (before 1990) 4 min (after 1990) • **Transmission Scan:** 10 min (before 1990) 3 min (after 1990) **Dose of FDG:** 10 mCi **Time between injection and performance:** 60 min **Reconstruction Algorithm used:** NS **Glucose Monitoring:** Fasting – 4 hours; Maximum glucose permitted – 200 mg/dL	**PET done:** Qualitatively and Semi-quantitatively **Criteria used for diagnosis:** Visual inspection – FDG-PET with activity greater than background determined as positive; On a subset of patients (n=18) SUV calculated semi-quantitatively as mean activity within a 1-cm circular ROI. SUV = Mean ROI activity / Injected dose/ bodyweight **Comparator Test:** CT **Done:** Qualitatively **Criteria used for diagnosis:** Nodes > 6 mm considered suspicious **Gold Standard test done:** Qualitatively **Criteria used for diagnosis:** Confirmed by percutaneous or endoscopic biopsy, or by histopathology in n=47 patients. In n=7 patients, clinical follow-up of at least 12 months was standard. **Blinding:** **Radiologist:** Yes **Gold Standard reader:** NS	PET (Cancer): +: 36, 1 -: 5, 12 Sensitivity = 88% Specificity = 92% CT (Cancer): +: 37, 5 -: 4, 8 Sensitivity = 90% Specificity = 62% Prevalence: 41/54 = 76% **Clinical Utility of FDG-PET:** **Local extension** – PET provided no additional information. FDG-PET did not predict vascular involvement. 7/41 patients had unresectable disease: proved by CT in 4, celiotomy in 3. **Nodal metastasis** – PET did not identify any nodal disease not detected by CT. N=6 increased FDG – 3 proven malignant; N=13 no increased FDG – all proven non-malignant. **Distant metastasis** – PET detected one distant metastasis missed by CT. N=17 increased FDG – 9 proven malignant, 7 not assessed, 1 false positive (benign cyst). **Change in management based on diagnosis of primary disease compared to CT** – FDG-PET detected one additional patient with cancer, management did not change. CT detected 37/41 malignancies. PET could have spared 4 patients unnecessary operation, but missed 3 cancers.	***Quality Score:*** **Rep.sample: 0** **Setting selection: 0** **Design minimizes diffs: 1** **Scanner: 1** **Interpretation criteria defined: 1** **Hist or clin confirmation: 1** **Blinded: 0** **Total Score = 4** **Notes:**

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Kato **1995** **PROCITE#** 7550 **Cancer Type:** Pancreatic **SOW Question(s) Addressed:** 1a **Frybeck et al. Level:** 2	**Dates of data collection:** **Geographic Location:** Nagoya, Japan **Prospective Study** **Enrolled Consecutively:** NS **Study Setting:** Academic/ Research **Patient Incl Crit:** • Clin Pres **Result led to incl:** • Abnormal only **Comparisons:** • No comp **Use of ref stand:** • Histology: n=21 • Prolonged follow-up: n=23	***Patients:*** **N =** 24 **Mean Age:** 55.0±10.6 years **Gender:** 83.3% Male **Inclusion criteria:** Pancreatic masses **Exclusion Criteria:** NS	**Scanner Model:** Headtome-IV (Shimadzu Corp) **Resolution:** • **Intrinsic:** NS • **Image:** NS **Acquisition Mode:** NS **Acquisition time per FOV:** • **Emission Scan:** NS • **Transmission Scan:** NS **Dose of FDG:** 121-287 MBq **Time between injection and performance:** 50 min **Reconstruction Algorithm used:** NS **Glucose Monitoring:** Fasting for unspecified amount of time	**PET done:** Quantitatively **Criteria used for diagnosis:** Different absorption ratios were calculated (DAR) = Tissue tracer concentration / Injected dose/ body weight DAR diagnosis of benign and malignant masses were compared **Comparator Test done:** CT **Criteria used for diagnosis:** NS **Comparator Test done:** MR **Criteria used for diagnosis:** NS **Gold Standard test done:** Histology and Clinical follow-up ≥ 3 years **Criteria used for diagnosis:** NS **Blinding:** **Radiologist:** NS **Gold Standard reader:** NS	Cancer PET | | + | - | | + | 14 | 2 | | - | 1 | 7 | Sensitivity = 93% Specificity = 78%	***Quality Score:*** **Rep.sample: 1** **Setting selection: 1** **Design minimizes diffs: 0** **Scanner: 1** **Interpretation criteria defined: 1** **Hist or clin confirmation: 1** **Blinded: 0** **Total Score = 5** **Notes:**

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Keogan **1998** **PROCITE#** 7370 **Cancer Type:** Pancreatic **SOW Question(s) Addressed:** 1a, 1b **Fryback et al. Level:** 2	**Dates of data collection:** 8/93 – 12/97 **Geographic Location:** Durham, NC **Prospective Study** **Enrolled Consecutively:** NS **Study Setting:** Academic/ Research **Patient Incl Crit:** • Clin Pres **Result led to incl:** • Abnorm and norm **Comparisons:** • Matched **Use of ref stand:** • Histology	***Patients:*** **N =** 37 **Mean Age:** 62 years **Age Range:** 44-80 years **Gender:** 59.5% Male **Inclusion criteria:** Patients with known or suspected pancreatic cancer, with suspicious findings on CT and ERCP **Exclusion Criteria:** NS	**Scanner Model:** GE Advance **Resolution:** • **Intrinsic:** 5 mm • **Image:** NS **Acquisition Mode:** 2-D **Acquisition time per FOV:** • **Emission Scan:** 10 min • **Transmission Scan:** NS **Dose of FDG:** 10 mCi **Time between injection and performance:** 60 min **Reconstruction Algorithm used:** NS **Glucose Monitoring:** Fasting – 4 hours; Glucose measured, maximum amount permitted 200 mg/dL	**PET done:** Quantitatively **Criteria used for diagnosis:** ROI and SUR values determined **Comparator Test:** CT **Done:** Qualitatively **Criteria used for diagnosis:** Positive, negative or equivocal **Comparator Test:** ERCP **Done:** NS **Criteria used for diagnosis:** NS **Gold Standard test done:** Quantitatively **Criteria used for diagnosis:** Histology - malignancy confirmed by fine-needle aspiration (n=18) or surgery (n=14) or both; Benign disease confirmed by fine-needle aspiration (n=6), surgery (n=5) and ERCP (n=1) **Blinding:** **Radiologist:** Yes **Gold Standard reader:** NS	Question 1a PET (Cancer): + 22, 2; - 3, 10 — Sensitivity = 88%, Specificity = 83% CT (Cancer): + 18, 2; - 6, 10 — Sensitivity = 75%, Specificity = 83% ERCP (Cancer): + 12, 5; - 2, 3 — Sensitivity = 86%, Specificity = 38% Prevalence: 25/37 = 68% Question 1b PET (Cancer): + 2, 0; - 2, 21 — Sensitivity = 50%, Specificity = 100% CT (Cancer): + 3, 0; - 1, 21 — Sensitivity = 75%, Specificity = 100% **Prevalence: 4/25 = 16%**	***Quality Score:*** **Rep.sample: 1** **Setting selection: 1** **Design minimizes diffs: 1** **Scanner: 1** **Interpretation criteria defined: 0** **Hist or clin confirmation: 1** **Blinded: 1** **Total Score = 6** **Notes:**

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Koyoma **2001** **PROCITE#** 7070 **Cancer Type:** Pancreatic **SOW Question(s) Addressed:** 1a **Fryback et al. Level:** 2	**Dates of data collection:** 10/93 – 7/99 **Geographic Location:** Osaka, Japan **Retrospective Study** **Enrolled Consecutively:** NS **Study Setting:** Academic/ Research **Patient Incl Crit:** • Clin Pres **Result led to incl:** • Abnormal only **Comparisons:** • Matched – US, CT and/or MRI **Use of ref stand:** • Histology (n=55) • Prolonged follow-up (n=31)	***Patients:*** **N =** 86 **Diagnosis:** N=21 benign N=65 malignant **Mean Age:** 64±9.6 years **Gender:** 58% Male **Inclusion criteria:** NS **Exclusion Criteria:** NS	**Scanner Model:** HEADTOME IV SET-1400W-10 (Shimadzu Corp.) **Resolution:** • **Spatial:** 14 mm FWHM **Acquisition Mode:** NS **Acquisition time per FOV:** • **Emission Scan:** NS • **Transmission Scan:** 15 min **Dose of FDG:** 180-370 MBq **Time between injection and performance:** 40-55 min **Reconstruction Algorithm used:** Filtered Backposition **Glucose Monitoring:** Fasting – 4 hours; Glucose measured, maximum amount permitted not specified	**PET done:** Quantitatively and Qualitatively **Criteria used for diagnosis:** Visual interpretation – FDG accumulation greater than background considered positive; SUV calculated as tissue concentration (mCi/g) divided by infected activity per body weight (mCi/g); SUV_{gluc} equal to SUV if blood sugar was less than or equal to 130 mg/dL. If BS > 130 mg/dL, SUV_{gluc} = SUV * (130/BS) **Comparator Test:** CT **Done:** Qualitatively **Criteria used for diagnosis:** 1) More than one of: Low-attenuating regions on dynamic contrast images; 2) Vascular invasion; 3) Invasion of contiguous organs **Comparator Test:** MRI **Done:** Qualitatively **Criteria used for diagnosis:** More than one of: 1) Low signal intensity tumor on TIWI; 2) Dynamic TIWI; 3) Vascular invasion; 4) Infiltration of peri-pancreatic tissue **Gold Standard test done:** Qualitatively	**Visual interpretation of PET*** Overall: Sensitivity = 82% Specificity = 81% SUV with 2.1 cut-off (SUV_{gluc}): Sensitivity = 89% Specificity = 76% SUV with 2.2 cut-off: Sensitivity = 91% Specificity = 76% **MRI** Sensitivity = 78% Specificity = 70% PET (Cancer): | | + | - | | + | 53 | 4 | | - | 12 | 17 | Sensitivity = 82% Specificity = 81% CT (Cancer): | | + | - | | + | 59 | 13 | | - | 6 | 8 | Sensitivity = 91% Specificity = 38% Prevalence: 65/86 = 76%	***Quality Score:*** **Rep.sample: 0** **Setting selection: 0** **Design minimizes diffs: 1** **Scanner: 1** **Interpretation criteria defined: 1** **Hist or clin confirmation: 1** **Blinded: 0** **Total Score = 4** **Notes:**

