Technology Assessment

Technology Assessment Program

Positron Emission Tomography for Nine Cancers (Bladder, Brain, Cervical, Kidney, Ovarian, Pancreatic, Prostate, Small Cell Lung, Testicular)

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Positron Emission Tomography for Nine Cancers (Bladder, Brain, Cervical, Kidney, Ovarian, Pancreatic, Prostate, Small Cell Lung, Testicular)

Technology Assessment Report

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University of Alberta Evidence-based Practice Center

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Chapter 1. Introduction

Background

Positron emission tomography (PET) is a form of nuclear medicine imaging that detects and establishes metabolic abnormalities in tissue. A PET scanner produces an image of the area of interest through the detection of radiation emitted from a positron-emitting radionuclide that is introduced into the patient and that accumulates in the target tissue.

Different radiotracers allow for various aspects of tumor metabolism to be imaged. The most commonly used radioisotope tracer is 18F-fluorodeoxyglucose (^{18}FDG), a glucose analog with the addition of a radioactive fluorine atom, which has a half-life of 109.8 minutes. The relatively long half-life of this radioisotope allows the operation of imaging sites up to 2 to 4 hours travelling distance from the production site.[1] Like glucose, ^{18}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. Images may be interpreted qualitatively by visual assessment for regions of increased uptake. Quantitative measurement of the glucose metabolism by cells in a region of interest is performed using the standardized uptake value (SUV). 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, time of image acquisition after radioisotope injection (later images will have higher SUVs as ^{18}FDG accumulates), the presence of hyperglycemia, method of normalization (use of body surface area or lean body mass), and the method of quantitative measurement.

Compared to structural imaging techniques (X-ray, CT, and MRI), ^{18}FDG-PET may be a more accurate technique for diagnosis, staging, and treatment decisions in oncology. PET imaging can differentiate between benign and malignant lesions (detecting malignancies as small as 6 mm, allowing for the early detection of disease before structural changes become apparent), establish the grade of malignancy (the stage of disease, the existence of recurrent or residual disease, the site of the disease and the primary site of a tumor for biopsy), evaluate a patient's response to therapy, and

can be used for radiotherapy planning in certain types of tumors.[2] Thus, ^{18}FDG-PET holds promise for decreasing the utilization of other diagnostic tests and invasive procedures, and providing more accurate knowledge of the extent of the disease. This information may influence patient management decisions, such as the aggressiveness of planned chemotherapy or radiotherapy, which, in turn may significantly impact patient mortality and quality of life.[3]

Several authors have discussed the sequence of evaluations that can be done in a diagnostic test study.[4,5] These include diagnostic test performance, therapeutic impact and clinical outcome.

The diagnostic performance of a test can be evaluated based on its sensitivity, specificity, accuracy or likelihood ratios (LR). Evaluating a test's performance involves comparing test results against a valid reference or "gold" standard which represents the actual or accepted disease status. Appropriate reference standards can include pathology findings (e.g., histopathological confirmation of the presence or absence of disease) or clinical outcome (e.g., subsequent disease progression or resolution of symptoms and signs).

Therapeutic impact is measured as the change in treatment decision, or decision for additional diagnostic workup, made by clinicians in response to the information provided by the test. The evaluation of outcome assesses if and the degree to which the patients who had the test have better health outcomes. This can be assessed by randomized clinical trials (RCT) of the test and subsequent management resulting from test information. Changes in outcome may also be reasonably inferred from a combination of evidence of improved diagnostic accuracy, evidence of changes in management and evidence of the effective treatment of a given condition. That is, in conjunction with evidence of improved diagnostic accuracy and changes in management, there should be evidence (ideally from RCTs) that alternative treatment or management result in improved long term health outcomes for patients. For example, if a diagnostic test allowed earlier diagnosis of a condition, evidence that earlier treatment is more effective than delayed treatment is needed to infer that improved outcomes result from the diagnostic test result.

^{18}FDG-PET is considered a potentially major advance in clinical practice because it may provide information about the behavior of tumors in addition to the anatomic extent and thus can provide evidence to guide therapeutic choices.[6] The use of ^{18}FDG-PET for the diagnosis of several cancers has been evaluated,[6-9] and it is estimated that applications of ^{18}FDG-PET in oncology may soon account for 80% to 90% of the technology's utilization.[2] In the United States, the Center for Medicaid and Medicare Services (CMS) has determined that there is sufficient evidence to show that

a ^{18}FDG-PET scan is reasonable and necessary for certain indications in the pretreatment and management phase of nonsmall cell lung cancer, esophageal cancer, colorectal cancer, lymphoma, melanoma, breast cancer, head and neck cancers and thyroid cancer.[10] Since the decision by the CMS to cover PET for these cancers, the use of PET scanning has increased anywhere from 80% for esophageal and brain cancer to 128%t for head and neck cancers, based on claims data from 2001-2004 (increases of over 1,000% were recorded for the initial coverage period 1999-2001 for lymphoma).[11] The issue of assessing ^{18}FDG-PET for a range of other cancers currently designated as "coverage with evidence development" remains unaddressed. "Coverage with evidence development" refers to the designation of a ^{18}FDG-PET scan being considered "reasonable and necessary" only when the provider is participating in, and patients are enrolled in a prospective clinical study designed to collect additional information to assist in patient management.[10]

With the exception of CNS neoplasms, PET for oncologic indications has only been in use since about 1995 when the first scanners capable of whole body imaging where introduced. Despite the rapidly expanding evidence for the use of PET,[2] researchers have noted the small number of high-quality ^{18}FDG-PET studies and uncertainty surrounding the possibility of publication bias.[3] There remain many unanswered questions with respect to the diagnostic accuracy of ^{18}FDG-PET for other cancers, the role of ^{18}FDG-PET in grading, restaging and monitoring response to treatment. In addition, because of its putative high cost,[12] ($179.4 million was paid by CMS to providers and facilities for 112,729 PET scans in 2002)[13] it would be beneficial to know the cost-effectiveness of ^{18}FDG-PET in light of the most recent reports of the technology's clinical effectiveness.

Scope of the report

In 2004, the Duke Evidence-based Practice Center (EPC) completed a technology assessment on PET for six cancers: brain, cervical, small cell lung, ovarian, pancreatic and testicular.[14] This technology assessment suggested that PET might be beneficial in helping physicians with clinical questions such as staging and detecting metastatic disease and recurrence. However, the literature had many limitations including the use of older generations of the technology, inclusion of heterogeneous groups of patients without presentation of results by clinically relevant subgroups, absence of data that would allow the reader to infer the information contributed by PET beyond that which was available from conventional studies, and in some cases, lack of a comparator.

The National Oncologic PET Registry (NOPR) was launched in May 2006 in response to the Center for Medicare and Medicaid Services' (CMS) "Coverage with Evidence Development" policy to collect data through a clinical registry to inform the center's ^{18}FDG-PET coverage determination decisions for currently non-covered cancer indications. Since then, NOPR has collected questionnaire data from referring physicians on intended patient management before and after a ^{18}FDG-PET scan. One publication from the NOPR Working Group[15] has reviewed survey data from referring physician regarding changes in treatment decisions before and after ^{18}FDG-PET. The authors found that clinicians report they often change their intended management based on the ^{18}FDG-PET results. ^{18}FDG-PET was associated with a 36.5% change in the treatment or no-treatment decision. One of the limitations of the NOPR database is the fact that the registry does not document whether the physicians actually completed the planned management changes. Therefore the information is based on an intention to treat, and the relative impact of ^{18}FDG-PET on the actual management of patients with cancer has not been assessed. Recently, NOPR has formally asked CMS to reconsider the current National Coverage decision on ^{18}FDG-PET and to end the data collection requirements for diagnosis, staging and restaging. CMS will review the published data and determine the next steps related to reimbursement for ^{18}FDG-PET scans now only covered through the NOPR.

The CMS, through the Agency for Healthcare Research and Quality (AHRQ), have commissioned the University of Alberta/Capital Health Evidence-based Practice Center (U of A EPC) to perform an evaluation of the available scientific evidence on the use of ^{18}FDG-PET for nine different cancers (bladder, brain, cervical, kidney, ovarian, pancreatic, prostate, small cell lung, and

testicular). This technology assessment is focused around four key questions provided to the U of A EPC by AHRQ and CMS.

Structure of the Report

To provide a framework for the report, we first present the key questions and our analytic approach to address them. A general methods section applicable to all the cancers considered in the report is presented. We describe the literature review methods, outline our inclusion and exclusion criteria, the search strategy for identifying articles relevant to the key questions, and the process for abstracting and synthesizing information from eligible studies. We also describe the methods for assessing the methodological quality of individual studies, the data analysis and synthesis.

The results are reported by type of cancer; each section addressing a particular cancer is organized so that it can be considered a stand-alone report. The bibliography of included studies and appendices including the search strings, data extraction and quality assessment forms, and detailed evidence tables for each cancer have been placed at the end of the document.

The following four key questions examine the degree to which current evidence supports confident judgments about the use of ^{18}FDG-PET in the assessment and treatment of nine types of cancer in clinical practice. It encompasses both dedicated PET and newer PET/CT technology that integrates PET and CT into one device.

Q1: ^{18}FDG-PET and ^{18}FDG-PET/CT diagnostic test performance

How does the diagnostic test performance of ^{18}FDG-PET and ^{18}FDG-PET/CT compare to conventional imaging modalities (e.g., CT and MRI) or other diagnostic procedures (e.g., biopsy, serum tumor markers) with respect to the following clinical situations:

1. Diagnosis
2. Staging
3. Restaging
4. Monitoring response to treatment

Q2: Diagnostic thinking impact of ^{18}FDG-PET and ^{18}FDG-PET/CT

What is the magnitude of the impact of ^{18}FDG-PET and ^{18}FDG-PET/CT on physician decision making regarding approaches to diagnosis and management with respect to the following clinical situations:

1. Diagnosis
2. Staging
3. Restaging
4. Monitoring response to treatment

Q3: ^{18}FDG-PET and ^{18}FDG-PET/CT as part of a management strategy

What is the impact of ^{18}FDG-PET and ^{18}FDG-PET/CT as part of a management strategy to improve patient-centered outcomes? What is the ability of ^{18}FDG-PET and ^{18}FDG-PET/CT to improve patient-centered outcomes when used as a diagnostic test to identify patients suitable for a particular treatment?

Q4: Cost-effectiveness of ^{18}FDG-PET and ^{18}FDG-PET/CT

What is the cost-effectiveness of ^{18}FDG-PET and ^{18}FDG-PET/CT with respect to the following clinical situations:

1. Diagnosis
2. Staging
3. Restaging
4. Monitoring response to treatment

The six-tiered efficacy model of technology assessment introduced by Fryback and Thornbury[16] was used as a framework to quantify the level of evidence available to address the questions of this report (Table 1). This report focuses on all evidence between hierarchies 2 and 6 (excluding technical imaging quality data).

Table 1. Hierarchy of Diagnostic Efficacy

Level of evidence	Description
Level 1: Technical	Resolution of line pairs Modulation transfer function change Gray-scale range Amounts of mottle Sharpness Computerized imaging parameters
Level 2: Diagnostic accuracy efficacy	Yield of abnormal or normal diagnoses in a case series Diagnostic accuracy (percentage of correct diagnoses in case series) Sensitivity, specificity, and positive/negative predictive value in a defined clinical problem setting Measures of area under the receiver operating characteristic (ROC) curve
Level 3: Diagnostic thinking efficacy	Number (percentage) of cases in a series in which image was judged "helpful" for making the diagnosis Entropy change in differential diagnosis probability distribution Difference in clinicians' subjectively estimated diagnosis probabilities before and after test information
Level 4: Therapeutic efficacy	Number (percentage) of times image was judged "helpful" in planning patient care in a case series Percentage of times medical or surgical procedure avoided due to image information Number or percentage of times planned therapy pretest changed after the image information was obtained (retrospectively inferred from clinical records) Number or percentage of times clinicians' prospectively stated therapeutic choices changed after test information
Level 5: Patient outcome efficacy	Percentage of patients improved with test vs. without test Morbidity (or procedures) avoided after having image information Change in quality-adjusted life expectancy Expected value of test information in quality-adjusted life years (QALYs) Cost per QALY saved with image information Patient utility assessment (e.g., Markov modeling, time trade-off)
Level 6: Societal efficacy	Benefit-cost analysis from societal viewpoint Cost-effectiveness analysis from societal viewpoint

Chapter 2. Methods

Overview

In this chapter, we document a prospectively designed protocol that the University of Alberta EPC used for this technology assessment report on the use of ^{18}FDG-PET and ^{18}FDG-PET/CT for nine cancers.

To accomplish the tasks as directed, a core research team composed of clinical investigators and methodologists was assembled. The core research team was trained and experienced in systematic review methodology or critical appraisal of the scientific literature in diagnostic tests.

In this chapter, we describe the technology assessment methods. We outline our inclusion and exclusion criteria, the study selection process for identifying relevant articles, and the process for abstracting information from eligible studies. Finally, we describe the methods for assessing the methodological quality of individual studies, the analysis and synthesis of the results.

Literature Search and Retrieval

Comprehensive searches of four biomedical electronic databases listed in Table 2 were conducted for the time periods specified. All search strategies were developed by a research librarian with input from the project team. The search strategy was comprised of both controlled vocabulary and keywords. Separate searches were done for each cancer. The search was not restricted by language and articles were retrieved from 2002 to the present. No study design filters were used since the research questions could be answered by a large variety of study types. See Appendix A for detailed search strings.

Table 2. Databases Searched for Relevant Studies

Database	Years/issues	Date of search
MEDLINE®	2003 - 2008	12 March, 2008
EMBASE	2003 - 2008	12 March, 2008
CENTRAL (Cochrane Central Register of Controlled Trials, NHS Economic Evaluation Database)	1st Quarter 2008	20 March, 2008
Scopus	2003-2008	19 March, 2008

Criteria for Selection of Studies

A set of inclusion and exclusion criteria was used to determine eligibility of studies for the technology assessment (Table 3). Briefly, eligible studies were published in English and evaluated the use of ^{18}FDG-PET or ^{18}FDG-PET/CT in a sample of more than 12 adult participants (older than 16 years of age) with primary cancer of the following type: bladder, brain, cervical, kidney, ovarian, pancreatic, prostate, small-cell lung, and testicular. Restrictions in terms of study design were not imposed and both prospective and retrospective studies were included.

Studies must have reported numeric data on at least one objective outcome of interest for the key questions of the technology assessment. For studies on the diagnostic performance of ^{18}FDG-PET and ^{18}FDG-PET/CT (Q1), the outcomes of interest were: sensitivity, specificity, positive and negative predictive values, and LR. Other outcomes that were examined for Q2, Q3 and Q4 included:

- additional diagnostic test work-up;
- treatment decisions and management strategy;
- changes in therapy;
- patient-centered outcomes (e.g., survival; quality of life, prognostic indicators, time until recurrence); and
- economic outcomes.

Table 3. Inclusion Criteria

Category	Criteria
Source	• English language studies reporting original research from 2003 to March 2008; • Study not duplicated or superseded by later study with the same purpose from the same institution
Population	• Studies ≥12 human participants; • The study provides separate data for a population consisting of adults (>16 years) with primary cancer of the following type: bladder, brain, cervical, kidney, ovarian, pancreatic, prostate, small-cell lung, and testicular
Test	• Studies of PET or PET/CT using ^{18}FDG as radioisotope tracer
Comparator	• ^{18}FDG-PET or ^{18}FDG-PET/CT should be compared to a reference standard (e.g., MRI, CT, biopsy/histology, X rays, ultrasound, PET with other radioisotope tracer, clinical followup) (Matched design)
Study design	• Both prospective and retrospective studies
Outcomes of interest	• Study should provide numeric data for the outcomes of interest in the review

CT=computer tomography; ^{18}FDG= fluorodeoxyglucose; MRI=magnetic resonance imaging; PET=positron emission tomography

Study Selection Process

Screening of titles and abstracts

Four reviewers evaluated the title and abstract of each study to select references potentially relevant to the topics of the report (Appendix B). The full-text of studies meeting the criteria was retrieved as was the full-text of those that reported insufficient information to determine eligibility.

Identification of studies eligible for the report

Two independent reviewers appraised the full-text of potentially relevant articles using a standard form (Appendix B). Disagreements about the inclusion or exclusion of studies were resolved by consensus among reviewers.

Evaluating the Methodological Quality of Studies and Grading the Evidence

The methodological quality of studies that assessed the diagnostic performance (Q1) and the diagnostic thinking impact (Q2) of ^{18}FDG-PET and ^{18}FDG-PET/CT was assessed using the Scottish Intercollegiate Guidelines Network (SIGN) assessment tool for diagnostic studies,[17] which is based on the Quality Assessment of Studies of Diagnostic Accuracy (QUADAS) tool.[18] Studies assessing the impact of ^{18}FDG-PET and ^{18}FDG-PET/CT as part of a management strategy to improve patient-centered outcomes (Q3) are different from diagnostic performance studies and they would be more akin to standard effectiveness studies (e.g., clinical trials, observational analytical cohort studies). Therefore, an individual components approach that considered important aspects of design, conduct, and reporting of effectiveness studies was used to assess the methodological quality of Q3 studies. Finally, the methodological quality of economic evaluations of ^{18}FDG-PET and ^{18}FDG-PET/CT was assessed using the Consensus on Health Economic Criteria (CHEC).[11] See Appendix B for the quality assessment instruments used in this technology report.

Evidence from the selected studies was graded using a system adopted by the Veterans Affairs Technology Assessment Program (VATAP) to classify the level of evidence regarding the clinical utility of studies on PET (Table 4).

Table 4. Grading Scheme for Diagnostic Studies

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

Adapted from Robert *et al* 1999[1]

Two reviewers assessed the methodological quality of studies independently. Disagreements were resolved by consensus or, when no consensus could be reached, a senior methodologist adjudicated.

Data Collection

Information regarding the study design and methods, characteristics of participants, PET and comparison tests, and outcomes of interest were extracted using a pretested data extraction form that was adapted to each of the four key questions (Appendix B).

General data relevant to the review was collected on a general data extraction form. General data collection included information on the country, year and type of publication, study design, setting, duration of the study, and number of participating centers. Data on characteristics of study participants included type of primary cancer, how participants were enrolled, inclusion and exclusion criteria, demographic characteristics, and stage or severity of their condition.

Data on characteristics of ^{18}FDG-PET and ^{18}FDG-PET/CT included a description of the purpose of their use within the study, technical details of the devices and administration procedures, and characteristics of the reference tests. Likewise, information on the criteria for interpretation was extracted. Specific forms were used to collect data for each of the four key questions of the report. Finally, information on study conclusions was collected as reported by the authors of the primary studies. Data from the primary studies were extracted by one reviewer and then independently verified for accuracy and completeness by a second reviewer. Any discrepancies in data extraction were resolved by consensus between the data extractor and the data verifier. Study selection, methodological quality assessment, and data extraction were managed with Microsoft Excel™

(Microsoft Corporation, Redmond, WA). Extraction of data from graphs was performed using Corel Draw®, version 9.0 (Vector Capital, San Francisco, CA).

Evidence Synthesis

Characteristics of the included studies were summarized using descriptive statistics (i.e., proportions and percentages for categorical data, means with standard deviations [SD], or medians with interquartile ranges [IQR], for continuous data).

Data were analyzed qualitatively. Evidence tables were constructed to report information on each article's source, study design, study population, characteristics of ^{18}FDG-PET and ^{18}FDG-PET/CT and reference tests, and outcomes. The evidence tables also included summaries of study quality and comments to help interpret the outcomes. Data were combined by type of cancer to provide summary information across studies for each of the key questions, if appropriate.

For each of the four key questions, the following study characteristics were summarized and discussed:

a. Inclusion criteria of studies (patients and disease characteristics)
b. PET technology used (^{18}FDG-PET alone, ^{18}FDG-PET/CT etc.) and comparator
c. Tests used prior to, concurrent with or after the PET scanning and whether the studies indicate the information contributed by PET beyond that provided by other tests
d. Overall quality of the body of evidence
e. The generalizability of the summarized evidence to the Medicare population (aged >65)
f. The generalizability of the summarized evidence to other cancers
g. Homogeneity of SUVs with respect to ^{18}FDG dose, timing of study, and scanner variability.

For the question related to ^{18}FDG-PET and ^{18}FDG-PET/CT diagnostic test performance, 2x2 tables (or 2 x 1 if only reference standard positive or reference standard negative subjects were included) were constructed for each comparison test or combination of tests within the individual studies. Sensitivity and specificity were calculated for each study using standard formulas. Results were graphed in forest plots for visual analysis, but not pooled statistically due to the different diagnostic thresholds of the various studies. Results were grouped when two or more studies assessed the same type of ^{18}FDG-PET (i.e., ^{18}FDG-PET or ^{18}FDG-PET/CT) for similar purposes (e.g., primary diagnosis, staging, restaging, recurrences), had similar study design (i.e. prospective or

retrospective), and had usable data for common outcomes of interest. Studies using different methods to confirm the final diagnosis were considered for grouping, but results were also presented separately by type of reference standard.

Summary estimates of the LR, both positive and negative were meta-analyzed using the DerSimonian and Laird random effects method.[19] The LRs are a measure of the performance of diagnostic tests, expressing the magnitude by which the odds of a diagnosis in a given patient is modified by the result of a test.[20] For example if an individual has probability of disease of 0.1 prior to taking a test (odds = 0.09) and the test has a positive LR of 4 and a negative LR of 0.2, the patients post test odds of having the disease would be 4*0.09 = 0.36 (probability = 0.27) if the test was positive and 0.2*0.09 = 0.02 (probability = 0.02) if the test was negative. A test with a higher positive LR and lower negative LR is considered a better test. Where studies presented more than one estimate of test performance for the same test, for example at different cut-off points or for different patient subgroups, we only included one estimate in the pooled analysis. We aimed to select the data set most similar to the estimates provided by the other studies in terms of patient population.

Homogeneity tests were carried out to evaluate the consistency of findings across the studies. We used the quantity I^2 to determine the percentage of total variation in the LR across the studies due to heterogeneity rather than to chance.[21] A value of 0% indicates no observed heterogeneity. Low, moderate, and high heterogeneity was assigned to I^2 values of 25%, 50%, and 75%, respectively,[21] with larger values increasing heterogeneity. Possible reasons for heterogeneity, such as patient characteristics and the nature of the reference method (biopsy/histology, clinical follow-up or a composite reference standard) were explored. Data on diagnostic performance were also synthesized using the summary receiver operating characteristic (SROC) approach.[22] All analyses were performed using RevMan software version 5.0 (Cochrane Collaboration, Oxford, UK).