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
				Criteria used for diagnosis: Classification of pancreatic carcinoma Japan Pancreatic Society First English Edition (1996). Clinical follow-up greater than 1 year. **Blinding:** **Radiologist:** Yes **Gold Standard reader:** NS		

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Mertz **2000** **PROCITE#** 7180 **Cancer Type:** Pancreatic **SOW Question(s) Addressed:** 1a, 1b **Fryback et al. Level:** 2	**Dates of data collection:** 8/96 – 1/99 **Geographic Location:** Nashville, TN **Retrospective Study** **Enrolled Consecutively:** No **Study Setting:** Academic/ Research **Patient Incl Crit:** • Clin Pres • Comp test result **Result led to incl:** • Abnormal only **Comparisons:** • Matched **Use of ref stand:** • Histology/ Cytology	***Patients:*** **N =** 35 **Final Diagnosis:** N = 31 malignant N = 4 benign **Mean(Median) Age:** NS **Gender:** NS **Inclusion criteria:** NS **Exclusion Criteria:** NS	**Scanner Model:** ECAT 933/08/16 (Siemens) **Resolution:** • **Intrinsic:** 4.8 mm • **Image:** NS **Acquisition Mode:** NS **Acquisition time per FOV:** • **Emission Scan:** 15 min per bed position • **Transmission Scan:** 10 min per bed position **Dose of FDG:** 370 MBq **Time between injection and performance:** NS **Reconstruction Algorithm used:** NS **Glucose Monitoring:** Fasting – 4 hours	**PET done:** Qualitatively and Quantitatively **Criteria used for diagnosis:** Visual – liver uptake referral (greater than liver uptake indicates malignancy); SUR (spontaneous uptake ratio) = $\frac{\text{Mean activity in ROI}}{\text{injected dose / body weight}}$ SUR > 2.8 indicates malignancy. **Comparator Test:** CT **Done:** Qualitatively **Criteria used for diagnosis:** A focal low attenuation mass is positive; Vascular invasion assessed. **Comparator Test:** Endoscopic Ultrasound **Done:** Qualitatively **Criteria used for diagnosis:** Discrete hypoechoic lesion considered positive; Vascular invasion assessed. **Gold Standard test done:** Histology **Criteria used for diagnosis:** NS **Blinding:** **Radiologist:** No **Gold Standard reader:** NS	PET Cancer | | + | - | | + | 27 | 2 | | - | 4 | 2 | Sensitivity = 87% Specificity = 50% CT Cancer | | + | - | | + | 16 | 3 | | - | 15 | 1 | Sensitivity = 52% Specificity = 25% EUS Cancer | | + | - | | + | 27 | 1 | | - | 2 | 3 | Sensitivity = 94% Specificity = 75% **Vascular invasion:** PET: Not capable CT: 32% EUS: 42% (3 additional cases) **Metastatic diagnosis:** PET: 7 cases /9 = 78% CT: 3 cases / 9 =33% CT for local and metastatic disease. EUS for local disease and vascular invasion. PET as an adjunct to CT for metastatic disease.	***Quality Score:*** **Rep.sample: 1** **Setting selection: 1** **Design minimizes diffs: 1** **Scanner: 1** **Interpretation criteria defined: 1** **Hist or clin confirmation: 1** **Blinded: 0** **Total Score = 6** **Notes:**

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Nakamoto **2000** **PROCITE#** 7140 **Cancer Type:** Pancreatic **SOW Question(s) Addressed:** 1a **Fryback et al. Level:** 2	**Dates of data collection:** NS **Geographic Location:** Kyoto, Japan **Retrospective Study** **Enrolled Consecutively:** NS **Study Setting:** Academic/ Research **Patient Incl Crit:** • Clin Pres **Result led to incl:** • Abnormal only **Comparisons:** • No comp **Use of ref stand:** • Histology: N=31 • Prolonged follow-up: N=16	***Patients:*** **N =** 47 **Mean Age:** 60.2 years **Gender:** 66% Male **Inclusion criteria:** NS **Exclusion Criteria:** NS	**Scanner Model:** PCT 3600W (Hitachi) **Resolution:** • **Intrinsic:** 4.6 mm • **Axial:** 7 mm • **Effective:** 10 mm **Acquisition Mode:** NS **Acquisition time per FOV:** • **Emission Scan:** 12 min • **Transmission Scan:** 11 min **Dose of FDG:** 10 mCi (370 MBq) **Time between injection and performance:** 1, 2 and 3 hours **Reconstruction Algorithm used:** NS **Glucose Monitoring:** Fasting – 5 hours Glucose measured, maximum amount permitted not specified	**PET done:** Quantitatively **Criteria used for diagnosis:** SUV in ROI value calculated Retention index calculated as: $\frac{SUV_{2\ hours} - SUV_{1\ hour}}{SUV_{1\ hour}}$ (Multiplied by 100) **Gold Standard test done:** Quantitatively **Criteria used for diagnosis:** Histopathology or clinical follow-up **Blinding:** **Radiologist:** No **Gold Standard reader**: **NS**	**Cut-off values: SUV: 2.3 and 2.4 at 2 hours and RI at -15** Final Diagnosis Malignant PET: + 27, 4; - 0, 16 Sensitivity = 100% Specificity = 80% **Cut-off values: SUV: 2.3 and 2.4 at 2 hours** Final Diagnosis Malignant PET: + 27, 5; - 0, 15 Sensitivity = 100% Specificity = 75% **Cut-off values: SUV: 2.8 at 1 hour** Final Diagnosis Malignant PET: + 26, 5; - 1, 15 Sensitivity = 96.3% Specificity = 75% **Cut-off values: RI at 0.0** Final Diagnosis Malignant PET: + 22, 3; - 5, 17 Sensitivity = 81.5% Specificity = 85% **Prevalence:** 27/47 = 57% **Retention Index:** Malignant = 12±13.37 Benign = -7.05±17.28 Difference statistically significant p< 0.0001	***Quality Score:*** **Rep.sample: 1** **Setting selection: 1** **Design minimizes diffs: 0** **Scanner: 1** **Interpretation criteria defined: 1** **Hist or clin confirmation: 1** **Blinded: 0** **Total Score = 5** **Notes:** No comparator test done. PET done on all patients with "suspected" malignancy.

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results/ Notes	Quality Score/Notes
Nakamoto **1999** **PROCITE#** 7310 **Cancer Type:** Pancreatic **SOW Question(s) Addressed:** 1b **Frybeck et al. Level:** 2	**Dates of data collection:** 6/95 – 12/97 **Geographic Location:** Hokkaido, Japan **Retrospective Study** **Enrolled Consecutively:** NS **Study Setting:** NS Patient Incl Crit: • Ref stand result – histologically proven pancreatic cancer **Result led to incl:** • Abnormal only **Comparisons:** • Matched **Use of ref stand:** • Histology • Prolonged follow-up	***Patients:*** **N =** 34 **Mean(Median) Age:** 64 years **Gender:** 65% Male **Inclusion criteria:** Histologically proven pancreatic cancer **Exclusion Criteria:** NS	**Scanner Model:** PET 3600W; Hitachi Medico **Resolution:** • **Intrinsic:** 7 mm • **Image:** 10 mm **Acquisition Mode:** NS **Acquisition time per FOV:** • **Emission Scan:** 15 min • **Transmission Scan:** 10 min **Dose of FDG:** 185-370 MBq **Time between injection and performance:** 55 min **Reconstruction Algorithm used:** NS **Glucose Monitoring:** Fasting – 5 hrs	**PET done:** Qualitatively and Quantitatively **Criteria used for diagnosis:** SUV > 3.3 considered positive for metastasis **Comparator Test done:** Ultrasound **Criteria used for diagnosis:** NS **Comparator Test done:** CT **Criteria used for diagnosis:** NS **Gold Standard test done:** Qualitatively and Quantitatively **Criteria used for diagnosis:** 29 patients had histological confirmation of pancreatic metastasis to liver; 5 patients had clinical follow-up confirming pancreatic metastasis to liver **Blinding:** **Radiologist:** Yes **Gold Standard reader:** NS	**Patient data:** PET (Metastasis): | | + | - | |---|---|---| | + | 11 | 2 | | - | 1 | 20 | Sensitivity = 92% Specificity = 91% US (Metastasis): | | + | - | |---|---|---| | + | 8 | 0 | | - | 4 | 22 | Sensitivity = 66.7% Specificity = 100% CT (Metastasis): | | + | - | |---|---|---| | + | 8 | 0 | | - | 4 | 22 | Sensitivity = 66.7% Specificity = 100% Overall Prevalence: 57% **Notes:** 1. Appears all patients had a positive PET for primary tumors which may detection for the metastatic lesions to the liver. 2. Only 17 patients with positive metastasis examined by ultrasound – not clear why, and not mentioned in the paper. 3. Recruitment of the patient population not described.	***Quality Score:*** **Rep.sample: 1** **Setting selection: 0** **Design minimizes diffs: 1** **Scanner: 1** **Interpretation criteria defined: 1** **Hist or clin confirmation: 1** **Blinded: 0** **Total Score = 5** **Notes:**

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Papos **2002** **PROCITE#** 7010 **Cancer Type:** Pancreatic **SOW Question(s) Addressed:** 1a **Fryback et al. Level:** 2	**Dates of data collection:** NS **Geographic Location:** Szeged, Hungary and Debrecen, Hungary **Prospective Study** **Enrolled Consecutively:** NS **Study Setting:** General outpatient clinics/ physician office; Academic/ Research **Patient Incl Crit:** • Clin Pres **Result led to incl:** • Abnorm and norm **Comparisons:** • Matched – US, CT, CRCP, CA **Use of ref stand:** • Histology • Prolonged follow-up	***Patients:*** **N =** 22 **Mean Age:** 39 years **Range:** 29-59 years **Gender:** 59% Male **Diagnosis:** N=16 benign N=6 malignant **Inclusion criteria:** NS **Exclusion Criteria:** NS	**Scanner Model:** GE 4096 plus **Resolution:** • **Spatial:** 6.5 mm FWHM **Acquisition Mode:** NS **Acquisition time per FOV:** • **Emission Scan:** NS • **Transmission Scan:** NS **Dose of FDG:** 232-418 MBq **Time between injection and performance:** 60 min **Reconstruction Algorithm used:** Filtered Backposition **Glucose Monitoring:** Fasting – overnight; Glucose measured, determined to be in "normal" range	**PET done:** Qualitatively **Criteria used for diagnosis:** Any FDG uptake over background in areas outside those with a normal FDG uptake or excretion was considered positive for cancer **Comparator Test:** CA 19-9 **Done:** Quantitatively **Criteria used for diagnosis:** CA level > 37 U/l considered positive **Comparator Test:** ERCP **Done:** Qualitatively **Criteria used for diagnosis:** Positive if complete duct obstruction, stricture, or dislocation of main pancreatic duct; Negative if chronic calcific pancreatitis, irregularity or dilation, or cyst filling and precipitate in main pancreatic duct **Comparator Test:** CT and US **Done:** Quantitatively **Criteria used for diagnosis:** Mass effect and loss of normal homogenous parechymal pattern on images of pancreas **Gold Standard test done:** Histology and follow-up > 6 months **Criteria used for diagnosis:** Histologic analysis after surgery (n=9) and clinical follow-up (n=13) **Blinding:** **Radiologist:** No **Gold Standard reader:** NS	PET Cancer | | + | - | | + | 6 | 2 | | - | 0 | 14 | Sensitivity = 100% Specificity = 87.5% CT Cancer | | + | - | | + | 6 | 7 | | - | 0 | 9 | Sensitivity = 100% Specificity = 56% US Cancer | | + | - | | + | 6 | 7 | | - | 0 | 8 | Sensitivity = 100% Specificity = 50% CA 19-9 Cancer | | + | - | | + | 4 | 4 | | - | 1 | 11 | Sensitivity = 80% Specificity = 73% ECRP Cancer | | + | - | | + | 3 | 1 | | - | 2 | 12 | Sensitivity = 60% Specificity = 92% Prevalence: 6/22 = 27%	***Quality Score:*** **Rep.sample: 1** **Setting selection: 1** **Design minimizes diffs: 1** **Scanner: 1** **Interpretation criteria defined: 1** **Hist or clin confirmation: 1** **Blinded: 0** **Total Score = 6** **Notes:**

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Rajput **1998** **PROCITE#** 7380 **Cancer Type:** Pancreatic **SOW Question(s) Addressed:** 1a **Fryback et al. Level:** 2	**Dates of data collection:** 3/95 – 8/96 **Geographic Location:** Cleveland, OH **Retrospective Study** **Enrolled Consecutively:** NS **Study Setting:** NS **Patient Incl Crit:** • Clin Pres – possible pancreatic disease **Result led to incl:** • Abnormal only **Comparisons:** • Matched **Use of ref stand:** • Histology	***Patients:*** **N =** 13 **Age Range: 22-83 years** **Gender:** 53.3% Male **Inclusion criteria:** Availability of tissue for final histological diagnosis **Exclusion Criteria:** NS	**Scanner Model:** ECAT EXACT (CTI) **Resolution:** • **Intrinsic:** 6 mm • **Image:** NS **Acquisition Mode:** 2-D **Acquisition time per FOV:** • **Emission Scan:** NS • **Transmission Scan:** NS **Dose of FDG:** 407-802 MBq **Time between injection and performance:** 45 min **Reconstruction Algorithm used:** NS **Glucose Monitoring:** Fasting – overnight	**PET done:** Qualitatively **Criteria used for diagnosis:** Focally increased activity considered malignant, diffuse uptake considered non-malignant inflammation **Comparator Test done:** CT **Criteria used for diagnosis:** NS **Comparator Test done:** ECRP **Criteria used for diagnosis:** NS **Comparator Test done:** EUS **Criteria used for diagnosis:** NS **Gold Standard test done:** Histology **Criteria used for diagnosis:** NS **Blinding:** **Radiologist:** Yes **Gold Standard reader:** NS	PET Cancer | | + | - | | + | 9 | 0 | | - | 2 | 2 | Sensitivity = 82% Specificity = 100% CT Cancer | | + | - | | + | 8 | 2 | | - | 3 | 0 | Sensitivity = 73% Specificity = 0% ERCP Cancer | | + | - | | + | 6 | 1 | | - | 4 | 1 | Sensitivity = 60% Specificity = 50% EUS Cancer | | + | - | | + | 5 | 2 | | - | 0 | 0 | Sensitivity = 100% Specificity = 0% Prevalence: 11/13 = 85%	***Quality Score:*** **Rep.sample: 0** **Setting selection: 0** **Design minimizes diffs: 1** **Scanner: 1** **Interpretation criteria defined: 1** **Hist or clin confirmation: 0** **Blinded: 0** **Total Score = 3** **Notes:** First 5 patients did not get the protocol for PET when PET imaging done. Not all patients received all tests since retrospective study. Not mentioned what qualified patients for inclusion in study.

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Rose **1999** **PROCITE#** 7300 **Cancer Type:** Pancreatic **SOW Question(s) Addressed:** 1a, 3 **Frybeck et al. Level:** 2, 4	**Dates of data collection:** 1995 – 1998 **Geographic Location:** Nashville, TN **Prospective Study** **Enrolled Consecutively:** NS **Study Setting:** Academic/ Research **Patient Incl Crit:** • Clin Pres **Result led to incl:** NS **Comparisons:** • Matched **Use of ref stand:** • Histology – 56 patients • Prolonged follow-up – 9 patients	***Patients:*** **N =** 65 satisfying Fryback 2, Q1A; 9 patients for assessment of response to chemotherapy – Fryback 4 Q3; 8 patients for detection of recurrence after treatment – Fryback 4 Q3 **Mean(Median) Age:** NS **Gender:** NS **Inclusion criteria:** Patients with suspected primary or recurrent pancreatic cancer who had undergone both CT and FDG-PET imaging. **Exclusion Criteria:** NS	**Scanner Model:** Siemens ECAT 933/08/16 **Resolution:** • **Intrinsic:** 4.8mm **Image:** 6.5x6.5x8.0 mm **Acquisition Mode:** NS **Acquisition time per FOV:** • **Emission Scan:** 15 min • **Transmission Scan:** 10 min **Dose of FDG:** 10 mCi **Time between injection and performance:** 60 min **Reconstruction Algorithm used:** NS **Glucose Monitoring:** Fasting > 4 hrs	**PET done:** Qualitatively and Quantitatively **Criteria used for diagnosis:** Focal area uptake in pancreas and SUR ≥ 2.8 considered positive for cancer. **Comparator Test:** CT **Done:** Qualitatively **Criteria used for diagnosis:** Either one considered positive for cancer: 1. Discrete low attenuation mass identified in pancreas. 2. In setting of metastases – enlargement of pancreatic head or uncinate process in the absence of a discrete low attenuation mass. **Gold Standard test done:** Histology (56 patients) or Clinical follow-up for 8 months (9 patients) **Blinding:** **Radiologist:** NS **Gold Standard reader:** NS	PET (Cancer): +: 48, 2 -: 4, 11 Sensitivity = 92% Specificity = 85% CT (Cancer): +: 34, 5 -: 18, 8 Sensitivity = 65% Specificity = 62% Prevalence = 80%	***Quality Score:*** **Rep.sample: 1** **Setting selection: 1** **Design minimizes diffs: 1** **Scanner: 1** **Interpretation criteria defined: 1** **Hist or clin confirmation: 1** **Blinded: 0** **Total Score = 6** **Notes:** No description of patient population or recruitment. Several questions were addressed by only sensitivity and specificity of detecting benign vs. malignant lesions had enough patients to include in the study.

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Sendler **2000** **PROCITE#** 7150 **Cancer Type:** Pancreatic **SOW Question(s) Addressed:** 1a **Fryback et al. Level:** 2	**Dates of data collection:** 1/94 – 2/96 **Geographic Location:** Munich, Germany **Prospective Study** **Enrolled Consecutively :** NS **Study Setting:** Academic/ Research **Patient Incl Crit:** • Clin Pres (mass) **Result led to incl:** • Abnormal only **Comparisons:** • Matched **Use of ref stand:** • Histology: N=38 • Prolonged follow-up: N=4	***Patients:*** **N =** 42 **MeanAge:** 54.2 years **Disease:** Adenocarcinoma: N=31 Chronic Pancreatitis: N=11 **Gender:** 50% Male **Inclusion criteria:** 1. Relative good condition (Karnofsky index>80); 2. Able to undergo PET without movement; 3. Underwent helical CT and conventional abdominal US for rutine staging before pancreatic surgery **Exclusion Criteria:** 1. Pregnancy; 2. Poorly controlled diabetes mellitus (blood glucose level > 250 mg/dl prior to PET imaging); 3. Younger than 18 years of age	**Scanner Model:** ECAT 951R/31 (Siemens) **Resolution:** • **Axial:** 5 mm FWHM • **Image:** 8 mm **Acquisition Mode:** NS **Acquisition time per FOV:** • **Emission Scan:** NS • **Transmission Scan:** 15 min **Dose of FDG:** 270-390 MBq **Time between injection and performance:** NS **Reconstruction Algorithm used:** Filtered Backposition **Glucose Monitoring:** Fasting overnight; Glucose measured – mean blood glucose level 113±30.4 mg/dl	**PET done:** Qualitatively and Quantitatively **Criteria used for diagnosis:** Qualitatively – visual analysis with a 5-point scale based on uptake relative to background activity: 1=normal (decreased compared to background) 3=equivocal (small focal uptake, low intensity) 5=definite (intense, focal uptake) Quantitatively: Standard ROI of 1.5 cm placed over all tumors. SUVs calculated – average (SUV_{avg}) and maximum (SUV_{max}) activity values of each ROI. Tumor/Non-tumor ratios (T/NT) calculated using normal pancreatic tissue as reference. **Comparator Test done:** Ultrasound **Criteria used for diagnosis:** NS **Comparator Test:** CT **Done:** Qualitatively **Criteria used for diagnosis:** Malignant lesions appear hypodense. Normal pancreas – homogenous arterial enhancement. **Gold Standard test done:** Qualitatively **Criteria used for diagnosis:** Histology and clinical follow-up **Blinding:** **Radiologist:** Yes **Gold Standard reader:** NS	Visual PET Cancer | | + | - | | + | 22 | 4 | | - | 9 | 7 | Sensitivity = 71% Specificity = 64% CT Cancer | | + | - | | + | 23 | 3* | | - | 8 | 8 | Sensitivity = 74% Specificity = 73% US Cancer | | + | - | | + | 18 | 5 | | - | 13* | 6 | Sensitivity = 58% Specificity = 55% * Apparent typographical error in Table 4, pg. 1125 where data is reported. Prevalence: 31/42 = 74% **Using an SUV cutoff of 2.5:** PET Cancer | | + | - | | + | 22 | 3 | | - | 9 | 8 | Sensitivity = 71% Specificity = 73%	***Quality Score:*** **Rep.sample: 1** **Setting selection: 1** **Design minimizes diffs: 1** **Scanner: 1** **Interpretation criteria defined: 1** **Hist or clin confirmation: 1** **Blinded: 0** **Total Score = 6** **Notes:**