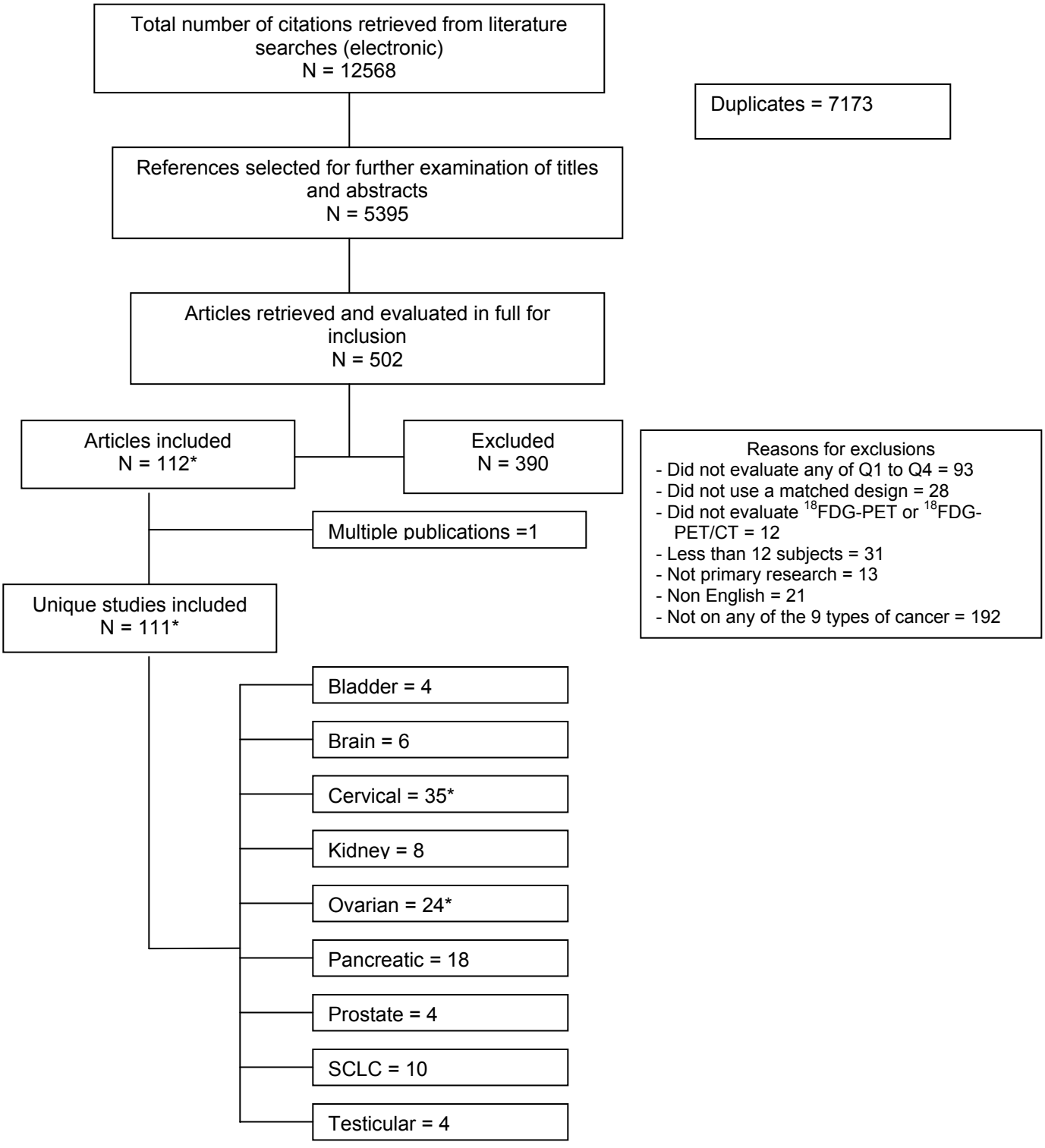
Chapter 3. Results

Search Results

Overall, the literature search (electronic and reference lists) resulted in the identification of 12,568 citations. After screening titles and abstracts (5,395 citations), the full-texts of 502 potentially relevant articles were retrieved and evaluated for inclusion. The application of the selection criteria to the 502 articles resulted in 390 articles being excluded, while 112 studies were relevant to the questions addressed in this review. Figure 1 outlines study retrieval and selection.

The primary reasons for exclusion of studies were as follows: (1) the study did not report on any of the nine types of cancer (n = 192), (2) the study did not evaluate the questions of interest (n = 93), (3) the study reported on less than 12 participants (n = 31), (4) the study did not use a matched design (n = 28), (5) the study did not evaluate ^{18}FDG-PET or ^{18}FDG-PET/CT (n = 12), (6) the study was not primary research (n = 13), and (7) the study was published in a language other than English (n=21) (Appendix C).

Figure 1. Flow Diagram for Study Retrieval and Selection for the Technology Report



*One study provided data for both cervical and ovarian cancer

1. Bladder Cancer

1.1. Background

Approximately five to 10% of all malignancies in men are bladder cancer. Throughout the United States and Europe it is the fourth most common cancer diagnosed.[131] It is also the most common cancer of the urinary tract.[132] Men are diagnosed with bladder cancer three to four times more frequently than women.[131] It is estimated that 68,810 new cases of bladder cancer will be diagnosed in the United States in 2008. Of these cases: 51,230 will be men and 17,580 will be women. Furthermore, approximately 14,100 deaths will occur as a result of this malignancy: 9,950 men and 4,150 women.[133] African Americans are at the half risk of Caucasian Americans in developing bladder cancer, but African Americans have a poorer overall survival.[131] Bladder cancer tends to present in an older age group, with the median age of diagnosis at 73 years of age.[133]

Bladder cancer is a heterogeneous disease and its natural history varies.[131] At one end of the spectrum bladder cancer may be of low-grade with slow progression, where on the other end it may be high-grade, highly malignant with significant progression and result in death.[131] The most frequently diagnosed form of bladder cancer (approximately 75%) is superficial disease contained in the mucosal and submucosal layers. The remaining patients are diagnosed with muscle-invasive disease, which extends outside the bladder. Bladder cancer patients have shown a 5-year cause-specific survival of more than 95%; however, recurrence occurs in more than 50% of patients and up to 20% develop invasive or metastatic disease.[134]

Several risk factors are known for the development of bladder cancer, of which smoking is the most well-established. Chemicals used in some industries account for up to 20% of bladder cancer and is considered the second most important risk factor. A patient's medical history may also increase their risk. Chronic urinary track infection, previous chemo or radiotherapy treatment and schistosomiasis are likely to elevate risk. Nulliparous women are at greater risk than women who have given birth. Familial bladder cancer is possible, but rare.[131]

The most frequent warning sign is painless hematuria, which occurs in 85% of patients. Microscopic hematuria may also be present and should be screened for in high-risk patients over the age of 50. Bladder irritability, urinary frequency, urgency and dysuria are common. Patients with advanced disease may experience weight loss and abdominal or bone pain.[131]

In order to plan appropriate patient care, accurate staging must be completed.[131] Bladder cancer

is staged using the TNMS (tumor, node, metastasis staging) system, approved by the Union International Contre le Cancer (UICC) in 2002 (Table 5). Tumors identified as Ta are considered noninvasive papillary carcinoma, whereas Tis refers to carcinoma in situ.[132] Any involvement in the lymph nodes is taken into consideration when staging bladder cancer as is distant metastasis.

Table 5: Bladder Cancer Stages

Stage	Description
T1	• subepithelial connective tissue invaded, not muscularis propria[131] • diagnosis difficult, variable prognosis[132]
T2a	• <50% of the depth of muscularis propria invaded[131]
T2b	• >50% of the depth of muscularis propria invaded[131]
T3a	• perivesical tissue invaded (microscopic)[132]
T3b	• perivesical tissue invaded (macroscopic)[132]
T4a	• tumor expansion to prostrate, uterus and vagina[132]
T4b	• tumor expansion to pelvic wall, abdominal wall[132]

Early detection of cancer can help improve survival, which is the main goal of screening. Usually only patients at elevated risk are screened on a regular basis. Ideal screening methods are noninvasive, inexpensive and are highly sensitive and accurate. Tests used to identify bladder cancer include hematuria testing, cystoscopy, bladder imaging, urine cytology and bladder tumor markers.[131] Diagnosis frequently depends on cystoscopic and histologic evaluation of resected tissue.[132] A high rate of incorrectly classified high-grade Ta tumors (grade 3 tumors or higher) has been noted.[135]

The standard method of detection of bladder cancer is cystoscopy. Cystoscopy effectively identifies most superficial disease; however, it is not always successful at detecting small or flat lesions. Additionally, cytoscopy is an invasive procedure. The use of a flexible fiberoscopy is preferred as it is less invasive and provides a clear picture of the bladder interior. Fluorescence endoscopy may also be used for viewing the intravesical area and is reported to have high sensitivity and reasonable specificity, especially for the small or flat lesions frequently missed by conventional cystoscopy.[134] Intravenous urography detects large tumors in the bladder, the upper urinary tract and defects in the kidney. It is unclear if this method of screening is useful as the detection of significant findings is low.[132] Often a combination of methods are required for an accurate diagnosis of small or flat lesions.[135]

Urine cytology is considered a good screening method for high-grade cancers.[131] Sensitivity and specificity are both greater than 90%, but it frequently does not detect low-grade papillary tumors. A positive result from urinary cytology indicates a tumor is present in the urinary tract, but does not

pinpoint where.[132] Cytology is inexpensive and minimally inconvenient to the patient.[131] There is uncertainty about whether cytology should be performed from a voided urine sample or from a bladder wash sample. Histology from the bladder biopsy is used to make the final diagnosis.[135]

For the purpose of detecting recurrent tumors in the pelvis, distinguishing local recurrent disease from postsurgical or postirradation fibrosis or necrosis and identifying metastases ^{18}FDG-PET can be useful. However, it is unlikely that PET can contribute to the management of low-grade or noninvasive tumors due to the excretion of ^{18}FDG by the kidneys and interference with imaging techniques by streak artifacts. Researchers have attempted to limit the amount of ^{18}FDG released in bladder. Thus far, work done with PET in bladder cancer is limited.

The first treatment for superficial bladder cancer is transurethral resection (TUR) of the tumor.[134] Establishing the correct diagnosis and removing all visible lesions is the aim of TUR. Small tumors may be resected together, while larger tumors need to be resected individually. Frequently bladder tumors are multifocal and therefore there is a risk that tumors may remain after initial TUR. Additionally, tumors may be understaged.[132] A second TUR reduces understaging and the risk of residual disease.[135] Recurrence and progression free survival may be improved by a second TUR.[132] Followup treatment for TUR is intravesical chemotherapy and it reduces the risk of reoccurrence. Efficacy of chemotherapy agents appears to be similar. In the case of muscle invasive cancer, radical cystectomy is performed. Immunotherapy with Bacillus Clamette-Guérin (BCG) is frequently used after TUR when the disease is confined to the mucosa or submocosa. While the exact mechanism of action is unknown, BCG forms a standard component of treatment for carcinoma in situ. The aim is to eradicate and prevent recurrence of superficial bladder cancer.[134]

1.2. Importance of Key Questions in the Clinical Management of Bladder Cancer

The most important factors in survival from bladder cancer are the stage and the tumor histological grade at diagnosis. Prognosis of bladder cancer is highly dependent on the depth of tumor penetration into the bladder wall. Errors in clinical staging are more likely as the tumor becomes more invasive. Problematic areas for diagnosis and staging of bladder cancer include determination of deep bladder wall invasion and presence of lymph-node metastases. Therefore, accurate staging is pivotal in optimal therapy planning and in avoiding radical surgery in bladder cancer patients. Some standard imaging methods (e.g., abdominal ultrasonography, CT and MRI) may not provide an accurate basis for therapeutic decisions. For example, tumor involvement is not

necessarily detected by changes in the shape or texture of an affected lymph node through CT and MRI. The clinical interpretation of very small lymph nodes on CT and MRI is also problematic as the presence of enlarged regional lymph nodes are not always indicative of metastasis but rather may be reactive to certain procedures such as transurethral biopsy. Procedures such as CT-guided fine-needle aspiration biopsy can increase the overall staging accuracy but they are subject to sampling errors. ^{18}FDG-PET can be a valuable test for the diagnosis of bladder cancer; however, the evidence about the accuracy and impact of ^{18}FDG-PET on therapeutic decisions and outcomes for bladder cancer patients is scarce. This is partly due to difficulties at interpreting the ^{18}FDG-PET images in the pelvis because ^{18}FDG is excreted by the kidneys and accumulated in ureters and the urinary bladder.

1.3. Results

Three studies[23-25] provided evidence on the use of ^{18}FDG-PET or ^{18}FDG-PET/CT for bladder cancer. All the three studies[23-25] evaluated the diagnostic accuracy of ^{18}FDG-PET or ^{18}FDG-PET/CT, and one study[24] reported on the diagnostic thinking impact. None of the studies evaluated the effects of ^{18}FDG-PET or ^{18}FDG-PET/CT as part of a management strategy on patient-centered outcomes. No economic evaluations on the use of ^{18}FDG-PET or ^{18}FDG-PET/CT for bladder cancer were identified. Characteristics of the populations, conditions of ^{18}FDG-PET administration, interpretation of results and methodological quality of the studies are summarized in appendices D to J.

1.3.1. Diagnostic accuracy of ^{18}FDG-PET and ^{18}FDG-PET/CT in bladder cancer

Characteristics of the studies

Three studies (two prospective,[23,25] one retrospective[24]) evaluated the diagnostic accuracy of ^{18}FDG-PET[23-25] and ^{18}FDG-PET/CT[24] on bladder cancer. Two studies used ^{18}FDG-PET for initial staging[23,25] and one used ^{18}FDG-PET/CT for both staging and restaging purposes.[24]

The studies contained a total of 136 patients with sample sizes ranging from 35 to 55. The participant ages ranged from 33 to 86 years. One study reported the distribution by stage of cancer: Clinical stage (CS) I = 16%, CS II = 47%, CS III = 31% and CS IV = 6%.[23] ^{18}FDG-PET was compared to a reference standard that varied across the studies. In two studies the reference standard was either histology/biopsy or clinical follow-up.[23,24] One study established the final diagnosis of all

patients using histology/biopsy.[25] One study reported the mean time between last treatment and ^{18}FDG-PET as 37 days.[23] Two studies used a fixed dose of ^{18}FDG (15 MCi[25] and 555 MBq[24]); one study used a weight based dose (6.5 MBq/kg).[23] The time between injection and PET scan was 60 minutes[23,24] and 20 minutes.[25] Patients fasted for six hours.[23,24] Two studies[23,24] measured glucose levels before administration of ^{18}FDG-PET; the maximum glucose level that was allowed was 120 mg/dL. Methods of interpretation of the images were qualitative in one study[23] and both qualitative and quantitative in a second.[24] Scans were interpreted qualitatively using visual analysis.[23,24] One study[24] reported using SUV but the criterion for abnormality was not reported.

Comparisons

Comparisons for which data were considered for meta-analysis are summarized in Table 6. Pooled data were obtained to evaluate the accuracy of ^{18}FDG-PET for the staging of bladder cancer. Individual study data are summarized in Appendix D.

Table 6. Summary of comparisons considered for meta-analyses of the accuracy of ^{18}FDG-PET for bladder cancer

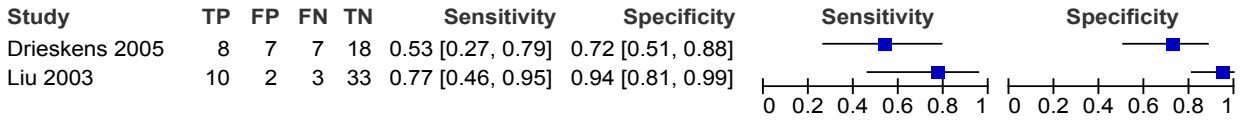
Indication	Studies	Design	Type of PET	Reference standard	Meta-analysis
Staging	Drieskens 2005[23]	P	FDG-PET	Histology/biopsy or clinical followup	1. FDG-PET vs. any reference standard (P studies) [23,25]
	Liu 2003[25]	P	FDG-PET	Histology/biopsy	
Staging and restaging	Jadvar 2008[24]	R	FDG-PET and FDG-PET/CT	Histology/biopsy or clinical followup	No

CT=computer tomography; FDG= fluorodeoxyglucose; P = prospective; PET=positron emission tomography; R = retrospective; vs.=versus

1. ^{18}FDG-PET for the staging of bladder cancer

Reference standard: any; prospective studies. Two prospective studies[23,25] totaling 88 participants provided data for a meta-analysis of the accuracy of ^{18}FDG-PET compared to any reference standard for the staging of bladder cancer. Individual 2x2 table results are presented in Figure 2. Sensitivity values in individual studies were 53%[23] and 77%.[25] Specificity values were 72%[23] and 94%.[25]

Figure 2. Results from 2x2 tables of individual prospective studies of 18FDG-PET versus any reference standard for the staging of bladder cancer



We found that ^{18}FDG-PET had a pooled positive LR of 4.68 (95% confidence interval [CI] 0.65, 33.90) and a pooled negative LR of 0.43 (95% CI = 0.15, 1.19) to accurately detect the stage of bladder cancer (Figures 3 and 4). Both the positive and negative LRs were not statistically significant, as the 95% CIs includes 1 and therefore, ^{18}FDG-PET does not seem to be helpful in identifying the stage of the disease. There was considerable heterogeneity in the positive ($p = 0.01$; $I^2 = 84$ percent) and negative ($p = 0.07$, $I^2 = 69$ percent) LRs across the studies. Liu[25] reported statistically significant results for both the positive and negative LRs whereas results in Drieskens[23] were not statistically significant. It is hard to draw definite conclusions based on the results of two small studies that provide heterogeneous results for the pooled estimates of the accuracy of ^{18}FDG-PET to identify the stage of bladder cancer.

Figure 3. Meta-analysis of the positive LR of ^{18}FDG-PET versus any reference standard for the staging of bladder cancer (prospective studies)

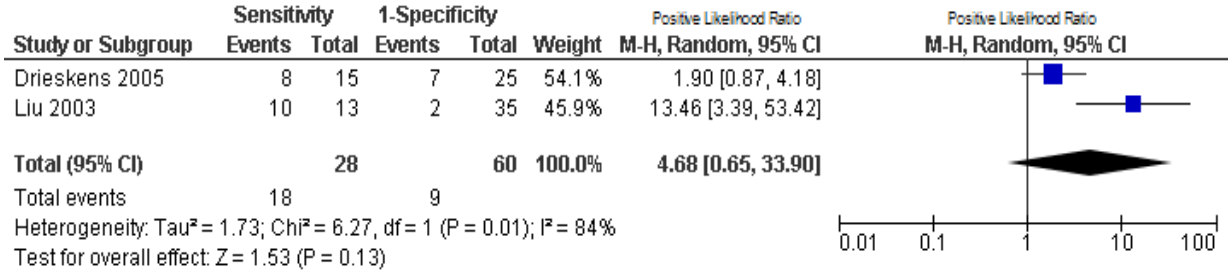


Figure 4. Meta-analysis of the negative LR of ^{18}FDG-PET versus any reference standard for the staging of bladder cancer (prospective studies)

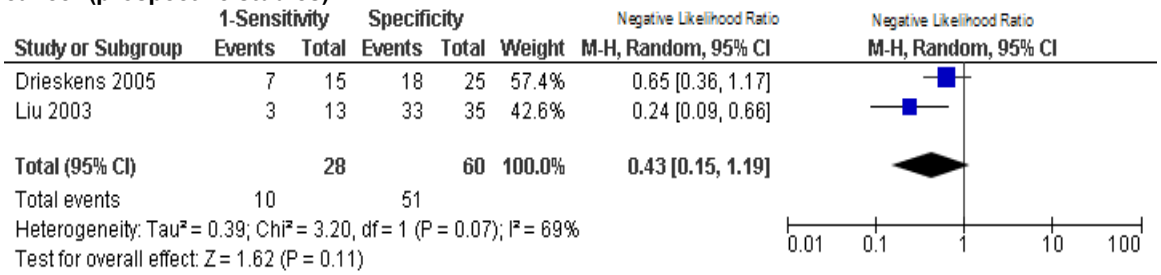
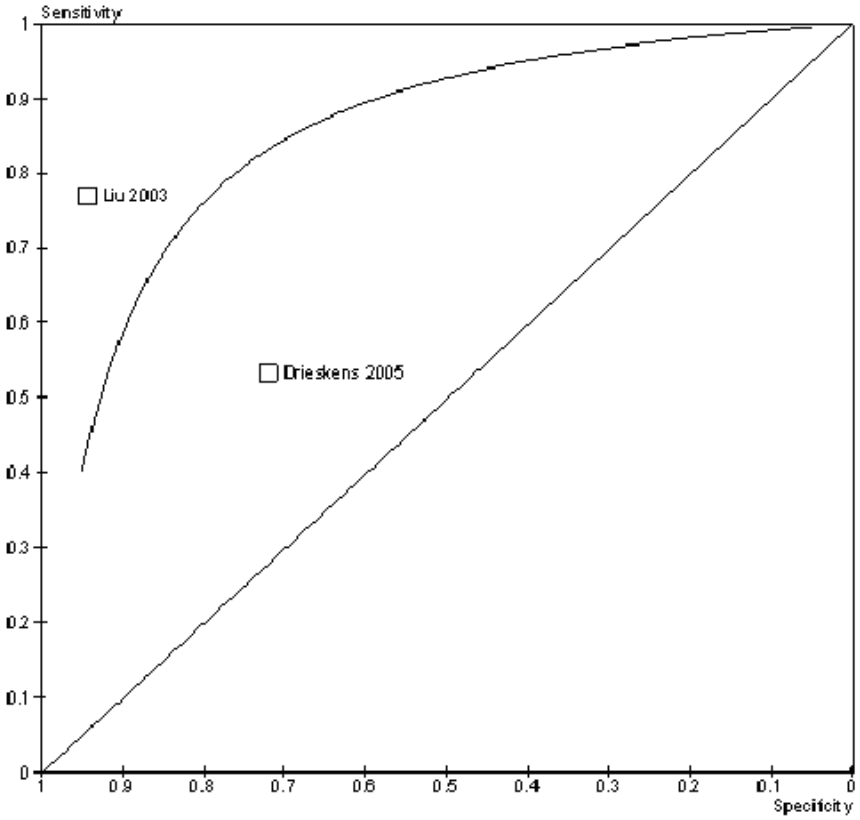


Figure 5 shows the estimates of sensitivity and 1-specificity plotted in ROC space for ^{18}FDG-PET versus any reference standard to identify the stage of bladder cancer.