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Sperti **2001** **PROCITE#** 7040 **Cancer Type:** Pancreatic **SOW Question(s) Addressed:** 1a **Fryback et al. Level:** 2, 4	**Dates of data collection:** 2/96 – 1/ 00 **Geographic Location:** Padua, Italy **Prospective Study** **Enrolled Consecutively:** NS **Study Setting:** Academic/ Research **Patient Incl Crit:** • Clin Pres **Result led to incl:** • Abnormal only – all cystic lesions, some (n=16) asymptomatic **Comparisons:** • Matched – CT, CA 19-9 and US (n=56), MRI (n=33) and ERCP (n=3) **Use of ref stand:** • Histology (n=55) • Prolonged follow-up (n=1)	***Patients:*** **Overall:** **N =** 56 **Mean Age:** 60.1 years **Age Range:** 31-86 years **Gender:** 38% Male **Malignant:** **N =** 17 (30%) **Mean Age:** 65.3 years **Age Range:** 31-78 years **Gender:** 23.5% Male **Benign:** **N =** 39 (70%) **Mean Age:** 57.6 years **Age Range:** 31-86 years **Gender:** 43.6% Male **Inclusion criteria:** Suspected cystic tumor of the pancreas or intraductal hypersecreting mucinous neoplasm	**Scanner Model:** ECAT EXACT 47 (Siemens) **Resolution:** • **Transaxial:** 6 mm at FWHM • **Axial:** 5 mm **Acquisition Mode:** NS **Acquisition time per FOV:** • **Emission Scan:** 2 scans, 15 min each • **Transmission Scan:** 2 scans, 15 min each **Dose of FDG:** 444 MBq (12 mCi) **Time between injection and performance:** 60 min **Reconstruction Algorithm used:** NS **Glucose Monitoring:** Fasting – overnight; Glucose measured, < 120 mg/dL permitted	**PET done:** Quantitatively **Criteria used for diagnosis:** Focal uptake with SUV of at least 2.5 **Comparator Test done:** CT **Criteria used for diagnosis:** NS **Gold Standard test done:** Pathologic findings **Criteria used for diagnosis:** Classified according to WHO histologic typing **Blinding:** **Radiologist:** Yes **Gold Standard reader:** Yes	PET Cancer | | + | - | | + | 16 | 1 | | - | 1 | 38 | Sensitivity = 94% Specificity = 97% CT Cancer | | + | - | | + | 11 | 5 | | - | 6 | 34 | Sensitivity = 65% Specificity = 87% CA 19-9 Cancer | | + | - | | + | 11 | 4 | | - | 6 | 35 | Sensitivity = 65% Specificity = 90% Prevalence: 17/56 = 30% **Notes:** Negative PET scans limited pancreatic resection (n=18) or avoided unnecessary splenectomy (n=9) or laparotomy in asymptomatic patients (n=6). In 5 patients with negative PET, percutaneous aspiration biopsy was done without the theoretical risk of seeding malignant cells.	***Quality Score:*** **Rep.sample: 1** **Setting selection: 1** **Design minimizes diffs: 1** **Scanner: 1** **Interpretation criteria defined: 1** **Hist or clin confirmation: 1** **Blinded: 1** **Total Score = 7** **Notes:** Limitation of PET – cannot replace anatomic imaging in the assessment of local tumor resectability.

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Zimny **1997** **PROCITE#** 7440 **Cancer Type:** Pancreatic **SOW Question(s) Addressed:** 1a **Fryback et al. Level: 2**	**Dates of data collection:** 1990 – 1996 **Geographic Location:** Aachen, Germany **Retrospective Study** **Enrolled Consecutively:** NS **Study Setting:** Academic/ Research **Patient Incl Crit:** • Clin Pres **Result led to incl:** • Abnormal only **Comparisons:** • Matched – results of comparator not reported in this study **Use of ref stand:** • Histology • Prolonged follow-up	***Patients:*** **N =** 122 **Mean Age:** 56.8 years **Gender:** 65.6% Male **Diabetics:** All: N = 27 IDDM: N = 11 **Inclusion criteria:** NS **Exclusion Criteria:** NS	**Scanner Model:** ECAT 953/15 **Resolution:** • **AxialFOV: 5.2 cm** **Acquisition Mode:** NS **Acquisition time per FOV:** • **Emission Scan:** 15 min • **Transmission Scan:** NS **Dose of FDG:** 190 MBq **Time between injection and performance:** 40 min **Reconstruction Algorithm used:** Iterative **Glucose Monitoring:** Fasting – 12 hours	**PET done:** Qualitatively and Quantitatively **Criteria used for diagnosis:** Visual analysis – focally increased FDG uptake considered positive; SUV calculated, values > 2.9 considered positive **Gold Standard test done:** Histology and/or Clinical follow-up **Criteria used for diagnosis:** NS **Blinding:** **Radiologist:** NS **Gold Standard reader:** NS	**PET (all)** Cancer PET: + 66, 15; - 8, 17 Sensitivity = 89% Specificity = 53% Prevalence = 70% **PET (euglycemia)** Cancer CT/MRI: + 43, 12; - 4, 13 Sensitivity = 91% Specificity = 52% Prevalence = 65% **PET (hyperglycemia)** Recurrence PET: + 23, 2; - 4, 5 Sensitivity = 85% Specificity = 71% Prevalence = 79% PET SUV cutoff: values > 2.9 considered positive	***Quality Score:*** **Rep.sample: 1** **Setting selection: 1** **Design minimizes diffs: 0** **Scanner: 0** **Interpretation criteria defined: 1** **Hist or clin confirmation: 1** **Blinded: 0** **Total Score = 4** **Notes:**

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Chin **2002** **PROCITE#** 10470 **Cancer Type:** Lung **SOW Question(s) Addressed:** 1a **Fryback et al. Level:** 2	**Dates of data collection:** 12/1/97 – 3/31/00 **Geographic Location:** Winston Salem, NC **Prospective Study** **Enrolled Consecutively:** Yes **Study Setting:** Academic/ Research **Patient Incl Crit:** • Ref stand result **Result led to incl:** • Abnormal only **Comparisons:** • Matched **Use of ref stand:** • Prolonged follow-up	***Patients:*** **N =** 18 **Mean Age:** NS **Gender:** NS **Inclusion criteria:** NS **Exclusion Criteria:** NS	**Scanner Model:** ECAT 951 (CTI) **Resolution:** • **Intrinsic:** NS • **Image:** NS **Acquisition Mode:** NS **Acquisition time per FOV:** • **Emission Scan:** 7 min per bed position • **Transmission Scan:** 4 min per bed position **Dose of FDG:** 20 mCi **Time between injection and performance:** 60 min **Reconstruction Algorithm used:** Filtered backprojection **Glucose Monitoring:** NS	**PET done:** Qualitatively **Criteria used for diagnosis:** Interpretation by one of two radiologists **Comparator Test done:** CT, MRI, bone scan, bone biopsy **Criteria used for diagnosis:** NS **Gold Standard test done:** Qualitatively **Criteria used for diagnosis:** Survival data obtained from comprehensive cancer center at Wake Forest University **Blinding:** **Radiologist:** No **Gold Standard reader:** No	**Staging results:** Positive Conventional Image: Pathology PET | | + | - | | + | 8 | 0 | | - | 1 | 0 | Sensitivity = 89% Specificity= NA Negative Conventional Image: Pathology PET | | + | - | | + | 2 | 0 | | - | 0 | 7 | Sensitivity = 100% Specificity= 100%	***Quality Score:*** **Rep.sample: 1** **Setting selection: 0** **Design minimizes diffs: 1** **Scanner: 1** **Interpretation criteria defined: 0** **Hist or clin confirmation: 0** **Blinded: 0** **Total Score = 3** **Notes:** No definitive outcome (“gold standard”) for determining diagnosis despite presentation of survival data. Multiple conventional imaging tests instead of one used for comparator.

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Pandit **2003** **PROCITE#** 10440 **Cancer Type:** Lung **SOW Question(s) Addressed:** 1a;1b **Fryback et al. Level:** 2	**Dates of data collection:** 1995 – 2000 **Geographic Location:** New York, NY **Retrospective Study** **Enrolled Consecutively:** Yes ("sequentially") **Study Setting:** Inpatient **Patient Incl Crit:** • Clin Pres • Ref stand result – histology **Result led to incl:** • Abnormal only **Comparisons:** • No comp **Use of ref stand:** • Histology • Prolonged follow-up or clinical exam	***Patients:*** **N =** 46 **Mean Age:** 63.8±9.6 years **Age Range:** 43-82 years **Gender:** 41.3% Male **8 patients with initial diagnosis** **38 patients post-treatment** **Inclusion criteria:** NS **Exclusion Criteria:** NS	**Scanner Model:** GE Advance Scanner **Resolution:** • **Transaxial:** 4.8 mm • **Image:** NS **Acquisition Mode:** 2-D **Acquisition time per FOV:** • **Emission Scan:** 4-5 min • **Transmission Scan:** 3-4 min **Dose of FDG:** 370 MBq **Time between injection and performance:** 60 min **Reconstruction Algorithm used:** Iterative **Glucose Monitoring:** Fasting – 4 hours	**PET done:** Qualitatively **Criteria used for diagnosis:** Focal intense uptake considered positive; No uptake or "ill-defined diffuse areas of low grade uptake" considered negative. **Gold Standard test done:** Qualitatively **Criteria used for diagnosis:** Pathology or "clinical follow-up – physical status, performance, radiological data, treatment history and survival history" **Blinding:** **Radiologist:** Yes **Gold Standard reader:** NS	**Initial Diagnosis:** Pathology PET | | + | - | | + | 8 | 0 | | - | 0 | 0 | Sensitivity = 100% **Post-Treatment:** Survival at 1 year PET | | + | - | | + | 23 | 13 | | - | 1 | 9 | Sensitivity = 96% Specificity= 41% **Collapsed across initial or post-treatment diagnosis:** **Histology Reference Standard:** Pathology PET | | + | - | | + | 19 | 4 | | - | 0 | 7 | **Clinical Follow-up Reference Standard:** Pathology PET | | + | - | | + | 19 | 1 | | - | 1 | 11 |	***Quality Score:*** **Rep.sample: 1** **Setting selection: 1** **Design minimizes diffs: 0** **Scanner: 1** **Interpretation criteria defined: 0** **Hist or clin confirmation: 1** **Blinded: 1** **Total Score = 5** **Notes:**

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Rees **2001** **PROCITE#** 3770 **Cancer Type:** Lung **SOW Question(s) Addressed:** 1c **Fryback et al. Level:** 2	**Dates of data collection:** 1996-2000 **Geographic Location:** London, England **Retrospective Study** **Enrolled Consecutively:** NS **Study Setting:** Inpatient; Academic/ Research **Patient Incl Crit:** • Clin Pres **Result led to incl:** • Abnorm and norm **Comparisons:** • No comp **Use of ref stand:** • Histology • Prolonged follow-up	***Patients:*** **N =** 43 **Mean(Median) Age:** NS **Gender:** 56% Male **Inclusion criteria:** Retrospective study – all patients with suspected paraneoplastic neurological syndrome in whom conventional imaging was negative **Exclusion Criteria:** NS	**Scanner Model:** Siemens/CTI ECAT 951/31R; GE Advance; Siemens ECAT EXACT 47 **Resolution:** • **Spatial:** 4.75-6.0 mm **Acquisition Mode:** NS **Acquisition time per FOV:** • **Emission Scan:** NS • **Transmission Scan:** NS **Dose of FDG:** 350 MBq **Time between injection and performance:** 60 min **Reconstruction Algorithm used:** NS **Glucose Monitoring:** NS	**PET done:** NS **Criteria used for diagnosis:** NS **Gold Standard test done:** Qualitatively **Criteria used for diagnosis:** Combination of positive CT, follow-up, surgery and diagnosis of malignancy. **Blinding:** **Radiologist:** Yes **Gold Standard reader:** NS	Cancer PET | | + | - | |---|---|---| | + | 9 | 3 | | - | 1 | 26* | Sensitivity = 90% Specificity = 90% Prevalence : 23% to 26% ** * 2 with paraneoplastic syndrome ** unconfirmed counted as negative	***Quality Score:*** **Rep.sample: 1** **Setting selection: 1** **Design minimizes diffs: 0** **Scanner: 1** **Interpretation criteria defined: 0** **Hist or clin confirmation: 1** **Blinded: 0** **Total Score = 4** **Notes:**

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Schumacher **2001** **PROCITE#** 4100 **Cancer Type:** Lung **SOW Question(s) Addressed:** 1a **Fryback et al. Level:** 2	**Dates of data collection:** NS **Geographic Location:** Freiburg, Germany **Retrospective/ ProspectiveStudy:** NS **Enrolled Consecutively:** NS **Study Setting:** Academic/ Research **Patient Incl Crit:** • Ref stand result – histology for SCLC **Result led to incl:** • Abnormal only **Comparisons:** • Matched **Use of ref stand:** • Prolonged follow-up	***Patients:*** **N =** 30 **Mean (Median) Age:** 57±13 yrs **Gender:** 77% Male **Inclusion criteria:** NS **Exclusion Criteria:** NS	**Scanner Model:** Siemens ECAT EXACT 921/31 **Resolution:** • **Intrinsic:** 6.0 mm • **Image:** NS **Acquisition Mode:** NS **Acquisition time per FOV:** • **Emission Scan:** 9 min • **Transmission Scan:** 3 min per bed position **Dose of FDG:** 5 MBq/kg **Time between injection and performance:** 90 min **Reconstruction Algorithm used:** Iterative **Glucose Monitoring:** Fasting – 12 hrs	**PET done:** Qualitatively and Quantitatively **Criteria used for diagnosis:** Classified as malignant if: 1. Focally increased tracer uptake exceeds normal limits of regional FDG uptake; 2. Lesion located at a metastatic site; 3. SUV > 4. **Comparator Test done:** CT/ MRI **Criteria used for diagnosis:** Unspecified "standard protocols" **Gold Standard test done:** Follow-up **Criteria used for diagnosis:** Diagnosis is all histologically confirmed. Staging based on follow-up and/or additional tests. **Blinding:** **Radiologist:** Yes **Gold Standard reader:** NS	**Comparisons of PET+ and OE (Other Examination – CT or MRI) for initial staging:** PET Pathology | | + | - | | ED | 20 | 0 | | LD | 0 | 6 | Sensitivity = 100% Specificity = 100% OE Pathology | | + | - | | ED | 13 | 0 | | LD | 7 | 6 | Sensitivity = 65% Specificity = 100% Note: "ED" – extensive disease, "LD" – limited disease. Prevalence: 20/30 = 67%	***Quality Score:*** **Rep.sample: 0** **Setting selection: 0** **Design minimizes diffs: 1** **Scanner: 1** **Interpretation criteria defined: 1** **Hist or clin confirmation: 0** **Blinded: 0** **Total Score = 3** **Notes:**

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Shen **2002** **PROCITE#** 3160 **Cancer Type:** Lung **SOW Question(s) Addressed:** 1a **Fryback et al. Level:** 2	**Dates of data collection:** NS **Geographic Location:** Taipei, Taiwan **Prospective Study** **Enrolled Consecutively:** NS **Study Setting:** Inpatient; Academic/ Research **Patient Incl Crit:** • Clin pres **Result led to incl:** • Abnormal only **Comparisons:** • Matched **Use of ref stand:** • Histology • Prolonged follow-up	***Patients:*** **N =** 25 **Age Range:** 45-68 years **Gender:** 72% Male **Disease:** Extensive: 60% Limited: 40% **Inclusion criteria:** Histologically confirmed SCLC **Exclusion Criteria:** Any prior radiotherapy or chemotherapy	**Scanner Model:** CTI EXACT HR+ (Siemens); GE Advance PET **Resolution:** • **Intrinsic:** NS • **Image:** NS **Acquisition Mode:** NS **Acquisition time per FOV:** • **Emission Scan:** 7 min per bed position • **Transmission Scan:** 3 min per bed position **Dose of FDG:** 10 mCi **Time between injection and performance:** 40-50 min **Reconstruction Algorithm used:** NS **Glucose Monitoring:** Fasting – 6 hours; Glucose measured, maximum glucose permitted 149 mg/dL	**PET done:** Qualitatively **Criteria used for diagnosis:** Agreement of at least two of three experienced specialists **Comparator Test done:** CT **Criteria used for diagnosis:** NS **Gold Standard test done:** Qualitatively **Criteria used for diagnosis:** Pathological findings from thoracotomy/ mediastinoscopy, other modalities and follow-up of at least one year **Blinding:** **Radiologist:** Yes **Gold Standard reader:** NS	**Results for PET and Conventional imaging** (ED = Extensive disease, LD = Limited disease): PET (Pathology): ED: + 15, - 0 LD: + 0, - 10 Sensitivity = 100% Specificity = 100% Conv (Pathology): ED: + 14, - 1 LD: + 1, - 9 Sensitivity = 93% Specificity = 90%	***Quality Score:*** **Rep.sample: 0** **Setting selection: 1** **Design minimizes diffs: 1** **Scanner: 1** **Interpretation criteria defined: 1** **Hist or clin confirmation: 1** **Blinded: 0** **Total Score = 5** **Notes:**

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Zhao **2002** **PROCITE#** 10450 **Cancer Type:** Lung **SOW Question(s) Addressed:** 1a, 1b **Fryback et al. Level:** 2	**Dates of data collection:** NS **Geographic Location:** Bronx, NY **Retrospective Study** **Enrolled Consecutively:** NS **Study Setting:** Academic/ Research **Patient Incl Crit:** • Ref stand result – Histologically confirmed SCLC (3 new patients, 12 past diagnosis) **Result led to incl:** • Abnormal only **Comparisons:** • Matched **Use of ref stand:** • Histology • Follow-up – not prolonged	***Patients:*** **N =** 15 **Mean Age:** 68 years **Age Range:** 50-81 years **Gender:** 53% Male **Inclusion criteria:** NS **Exclusion Criteria:** NS	**Scanner Model:** ADAC Laboratories C-PET PLUS scanner **Resolution:** • **Intrinsic:** NS • **Image:** NS **Acquisition Mode:** NS **Acquisition time per FOV:** • **Emission Scan:** NS • **Transmission Scan:** NS **Dose of FDG:** 3.4 – 4.14 mCi **Time between injection and** performance**:** 50 min **Reconstruction Algorithm used:** Iterative **Glucose Monitoring:** Fasting – 4 hours	**PET done:** NS **Criteria used for diagnosis:** NS **Comparator Test done:** CT **Criteria used for diagnosis:** NS **Gold Standard test done:** Qualitatively **Criteria used for diagnosis:** Surgery and Clinical follow-up **Blinding:** **Radiologist:** NS **Gold Standard reader:** NS	**New Patients (N = 3):** N = 3 PET positive N = 0 PET negative Sensitivity: 100% **Patients with previously diagnosed SCLC (N = 12):** Recurrence PET: + 7 1; - 0 4 Sensitivity = 100% Specificity = 80% **Collapsed across new or previously diagnosed patients with SCLC (N = 15):** Pathology PET: + 10 1; - 0 4 Sensitivity = 100% Specificity = 80% CT: + 9 3; - 1 2 Sensitivity = 90% Specificity = 40%	***Quality Score:*** **Rep.sample: 0** **Setting selection: 0** **Design minimizes diffs: 1** **Scanner: 1** **Interpretation criteria defined: 0** **Hist or clin confirmation: 0** **Blinded: 0** **Total Score = 2** **Notes:** Data and text do not provide enough data to construct table for CT results by patient type.