Figure 5. Summary ROC plot of ^{18}FDG-PET versus any reference standard for the staging of bladder cancer (prospective studies)



Summary of the results

A meta-analysis was calculated to evaluate the accuracy of ^{18}FDG-PET to identify the stage of bladder cancer. The pooled LRs were not statistically significant and therefore, ^{18}FDG-PET does not seem to be helpful for detecting the stage of the disease (Table 7). Heterogeneity across the studies was significant, precluding us from making strong inferences from the pooled overall results.

Table 7. Results of meta-analysis of the accuracy of ^{18}FDG-PET for bladder cancer

PET Purpose	Type	Design	Reference standard	Studies	N	Effect estimate M-H, Random, 95% CI
Staging	FDG-PET	P	Any reference standard	2	88	PLR=4.88 [0.65, 33.90]
						NLR=0.43 [0.15, 1.19]

95% CI=95% confidence interval; FDG= fluorodeoxyglucose; M-H = Mantel Hantzel; NLR=negative likelihood ratio; P=prospective; PET=positron emission tomography; PLR=positive likelihood ratio

1.3.2. Diagnostic thinking impact of ^{18}FDG-PET and ^{18}FDG-PET/CT on physician decision making with respect to diagnosis and management strategy for patients with bladder cancer

One study evaluated the diagnostic thinking impact of ^{18}FDG-PET on the treatment of bladder cancer. A retrospective study by Jadvar *et al*[24] evaluated the influence of ^{18}FDG-PET and ^{18}FDG-PET/CT on the management of patients who had been previously treated for transitional cell carcinoma and who were under evaluation for staging and restaging. Both ^{18}FDG-PET and ^{18}PET/CT were used in this study; however the results were not separated by the mode of imaging used. The population enrolled was of moderate size (N=35) and encompassed a wide age range (39-86 yrs). The subjects were predominately male (71%), nondiabetic, with a history of bladder transitional cell carcinoma at initial stages (B2 and C). ^{18}FDG-PET was performed in 17 patients and ^{18}FDG-PET/CT in 18 patients, but mixed results were presented from the two devices.

The diagnostic thinking impact of ^{18}FDG-PET was reported as changes in the clinical management of patients. Overall, 17% of the patients in the study had their treatment course altered as a result of the ^{18}FDG-PET imaging analysis five patients underwent additional courses of chemotherapy, and one patient was under a regime of observation. While the remaining 29 patients did not have their care significantly altered by ^{18}FDG-PET, the authors noted that there was more precise localization of hypermetabolic disease. The authors concluded that combined ^{18}FDG-PET and CT diagnostic information was useful in detecting, localizing and characterizing the extent of metastatic disease.

Overall, the quality of the study was graded as moderate using the SIGN Methodology Checklist tool. As the study was retrospective, it received a C for the grade of evidence (several methods flaws). Significant issues with the quality of this study included the unblinded interpretation of the ^{18}FDG-PET and the use of multiple modalities to verify the presence of disease (e.g. histology, serial imaging). Additionally, the selection criteria for the patients included in this retrospective analysis was not specified, raising the possibility of selection bias. Finally, as there was no clearly defined time period between the ^{18}FDG-PET and the reference standard, disease progression may have occurred between the assessment of the ^{18}FDG-PET and the final designation of disease status.

Because of the relatively small number of patients included in the Jadvar *et al*[24] study, further studies are necessary to assess the role of ^{18}FDG-PET/CT to make clinical management decisions for bladder cancer patients. Table 8 provides a summary of the main findings and the types of bias that

affected the evidence on the diagnostic thinking impact of ^{18}FDG-PET and ^{18}FDG-PET/CT on bladder cancer

Table 8. Main findings and types of bias that affected the evidence on the diagnostic thinking impact of ^{18}FDG-PET and ^{18}FDG-PET/CT for bladder cancer

Study	Results of FDG-PET imaging on Patient Diagnosis and Treatment	Types of Bias
Jadvar H, 2008[24]	**Management decision:** Treatment	Selection Bias (unclear) Disease progression bias (unclear)
Study type: Retrospective	Changes in clinical management after PET/CT: 6 / 35 (17%): Additional chemotherapy: n=5 Wait-and-watch regiment: n=1	Verification Bias (+1 RS) Review Bias (PET, unblinded; RS unclear if blinded)

CT = computer tomography; FDG = fluorodeoxyglucose F18; PET = positron emission tomography; RS = reference standard

2. Brain Cancer

2.1. Background

An estimated 21,810 new cases of brain cancer will be diagnosed in the US in 2008 and 13,070 patients will die from the disease.[133] Primary brain tumors represent a small number of all primary malignant cancers diagnosed, approximately 1.35%. Brain cancer as a result of metastases is more common.[136] Brain cancer incidence has increased over time; however, this is largely due to improvements in diagnostic tools, health care, changes in the treatment of elderly patients and changes to the classification of brain tumors.[137] The incidence of brain cancer between 2001 and 2005 was 6.0/100,000[133] in the United States. Caucasians experience certain types of brain tumors (glioma and germ cell tumors) twice as often as African-Americans. In the United States, incidence rates vary from 9.6/100,000 in Virginia to 21.9/100,000 in Colorado. The high rates of brain cancer detected may be linked to greater access to health care and better health care.[137]

Malignant brain tumors encompass a wide range of neoplasms.[136] Patients who are diagnosed with glioblastoma tumors tend to have the shortest survival time of brain cancer patients (less than one third of patients survive one year) as do older patients.[137] The median age for diagnosis of brain cancer is 56 years, while the median age at death is 64 years.[133] According to numbers recorded between 1998 and 2003, 37.7% of patients diagnosed with a primary malignant brain tumor survived for 2 years and 30.2% survived for 5 years.[137] Primary brain malignancies tend to remain local and rarely spread outside the central nervous system.[136]

Many risk factors are suspected to cause brain cancer, but few are confirmed. Cellular phones showed no evidence of association with brain tumors when first investigated; however, recent studies suggest a link between long-term use and gliomas is possible. Other suspicions include: head injury and trauma; dietary intake of calcium, N-nitroso compound and antioxidants; smoking; alcohol consumption and exposure to electromagnetic fields. Women have been shown to experience lower rates of glioma, which may be associated to menarche and childbirth. These lower rates appear to wane after menopause. Evidence has demonstrated a reduced risk of glioma and glioblastoma in patients with allergies, autoimmune diseases and a history of infections such as varicella-zoster virus. A genetic link is also possible.[137]

Brain tumors may present differently depending on the location of the lesion, rate of growth and

histology.[136] In the initial stages of the disease most symptoms are focal. As tumor size increases, more generalized symptoms occur.[138] Approximately 50% of patients will present with headache,[136] which can last for six months or more. Increased intracranial pressure may cause nausea and vomiting and in patients with low-grade gliomas, seizures are common.[136] Cognitive dysfunction may also occur, which is demonstrated by changes in memory, attention, language use and personality.[138]

Patient prognosis is linked to a number of factors, as are treatment strategies.[137] Increased survival is associated with patient age less than 60, presence of seizures, frontal lobe tumors, low-grade tumors, no tumor necrosis, limited tumor activity, performance scores greater than 70 and total or near-total resection. The World Health Organization (WHO) classifies brain tumors according to type of cell and histological appearance.[138] The major histological groups are: neuroepithelial tissue or gliomas, tumor of meninges, germ cell tumors and tumors of sellar regions.[137] More than 80% of primary brain tumors are gliomas, tumors of the meninges make up much of the rest.[138]

Diagnosis starts with a complete medical history, physical examination and a careful neurological assessment.[136] In addition, funduscopy and a focused neurologic examination should be performed. Appropriate brain imaging is required followed by histopathology to confirm diagnosis.[138]

MRI is preferred for the initial screening of brain tumors. It produces higher resolution images and can access more areas of the brain than CT scan and is used for neurosurgical planning and risk assessment.[138] To distinguish infiltrative brain tumors from nonneoplastic conditions, high-grade from low-grade tumors, and primary tumors from metastastic tumors, magnetic resonance spectroscopy (MRS) may be used.[136]

Biochemical and metabolic information about tumors and the brain can be determined by MRS. ^{18}FDG-PET provides a noninvasive method to diagnose and grade gliomas and differentiate between tumor recurrence and radiation necrosis. It can also predict tumor response to chemotherapy compared to radiochemotherapy.[138] The diagnostic standard is still tissue biopsy. More recently developed stereotactic biopsy techniques are minimally invasive, with decreased morbidity and mortality relative to traditional neurosurgery. Stereotactic biopsy should be obtained to help confirm diagnosis of low-grade gliomas. MRI, MRS and ^{18}FDG-PET assist in tumor localization for biopsy. Testing for biomarkers may also assist in diagnosis, treatment planning and predicting prognosis.[136]

If it is possible to perform a complete resection, surgery is the treatment of choice;[138] there are no clear guidelines on degree or timing of the resection.[136] The decision is based on tumor location, extent, histopathology and comorbid conditions. In the case of high-grade gliomas, a near to total resection aims to decrease tumor burden, by lowering intracranial pressure and improving survival. The patient should be screened for residual tumors within the first three days after surgery. Radiation, chemotherapy or a combination of both treatments frequently follows surgery.[138] As of yet, it is unclear whether it is best to immediately proceed with postoperative radiotherapy, or whether the patient should be observed before proceeding with additional treatment. Early radiation therapy may improve survival times, but it can also lead to radiation-related neurotoxicity. Older patients, whose risk of recurrence is high, may be offered radiotherapy immediately after surgery.[136] Combined chemo and radiotherapy helps improves survival over standard radiation. Patients who are not candidates for surgery or chemotherapy should be considered for palliative care.[138]

2.2. Importance of Key Questions in the Clinical Management of Brain Cancer

Imaging of brain tumors with ^{18}FDG was the first oncologic application of PET for tumor detection, grading of cerebral tumors and assessment of peritumor or remote metabolic alterations. The application of ^{18}FDG-PET for tumor imaging of the brain is based on increased glycolysis in neoplastic cells. There is, however, no consensus regarding the utility of ^{18}FDG-PET in predicting histological grading and survival of brain tumors. Differentiation between inflammatory tissue and malignancies is sometimes difficult due to the high degree of physiologic glucose metabolism in normal brain tissue, making the interpretation of increased ^{18}FDG accumulation in both processes difficult. For example, when a hypermetabolic lesion is at the cortical or subcortical gray matter, tumor ^{18}FDG uptake and normal ^{18}FDG uptake are hard to differentiate. Because brain tumors are histologically heterogeneous, CT- or MRI-guided stereotactic brain biopsy does not always yield a valid diagnosis or grading. The correct diagnosis of a relapse is crucial for optimal further treatment. For example, ^{18}FDG may help to distinguish between recurrences and radiation necrosis in cases of glioblastoma multiforme (GBM), and detection of early relapse can help to increase the benefit of interventions such as stereotactic irradiation or gamma knife treatment. Therefore, although the prognosis of GBM tumors remains poor, the use of ^{18}FDG-PET may still have benefits in terms of patient survival time.

2.3. Results

Six studies[26-30,129] provided evidence on the use of ^{18}FDG-PET or ^{18}FDG-PET/CT. Five studies[26-30] evaluated the diagnostic accuracy of ^{18}FDG-PET or ^{18}FDG-PET/CT for brain cancer. None of the studies reported on the diagnostic thinking impact of ^{18}FDG-PET or ^{18}FDG-PET/CT. One study[129] evaluated the effects of ^{18}FDG-PET as part of a management strategy on patient-centered outcomes. No economic evaluations on the use of ^{18}FDG-PET or ^{18}FDG-PET/CT for brain cancer were identified. Characteristics of the populations, conditions of ^{18}FDG-PET administration, interpretation of results and methodological quality of the studies are summarized in appendices D to J.

2.3.1. Diagnostic accuracy of ^{18}FDG-PET and ^{18}FDG-PET/CT in brain cancer

Characteristics of the studies

Five studies (three prospective, [26-28] two retrospective[29,30]) evaluated the diagnostic accuracy of ^{18}FDG-PET on brain cancer. ^{18}FDG-PET was used for initial staging in three studies,[27,28,30] for assessment of recurrences in one study,[29] and for establishing both primary diagnosis and recurrences in the remaining study.[26] The studies contained a total of 217 patients with sample sizes ranging from 17 to 81. The participant ages ranged from 20 to 76 years. Four studies reported the distribution by stage of cancer: CS I = 64%, CS II = 36%;[30] CS II = 22%, CS III = 16%, CS IV = 42%;[26] CS II = 27%, CS III = 42%, CS IV = 31%;[28] and CS I = 7%, CS II = 20%, CS III = 20%, CS IV = 47%.[27] ^{18}FDG-PET was compared to a reference standard that varied across the studies. Three studies established the final diagnosis of all patients using histology/biopsy.[27,28,30] In one study the reference standard was either histology/biopsy or clinical follow-up.[26] One study used MRI and MET-PET as reference standards in all patients.[29] One study reported the mean time between last treatment and ^{18}FDG-PET as 4 months for chemotherapy, 12 months for radiotherapy and 13 months for surgery.[29] Two studies used a fixed dose of 370 MBq of ^{18}FDG.[28,30] One study used a weight based dose (2.4 MBq/kg),[26] while another study reported a dose range of 200-300 MBq.[29] The time between injection and PET scan was 30 minutes,[29] 45 minutes,[28] and 60 minutes.[26,30] Patients fasted for four,[28,29] six,[27] or twelve[30] hours. Two studies[29,30] measured glucose levels before administration of ^{18}FDG-PET; the maximum glucose level that was allowed was normal levels[29] and 5.6 mmol/L.[30] Methods of interpretation of the images were qualitative in two study[27,30] and both qualitative and

quantitative in three.[26,28,29] Scans were interpreted qualitatively using visual analysis.[26-29] Two studies[28,29] reported using SUV but the criterion for abnormality was not reported.

Comparisons

Comparisons for which data were considered for a meta-analysis are summarized in Table 9. Pooled data were obtained to evaluate the accuracy of ^{18}FDG-PET in detecting the stage of brain cancer. Individual study data are summarized in Appendix D.

Table 9. Summary of comparisons considered for meta-analyses of the accuracy of ^{18}FDG-PET for brain cancer

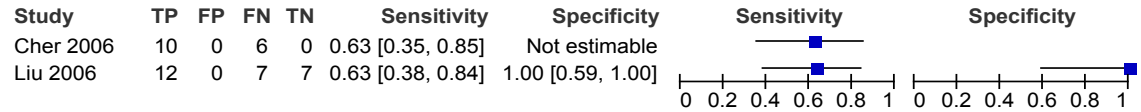
Indication	Studies	Design	Type of PET	Reference standard	Meta-analysis
Primary diagnosis and recurrences	Chen 2006[26]	P	FDG-PET	Histology/biopsy or clinical followup	No
Recurrences	Potzi 2007[29]	R	FDG-PET	MRI, MET-PET	No
Staging	Cher 2006[27]	P	FDG-PET	Histology/biopsy	1. FDG-PET vs. histology/biopsy (P studies)[27,28]
	Liu 2006[28]	P	FDG-PET	Histology/biopsy	
	Stockhammer 2007[30]	R	FDG-PET	Histology/biopsy	

FDG= fluorodeoxyglucose; MET=carbon-11 methionine; MRI=magnetic resonance imaging; P = prospective; PET=positron emission tomography; R = retrospective; vs.=versus

1. ^{18}FDG-PET for the staging of brain cancer

Reference standard: histology/biopsy; prospective studies. Two prospective studies[27,28] totaling 42 participants provided data for a meta-analysis of the accuracy of ^{18}FDG-PET compared to histology for the staging of brain cancer. Individual 2x2 table results are presented in Figure 6. The sensitivity value in both of the individual studies was 63%.[27,28] Specificity data was provided by one study only[28] and the value was 100%.

Figure 6. Results from 2x2 tables of individual prospective studies of ^{18}FDG-PET versus histology for the staging of brain cancer



We could not calculate a pooled estimate of the positive and negative LRs for the accuracy of the staging of brain cancer because the study by Cher[27] provided sensitivity data only. Therefore, the positive and negative likelihood values are based in the study by Liu.[28] ^{18}FDG-PET had a positive LR of 10 (95% CI 67, 149.57), that was not statistically significant, and a negative LR of 0.40 (95% CI = 0.22, 0.72) that was statistically significant to detect the stage of the disease. However, the 95% confidence interval of the negative LR was too wide to have confidence in these results (Figures 7 and 8).

Figure 7. Meta-analysis of the positive LR of ^{18}FDG-PET versus histology for the staging of brain cancer (prospective studies)

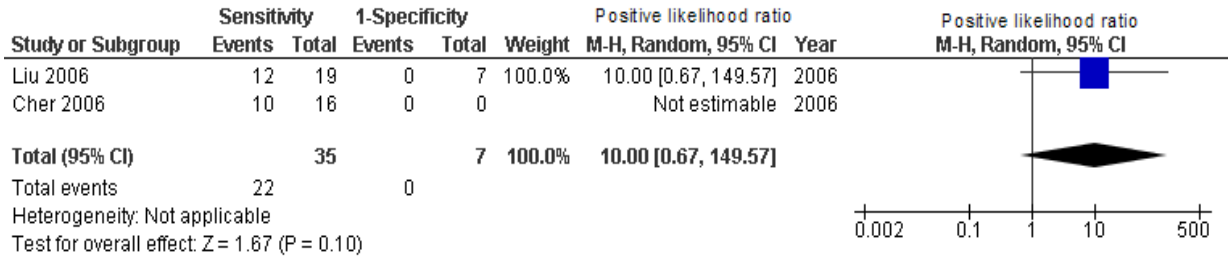
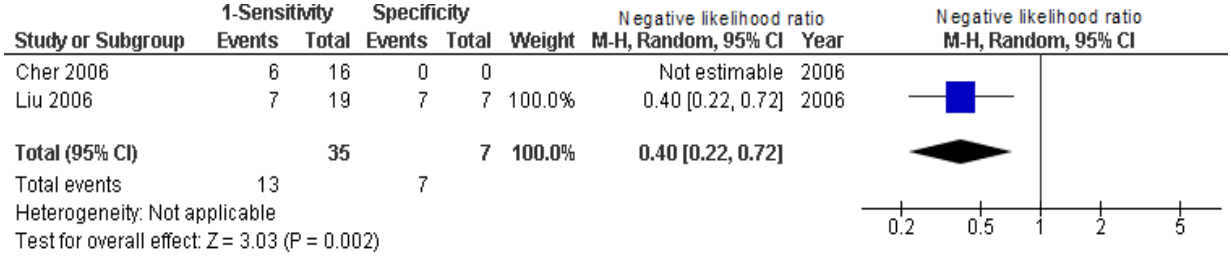
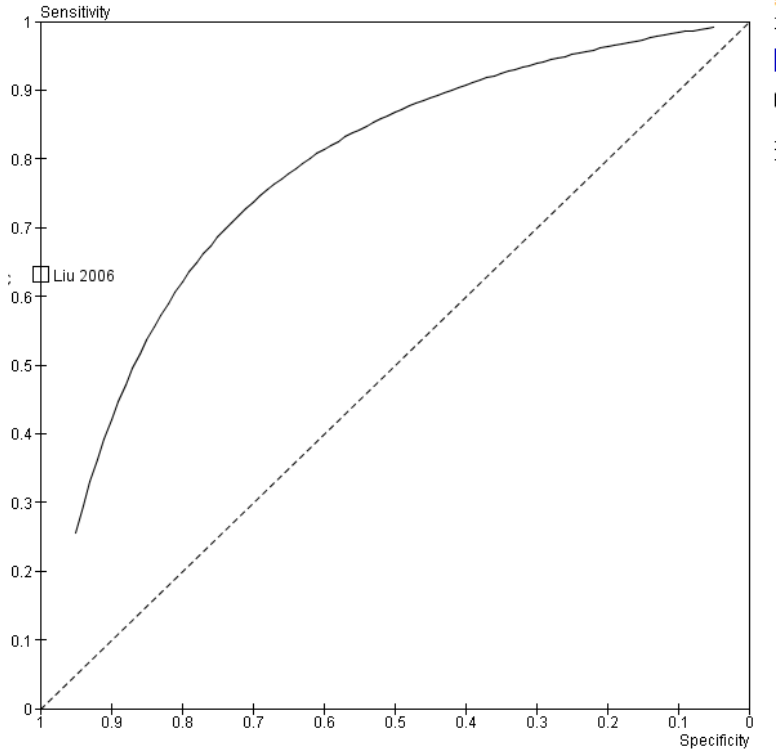


Figure 8. Meta-analysis of the negative LR of ^{18}FDG-PET versus histology for the staging of brain cancer (prospective studies)



The ROC plot analysis for ^{18}FDG-PET versus histology for the staging of brain cancer was based on one prospective study only[28] (Figure 9).

Figure 9 Summary ROC Plot of ^{18}FDG-PET versus histology for the staging of brain cancer (prospective studies)



2.3.2. ^{18}FDG-PET and ^{18}FDG-PET/CT as part of a management strategy in brain cancer

One study assessed the impact of ^{18}FDG-PET as part of a management strategy of brain cancer at various stages of treatment. Padma *et al*[129] conducted a retrospective study that evaluated the value of ^{18}FDG-PET results for predicting the survival of patients with brain cancer. The study included 331 patients with a mean age of 47 years (59% males), histologically-proven brain tumors according to WHO criteria, and should have been followed up until death or at least one year after ^{18}FDG-PET.

Prognostic value was assessed with respect to the ability of ^{18}FDG-PET to predict the grade of glioma and patient survival. Patients were followed up for an average of 3.6 years after ^{18}FDG-PET. One hundred and thirty-seven (41%) of the patients underwent ^{18}FDG-PET prior to histological diagnosis and any therapeutic intervention, while 194 patients underwent ^{18}FDG-PET between 2 months and 10 years following the histological diagnosis.