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Albers **1999** **PROCITE#** 9030 **Cancer Type:** Testicular **SOW Question(s) Addressed:** 1a **Frybeck et al. Level:** 2	**Dates of data collection:** **1/95 – 7/97** **Geographic Location:** Bonn, Germany **Retrospective/ Prospective Study: NS** **Enrolled Consecutively:** 37 **Study Setting:** Inpatient; Academic/ Research **Patient Incl Crit:** • Clin Pres **Result led to incl:** • Abnormal only **Comparisons:** • Matched • PET and comp – random • PET and comp – not random • No comp **Use of ref stand:** • Histology • Prolonged follow-up	***Patients:*** **N =** 35 **Stage:** **I: N=25** **II: 12** **Tumor:** N = 24 NSGCT N = 13 seminoma **Mean Age:** NS **Inclusion criteria:** NS **Exclusion Criteria:** NS	**Scanner Model:** Siemens ECAT EXACT **Resolution:** • **Intrinsic:** NS • **Image:** NS **Acquisition Mode:** NS **Acquisition time per FOV:** • **Emission Scan:** 10 min • **Transmission Scan:** 10 min **Dose of FDG:** 5-10 mCi **Time between injection and performance:** 45 min **Reconstruction Algorithm used:** Filtered backprojection **Glucose Monitoring:** Fasting – 12 hours; Glucose measured, maximum amount permitted not specified	**PET done:** Qualitatively and Quantitatively **Criteria used for diagnosis:** Visual analysis; **SUV > 2.0 considered positive** **Comparator Test:** CT **Done:** Quantitatively **Criteria used for diagnosis:** Solitary nodules ≥ 1.0 cm or group of ≥ 5 sub-centimeter nodes considered positive **Gold Standard test done:** Quantitatively **Criteria used for diagnosis:** Histology or clinical follow-up > 6 months **Blinding:** **Radiologist:** Yes **Gold Standard reader:** NS	PET (Metastasis): + / + : 7 + / - : 0 - / + : 3 - / - : 27 Sensitivity = 70% Specificity = 100% CT (Metastasis): + / + : 4 + / - : 2 - / + : 6 - / - : 25 Sensitivity = 40% Specificity = 93% Prevalence: 10/37 = 27%	***Quality Score:*** **Rep.sample: 1** **Setting selection: 1** **Design minimizes diffs: 1** **Scanner: 1** **Interpretation criteria defined: 1** **Hist or clin confirmation: 1** **Blinded: 1** **Total Score = 7** **Notes:**

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Cremerius **1999** **PROCITE#** 9150 **Cancer Type:** Testicular **SOW Question(s) Addressed:** 1a **Frybeck et al. Level:** 2	**Dates of data collection:** NS **Geographic Location:** Aachen, Germany **Retrospective/ Prospective Study: NS** **Enrolled Consecutively:** NS **Study Setting:** Inpatient; Academic/ Research **Patient Incl Crit:** • Clin Pres **Result led to incl:** • Abnorm and norm **Comparisons:** • Matched **Use of ref stand:** • Histology • Prolonged follow-up	***Patients:*** **N =** 50 **Median Age:** 31 years **Age Range:** 20-76 years **Inclusion criteria:** NS **Exclusion Criteria:** NS	**Scanner Model:** ECAT EXACT 922/47; ECAT 953/15 **Resolution:** • **Intrinsic:** NS • **Image:** NS **Acquisition Mode:** 2-D **Acquisition time per FOV:** • **Emission Scan:** NS • **Transmission Scan:** NS **Dose of FDG:** 221±62 MBq **Time between injection and performance:** 30-60 min **Reconstruction Algorithm used:** Cited in references **Glucose Monitoring:** Glucose measured, maximum amount allowed not specified	**PET done:** Qualitatively **Criteria used for diagnosis:** Visual analysis – foci of unphysiologic FDG uptake considered positive. SUV calculated **Comparator Test:** CT **Done:** Quantitatively **Criteria used for diagnosis:** Node > 10 mm in size considered positive **Gold Standard test done:** Histology and/or clinical follow-up **Criteria used for diagnosis:** All available sources of clinical data used to determine gold standard diagnosis **Blinding:** **Radiologist:** Yes **Gold Standard reader:** No	PET Metastasis | | + | - | | + | 13 | 2 | | - | 2 | 33 | Sensitivity = 87% Specificity = 94% CT Metastasis | | + | - | | + | 11 | 2 | | - | 4 | 33 | Sensitivity = 73% Specificity = 94% Tumor Markers Metastasis | | + | - | | + | 10 | 0 | | - | 5 | 35 | Sensitivity = 67% Specificity = 100% Prevalence: 15/50 = 30%	***Quality Score:*** **Rep.sample: 1** **Setting selection: 1** **Design minimizes diffs: 1** **Scanner: 1** **Interpretation criteria defined: 1** **Hist or clin confirmation: 1** **Blinded: 0** **Total Score = 6** **Notes:**

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Cremerius **1998** **PROCITE#** 9380 **Cancer Type:** Testicular **SOW Question(s) Addressed:** 1a, 1b **Fryback et al. Level:** 2	**Dates of data collection:** 9/90 – 8/96 **Geographic Location:** Aachen, Germany **Retrospective/ Prospective Study: NS** **Enrolled Consecutively:** NS **Study Setting:** Inpatient; Academic/ Research **Patient Incl Crit:** • Clin Pres **Result led to incl:** • Abnormal only **Comparisons:** • Matched **Use of ref stand:** • Histology • Prolonged follow-up	***Patients:*** **N =** 33 **Mean Age:** 30 years **Age Range:** 19-71 years **Disease:** N = 14 seminoma N = 18 non-seminoma **Inclusion criteria:** Histopatho-logically proven germ cell tumor **Exclusion Criteria:** NS	**Scanner Model:** Siemens ECAT 953/15 **Resolution:** • **In-plane:** 7 mm • **Image:** NS **Acquisition Mode:** NS **Acquisition time per FOV:** • **Emission Scan:** 45-80 min • **Transmission Scan:** 12-15 min per bed position **Dose of FDG:** 120-309 MBq **Time between injection and performance:** 40-60 min **Reconstruction Algorithm used:** Iterative **Glucose Monitoring:** Fasting – overnight (n=42) or 3-6 hours (n=12)	**PET done:** Qualitatively and Quantitatively **Criteria used for diagnosis:** Visual analysis, hypermetabolic lesion considered positive; SUV values calculated **Comparator Test:** CT **Done:** Qualitatively **Criteria used for diagnosis:** Stable or progressive disease considered positive, complete response or partial response considered negative. Tumors greater than 1.5 cm considered positive. **Gold Standard test done:** Histology or clinical follow-up more than 180 days **Criteria used for diagnosis:** Residual viable tumor if: Lesions documented by CT and either tumor markers positive at time of PET, or Progression found in CT during follow-up **Blinding:** **Radiologist:** No **Gold Standard reader:** NS	**Initial Staging:** PET (Metastasis): TP 5, FP 1, FN 1, TN 5 — Sensitivity = 83%, Specificity = 83% CT (Metastasis): TP 5, FP 1, FN 1, TN 5 — Sensitivity = 83%, Specificity = 83% **Less than 2 weeks after chemotherapy:** PET (Metastasis): TP 4, FP 0, FN 5, TN 4 — Sensitivity = 44%, Specificity = 100% CT (Metastasis): TP 7, FP 2, FN 2, TN 2 — Sensitivity = 78%, Specificity = 50% **More than 2 weeks after chemotherapy**: PET (Metastasis): TP 7, FP 2, FN 2, TN 18 — Sensitivity = 78%, Specificity = 90% CT (Metastasis): TP 6, FP 9, FN 3, TN 11 — Sensitivity = 67%, Specificity = 55%	***Quality Score:*** **Rep.sample: 1** **Setting selection: 1** **Design minimizes diffs: 1** **Scanner: 1** **Interpretation criteria defined: 1** **Hist or clin confirmation: 1** **Blinded: 0** **Total Score = 6** **Notes:**

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
DeSantis **2001** **PROCITE#** 8230 **Cancer Type:** Testicular **SOW Question(s) Addressed:** 1b **Fryback et al. Level:** 2	**Dates of data collection:** NS **Geographic Location:** Austria and Germany **Prospective Study** **Enrolled Consecutively:** Yes – prospective study **Study Setting:** Inpatient; Academic/ Research **Patient Incl Crit:** • Clin Pres • Comp test result **Result led to incl:** • Abnormal only • Abnorm and norm **Comparisons:** • Matched **Use of ref stand:** • Histology: N=9 • Prolonged follow-up: N=28	***Patients:*** **N =** 33 patients (37 scans) **Median Age:** 37 years **Age Range:** 22-59 years **Inclusion criteria:** Patients with metastases of pure testicular or extragonadal seminomas who had negative tumor markers on completion of platinum-containing first-line or salvage chemotherapy, but showed CT evidence of clearly defined and measurable residual masses > 1 cm diameter **Exclusion Criteria:** Patients not meeting inclusion criteria, along with those scheduled for radiotherapy at the site of the residual lesions	**Scanner Model:** GE Advance (N=32); ECAT ART – Siemens/CTI (N=1) **Resolution:** • **Axial:** 4.0 mm • **Transaxial:** 3.8 mm **Acquisition Mode:** NS **Acquisition time per FOV:** • **Emission Scan:** NS • **Transmission Scan:** NS **Dose of FDG:** 10 mCi (370 MBq) **Time between injection and performance:** ≥ 45 min **Reconstruction Algorithm used:** Filtered Backprojection; Iterative **Glucose Monitoring:** Fasting – 4 hours	**PET done:** Qualitatively **Criteria used for diagnosis:** Visual interpretation – localization, shape, intensity of increased uptake **Comparator Test:** CT **Done:** Quantitatively **Criteria used for diagnosis:** Size >3cm considered positive **Gold Standard test done:** Quantiatively **Criteria used for diagnosis:** Histology or clinical follow-up ≥ 2 years or other imaging study **Blinding:** **Radiologist:** NS **Gold Standard reader:** NS	**Results reflect N = 37 lesions (scans):** Viable Residual Tumor PET | | + | - | | + | 8 | 0 | | - | 1 | 28 | Sensitivity = 89% Specificity = 100% Viable Residual Tumor CT | | + | - | | + | 7 | 7 | | - | 2 | 21 | Sensitivity = 78% Specificity = 75% Prevalence: 9/37 – 24%	***Quality Score:*** **Rep.sample: 1** **Setting selection: 1** **Design minimizes diffs: 1** **Scanner: 1** **Interpretation criteria defined: 1** **Hist or clin confirmation: 1** **Blinded: 0** **Total Score = 6** **Notes:**