The influence of ^{18}FDG-PET in predicting survival was found to be significant. Overall, the median survival of patients with high uptake scores on ^{18}FDG-PET was 11 months versus 28 months in patients with low uptake scores. High ^{18}FDG-PET uptake was strongly associated with poor survival; while cases with low uptake had increased likelihood of long term (4-5 yr) survival. The

authors concluded that ^{18}FDG-PET may help in the stratification of patients entered in protocols that evaluate therapeutic strategies in brain tumors. Additionally, the authors discuss the utility of ^{18}FDG-PET versus grading by histology for predicting the survival of patients in whom the ^{18}FDG-PET was done prior to surgery and any mode of therapeutic intervention.

Overall, the study was graded as level D of evidence (multiple flaws in methods). A detailed description of the methodological quality of this study is presented in appendix H. The issues with the quality in the study included the lack of a comparator group who did not receive the ^{18}FDG-PET as a component of their disease monitoring. The selection criteria were only partially described, raising the possibility of selection bias. While the study had a large population, there is only partial description of the study population and their selection. The methods of executing ^{18}FDG-PET test were not well described to permit reproducibility. Two different types of scans were used over the study period, and it is unknown how the use of different types of scan may affect the detection of low or high ^{18}FDG uptake and therefore, affect outcome assessment. Additionally, while this study was relevant to management strategy, a matched design was not employed.

Table 10 provides a summary of the main findings and the types of bias that affected the evidence on ^{18}FDG-PET as part of a management strategy in brain cancer

Table 10. Main findings and types of bias that affected the evidence on 18FDG-PET as part of a management strategy in brain cancer

Study	Patient Centered Outcomes	Types of Bias
Padma 2003[129] Study type: Retrospective	FDG-PET used for: Predicting survival High FDG-uptake (n = 166) Low FDG-PET uptake (n = 165)	Selection Bias (unclear) Disease progression bias (unclear) Review Bias (ref std, unclear)

Survival	High uptake	Low Uptake
< 1 y	117/165	10/166
> 1 y	48/165	156/166
> 2 y	0/165	104/166
> 3 y	0/165	65/166
4 and 5 y	0/165	49 and 26/166

FDG=Fluorodeoxyglucose F18; PET=positron emission tomography; RS=reference standard; yr = years

3. Cervical Cancer

3.1. Background

In the United States in 2008, 11,070 women are expected to be diagnosed with new cases of cervical cancer and approximately 3,870 will die from the disease.[133] Incidence of cervical cancer varies greatly across subpopulations within the country.[139] Between 2000 and 2004 incidence rates of cervical cancer for Caucasian American women were 8.5/100,000. For African American women the numbers increase to 11.4/100,000 and the highest rate occurs in Hispanic American women at 13.8/100,000.[133] Cervical cancer appears earlier in life than other malignancies. The median age at diagnosis is 48 years and the median age of death is 57 years. On average, cervical cancer accounts for 26.3 years of life lost in women diagnosed with this condition in the United States.[133]

Sexual intercourse at an early age, multiple male sexual partners who also have multiple partners and smoking are considered risks for the disease.[140] The vast majority of cervical cancer cases (99.7%) are associated with human papilloma virus (HPV).[141] There are many different types of HPV. High risk viral subtypes of HPV raise the risk of developing high-grade cervical dysplasia and cancer. Immunosuppression due to renal-allograft transplantation or Hodgkin's disease is also linked to cervical cancer. Precursors to cervical cancer known as cervical intraepithelial neoplasia (CIN) can occur in women less than 40 years of age.[140] HPV vaccines have helped to decrease rates of CIN significantly. Screening for cervical cancer using the Pap smear to assess for abnormal cervical cytology is commonplace in the United States. The Pap smear facilitates detection of precursor lesions, prior to the progression of disease to a more invasive cancer. Abnormal Pap findings require further evaluation with colposcopy and directed biopsies being required.[141]

If diagnosed in the early stages of disease, a high cure rate can be achieved. However, cervical cancer is often asymptomatic[140] and when left untreated, cervical cancer grows and frequently will metastasize into regional lymph nodes.[142] A patient may report vaginal discharge or postcoital vaginal bleeding. In cases of advanced disease lower extremity edema, deep vein thrombosis or ureteral obstruction may occur.[140] Two thirds of all cervical cancers are composed of squamous cell carcinoma, while much of the remaining 25% are adenocarcinoma. Tumors are staged using the International Federation of Gynaecology (FIGO) system, which takes tumor grade, depth, width and extent of invasion into consideration (Table 11).[143]

Table 11. FIGO Staging of Cervical Cancer

Stage	Description
Stage 0	Carcinoma in situ
Stage Ia1	Invasive carcinoma, confined to cervix, lesion ≤3 mm deep, ≤ 7 mm wide
Stage Ia2	Invasive carcinoma, confined to cervix, lesion >3 mm and ≤ 5 mm deep, ≤ 7 mm wide
Stage Ib1	Invasive carcinoma, confined to cervix, lesion ≤ 4 cm
Stage Ib2	Invasive carcinoma, confined to cervix, lesion > 4 cm
Stage IIa	Tumor extended beyond cervix to vagina (but not lower 1/3)
Stage IIb	Tumor extended beyond cervix, parametrial invasion (but not to pelvic side wall or lower 1/3 of vagina)
Stage IIIa	Tumor extended to lower 1/3 of vagina (but not to pelvic side wall)
Stage IIIb	Tumor extended to pelvic side wall, interferes with kidney function
Stage IVa	Tumor extended into bladder or rectum
Stage IVb	Distant metastasis

Taken from Petignat et al.[143]

Limitations to current screening and imaging modalities exist. Pap tests are commonly used to cytologically evaluate the cervix, but are subject to errors occurring during sample collection or evaluation. An alternative to conventional Pap testing is liquid-based cytology. Findings do not consistently demonstrate if liquid-based cytology is more effective than conventional Pap testing.[139] Regardless, screening is a useful tool and has dramatically reduced the incidence and mortality of cervical cancer. Colposcopy and directed biopsies provide followup screening for an abnormal Pap test to confirm the presence and determine the scope of the disease.[141]

Testing may also be conducted to detect HPV DNA. The United States and some European countries screen for specific biomarkers, which improves efficiency and maximizes sensitivity. It is an adjunctive test with cytology for women 20 years of age or older. Although screening for biomarkers is more sensitive and has high negative predictive values, it suffers from lower specificity than Pap tests as HPV infections are common in sexually active women.[139]

When local disease is diagnosed, screening with CT or MRI is helpful for defining lymph node status and determining the extent of disease. Identifying involved nodes can be difficult as their identification relies on size and morphological criteria. Surgery provides another method for staging. Pelvic lymphadenectomy and para-aortic lymphadenectomy are two techniques frequently used. Many studies demonstrate excellent patient results after surgical staging. Imaging techniques such as CT, MRI and PET, in addition to surgical staging are more effective in identifying the true extent of disease than clinical testing. However, these techniques have yet to be incorporated into FIGO staging system.[143]

^{18}FDG-PET has been shown to have an advantage over CT in the imaging of cervical cancer.

Lesion location can be identified with CT, but ^{18}FDG-PET is capable of detecting nodal involvement when CT is not. In regards to nodal staging, MRI appears to have insufficient accuracy, whereas ^{18}FDG-PET has demonstrated a high positive predictive value of ^{18}FDG-PET, which can eliminate the need for nodal sampling. ^{18}FDG-PET may also be useful in diagnosing recurrent and metastatic disease.[144]

Cure can be achieved in 80 to 90 % of patients with stage I and II disease when treated with surgery or chemoradiotherapy.[143] Surgery is usually performed first followed by chemotherapy or radiotherapy, which helps decrease the risk of reoccurrence.[140] Conisation is performed in woman with stage I disease if fertility to be preserved; if that is not the case simple hysterectomy is performed. Radical hysterectomy is performed for higher grade tumours; radical trachelctomy may provide a surgical option for younger women who wish to preserve fertility.[143] Relapse occurs frequently in patients with stages IIb III and IV even after treatment with surgery and radiotherapy.[140] Recurrences usually occur place within two years after the completion of primary treatment.[143] Approximately 30% of women with invasive cancer die from recurrence.[140] The goal for treatment of patients with stage IVB cancer is palliative. How treatment affects quality of life and toxicity influences choice of treatment.[143]

3.2. Importance of Key Questions in the Clinical Management of Cervical Cancer

Cervical cancer spreads directly through the lymphatic system, with pelvic node metastasis preceding aortic node metastasis in the majority of the cases. Sensitive and specific imaging modalities that identify occult lymph node metastasis may allow avoidance of morbid surgical procedures and facilitate treatment planning with novel modalities. Earlier detection of recurrent cervical cancer has the potential to improve survival, since some patients may be salvaged using radiotherapy or radical surgery. Local recurrences may be difficult to detect by anatomical examination because the soft tissue structures are thickened following radiation or surgery. Anatomical imaging techniques such as CT and MRI can be fairly inaccurate in detecting retroperitoneal nodal metastasis and therefore, it is important to explore whether functional imaging methods such as ^{18}FDG-PET can help to improve the accuracy of pretreatment staging and have a positive impact on patient survival. It is important to determine whether the use of ^{18}FDG-PET in patients with cervical cancer can improve patient-centered outcomes by altering the primary management strategies. As the available treatments for cervical cancer recurrence improve, such as

radical resection in combination with intraoperative high-dose-rate brachytherapy, the improvement of imaging modalities to identify recurrences early becomes more important.

3.3. Results

Thirty-five studies[31-63,145,146] provided evidence on the use of ^{18}FDG-PET or ^{18}FDG-PET/CT for cervical cancer. Thirty-three studies[31-63] evaluated the diagnostic accuracy of ^{18}FDG-PET or ^{18}FDG-PET/CT for cervical cancer. Six studies reported on the diagnostic thinking impact of ^{18}FDG-PET[33,42,43,61] and ^{18}FDG-PET/CT,[32,38] and two studies[33,42] evaluated the impact of ^{18}FDG-PET as part of a management strategy on patient-centered outcomes. No economic evaluations on the use of ^{18}FDG-PET and ^{18}FDG-PET/CT for cervical cancer were identified. Characteristics of the populations, conditions of ^{18}FDG-PET administration, interpretation of results and methodological quality of the studies are summarized in appendices D to J.

3.3.1. Diagnostic accuracy of ^{18}FDG-PET and ^{18}FDG-PET/CT in cervical cancer

Characteristics of the studies

Thirty-three studies (21 prospective, [31-33,35-37,41-46,48,50-52,59-63]12 retrospective [34,38-40,47,49,53-58]) evaluated the diagnostic accuracy of ^{18}FDG-PET [33-35,37,39-44,46-50,53-61,63] and ^{18}FDG-PET/CT [31,32,36,38,45,51,52,58,62] on cervical cancer. Ten studies[37,41,44,46-48,53,55,58,60] used ^{18}FDG-PET for initial staging, one for primary diagnosis and recurrence,[35]11 for recurrence,[33,34,39,40,43,49,50,54,56,59,61]1 for restaging[42] one for staging and recurrence,[63] and one for staging and restaging.[57] Six studies used ^{18}FDG-PET/CT for initial staging, [31,36,45,51,58,62] two for recurrence[38,52]and one for staging and restaging purposes.[32] The studies contained a total of 2,767 patients with sample sizes ranging from 14 to 517. The participant ages ranged from 20 to 87 years. Twenty-seven studies reported the distribution by stage of cancer[32-43,45,47-52,54-56,58-62] and included variously all stages from IA1 to stage IV. ^{18}FDG-PET was compared to histology/biopsy in all studies, but in 19 studies the reference standard was also clinical follow-up,[31-35,38,39,42,43,45,49,52,54,56,57,59-61,63] and in one[46] it was also imaging follow-up. Twelve studies[32-34,38,43,46,50-52,54,56,62] reported the mean time between last treatment and ^{18}FDG-PET, which ranged from 7 days[51] to 42 months.[46] Seventeen studies reported using a fixed dose of ^{18}FDG (322MBq,[47]370MBq,[33-35,37,42-44,46,51,52,56,60,61]400MBq,[45] 550MBq[54,55]); four studies used a weight based dose (0.14mCi/kg,[40]0.22mCi/kg,[38] 5MBq/kg,[47]5.2MBq/kg[57]). The time between injection and PET from scan ranged from 30 minutes[34] to 3 hours.[46] Patients fasted anywhere from 4 hours[31,32,34,38,44,50,54,55,62,63] to overnight.[147] Seven studies[31,32,35,46,51,52,56] measured glucose levels

before administration of ^{18}FDG-PET; the maximum glucose level permitted was 200 mg/dL.[31,52] Methods of interpretation of the images were quantitative in 1 study, [50] qualitative in 16 studies[32-34,37,38,40,43,44,46,49,51,52,54,56,57,61] and both qualitative and quantitative in 8 studies.[35,36,39,42,47,48,59,60] Scans were interpreted qualitatively using visual analysis in 26 studies.[32-40,42-44,46-52,54,56-61] Four studies[36,39,46,48] reported using both visual analysis and SUV and one[50] used SUV only.

Comparisons

Comparisons for which data were considered for meta-analysis are summarized in Table 12. Pooled data were obtained to evaluate the accuracy of ^{18}FDG-PET in cervical cancer for staging and for detection of recurrences. Pooled data were also obtained to evaluate the accuracy of ^{18}FDG-PET/CT for staging of cervical cancer. Individual study data are summarized in Appendix D.

Table 12. Summary of comparisons considered for meta-analyses of the accuracy of ^{18}FDG-PET and ^{18}FDG-PET/CT for cervical cancer

Indication	Studies	Design	Type of PET	Reference standard	Meta-analysis
Primary diagnosis and recurrences	Chang 2005[35]	P	FDG-PET	Histology/biopsy or clinical followup	No
Staging and recurrences	Grisaru 2004[63]	P	FDG-PET	Histology/biopsy	No
Staging and restaging	Bjurberg 2007[32]	P	FDG-PET/CT	Histology/biopsy or clinical followup	No
	Wong 2004[57]	R	FDG-PET	Histology/biopsy or clinical followup	
Recurrences	Chang 2004[33]	P	FDG-PET	Histology/biopsy or clinical followup (local vs. distant)	1. FDG-PET vs. histology/biopsy or clinical followup (P studies) [43,59,61]
	Chang 2004[34]	R	FDG-PET	Histology/biopsy or clinical followup (lesion-based)	
	Chung 2007[38]	R	FDG-PET/CT	Histology/biopsy or clinical followup	2. FDG-PET vs. histology/biopsy or clinical followup (R studies) [39,49,54]
	Chung 2006[39]	R	FDG-PET	Histology/biopsy or clinical followup	
	Havrilesky 2003[40]	R	FDG-PET	Histology/biopsy (lesion-based)	
	Lin 2006[43]	P	FDG-PET	Histology/biopsy or clinical followup	
	Ryu 2003[49]	R	FDG-PET	Histology/biopsy or clinical followup	
	Sakurai 2006[50]	P	FDG-PET	Histology/biopsy (lesion-based)	
	Sironi 2007[52]	P	FDG-PET/CT	Histology/biopsy or clinical followup	
	Unger 2004[54]	R	FDG-PET	Histology/biopsy or clinical followup	
	Van Der Veldt 2006[56]	R	FDG-PET	Histology/biopsy or clinical followup (lesion-based)	
	Yen 2006[59]	P	FDG-PET	Histology/biopsy or clinical followup	

Table 12. Summary of comparisons considered for meta-analyses of the accuracy of ^{18}FDG-PET and ^{18}FDG-PET/CT for cervical cancer (cont')

Indication	Studies	Design	Type of PET	Reference standard	Meta-analysis
Recurrences (cont')	Yen 2004[61]	P	FDG-PET	Histology/biopsy or clinical followup	
Restaging	Lai 2004[42]	P	FDG-PET	Histology/biopsy or clinical followup	No
Staging	Amit 2006[31]	P	FDG-PET/CT	Histology/biopsy or clinical followup	1. FDG-PET vs. any reference standard (P studies)[37,41,44,46,48]
	Choi 2006[36]	P	FDG-PET/CT	Histology/biopsy (lesion-based)	
	Chou 2006[37]	P	FDG-PET	Histology/biopsy	2. FDG-PET vs. histology (P studies) [37,41,44,48]
	Hope 2006[41]	P	FDG-PET	Histology/biopsy	
	Lin 2003[44]	P	FDG-PET	Histology/biopsy	
	Loft 2007[45]	P	FDG-PET/CT	Histology/biopsy or clinical followup	3. FDG-PET vs. histology (R studies)[47,53,55]
	Ma 2003[46]	P	FDG-PET	Histology/biopsy and imaging follow-up	4. FDG-PET/CT vs. any reference standard (P studies) [31,45,62]
	Park 2005[47]	R	FDG-PET	Histology/biopsy	
	Roh 2005[48]	P	FDG-PET	Histology/biopsy	
	Sironi 2006[51]	P	FDG-PET/CT	Histology/biopsy (node-based)	5. FDG-PET/CT vs. histology/biopsy or clinical followup (P studies) [31,45]
	Tran 2003[53]	R	FDG-PET	Histology/biopsy	
	Unger 2005[55]	R	FDG-PET	Histology/biopsy	
	Wright 2005[58]	R	FDG-PET and FDG-PET/CT	Histology/biopsy	
	Yen 2003[60]	P	FDG-PET	Histology/biopsy or clinical followup (lesion-based)	
	Yildirim 2008[62]	P	FDG-PET/CT	Histology/biopsy	

CT=computer tomography; FDG= fluorodeoxyglucose; P = prospective; PET=positron emission tomography; R = retrospective

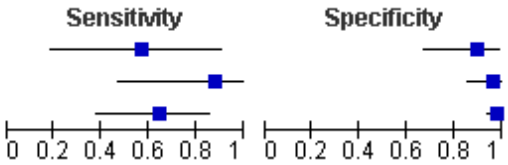
1. ^{18}FDG-PET for recurrences of cervical cancer

Reference standard: histology/biopsy or clinical followup; prospective studies. Three prospective studies[43,59,61] totaling 231 participants provided data for a meta-analysis of the accuracy of ^{18}FDG-PET compared to histology/biopsy or clinical followup for detecting recurrences of cervical cancer. Recurrences were identified by site including peritoneum, bone, liver/spleen, lung, mediastinal lymph node (MLN), supraclavicular lymph node (SLN), para-aortic lymph node (PALN), pelvic lymph node (PLN), and inguinal lymph node (ILN). Individual 2x2 table results are presented in Figure 10. Sensitivity values in individual studies ranged from 50%[43] for bone and PLN sites to 100% for liver/spleen, [43,59] MLN[43,59,61] and ILN[43,59] sites. Specificity ranged from 88% for MLN[43] to 100% for liver/spleen,[43] lung,[43,59] PALN,[59] PLN[43] and ILN.[43,59]

Figure 10. Results derived from the 2x2 tables of individual prospective studies of ^{18}FDG-PET versus histology/biopsy or clinical followup to detect recurrences of cervical cancer

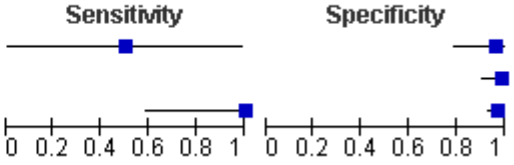
Peritoneum

Study	TP	FP	FN	TN	Sensitivity	Specificity
Lin 2006	4	2	3	17	0.57 [0.18, 0.90]	0.89 [0.67, 0.99]
Yen 2004	7	2	1	45	0.88 [0.47, 1.00]	0.96 [0.85, 0.99]
Yen 2006	11	3	6	129	0.65 [0.38, 0.86]	0.98 [0.94, 1.00]



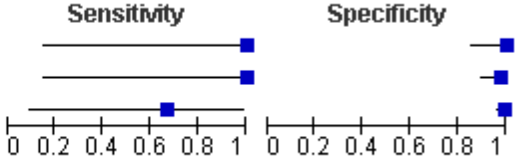
Bone

Study	TP	FP	FN	TN	Sensitivity	Specificity
Lin 2006	1	1	1	23	0.50 [0.01, 0.99]	0.96 [0.79, 1.00]
Yen 2004	0	1	0	54	Not estimable	0.98 [0.90, 1.00]
Yen 2006	7	4	0	139	1.00 [0.59, 1.00]	0.97 [0.93, 0.99]



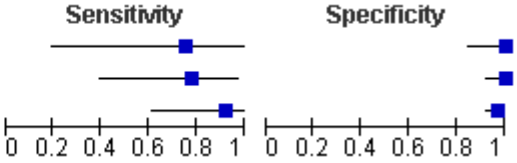
Liver/spleen

Study	TP	FP	FN	TN	Sensitivity	Specificity
Lin 2006	2	0	0	24	1.00 [0.16, 1.00]	1.00 [0.86, 1.00]
Yen 2004	2	1	0	52	1.00 [0.16, 1.00]	0.98 [0.90, 1.00]
Yen 2006	2	1	1	144	0.67 [0.09, 0.99]	0.99 [0.96, 1.00]



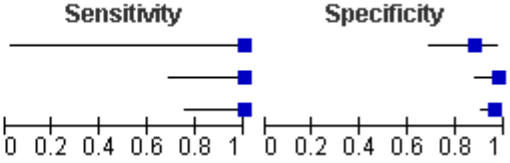
Lung

Study	TP	FP	FN	TN	Sensitivity	Specificity
Lin 2006	3	0	1	22	0.75 [0.19, 0.99]	1.00 [0.85, 1.00]
Yen 2004	7	0	2	46	0.78 [0.40, 0.97]	1.00 [0.92, 1.00]
Yen 2006	11	4	1	129	0.92 [0.62, 1.00]	0.97 [0.92, 0.99]



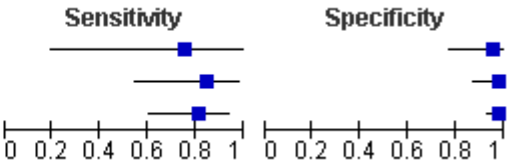
MLN

Study	TP	FP	FN	TN	Sensitivity	Specificity
Lin 2006	1	3	0	22	1.00 [0.03, 1.00]	0.88 [0.69, 0.97]
Yen 2004	10	1	0	44	1.00 [0.69, 1.00]	0.98 [0.88, 1.00]
Yen 2006	13	5	0	118	1.00 [0.75, 1.00]	0.96 [0.91, 0.99]



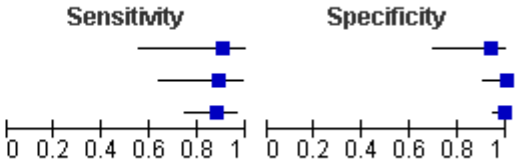
SLN

Study	TP	FP	FN	TN	Sensitivity	Specificity
Lin 2006	3	1	1	21	0.75 [0.19, 0.99]	0.95 [0.77, 1.00]
Yen 2004	11	1	2	41	0.85 [0.55, 0.98]	0.98 [0.87, 1.00]
Yen 2006	21	3	5	118	0.81 [0.61, 0.93]	0.98 [0.93, 0.99]



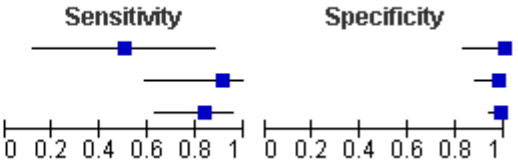
PALN

Study	TP	FP	FN	TN	Sensitivity	Specificity
Lin 2006	9	1	1	15	0.90 [0.55, 1.00]	0.94 [0.70, 1.00]
Yen 2004	15	0	2	38	0.88 [0.64, 0.99]	1.00 [0.91, 1.00]
Yen 2006	37	1	5	102	0.88 [0.74, 0.96]	0.99 [0.95, 1.00]



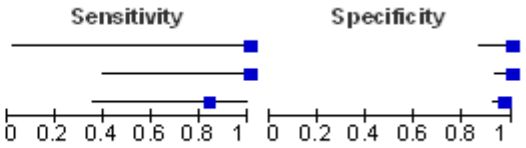
PLN

Study	TP	FP	FN	TN	Sensitivity	Specificity
Lin 2006	3	0	3	20	0.50 [0.12, 0.88]	1.00 [0.83, 1.00]
Yen 2004	10	1	1	43	0.91 [0.59, 1.00]	0.98 [0.88, 1.00]
Yen 2006	20	2	4	117	0.83 [0.63, 0.95]	0.98 [0.94, 1.00]



ILN

Study	TP	FP	FN	TN	Sensitivity	Specificity
Lin 2006	1	0	0	25	1.00 [0.03, 1.00]	1.00 [0.86, 1.00]
Yen 2004	4	0	0	51	1.00 [0.40, 1.00]	1.00 [0.93, 1.00]
Yen 2006	5	5	1	136	0.83 [0.36, 1.00]	0.96 [0.92, 0.99]



Figures 11 and 12 present the positive and negative LRs of ^{18}FDG-PET versus histology/biopsy or clinical followup to detect recurrences of cervical cancer. We found that all the positive LR by site of recurrence were statistically significant ranging from 15.24 (95% CI = 5.63, 41.27) for MLN to 45.89 (95% CI = 14.09, 149.49 for liver/spleen. Overall, the positive LRs across the studies were homogeneous except for MLN, where moderate heterogeneity was found across the studies (p = 0.12; I^2 = 53 percent). All the negative LRs by site of recurrence were statistically significant except for the identification of bone recurrences. Negative LR ranged from 0.09 (95% CI = 0.02, 0.40) for MLN to 0.37 95% CI = 0.22, 0.60) for peritoneum. The negative LR across the studies were homogeneous except for the identification of recurrences in bone (p = 0.07; I^2 = 70 percent) and PLN (p = 0.03; I^2 = 71 percent).

Figure 11. Meta-analysis of the positive LR of ^{18}FDG-PET versus histology/biopsy or clinical followup to detect recurrences of cervical cancer

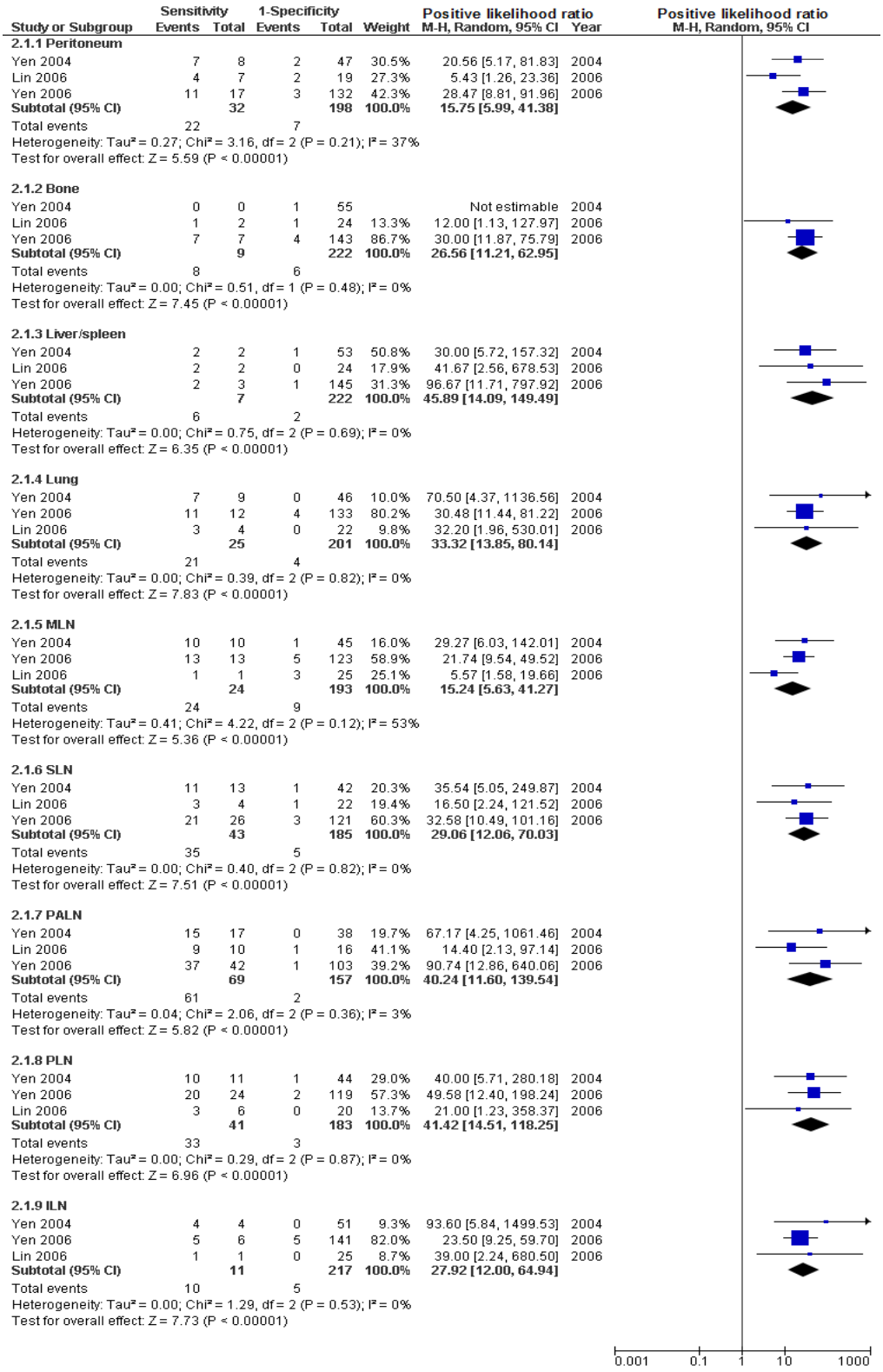
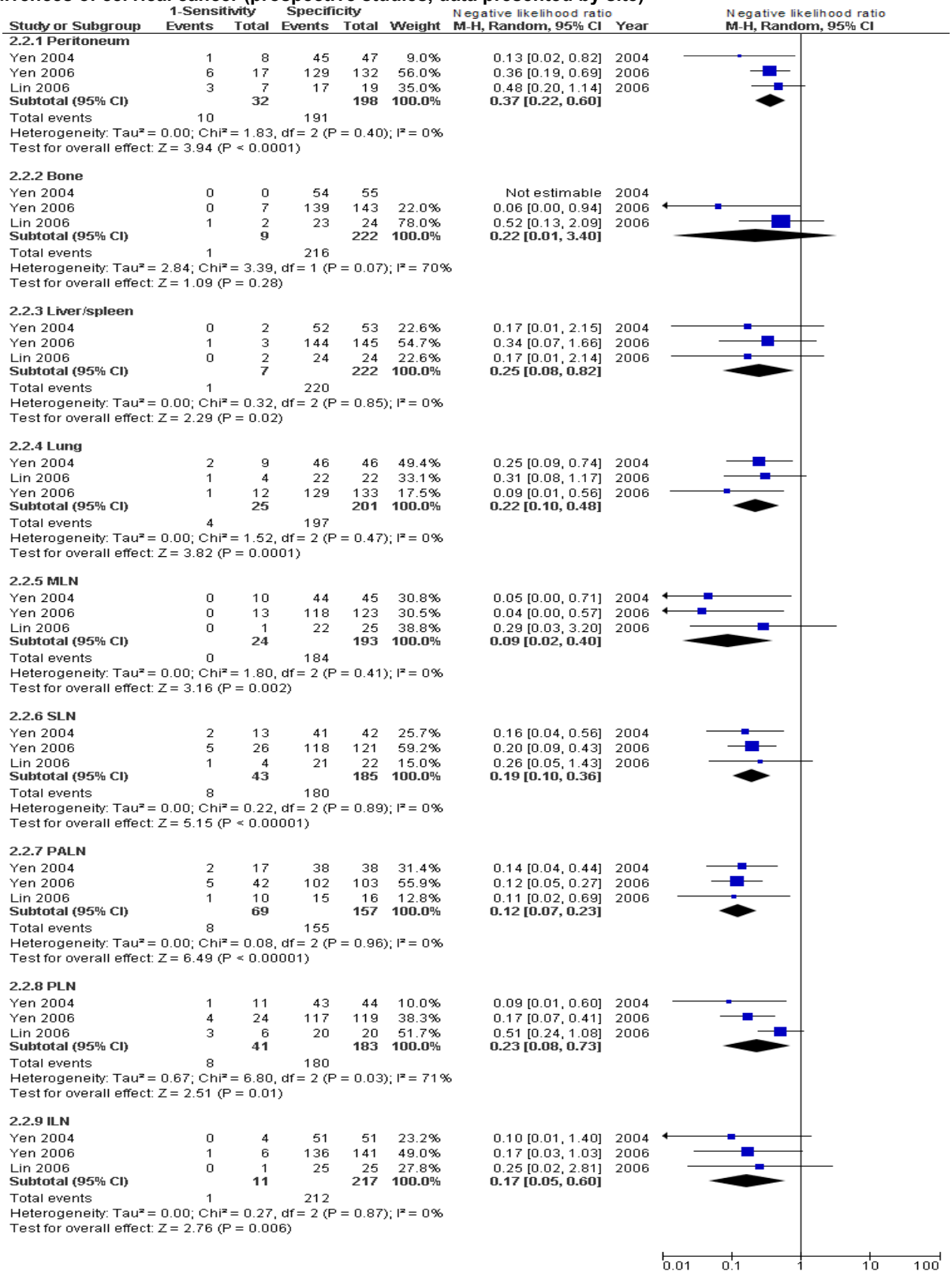


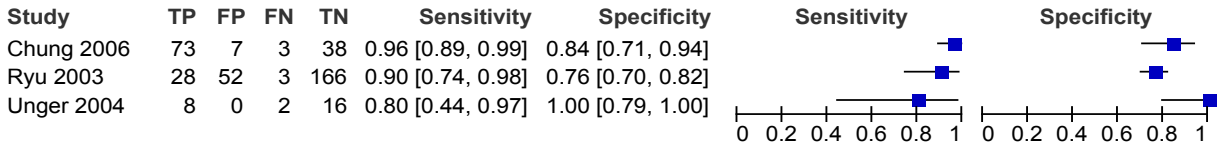
Figure 12. Meta-analysis of the negative LR of ^{18}FDG-PET versus histology/biopsy or clinical followup to detect recurrences of cervical cancer (prospective studies, data presented by site)



Estimates of sensitivity and 1-specificity plotted in ROC space for ^{18}FDG-PET versus histology/biopsy or clinical followup to detect recurrences of cervical cancer based on prospective studies were not calculated per site of lesion.

Reference standard: histology/biopsy or clinical followup; retrospective studies. Separate meta-analyses were conducted for retrospective studies Three retrospective studies[39,49,54] totaling 396 participants provided data for a meta-analysis of the accuracy of ^{18}FDG-PET compared to histology/biopsy or clinical followup for detecting recurrences of cervical cancer. Individual 2x2 table results are presented in Figure 13. Sensitivity values in individual studies ranged from 80%[54] to 96%.[39] Specificity ranged from 76%[49] to 100%.[54]

Figure 13. Results from 2x2 tables of individual retrospective studies of ^{18}FDG-PET versus histology/biopsy or clinical followup for detecting recurrences of cervical cancer



Based on the analysis of retrospective studies, we found that ^{18}FDG-PET had a pooled positive LR of 5.33 (95% CI 2.36, 12.05) and a pooled negative LR of 0.11 (95% CI = 0.04, 0.28) to accurately detect recurrences of cervical cancer (Figures 14 and 15). The positive and negative LRs were statistically significant and therefore, ^{18}FDG-PET/CT seems to be helpful to identify recurrences of the disease. However, both the positive ($p = 0.03$; $I^2 = 70$ percent) and the negative ($p = 0.12$; $I^2 = 53$ percent) LRs were heterogeneous across the studies precluding firm conclusions based on these results.

Figure 14. Meta-analysis of the positive LR of ^{18}FDG-PET versus histology/biopsy or clinical followup for detecting recurrences of cervical cancer (retrospective studies)

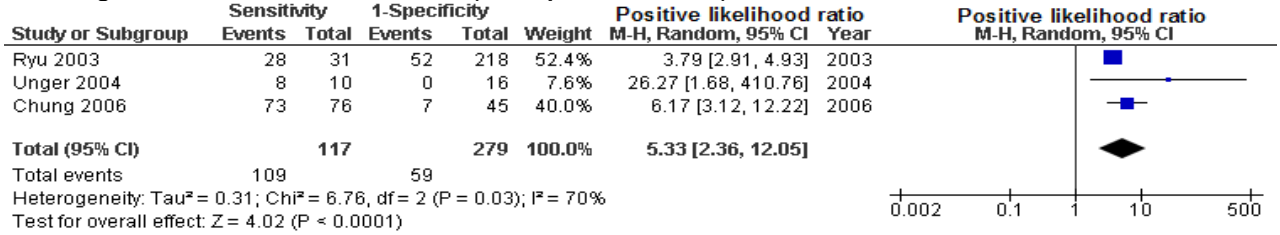


Figure 15. Meta-analysis of the negative LR of ^{18}FDG-PET versus histology/biopsy or clinical followup for detecting recurrences of cervical cancer (retrospective studies)

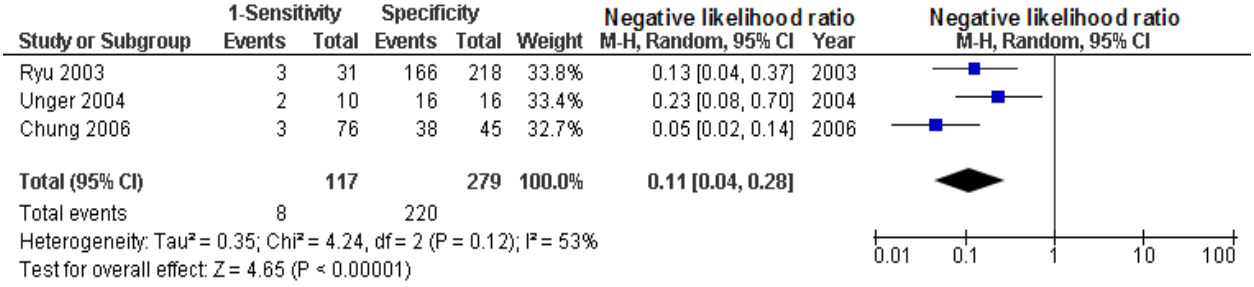
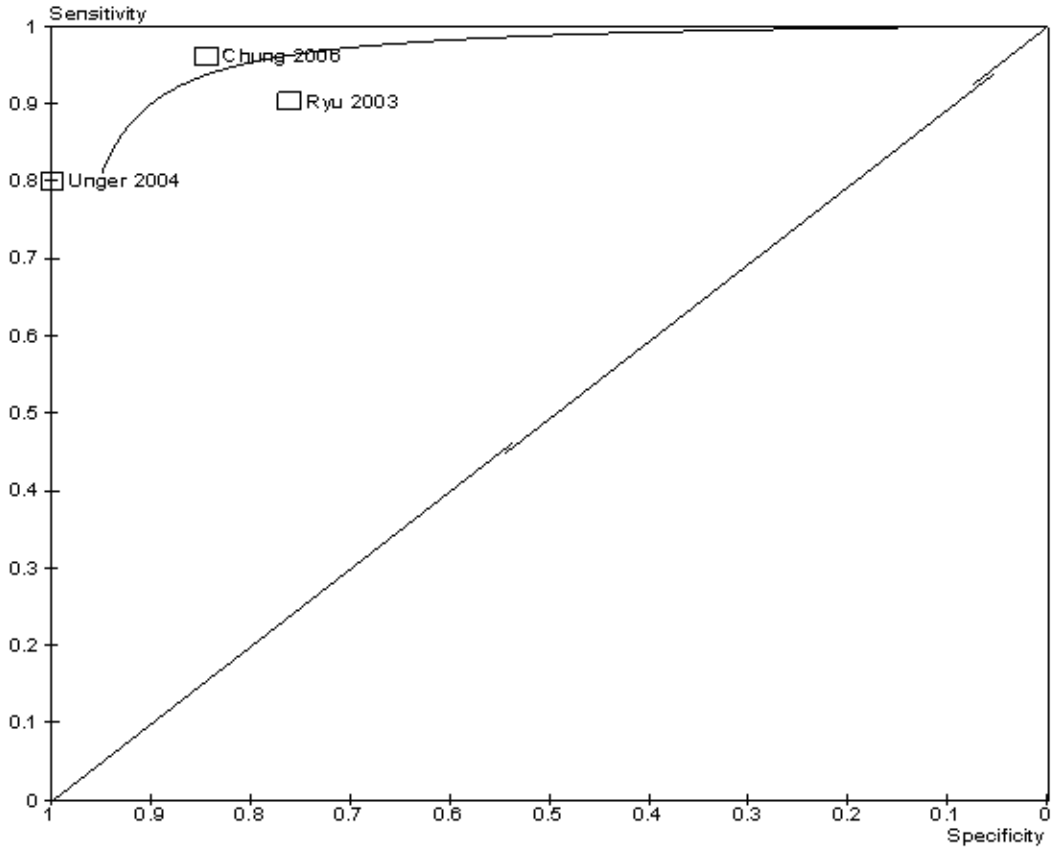


Figure 16 shows the estimates of sensitivity and 1-specificity plotted in ROC space for ^{18}FDG-PET versus histology/biopsy or clinical followup for detecting recurrences of cervical cancer.

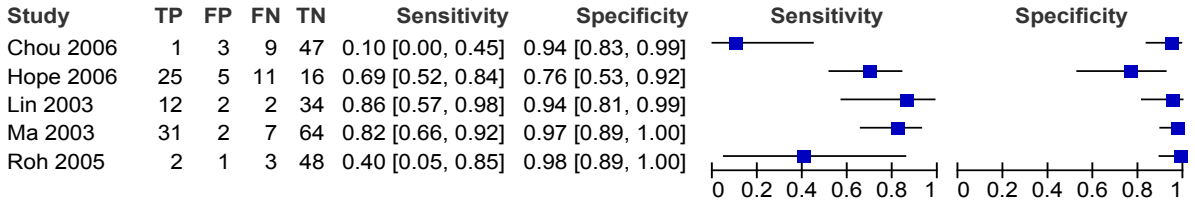
Figure 16. Summary ROC plot of ^{18}FDG-PET versus any reference standard for detecting recurrences of cervical cancer (retrospective studies)



2. ^{18}FDG-PET for the staging of cervical cancer

Reference standard: any; prospective studies. Five prospective studies[37,41,44,46,48] totaling 325 participants provided data for a meta-analysis of the accuracy of ^{18}FDG-PET compared to a variety of reference standards for the staging of cervical cancer. Individual 2x2 table results are presented in Figure 17. Sensitivity ranged from 10%[37] to 86%.[44] Specificity ranged from 76%[41] to 98%.[48]

Figure 17. Results from 2x2 tables of individual prospective studies of ^{18}FDG-PET versus any reference standard for the staging of cervical cancer



We found that^{18}FDG-PET had a pooled positive LR of 8.22 (95% CI 2.59, 26.08) and a pooled negative LR of 0.38 (95% CI = 0.12, 1.20) to accurately identify the stage of cervical cancer (Figures 18 and 19). The pooled positive LR was statistically significant and therefore, ^{18}FDG-PET seems to be helpful to detect the stage of the disease. The negative LR was not statistically significant and therefore ^{18}FDG-PET does not seem to be helpful to ruling out the presence of particular stages of the disease. There was high heterogeneity in the positive LR (p = 0.01; I^2 = 69 percent) and negative LR (p=<0.000001; I^2 = 95 percent) across the studies.