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Ganjoo 1999 **PROCITE#** 10500 **Cancer Type:** Testicular **SOW Question(s) Addressed:** 1b **Frybeck et al. Level:** 2	**Dates of data collection:** 2/96 – 3/98 **Geographic Location:** Indianapolis, IN **Prospective Study** **Enrolled Consecutively:** Yes – prospective enrollment **Study Setting:** Academic/ Research **Patient Incl Crit:** • Clin Pres **Result led to incl:** • Abnorm and norm **Comparisons:** • Matched **Use of ref stand:** • Histology	***Patients:*** **N =** 29 – all seminoma patients **Median Age:** 38 years **Age Range:** 24-67 years **Chemotherapy:** Initial: n=19 Salvage: n=10 **Primary Tumor:** Testicular I: n=12 Testicular II: n=7 Retroperitoneal: n=6 Mediastinal: n=4 **Residual Mass:** < 3 cm: n=8 ≥ 3 cm: n=18 Unknown: n=3 **Inclusion criteria:** NS **Exclusion Criteria:** NS	**Scanner Model:** NS **Resolution:** • **Intrinsic:** NS • **Image:** NS **Acquisition Mode:** NS **Acquisition time per FOV:** • **Emission Scan:** NS • **Transmission Scan:** NS **Dose of FDG:** 10 mCi **Time between injection and performance:** NS **Reconstruction Algorithm used:** NS **Glucose Monitoring: NS**	**PET done:** Quantitatively **Criteria used for diagnosis:** SUV ≥ 4 **Comparator Test:** CT **Done:** Quantitatively **Criteria used for diagnosis:** size ≥ 3 cm considered abnormal (positive) **Gold Standard test done:** Quantitatively **Criteria used for diagnosis:** Histology or prolonged follow-up **Blinding:** **Radiologist:** NS **Gold Standard reader:** NS	PET (Cancer) | | + | - | | + | 0 | 1 | | - | 5 | 23 | Sensitivity = 0% Specificity = 96% CT (Cancer) | | + | - | | + | 2 | 14 | | - | 2 | 10 | Sensitivity = 50% Specificity = 42%	***Quality Score:*** **Rep.sample: 1** **Setting selection: 1** **Design minimizes diffs: 1** **Scanner: 0** **Interpretation criteria defined: 1** **Hist or clin confirmation: 1** **Blinded: 0** **Total Score = 5** **Notes:**

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Hain **2000a** **PROCITE#** 8730 **Cancer Type:** Testicular **SOW Question(s) Addressed:** 1a **Fryback et al. Level:** 2, 3	**Dates of data collection:** 1994 – 1998 **Geographic Location:** London, UK **Retrospective Study** **Enrolled Consecutively:** No – retrospective review **Study Setting:** Inpatient; Academic/ Research **Patient Incl Crit:** • Clin Pres **Result led to incl:** • Abnorm and norm **Comparisons:** • Matched **Use of ref stand:** • Histology • Prolonged follow-up	***Patients:*** **N =** 31 **Tumor Type:** N=13 seminomas N=18 NSGCT **Mean Age:** 31.6 years **Age Range:** 17-51 years **Inclusion criteria:** None **Exclusion Criteria:** None	**Scanner Model:** Siemens ECAT 951 **Resolution:** • **Spatial:** 8 mm FWHM **Acquisition Mode:** NS **Acquisition time per FOV:** • **Emission Scan:** 5 min • **Transmission Scan:** 5 min **Dose of FDG:** 320 MBq **Time between injection and performance:** NS **Reconstruction Algorithm used:** **Glucose Monitoring:** Fasting – 6 hours	**PET done:** NS **Criteria used for diagnosis:** Scans reported by two nuclear medicine physicians blinded to CT/MRI reports **Comparator Test done:** CT/ MRI **Criteria used for diagnosis:** NS **Gold Standard tests done:** Qualitatively and Quantitatively **Criteria used for diagnosis:** Histology or clinical follow-up ≥ 18 months **Blinding:** **Radiologist:** Yes **Gold Standard reader:** NS	PET Metastasis | | + | - | | + | 10 | 0 | | - | 5 | 16 | Sensitivity = 67% Specificity = 100% CT Metastasis | | + | - | | + | 13 | 7 | | - | 2 | 9 | Sensitivity = 87% Specificity = 56% Prevalence: 15/31 = 48%	***Quality Score:*** **Rep.sample: 1** **Setting selection: 0** **Design minimizes diffs: 1** **Scanner: 1** **Interpretation criteria defined: 0** **Hist or clin confirmation: 1** **Blinded: 0** **Total Score = 4** **Notes:**

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Hain **2000b** **PROCITE#** 8640 **Cancer Type:** Testicular **SOW Question(s) Addressed:** 1c **Frybeck et al. Level:** 2, 3, 4	**Dates of data collection:** 1994-1998 **Geographic Location:** London, UK **Retrospective Study** **Enrolled Consecutively:** Yes **Study Setting:** Academic/ Research **Patient Incl Crit:** • Clin Pres – abnormal CT or increased markers **Result led to incl:** • Abnormal only **Comparisons:** • Matched **Use of ref stand:** • Histology • Prolonged follow-up	***Patients:*** **N =** 55 patients 70 total PET scans: 23 scans for patients with increased markers and normal CT; 47 scans (in 39 patients) for abnormal CT **Mean Age:** 30 years **Age Range:** 15-55 years **Inclusion criteria:** Patients with previous germ cell tumor(s) **Exclusion Criteria:** NS	**Scanner Model:** Siemens ECAT 951 **Resolution:** • **Spatial:** 8 mm FWHM • **Image:** NS **Acquisition Mode:** NS **Acquisition time per FOV:** • **Emission Scan:** NS • **Transmission Scan:** NS **Dose of FDG:** 320 MBq **Time between injection and performance:** NS **Reconstruction Algorithm used:** NS **Glucose Monitoring:** Fasting – 6 hours	**PET done:** NS **Criteria used for diagnosis:** NS **Comparator Test:** CT **Done:** NS **Criteria used for diagnosis:** NS **Comparator Test:** Tumor Markers **Done:** Quantitatively **Criteria used for diagnosis:** BHCG > 5 ku/l and AFP > u/l **Gold Standard test done:** Qualitatively and Quantitatively **Criteria used for diagnosis:** Histology or extended clinical follow-up **Blinding:** **Radiologist:** NS **Gold Standard reader:** NS	Patients with residual masses after chemotherapy (N=47 scans): PET: Cancer + 25, Cancer - 1, Non-Cancer + 3, Non-Cancer - 18 Sensitivity = 89% Specificity = 95% CT: Cancer + 28, Cancer - 19, Non-Cancer + 0, Non-Cancer - 0 Sensitivity = 100% Specificity = 0% Prevalence: 28/47 = 60% Patients with elevated tumor markers (N=41 scans): PET: Cancer + 27, Cancer - 1, Non-Cancer + 6, Non-Cancer - 7 Sensitivity = 82% Specificity = 88% CT: Cancer + 18, Cancer - 0, Non-Cancer + 15, Non-Cancer - 8 Sensitivity = 55% Specificity = 100% Prevalence: 33/41 = 80% Patients with elevated tumor markers and negative CT (N=23 scans): PET: Cancer + 11, Cancer - 1, Non-Cancer + 4, Non-Cancer - 7 Sensitivity = 73% Specificity = 88%	***Quality Score:*** **Rep.sample: 1** **Setting selection: 1** **Design minimizes diffs: 1** **Scanner: 1** **Interpretation criteria defined: 0** **Hist or clin confirmation: 1** **Blinded: 0** **Total Score = 5** **Notes:** Therapy was changed in 57% (27/47) of patients based on PET compared with care plan established based on CT alone.

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Kollmannsberger **2002** **PROCITE#** 7870 **Cancer Type:** Testicular **SOW Question(s) Addressed:** 1b **Fryback et al. Level:** 2	**Dates of data collection:** 9/95 – 10/99 **Geographic Location:** Tuebingen, Germany **Prospective Study** **Enrolled Consecutively:** Yes **Study Setting:** Inpatient; Academic/ Research **Patient Incl Crit:** • Clin Pres **Result led to incl:** • Abnorm and norm **Comparisons:** • Matched **Use of ref stand:** • Histology • Prolonged follow-up	***Patients:*** **N =** 45 **Median Age:** 33 years **Age Range:** 21-57 years **Tumor localization:** N=37 Gonadal N=8 Extragonadal **Inclusion criteria:** Newly diagnosed, metastatic, poor prognosis NSGCT OR recurrent disease after cisplatin-based chemotherapy and at least one residual mass ≥ 1 cm on a CT scan **Exclusion Criteria:** NS	**Scanner Model:** GE Advance **Resolution:** • **Intrinsic:** NS • **Image:** 8 mm **Acquisition Mode:** NS **Acquisition time per FOV:** • **Emission Scan:** 5-15 min per FOV • **Transmission Scan: 3-20 min per FOV** **Dose of FDG:** 250 MBq **Time between injection and performance:** 45-60 min **Reconstruction Algorithm used:** Filtered backprojection; Iterative **Glucose Monitoring:** Fasting – 12 hours; Glucose measured, maximum amount allowed not specified	**PET done:** Qualitatively and Quantitatively **Criteria used for diagnosis:** Visual analysis; SUV ≥ 2 **Comparator Test:** CT **Done:** Quantitatively **Criteria used for diagnosis: Less than** 50%decrease in tumor size, and persistent/increased contrast medium uptake considered positive **Comparator Test:** MRI/Serum tumor marker **Done:** NS **Criteria used for diagnosis: NS** **Gold Standard test done:** Histology or survival **Criteria used for diagnosis:** Histological results or survival > 6 months **Blinding:** **Radiologist:** Yes **Gold Standard reader:** No	Results reported for lesions (not patients) Visual analysis: PET (Cancer): | | + | - | |---|---|---| | + | 29 | 3 | | - | 20 | 33 | Sensitivity = 59% Specificity = 92% CT/ MRI (Cancer): | | + | - | |---|---|---| | + | 27 | 5 | | - | 22 | 31 | Sensitivity = 55% Specificity = 86% CT/ MRI/ Serum (Cancer): | | + | - | |---|---|---| | + | 38 | 3 | | - | 11 | 33 | Sensitivity = 77.5% Specificity = 92% Prevalence: 49/85 = 57.6%	***Quality Score:*** **Rep.sample: 1** **Setting selection: 1** **Design minimizes diffs: 1** **Scanner: 1** **Interpretation criteria defined: 1** **Hist or clin confirmation: 1** **Blinded: 0** **Total Score = 6** **Notes:**