Figure 18. Meta-analysis of the positive LR of ^{18}FDG-PET versus any reference standard for the staging of cervical cancer (prospective studies)

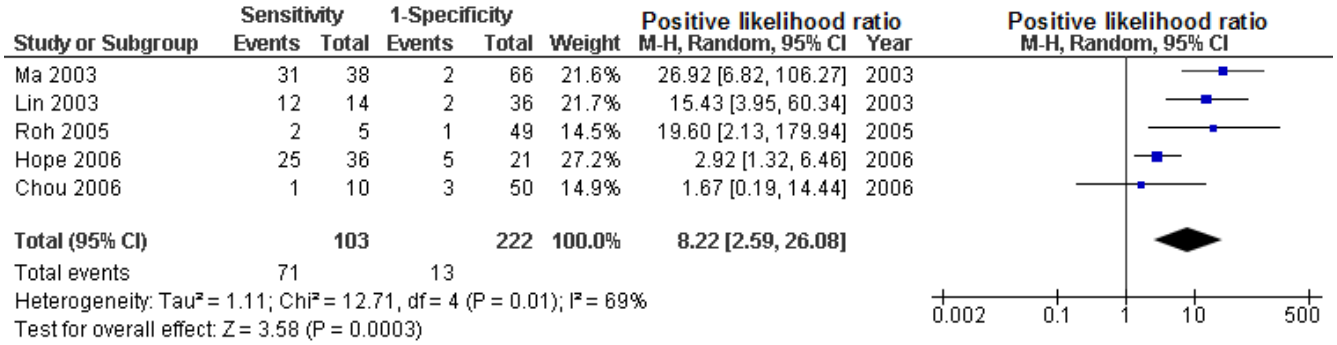


Figure 19. Meta-analysis of the negative LR of ^{18}FDG-PET versus any reference standard for the staging of cervical cancer (prospective studies)

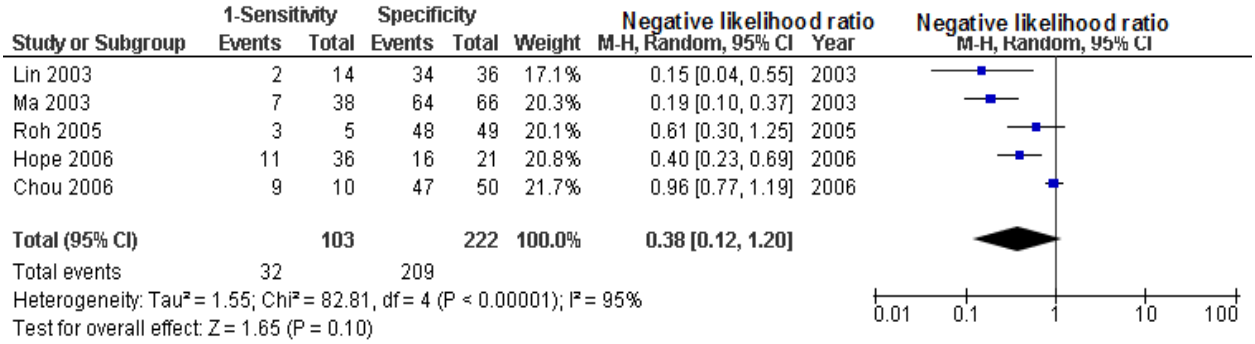
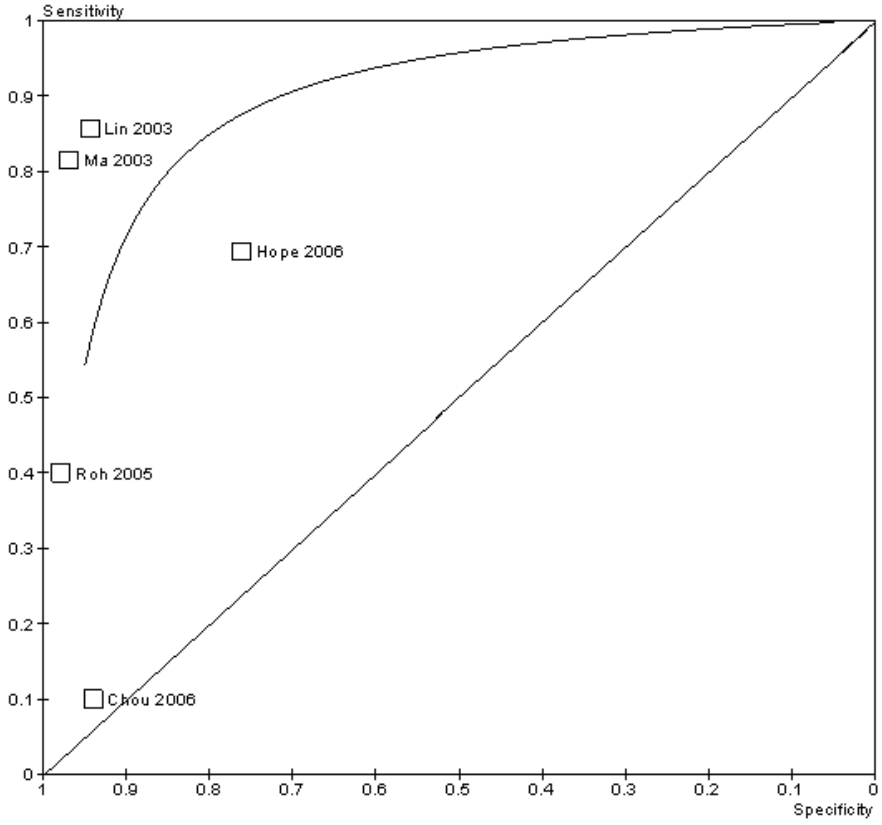


Figure 20 shows the estimates of sensitivity and 1-specificity plotted in ROC space for ^{18}FDG-PET versus any reference standard for the staging of cervical cancer based on prospective studies.

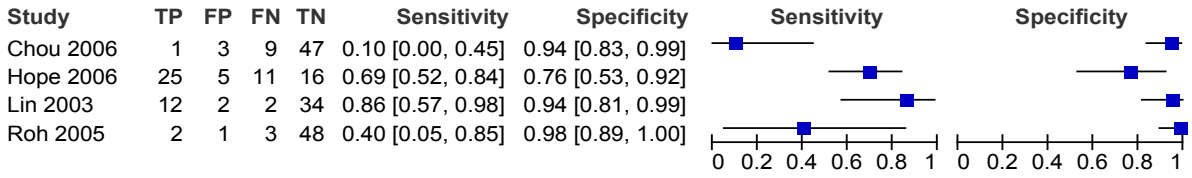
Figure 20. Summary ROC plot of ^{18}FDG-PET versus any reference standard for the staging of cervical cancer (prospective studies)



Reference standard: histology/biopsy; prospective studies. Four prospective studies[37,41,44,48] totaling 221 participants provided data for a subgroup analysis of the accuracy of ^{18}FDG-PET when

histology/biopsy or clinical followup were used as the reference standard for the staging of cervical cancer. Individual 2x2 table results are presented in Figure 21. Sensitivity ranged from 10%[37] to 86%.[44] Specificity ranged from -76%[41] to 98%.[48]

Figure 21. Results from 2x2 tables of individual prospective studies of ^{18}FDG-PET versus histology/biopsy or clinical followup for the staging of cervical cancer



We found that when only histology/biopsy were considered as reference standard, ^{18}FDG-PET had a pooled positive LR of 5.79 (95% CI 1.88, 17.88) and a pooled negative LR of 0.47 (95% CI = 0.17, 1.32) to accurately identify the staging of cervical cancer (Figures 22 and 23). Both the positive and negative LRs were statistically significant and therefore, ^{18}FDG-PET seems to be helpful to identify help to classify the stage of the disease. However, both the positive ($p = 0.08$; $I^2 =$ 56 percent) and the negative ($p < 0.000001$; $I^2 = 92$ percent) LRs were heterogeneous across the studies precluding firm conclusions based on these results.

Figure 22. Meta-analysis of the positive LR of ^{18}FDG-PET versus histology/biopsy or clinical followup for the staging of cervical cancer (prospective studies)

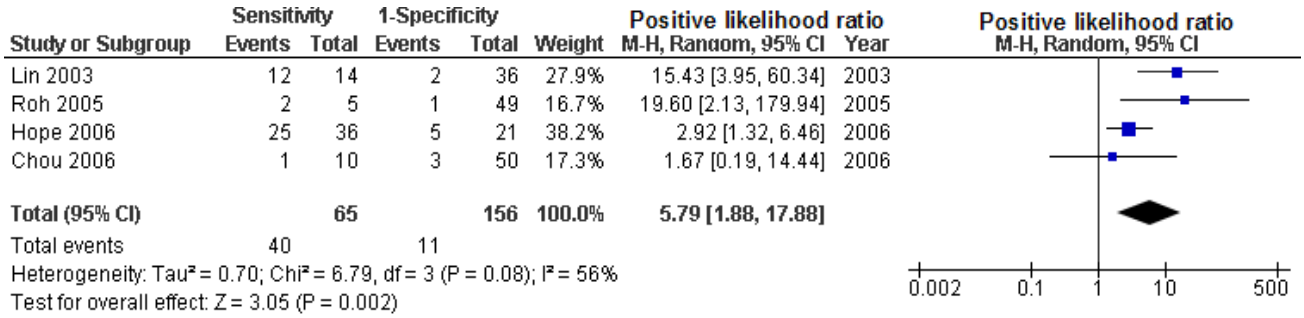


Figure 23. Meta-analysis of the negative LR of ^{18}FDG-PET versus histology/biopsy or clinical followup for the staging of cervical cancer (prospective studies)

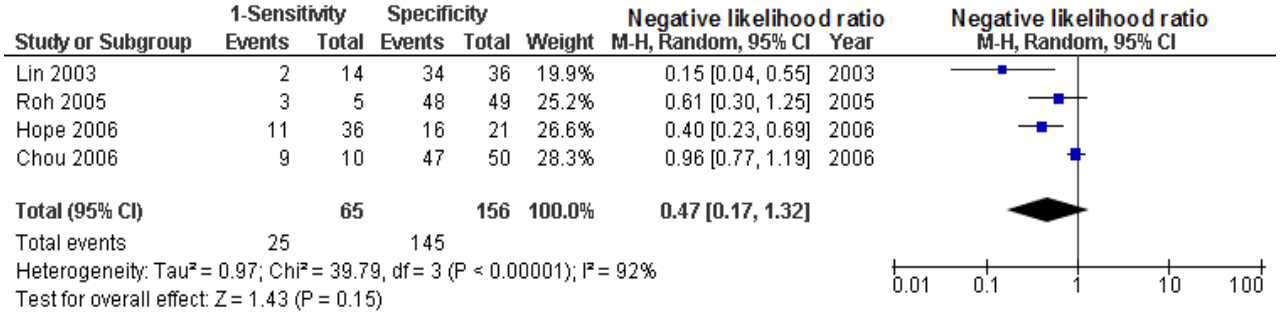
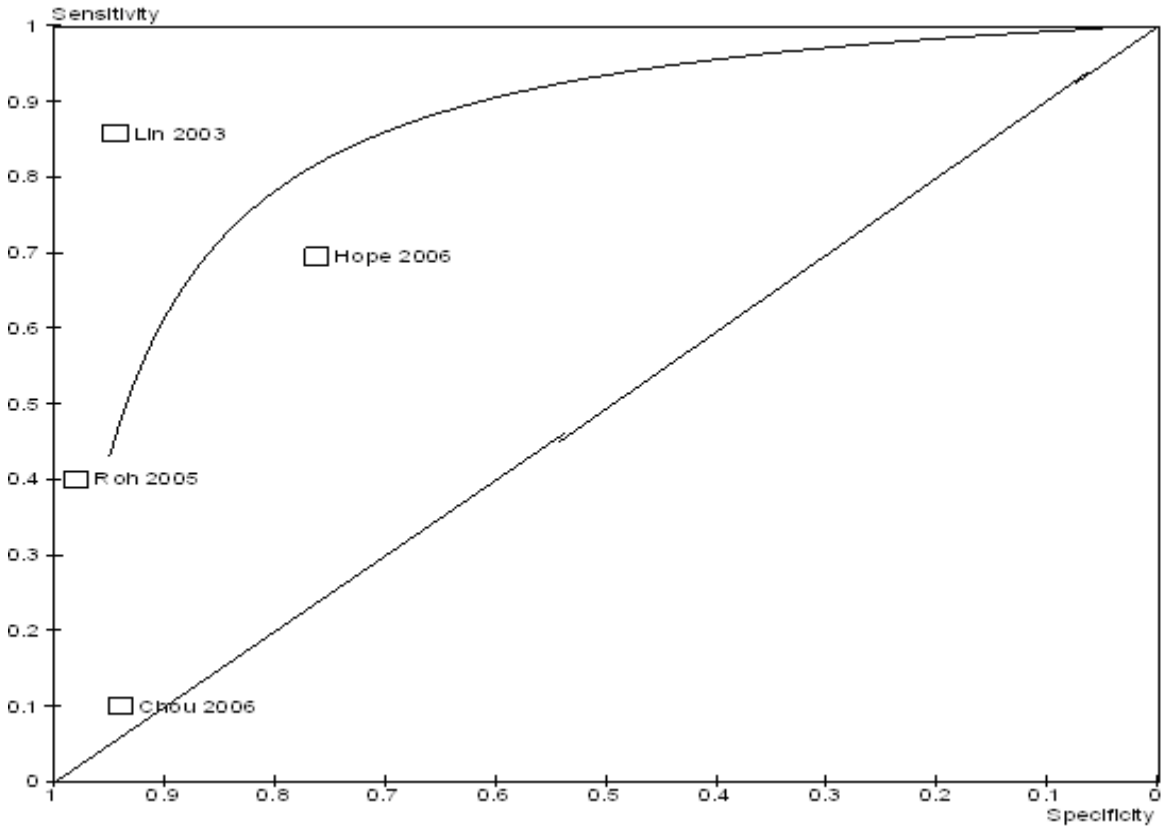


Figure 24 shows the estimates of sensitivity and 1-specificity plotted in ROC space for ^{18}FDG-PET versus histology/biopsy or clinical followup for the staging of cervical cancer.

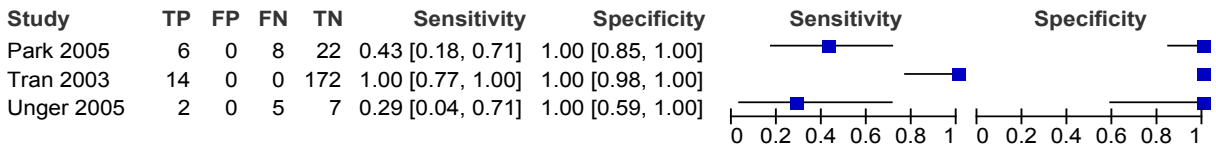
Figure 24. Summary ROC plot of ^{18}FDG-PET versus histology/biopsy or clinical followup for the staging of cervical cancer (prospective studies)



Reference standard: histology/biopsy; retrospective studies. A separate meta-analysis of studies was conducted for retrospective studies of ^{18}FDG-PET compared to histology/biopsy for the

staging of cervical cancer. Three retrospective studies[47,53,55] totaling 236 participants provided data for a meta-analysis of the accuracy of ^{18}FDG-PET compared to histology/biopsy for the staging of cervical cancer. Individual 2x2 table results are presented in Figure 25. Sensitivity values ranged from 29%[55] to 100%.[53] Specificity was 100% in the three studies.

Figure 25. Results from 2x2 tables of individual retrospective studies of ^{18}FDG-PET versus histology/biopsy or clinical followup for the staging of cervical cancer



Based on the analysis of retrospective studies, we found that ^{18}FDG-PET had a pooled positive LR of 32.90 (95% CI 2.89, 375.25) and a pooled negative LR of 0.41 (95% CI = 0.11, 1.55) to accurately identify the stage of cervical cancer (Figures 26 and 27). The positive LR was statistically significant; however, the results were moderately heterogeneous across the studies (p = 0.11; I^2 = 55 percent). The negative LR was not statistically significant and therefore, the test does not seem to be helpful to ruling out the presence of particular stages of the disease.

Figure 26. Meta-analysis of the positive LR of ^{18}FDG-PET versus histology/biopsy or clinical followup for the staging of cervical cancer (retrospective studies)

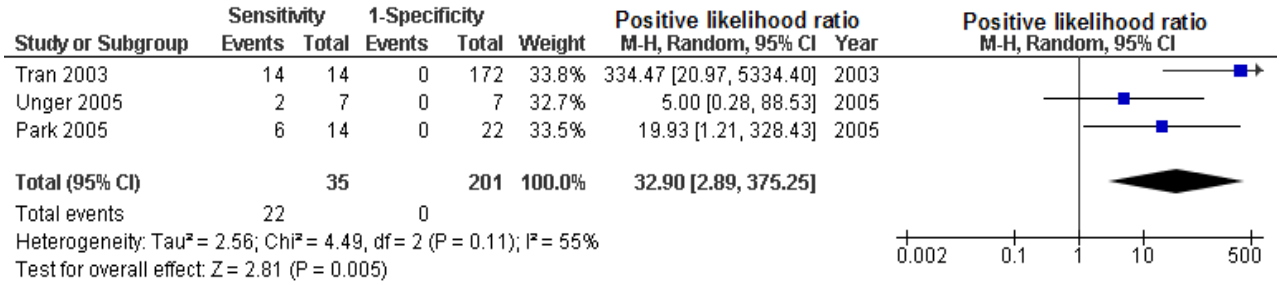


Figure 27 Meta-analysis of the negative LR of ^{18}FDG-PET versus histology/biopsy or clinical followup for the staging of cervical cancer (retrospective studies)

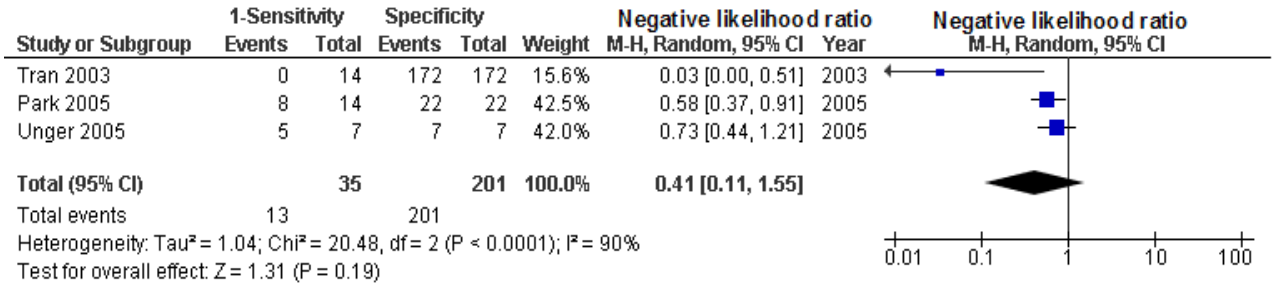
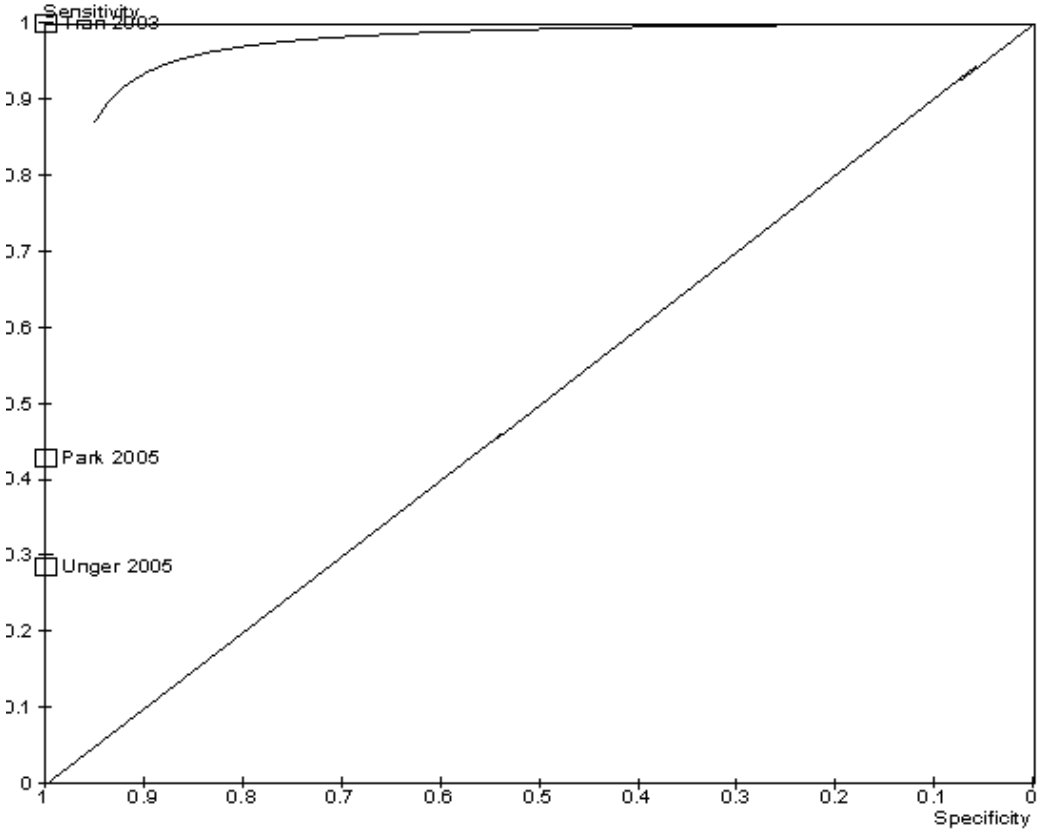


Figure 28 shows the estimates of sensitivity and 1-specificity plotted in ROC space for ^{18}FDG-PET versus histology/biopsy or clinical followup for the staging of cervical cancer based on retrospective studies.

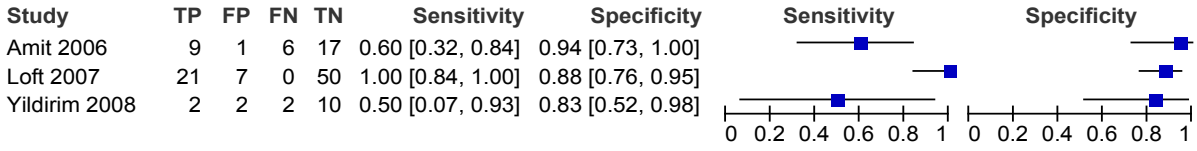
Figure 28. Summary ROC plot of ^{18}FDG-PET versus histology/biopsy or clinical followup for the staging of cervical cancer (retrospective studies)



3. ^{18}FDG-PET/CT for the staging of cervical cancer

Reference standard: any; prospective studies. Three prospective studies[31,45,62] totaling 127 participants provided data for a meta-analysis of the accuracy of ^{18}FDG-PET/CT compared to a variety of reference standards for the staging of cervical cancer. Individual 2x2 table results are presented in Figure 29. Sensitivity values ranged from 50%[62] to 100%.[45] Specificity ranged from 83%[62] to 94%.[31]

Figure 29. Results from 2x2 tables of individual prospective studies of ^{18}FDG-PET/CT versus any reference standard for the staging of cervical cancer



We found that ^{18}FDG-PET/CT had a pooled positive LR of 6.89 (95% CI 3.82, 12.42) and a pooled negative LR of 0.28 (95% CI = 0.06, 1.38) to accurately identify the stage of cervical cancer (Figures 30 and 31). The positive LR was statistically significant and the results were homogeneous across the studies and therefore, it can be said that ^{18}FDG-PET/CT seems to be helpful to identify the stage of the disease. The negative LR was not statistically significant, and the results were quite heterogeneous across the studies ($p = 0.004$; $I^2 = 82$ percent) and therefore, ^{18}FDG-PET/CT does not seem to be helpful rule out particular stages of the disease.

Figure 30. Meta-analysis of the positive LR of ^{18}FDG-PET/CT versus any reference standard for the staging of cervical cancer (prospective studies)

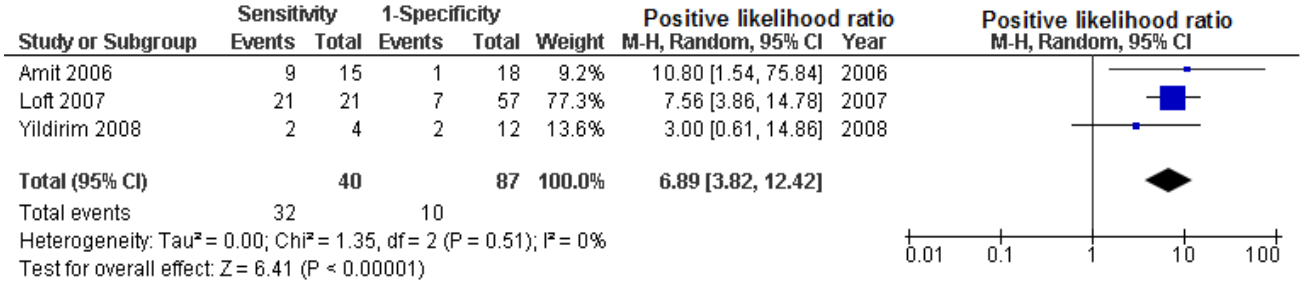


Figure 31. Meta-analysis of the negative LR of ^{18}FDG-PET/CT versus any reference standard for the staging of cervical cancer (prospective studies)

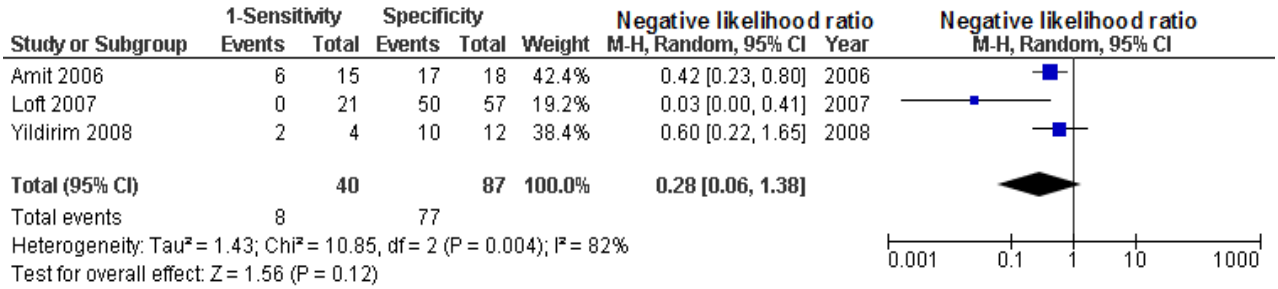
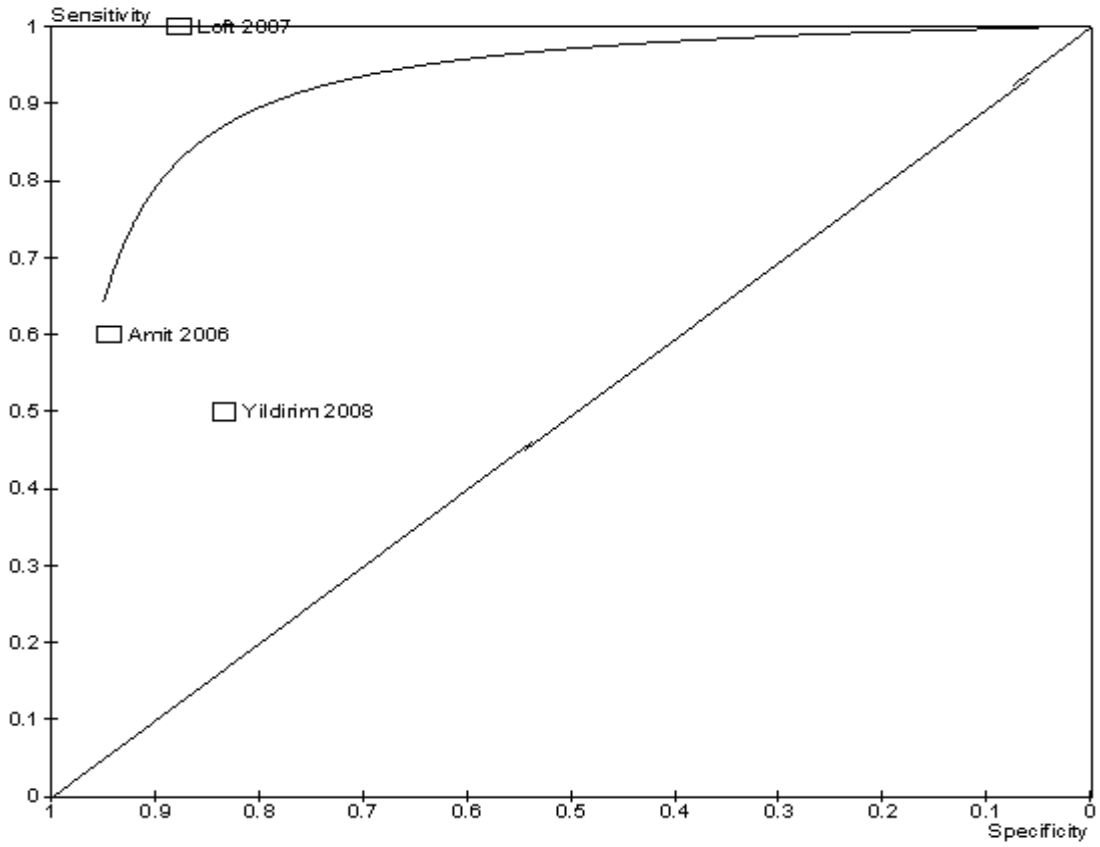


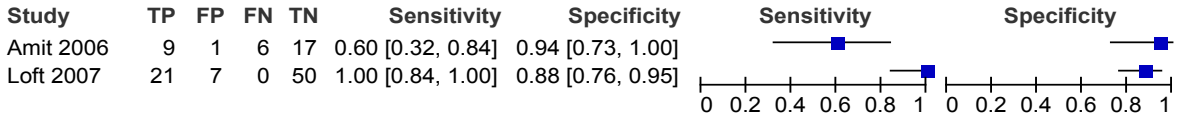
Figure 32 shows the estimates of sensitivity and 1-specificity plotted in ROC space for ^{18}FDG-PET/CT versus any reference standard for the staging of cervical cancer.

Figure 32. Summary ROC plot of ^{18}FDG-PET/CT versus any reference standard for the staging of cervical cancer (prospective studies)



Reference standard: histology/biopsy or clinical followup; prospective studies. Two prospective studies[31,45] totaling 111 participants provided data for a subgroup analysis of the accuracy of ^{18}FDG-PET/CT compared to histology/biopsy or clinical followup for the staging of cervical cancer. Individual 2x2 table results are presented in Figure 33. Sensitivity values were 60%[31] and 100%.[45] Specificity values were 88%[45] and 94%.[31]

Figure 33. Results from 2x2 tables of individual prospective studies of ^{18}FDG-PET/CT versus histology/biopsy or clinical followup for the staging of cervical cancer



We found that when only histology/biopsy were considered as reference standard, ^{18}FDG-PET/CT had a pooled positive LR of 7.85 (95% CI 4.16, 14.80) and a pooled negative LR of 0.12 (95% CI = 0.00, 10.08) to accurately identify the stage of cervical cancer (Figures 34 and 35). The positive LR was statistically significant and the results were homogeneous across the studies and therefore, it can be said that ^{18}FDG-PET/CT seems to be helpful to identify the stage of the disease. The negative LR was not statistically significant, and the results were quite heterogeneous across the studies (p = 0.002; I^2 = 90 percent) and therefore, ^{18}FDG-PET/CT does not seem to be helpful to rule out particular stages of the disease.

Figure 34. Meta-analysis of the positive LR of ^{18}FDG-PET/CT versus histology/biopsy or clinical followup for the staging of cervical cancer (prospective studies)

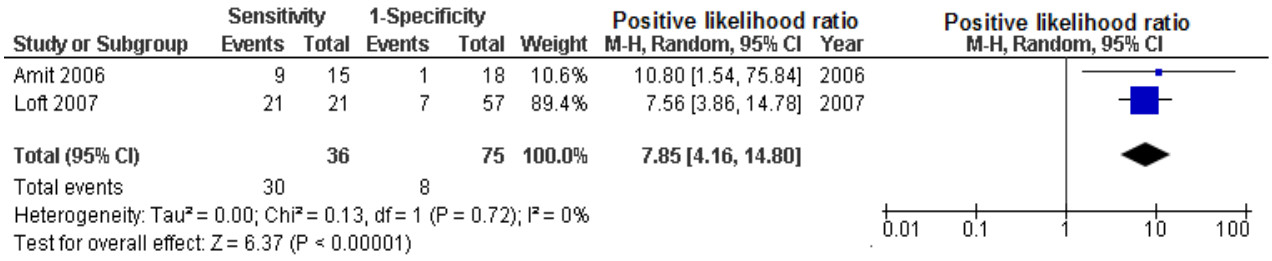


Figure 35. Meta-analysis of the negative LR of ^{18}FDG-PET/CT versus histology/biopsy or clinical followup for the staging of cervical cancer (prospective studies)

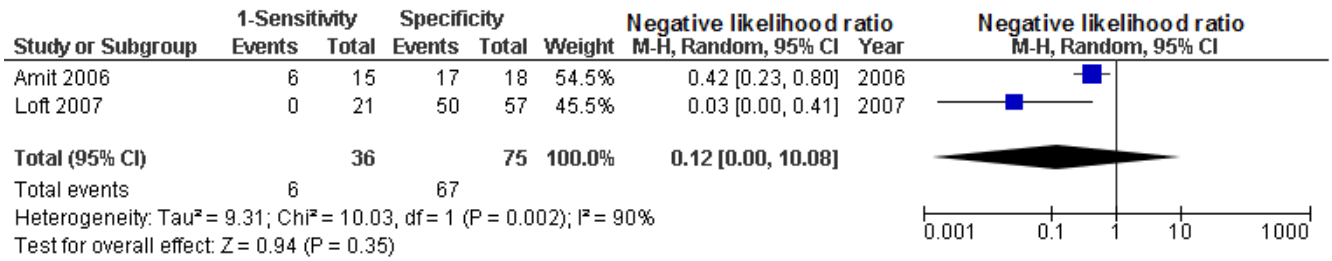
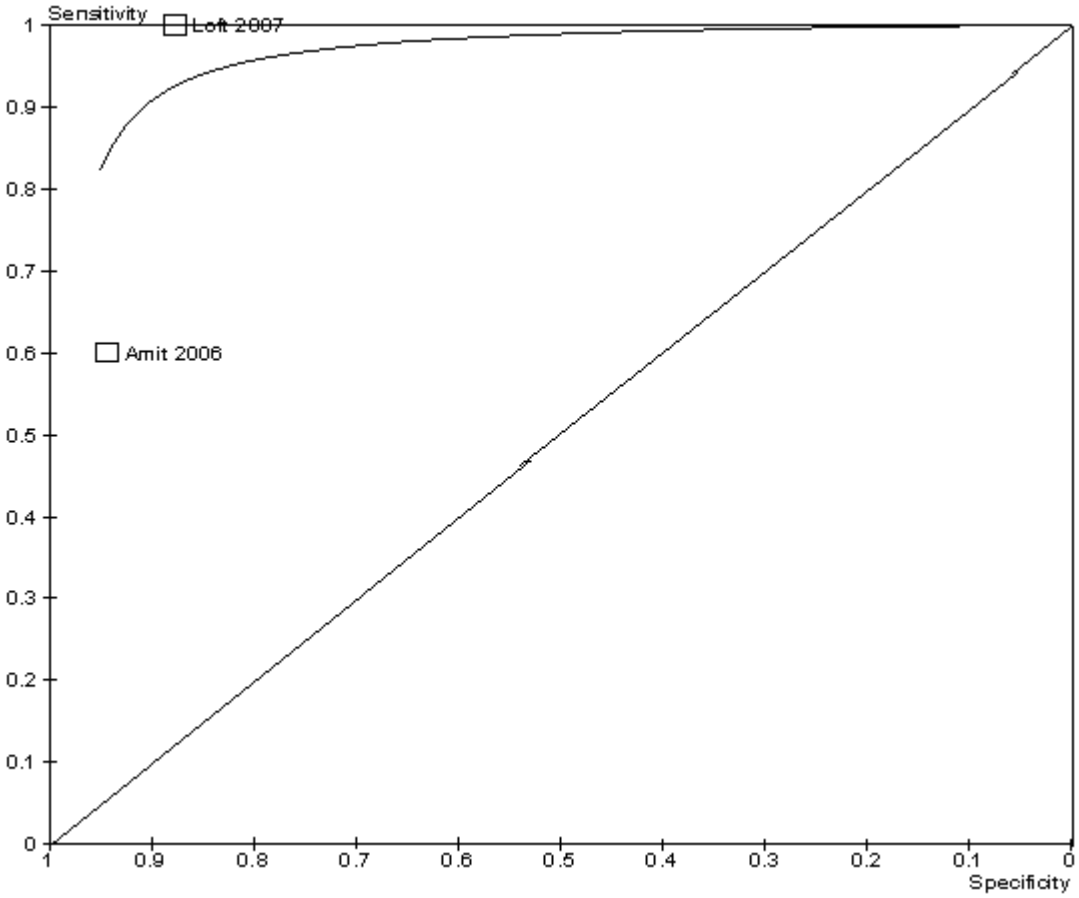


Figure 36 shows the estimates of sensitivity and 1-specificity plotted in ROC space for ^{18}FDG-PET/CT versus histology/biopsy or clinical followup for the staging of cervical cancer.

Figure 36. Summary ROC plot of ^{18}FDG-PET/CT versus histology/biopsy or clinical followup for the staging of cervical cancer (prospective studies)



Summary of the results

Meta-analyses were calculated to evaluate the accuracy of ^{18}FDG-PET and ^{18}FDG-PET/CT to detect recurrences and identify the staging of cervical cancer (Table 13) The largest estimate of the positive LR to detect recurrences of cervical cancer was obtained for ^{18}FDG-PET when compared to histology/biopsy or clinical followup to detect recurrences in liver/spleen (PLR=45.89). The confidence interval indicates that more data should be collected before anything definite can be said about the parameter. The smallest estimate of the negative LR was obtained to identify recurrences in MLN (NLR=0.09); however, the results were heterogeneous and firm conclusions cannot be drawn based on this pooled estimate. When ^{18}FDG-PET and ^{18}FDG-PET were evaluated for staging purposes, we found that the values in the positive and negative LRs were similar for both techniques. Significant results were reported for the positive LR, indicating that both techniques seem to be useful to detect the stage of the disease. The results for the negative LR were not statistically

significant and therefore, it can be said that a negative result both in ^{18}FDG-PET and ^{18}FDG-PET is not useful to identify the stage of cervical cancer.

Table 13. Results of meta-analyses of the accuracy of ^{18}FDG-PET and ^{18}FDG-PET/CT for cervical cancer

PET Purpose	Type of PET	Reference standard	Design	Studies	N	Effect estimate M-H, Random, 95% CI
Recurrences	FDG-PET	Histology/biopsy or clinical followup	P	3	230	Peritoneum: PLR=15.75 [5.99, 41.38]
						NLR=0.37 [0.22, 0.60]
						Bone: PLR=26.56 [11.21, 62.95]
						NLR=0.22 [0.01, 3.40]
						Liver/spleen: PLR=45.89 [14.09, 149.49]
						NLR=0.25 [0.08, 0.82]
						Lung: PLR=33.32 [13.85, 80.14]
						NLR=0.22 [0.10, 0.48]
						MLN: PLR= 15.24 [5.63, 41.27]
						NLR=0.09 [0.02, 0.40]
						SLN: PLR=29.06 [12.06, 70.03]
						NLR=0.19 [0.10, 0.36]
						PALN: PLR=40.24 [11.60, 139.54]
						NLR=0.12 [0.07, 0.23]
						PLN: PLR=41.42 [14.51, 118.25]
						NLR=0.23 [0.08, 0.73]
						ILN: PLR=27.92 [12.00, 64.94]
						NLR=0.17 [0.05, 0.60]
			R	3	396	PLN=5.33 [2.36, 12.05]
						NLR=0.11 [0.04, 0.28]
Staging	FDG-PET	Any reference standard	P	5	325	PLR=8.22 [2.59, 26.08]
						NLR=0.38 [0.12, 1.20]
		Histology/biopsy	P	4	221	PLR=5.79 [1.88, 17.88]
						NLR=0.47 [0.17, 1.32]
			R	3	236	PLR=32.90 [2.89, 375.25]
						NLR=0.41 [0.11, 1.55]
	FDG-PET/CT	Any reference standard	P	3	127	PLR=6.89 [3.82, 12.42]
						NLR=0.28 [0.06, 1.38]
		Histology/biopsy or clinical followup	P	2	111	PLR=7.85 [4.16, 14.80]
						NLR=0.12 [0.00, 10.08]

95% CI=95% confidence interval; FDG= fluorodeoxyglucose; ILN= inguinal lymph node; M-H = Mantel Hantzel; MLN= mediastinal lymph node ; NLR=negative likelihood ratio; P=prospective; PALN= para-aortic lymph node ; PET=positron emission tomography; PLN= pelvic lymph node; PLR=positive likelihood ratio; R=retrospective; SLN= supraclavicular lymph node

3.3.2. Diagnostic thinking impact of ^{18}FDG-PET and ^{18}FDG-PET/CT on physician decision making with respect to diagnosis and management strategy for patients with cervical cancer

Six studies reported on the diagnostic thinking impact of ^{18}FDG-PET[33,42,43,61] and ^{18}FDG-PET/CT.[32,38]

The study by Bjurberg *et al*[32] evaluated the treatment decision and diagnostic testing impact of ^{18}FDG-PET for assessment of staging and restaging of cervical cancer. This prospective study

enrolled 42 patients with biopsy-proven cervical cancer that were included in three sub-groups for analysis: 1) early disease, follow-up after surgical treatment (n=10), FIGO stage IA:2-IIA; 2) locally advanced disease scheduled for radical radiotherapy (n=17), FIGO stage IB:2-IVB; and 3) relapsing disease (n=15). The mean age of the patients in the three groups was 38.8 yrs, 55.5 yrs and 50.3 yrs respectively. Changes in treatment management were reported in groups 2 and 3. Of the 17 patients in group 2, 4 had their treatment strategy changed following ^{18}FDG-PET detection of new metastases (24%). In the 15 group 3 patients, there were three cases deemed to be benign by ^{18}FDG-PET imaging. Subsequent follow-up testing verified that ^{18}FDG-PET had correctly identified the patients to be free from recurrent disease. Additionally, ^{18}FDG-PET led to a change in the treatment plan for three of the 12 patients deemed to be positive for recurrent disease (25%). Additional diagnostic testing was performed in six of the 12 recurrent cases.

The study concluded that ^{18}FDG-PET provided detail about the extent of disease which contributed to the restaging and appropriate management of the patients with locally advanced or recurrent cervical cancer. However, they felt that there was not added value to patient management when ^{18}FDG-PET was used in follow-up for patients with early stage disease. They based this statement on their current results, and point out that the follow-up period was short and the number of patients was very small.

Chung *et al*[38] examined the treatment decision impact of ^{18}FDG-PET/CT on assessing the recurrence of cervical cancer. The medical records of 52 women with suspected recurrence of cervical cancer were retrospectively reviewed. The mean age of patients was 53 years (range: 32-77), with primarily stage I (50%) and II (40%) cancer. Treatment management was altered on the basis of ^{18}FDG-PET/CT findings for 12 patients (23%). In three patients, previously unplanned treatment was initiated, while in five patients, ^{18}FDG-PET/CT prompted change to the previously planned therapeutic approach. The need for previously planned diagnostic procedures was eliminated in the final three patients. In addition, ^{18}FDG-PET/CT provided valuable information for 12 patients, by identifying the exact location of lymph nodes (5 patients), showing precise location of pelvic-wall or bone infiltration (5 patients) and the exact location of distant metastases. In nine patients, ^{18}FDG-PET/CT guided additional invasive diagnostic procedures.

The authors also reported the prognostic outcomes of patients undergoing ^{18}FDG-PET/CT. The 2-year disease-free survival rate of patients who had negative ^{18}FDG-PET/CT results was

significantly better than that of patients who tested positive on ^{18}FDG-PET/CT (85% versus 10.9%, p=0.002).

The authors concluded that ^{18}FDG-PET/CT provides good anatomical and functional localization of suspicious lesions. The superior diagnostic interpretation of ^{18}FDG-PET/CT has a positive impact on clinical management, treatment planning and on patient disease-free survival rate.

This retrospective study was rated as having moderate quality. The greatest methodological weaknesses of this study include only partial reporting of the spectrum of patients enrolled, thereby presenting the risk of spectrum bias, and lack of clarity on the period between the index and reference standard.