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Nuutinen **1997** **PROCITE#** 9600 **Cancer Type:** Testicular **SOW Question(s) Addressed:** 1b **Fryback et al. Level:** 2	**Dates of data collection:** 5/95 – 5/96 **Geographic Location:** Turku, Finland **Retrospective/ Prospective Study: NS** **Enrolled Consecutively:** No **Study Setting:** Inpatient; Academic/ Research **Patient Incl Crit:** • Clin Pres **Result led to incl:** • Abnormal only – abnormal CT after chemotherapy **Comparisons:** • No comp **Use of ref stand:** • Histology • Prolonged follow-up	***Patients:*** **N =** 15 **Median Age:** 32 years **Age Range:** 21-54 years **Inclusion criteria:** Abnormal CT after chemotherapy for metastatic testicular cancer **Exclusion Criteria:** NS	**Scanner Model:** Siemens ECAT 931/08-12 **Resolution:** • **Intrinsic:** NS • **Image:** NS **Acquisition Mode:** NS **Acquisition time per FOV:** • **Emission Scan:** 15 min • **Transmission Scan:** NS **Dose of FDG:** 311-446 MBq **Time between injection and performance:** 45 min **Reconstruction Algorithm used:** NS **Glucose Monitoring:** Fasting – 6 hours; Plasma glucose level measured.	**PET done:** Qualitatively and Quantitatively **Criteria used for diagnosis:** Visual analysis: ++ = clearly positive + = suspect – = normal; SUV calculated. **Gold Standard test done:** Histology and clinical follow-up **Criteria used for diagnosis:** Morphological studies, serum tumor markers and length of event-free follow-up time (median 16 months, range 8-20 months). **Blinding:** **Radiologist:** NS **Gold Standard reader:** NS	Analysis based on N = 13 (rather than N = 20 scans). Patients 1 and 11 eliminated due to conflicting secondary results. Cancer PET | | + | - | |---|---|---| | + | 3 | 2 | | - | 1 | 7 | Sensitivity = 75% Specificity = 78%	***Quality Score:*** **Rep.sample: 1** **Setting selection: 1** **Design minimizes diffs: 1** **Scanner: 1** **Interpretation criteria defined: 1** **Hist or clin confirmation: 1** **Blinded: 0** **Total Score = 6** **Notes:**

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Stephens 1996 **PROCITE# 10490** **Cancer Type:** Testicular **SOW Question(s) Addressed:** 1b **Frybeck et al. Level:** 2	**Dates of data collection:** NS **Geographic Location:** Indianapolis, IN **Retrospective/ Prospective Study: NS** **Enrolled Consecutively:** NS **Study Setting:** Academic/ Research **Patient Incl Crit:** • Clin Pres – residual post-chemotherapy mass **Result led to incl:** • Abnormal only **Comparisons:** • Matched – no SN or SP reported for CT, all patients had abnormal CT **Use of ref stand:** • Histology: n=30	***Patients:*** **N =** 30 **Median Age:** 31.5 years **Age Range:** 16-46 years **Chemotherapy status:** 1st line: n=22 Salvage: n=8 **Inclusion criteria:** All patients non-seminoma Tumor markers normal in all patients **Exclusion Criteria:** NS	**Scanner Model:** Siemens 951/31R **Resolution:** • **Intrinsic:** NS • **Image:** NS **Acquisition Mode:** NS **Acquisition time per FOV:** • **Emission Scan:** NS • **Transmission Scan:** NS **Dose of FDG:** 10 mCi **Time between injection and performance:** 60 min **Reconstruction Algorithm used:** NS **Glucose Monitoring:** NS	**PET done:** Quantitatively **Criteria used for diagnosis:** SUV > 5 considered positive **Comparator Test:** CT **Done:** Quantitatively **Criteria used for diagnosis:** NS – inferred criteria for abnormality was mass > 1 cm **Gold Standard test done:** Quantitatively **Criteria used for diagnosis:** Histological results **Blinding:** **Radiologist:** NS **Gold Standard reader:** NS	PET Cancer | | + | - | | + | 3 | 1 | | - | 16 | 10 | Sensitivity = 16% Specificity = 91% CT Cancer * | | + | - | | + | 12 | 2 | | - | 13 | 11 | Sensitivity = 48% Specificity = 85% * Teratoma scored as "cancer"	***Quality Score:*** **Rep.sample: 1** **Setting selection: 1** **Design minimizes diffs: 1** **Scanner: 1** **Interpretation criteria defined: 1** **Hist or clin confirmation: 1** **Blinded: 0** **Total Score = 6** **Notes:**

<table>
<tr><th>Study, Year/ General Inclusion Criteria</th><th>Study Design</th><th>Patients/ Subject Characteristics</th><th>PET Technical Characteristics</th><th>Criteria for Abnormality</th><th>Results</th><th>Quality Score/Notes</th></tr>
<tr>
<td>
Sugawara

1999

PROCITE# 9040

Cancer Type: Testicular

SOW Question(s) Addressed: 1b

Frybeck et al. Level: 2
</td>
<td>
Dates of data collection: NS

Geographic Location: Ann Arbor, MI

Retrospective/ Prospective Study: NS

Enrolled Consecutively: NS

Study Setting: Inpatient; Academic/ Research

Patient Incl Crit:
• Clin Pres

Result led to incl:
• Abnormal only – all patients had abnormal CT results

Comparisons:
• No comp

Use of ref stand:
• Histology, or increased mass with positive biomarkers
</td>
<td>
Patients:

N = 21 overall

N = 15 patients

Tumors
Primary: n=15
Retroperitoneal or mediastinal: n=6

Mean Age: 29 years

Age Range: 19-42 years

Inclusion criteria: NS

Exclusion Criteria: NS
</td>
<td>
Scanner Model: Siemens ECAT 931

Resolution:
• Intrinsic: 120 mm
• Image: NS

Acquisition Mode: NS

Acquisition time per FOV:
• Emission Scan: 2-10 min per FOV
• Transmission Scan: 10 min

Dose of FDG: 370 MBq

Time between injection and performance: 0 min

Reconstruction Algorithm used: NS

Glucose Monitoring: Fasting – 4 hours
</td>
<td>
PET done: Qualitatively and Quantitatively

Criteria used for diagnosis:
Grading scale:
0 = no uptake
1 = equivocal uptake
2 = intense uptake; SUV calculated by dividing decay-corrected tissue activity by injected dose per patient body weight corrected by predicted lean body mass.

Gold Standard test done: Quantitatively

Criteria used for diagnosis:
Histology results

Blinding:
Radiologist: No
Gold Standard reader: NS
</td>
<td>
Equivocal PET results (Visual Grade 1) reported for N = 3 patients.

Data reflecting Visual Grade 1 results as PET positive:
<table>
<tr><td></td><td>Viable Tumor</td><td></td></tr>
<tr><td></td><td>+</td><td>-</td></tr>
<tr><td>PET</td><td>+</td><td>8</td><td>1</td></tr>
<tr><td></td><td>-</td><td>4</td><td>8</td></tr>
</table>
Sensitivity = 67%
Specificity = 89%

Data reflecting Visual Grade 1 results as PET negative, and teratomas considered positive Viable Tumors:
<table>
<tr><td></td><td>Viable Tumor</td><td></td></tr>
<tr><td></td><td>+</td><td>-</td></tr>
<tr><td>PET</td><td>+</td><td>10</td><td>0</td></tr>
<tr><td></td><td>-</td><td>6</td><td>11</td></tr>
</table>
Sensitivity = 67%
Specificity = 100%
</td>
<td>
Quality Score:

Rep.sample: 1

Setting selection: 1

Design minimizes diffs: 1

Scanner: 1

Interpretation criteria defined: 1

Hist or clin confirmation: 1

Blinded: 0

Total Score = 6

Notes:
</td>
</tr>
</table>

Study, Year/ General Inclusion Criteria	Study Design	Patients/ Subject Characteristics	PET Technical Characteristics	Criteria for Abnormality	Results	Quality Score/Notes
Tsatalpas **2002** **PROCITE#** 7990 **Cancer Type:** Testicular **SOW Question(s) Addressed:** 1a, 1b **Fryback et al. Level:** 2	**Dates of data collection:** NS **Geographic Location:** Dresden, Germany **Retrospective/ Prospective Study: NS** **Enrolled Consecutively:** NS **Study Setting:** General outpatient clinics/ physician office; Academic/ Research **Patient Incl Crit:** • Clin Pres **Result led to incl:** • Abnorm and norm **Comparisons:** • Matched **Use of ref stand:** • Histology • Prolonged follow-up	***Patients:*** **N =** 21 patients scanned for staging **N =**11 patients scanned to assess for response to therapy **Mean(Median) Age:** NS **Inclusion criteria:** Patients with diagnosed testicular cancer **Exclusion Criteria:** NS	*Set 1 = 15/21 scans* **Scanner Model:** Siemens ECAT EXACT HR+ **Resolution:** • **Intrinsic:** NS • **Image:** 4-5 mm FWHM **Acquisition Mode:** NS **Acquisition time per FOV:** • **Emission:** 50-60 min • **Transmission:** NS **Dose of FDG:** 266-390 MBq **Time between injection and performance:** 60 min **Reconstruction Algorithm used:** Filtered Backposition **Glucose Monitoring:** Fasting – 6-12 hours *Set 2 = 6/21 scans* **Scanner Model:** Solus EPIC MCD (ADAC) **Resolution:** • **Intrinsic:** NS • **Image:** 4 mm FWHM **Acquisition Mode:** NS **Acquisition time per FOV:** • **Emission:** 60-90 min • **Transmission:** NS **Dose of FDG:** 100-140 MBq **Time between injection and performance:** 60 min **Reconstruction Algorithm used:** Iterative **Glucose Monitoring:** Fasting – 6-12 hours	**PET done:** Qualitatively Quantitatively **Criteria used for diagnosis:** Area determined to be "Hot or not", SUV calculation, cutoff not mentioned. **Comparator Test:** CT Scan **Done:** Quantitatively **Criteria used for diagnosis:** Node> 1.5 cm. Contrast-enhancement of suspected organ metastasis. **Gold Standard test done:** Quantitatively **Criteria used for diagnosis:** Histology gold standard for n= 7. Clinical follow-up (6-11 mos after last PET) gold standard for n=16. **Blinding:** **Radiologist:** Yes **Gold Standard reader:** NS	**SOW Question 1a** Metastasis PET: + 9, - 0; + 1, - 11 Sensitivity = 90% Specificity = 100% Metastasis CT: + 6, - 0; + 4, - 11 Sensitivity =60% Specificity = 100% Prevalence = 10/21 = 48% **SOW Question 1b** Viable Tumor PET: + 1, - 4; + 0, - 6 Sensitivity = 100% Specificity = 60% Viable Tumor CT: + 1, - 4; + 0, - 6 Sensitivity = 100% Specificity = 60% Prevalence = 1/11 = 9%	***Quality Score:*** **Rep.sample: 1** **Setting selection: 1** **Design minimizes diffs: 1** **Scanner: 1** **Interpretation criteria defined: 1** **Hist or clin confirmation: 1** **Blinded: 0** **Total Score = 6** **Notes:**

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