Chang *et al*[33] evaluated the treatment decision impact of ^{18}FDG-PET on disease recurrence of cervical cancer. Consecutive outpatients were prospectively enrolled between February 2001 and January 2003. A historical control group that did not undergo ^{18}FDG-PET was used for comparison. Eligible patients had a history of histologically confirmed squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma of the uterine cervix that had complete remission after primary treatment or salvage therapy. In addition, patients had elevated serum SCC-Ag levels greater than 2.0 ng/mL over the last two weeks of the study, but no evidence of recurrent disease on physical examination, Pap smear, chest X-ray, CT or MRI of the pelvis and abdomen, or histological evaluation. Patients who received cytotoxic therapy within the previous 3 months, were previously diagnosed with malignant disease other than nonmelanoma skin malignancy, or had skin or pulmonary lesions, were ineligible. The study population consisted of 27 females, with a mean age of 53.9 years (range: 34.8-75.8 years). The disease stage at initial diagnosis was mainly stage I (44%) and II (42%). It should be noted that 15 of the patients in this study, who had documented relapse after PET, were also included as a subset of the population in another study by Yen *et al*,[61] reported below. Although these studies were conducted by the same authors and institutions and have overlap in the patient populations, different outcomes were reported in the latter study and therefore this study is included in our review. Final diagnosis was established through histological or cytological confirmation via CT or sonar-guided biopsy before treatment. Laparoscopic or exploratory surgery was performed if it was judged as potentially useful for patient management purposes. Patients with inconsistent findings underwent clinical followup for 6 months. ^{18}FDG-PET images were interpreted through visual analysis. Diagnosis and treatment decisions were made by consensus among a multidisciplinary panel.

Of the 17 patients with recurrent disease identified by ^{18}FDG-PET, seven received therapy with curative intent, four received palliative chemotherapy, and six received supportive care. One patient with negative PET findings had recurrent disease diagnosed at 2 months of clinical followup and received palliative therapy. Compared to the 39% (7/18) of patients with recurrence who received treatment with curative intent based on PET findings, only 53% (16/30) of patients in the historical control group received treatment with curative intent.

The authors concluded that ^{18}FDG-PET is a valuable tool for detecting recurrent disease. They suggest that ^{18}FDG-PET findings allow the selection of patients for treatment with curative intent and also avoid administering unnecessary treatment to patients with incurable disease. Finally, the authors conclude that ^{18}FDG-PET has the possibility of improving the survival as well as the quality of life in patients with recurrent cervical malignancies.

Components that were well reported in this study include selection criteria, choice and execution of reference standard, execution of index test, intermediate test results and withdrawals from the study. In addition, the period between the index test and reference standard was sufficiently short to prevent disease progression, and a reference standard was applied to all patients, albeit not the same standard across all patients. The spectrum of patients enrolled in the study was only partially described, therefore the possibility of spectrum bias cannot be ruled out. This study is also vulnerable to review bias, since the reference standard was not blinded to the findings of the index test, and it is unclear whether the interpretation of the index test was blinded to the reference.

A study by Lai *et al*[42] examined the treatment decision impact of ^{18}FDG-PET for assessing restaging and recurrence of cervical cancer. The study population consisted of 45 females with a median age of 51 years (range 25-87) whose initial diagnosis was mainly stage I (33%) and II (50%). Along with a subset of patients from the study by Chang *et al,*[33] all of these 45 enrolled patients were also included in the study by Yen *et al,*[61] reported below. Although these studies were conducted by the same authors and institutions, and the patient populations overlap, different outcomes were reported in the latter study and therefore this study is also reported in our review. Of the 40 patients included in the analysis, 22 (55%) had a change in treatment planning as a result of ^{18}FDG-PET findings. Fifteen patients had their management shifted from curative to palliative treatment, while seven continued to be treated with curative intent but had a change in their treatment field or modality. Thus, prior to PET scanning, 23 patients planned to undergo concurrent chemotherapy and radiotherapy (CCRT), 17 planned to undergo surgery, and none to receive

treatment with palliative intent. After PET, 12 patients received CCRT, 13 received surgery and 15 received treatment with palliative intent. In addition, 14 patients underwent an additional guided biopsy (n=11) or exploratory surgery (n=3) due to the findings of ^{18}FDG-PET.

The authors concluded the ^{18}FDG-PET is better than CT/MRI in restaging cancer recurrence. ^{18}FDG-PET may significantly reduce the number of unnecessary salvage attempts compared to conventional assessment. Therefore, the authors conclude that use of ^{18}FDG-PET in restaging allows the clinician to offer optimal management of recurrent cervical carcinoma.

The quality of this prospective study was assessed as moderate. The selection criteria were clearly described, as was the choice of reference standard and the execution of both index and reference tests. All test results and study participants were accounted for. The period between the index and reference test was sufficiently short that it is unlikely that disease progressed between tests. The whole sample received disease verification using a reference standard; however, the same reference standard was not used for all patients, raising the possibility of verification bias. There was only a partial description of the spectrum of patients included in the study. Finally, it was unclear whether the index test or the reference standard was interpreted while blind to other test results. Due to the lack of clarity in reporting, it is uncertain to what degree review bias may have affected the study findings.

Lin *et al*[43] prospectively investigated the benefit of adding ^{18}FDG-PET to the diagnostic workup in patients with histologically documented re-recurrent cervical cancer after curative salvage or unexplained elevations in tumor markers. The study sample consisted of 26 female patients (median age: 56 years). The disease stage at initial diagnosis was mainly stage I (42%) and II (38%). Of the 26 patients, 24 had a second recurrence, and two had a third recurrence. The median time between salvage therapy and documented re-recurrence was 12.8 months. Of the 26 patients enrolled, ^{18}FDG-PET had a positive clinical impact on 12 (46%). Among these 12 patients, nine were changed from curative to palliative treatment and three had an isolated in field failure successfully resected due to ^{18}FDG-PET. In contrast, ^{18}FDG-PET led to unnecessary and invasive additional procedures, such as biopsies, in four patients. As a result of these additional procedures, ^{18}FDG-PET was stated to have had an overall negative impact in the management of two patients.

The authors concluded that ^{18}FDG-PET may facilitate the selection of suitable management strategies for individual patients with re-recurrent cervical cancer.

This prospective study was assessed as being of high quality. Both the selection criteria and choice of reference standard were clearly described, and all test results and study participants were accounted for. The period between the index and reference test was short enough that it is unlikely that disease progressed between tests. The whole sample received disease verification using a reference standard; however, the same reference standard was not used for all patients, raising the possibility of verification bias. The execution of the reference test was well described and the execution of the index test was partially described. There was insufficient detail in reporting the recruitment of patients into the study, therefore it uncertain whether spectrum bias may have occurred. Finally, the index test results were interpreted without knowledge of the results of the reference standard; however, it was unclear whether the interpretation of the reference standard was also blinded. Therefore, it remains unclear whether review bias may have affected the results of this study.

Yen *et al*[61] investigated the treatment decision impact of ^{18}FDG-PET for assessing the recurrence of cervical cancer. Patients were enrolled from two separate prospective studies examining the role of ^{18}FDG-PET in cervical cancer patients; there were 40 included patients who had documented treatment failure (Lai *et al*[42]), while 15 patients had unexplained elevated tumor marker squamous cell carcinoma antigen or carcinoembryonic antigen serum level (Chang *et al*[33]). Although 27 patients were included in the study by Chang *et al,*[33] 12 were excluded due to lack of evidence of lesion presence, and the remaining 15 were enrolled in the present study. Along with the 40 patients enrolled from Lai *et al,*[42] a total of 55 females. The median age of patients was 51 years (range 25-86). Forty-five percent of patients had initial stages of Ib or IIa, while 55% had stages between IIb and IVa.

Of the 55 enrolled patients, 36 (65%) had their treatment plans modified based on the findings of ^{18}FDG-PET, while 19 (35%) were treated according to their prePET plan. Among these 36 patients, nine (25%) had treatment that remained with a curative intent although the field or modality of radiation changed, while 27 (75%) received palliative therapy. Three of the nine patients whose treatment was changed were downstaged.

A prognostic scoring system was used to categorize patients as having low, moderate or high risk of mortality. Based on the findings of ^{18}FDG-PET, 10 patients in the low-risk group were changed to palliative treatment, while 17 stayed at curative treatment (seven with changes in treatment plan, 10 with no changes). In the intermediate-risk group, 12 patients were changed to palliative care, and

seven stayed on curative therapy (two with changes in treatment plan, five with no change). Five patients were changed to palliative treatment in the high risk group, whereas one patient stayed on curative treatment.

The authors concluded that ^{18}FDG-PET is useful in the management of recurrent cervical cancer because it allows for a more precise restaging than CT or MRI. ^{18}FDG-PET may offer maximal benefit by identifying patients suitable for therapy with precise restaging information.

This prospective study was assessed to be of moderate quality. The selection criteria and choice of reference standard were clearly described, and all test results and study participants were accounted for. The time interval between the index and reference test was sufficiently brief that it is unlikely that disease progressed between tests. The whole sample received disease verification using a reference standard; however, the same reference standard was not used for all patients, raising the possibility of verification bias. The execution of both the index and reference standard was only partially described. In addition, it was unclear whether there was blind interpretation of the tests, which may have introduced review bias. Finally, there was lack of clarity in the description of how patients were recruited into the study, creating the potential for spectrum bias.

3.3.3. ^{18}FDG-PET and ^{18}FDG-PET/CT as part of a management strategy in cervical cancer

Two studies[33,42] evaluated the impact of ^{18}FDG-PET as part of a management strategy on patient-centered outcomes. Chang *et al.*[33] compared the mean overall survival between a group that underwent ^{18}FDG-PET and a historical control group. The followup times were similar for both groups (11.9 months and 14 months, respectively). Characteristics of the population and ^{18}FDG-PET have been described above. Compared to the historical control group, overall survival was improved in the group pf patients that had ^{18}FDG-PET as part of their diagnostic work-up (^{18}FDG-PET group = 22.0 months; 95% CI: 17.3 to 26.7 months; Historical cohort: 12.7 months; 95%CI: 7.9 to 17.5; p = 0.02). Due to the observational nature of this study, reliable conclusions cannot be made regarding the effectiveness of ^{18}FDG-PET as part of a management strategy to improve patients overall survival. It is unknown whether factors other than the exposure to the intervention (e.g., ^{18}FDG-PET) are equally distributed among the groups.

The study by Lai *et al*[42] compared the 2-yr overall survival rate between a group of patients that underwent ^{18}FDG-PET as part of their diagnostic work-up and a group of comparable previously

treated patients who did not undergo disease restaging with PET. Characteristics of the population and ^{18}FDG-PET have been described above. All seven patients who continued with curative treatment but who had their treatment field altered remained alive. In the primary surgery group, a significantly 2-year overall survival rate was noted among the ^{18}FDG-PET group compared to a historical cohort of patients whose disease was restaged without ^{18}FDG-PET (Hazard ratio: [HR]: 0.21; 95% CI: 0.05-0.83; p=0.02). Among patients receiving primary RT or CCRT there was no differences among the two groups in 2-year overall survival (HR: 0.99; 95% CI: 0.53, 1.85; p=0.99). The authors reported that clinical characteristics were similar for study participants and historical control patients in the primary surgery group and they suggest that the observed benefit in overall survival probably is not due to other prognostic factors. Lai *et al*[42] was an observational study and therefore, conclusions about the effectiveness of ^{18}FDG-PET on patient-survival are limited.

Table 14 provides a summary of the main findings and the types of bias that affected the evidence on the diagnostic thinking impact and effect on patient-centered outcomes of ^{18}FDG-PET and ^{18}FDG-PET/CT for cervical cancer

Table 14 Main findings and types of bias that affected the evidence on the diagnostic thinking impact and effect on patient-centered outcomes of ^{18}FDG-PET and ^{18}FDG-PET/CT for cervical cancer

Study	Results of FDG-PET imaging on Patient Diagnosis, Treatment and Outcomes	Types of Bias
Bjurberg 2007[32] Study type: Prospective	**Management decision:** Treatment and diagnostic testing impact -Treatment strategy changed due to identification of new metastasis for 4 / 17 cases (24%) -PET did not confirm clinical suspicion of recurrence. PET deemed to be true negative upon follow-up 3 / 15 cases; -Treatment strategy changed for 3 / 12 positive recurrence cases (25%) Additional diagnostic testing occurred in 6 / 12 positive recurrence cases	Spectrum bias (unclear) Selection bias (unclear) Verification bias (+1 RS) Review bias (PET; unblinded; RS, unblinded)
Chang 2004[33] Study type: Prospective	**Management decision:** Treatment Treatment plan changed in 17 / 27 cases (63%) Curative therapy (n=7) Palliative chemotherapy (n=4) Supportive care (n=6) 7/18 (39%) patients with recurrence received curative therapy based on PET, compared to 53% (16/30) in historical control **Patient-centered Outcomes:** Mean overall survival PET group: 12.7 mo (95%CI: 7.9,17.5) vs. historical control: 22 mo (95%CI: 17.3, 26.7)	Spectrum bias (unclear) Verification bias (+1 RS) Review bias (PET; unclear if blinded; RS, unblinded)
Chung 2007[38] Study type: Retrospective	**Management decision:** Treatment & Diagnostic Testing Impact Treatment management change in 12 patients (23%): Initiated previously unplanned treatment (n=4), Changed previously planned therapeutic approach (n=5) Eliminate previously planned diagnostic procedure (n=3) PET/CT guided additional invasive diagnostic procedures (n=9).	Spectrum bias (unclear) Selection bias (unclear) Disease progression bias (unclear) Verification bias (+1 RS) Review bias (RS, unclear)
Lai 2004[42] Study type: Prospective	**Management decision:** Treatment & Diagnostic Testing Impact Treatment plan change in 22 / 40 patients (55%): Shifted from curative to palliative treatment (n=15), Curative treatment continued; altered treatment field or modality (n=7) Diagnostic testing impact due to PET findings in 14 patients: Additional guided biopsy (n=11); exploratory surgery (n=3) **Patient-centered Outcomes** Patients treated with altered treatment field remained alive (n=7). Primary surgery group, had a significant 2-yr overall survival rate in the PET group compared to those restaged without PET. Patients receiving primary RT or CCRT had no significant differences among the two groups.	Spectrum bias (unclear) Verification bias (+1 RS) Review bias (PET and RS; unclear if blinded)
Lin 2006[43] Study type: Prospective	**Management decision:** Treatment PET had positive clinical impact on 12 / 26 patients (46%); Changed from curative to palliative treatment (n=9), Isolated in field failure successfully resected due to PET (n=3) PET led to unnecessary and invasive additional procedures, (n=4) (e.g. biopsies). PET stated to have had overall negative impact in management (n=2)	Spectrum bias (unclear) Verification bias (+1 RS) Review bias (RS; unclear if blinded)
Yen 2004[61] Study type: Prospective	**Management decision:** Treatment Treatment plans modified based on PET in 36 / 55 patients (65%): Field or modality of radiation changed (n=9) Changed from curative to palliative therapy (n=27)	Spectrum bias (unclear,) Verification bias (+1 RS) Review bias (PET and RS; unclear if blinded)

CCRT= concurrent chemotherapy and radiotherapy; FDG=Fluorodeoxyglucose F18; mo=months; PET=positron emission tomography; RS=reference standard; RT=radiotherapy; vs.=versus

4. Kidney Cancer

4.1. Background

Approximately 54,390 new cases of kidney and renal pelvis cancer will be diagnosed in the United States during 2008. Sixty percent of these cases will occur in men.[133] The National Cancer Institute indicates that kidney cancer has been increasing at a rate of 2% per year for the last 65 years. Mortality has also increased, but to a lesser degree then incidence, during this same time period.[133] An estimated 13,101 deaths will be caused by kidney cancer in 2008.[133] Native Americans suffer the highest rates of kidney cancer (20.9 and 10.0 cases per 100 00 for men and women respectively) however African-Americans also show higher rates of cancer incidence then what is observed among Caucasians.[148] In Europe renal cancer ranks as the seventh most common kind of cancer among men and the twelfth most common among women with overall incidence being higher in economically richer societies.[149] Renal cancer has a median age of onset of 65 years.[133] Five year survival is 71% in individuals under 45 years of age where kidney cancer is rare but decreases to 45% in patients over 74 years in Europe.[149]

Cigarette smoking and obesity are the two strongest risk factors associated with renal cancer.[148] Cigarettes may be associated with 1/3 of all kidney cancers and eliminating cigarette smoking may reduce the incidence of kidney cancer by 16-28% in the adult population.[149] The relationship between kidney cancer and obesity is linear with risk increasing as body weight increases. This relationship is mirrored by increasing mortality rates particularly in women.[149] Hypertension and family history are also associated with the disease.[148] Environmental exposure to certain chemicals has been found to increase risk in epidemiological studies; these chemicals include: iron; steel; petroleum; asbestos; cadmium; and dry cleaning solvent.[149] Conflicting evidence concerning a protective effect of a diet high in fruits and vegetables has been reported. There may be an association between fatty fish or a higher intake of omega-3 fatty acids associated with a decreased risk of kidney cancer.[148]

The early diagnosis of renal carcinoma is hampered by the observation that tumors can grow quite large before the patient exhibits any symptoms. Pain, haematuria, and flank masses have been traditional symptoms but these appear in only 9% of patients and are often indicative of advanced disease.[149] Approximately 30% of patients have with metastatic disease.[149] Hyprochromic anaemia, fever, cachexia, fatigue, and weight loss may also be symptomatic of renal carcinoma.[149]

Specific early screening programs for kidney cancer are not realistic as the populations that would be targeted are too large and there is no evidence that could be used to recommend a screening program.[149] Small renal masses are being detected through routine imaging with increasing frequency, but imaging is not specific enough to accurately discriminate between benign and malignant tumors. Local symptoms are the best predictive tool in determining malignancy.[148]

Computed tomography has shown to be the most effective tool in the staging of renal carcinomas with a sensitivity of 90% for small tumors and 95% for tumors larger then 3cm.[149] Ultrasonography is often used as well, having a sensitivity of 60% for detecting small tumors and 85% for larger tumors.[149] Magnetic resonance imaging (MRI) has not been shown to be effective in characterising tumors in renal carcinoma patients but may still be employed to provide information about the tumor involvement with the vena cava or when surgical removal of tumors is being planned.[149] Staging of renal carcinoma is commonly done using the Robson classification scheme within the United States (Table 15). While this staging system is uncomplicated, a weakness of the system is that it combines stages which may have widely varied survival prognoses. The Robson stages of renal carcinoma are outlined below:

Table 15. Robson Stages of Renal Carcinoma

Stage	Description
I	Renal carcinoma is localized to the kidney only.
II	Cancer extends to renal capsule but is confined to the Gerota's fascia.
III	Tumor is associated with the inferior vena cava or renal vein (stage IIIa) or local hiliar lymph notes (stage IIIb).
IV	Cancer has spread to other local organs or distant sites.

Taken from Corgna *et al*[149]

The TNM classification offers more complete stratification of patients and a more accurate assessment of their prognosis. As with the bladder cancer TNM classification, the T refers to the tumor size and whether or not it has spread to adjacent tissues; the N represents whether or not there has been spread to the lymph nodes; while the M is indicative of whether or not the cancer has metastasised.

Surgical resection is the primary method of curative therapy for kidney cancer. Two common types of surgery performed are laparoscopic and radical nephrectomy.[148] Radical nephrectomy is the main operation performed but new organ-sparing approaches have increased research interest in laparoscopic nephrectomy.[148,149] Palliative surgery is also frequent.[149] There are no standard chemotherapy or immunotherapy treatments for renal cell carcinoma and it may be unadvisable to

use such treatments outside of a clinical trial.[149] Radiation therapy in patients with metastatic disease may allow the resolution of symptoms in some patients.[149]

4.2. Importance of Key Questions in the Clinical Management of Kidney Cancer

Survival is very much related to the stage of cancer when it is diagnosed. The ability to detect and characterize renal masses more accurately and to stage malignant renal tumors is crucial for the management of patients. The identification of a single or several metastatic lesions can lead to differing therapeutic approaches (e.g., surgery or systemic treatment). If detected early, renal tumors can be treated with alternatives other than standard radical nephrectomy, such as minimally invasive surgery and partial nephrectomy. Although solid renal masses are considered malignant tumors, benign solid renal masses are not uncommon. Morphological imaging methods present several diagnostic problems in differentiating between benign and malignant solid renal tumors. They also show some limitations evaluating kidney cancer with regards to local spread and distant disease. Improving the diagnostic yield of these investigations while precluding the need for obtaining a tissue diagnosis would have obvious implications in management. The role of ^{18}FDG-PET in the diagnosis, staging, and management of kidney cancer has not been clearly defined. Due to the potential problem of physiological excretion of ^{18}FDG through the kidneys, the usefulness of ^{18}FDG-PET has been documented mainly in detection of distant metastasis of renal tumors and the literature regarding the evaluation of primary solid renal masses is still not clear.

4.3. Results

Eight studies[64-71] provided evidence on the use of ^{18}FDG-PET or ^{18}FDG-PET/CT for kidney cancer. All the eight studies evaluated the diagnostic accuracy of ^{18}FDG-PET or ^{18}FDG-PET/CT for kidney cancer. Three studies[67,69,70] reported on the diagnostic thinking impact of ^{18}FDG-PET. None of the studies evaluated the impact of ^{18}FDG-PET or ^{18}FDG-PET/CT as part of a management strategy on patient-centered outcomes. No economic evaluations on the use of ^{18}FDG-PET or ^{18}FDG-PET/CT for kidney cancer were identified. Characteristics of the populations, conditions of ^{18}FDG-PET administration, interpretation of results and methodological quality of the studies are summarized in appendices D to J.

4.3.1. Diagnostic accuracy of ^{18}FDG-PET and ^{18}FDG-PET/CT in kidney cancer

Characteristics of the studies

Eight studies (three prospective, [64,65,67] five retrospective[66,68-71]) evaluated the diagnostic accuracy of ^{18}FDG-PET on kidney cancer. One study used ^{18}FDG-PET for initial staging,[67] one for primary diagnosis,[65] one for restaging,[68] one for initial staging and recurrences,[71] and four used ^{18}FDG-PET for both primary diagnosis and initial staging.[64,66,69,70] The studies contained a total of 250 patients with sample sizes ranging from 15 to 66. The participant ages ranged from 23 to 87 years. In five studies ^{18}FDG-PET was compared to histology/biopsy or clinical follow-up as the reference standard,[64,67-70] in the three remaining studies histology/biopsy was used exclusively as the reference standard.[65,66,71] One study reported the mean time between last treatment and ^{18}FDG-PET as 3 to 24 months.[68] Three studies used a fixed dose of ^{18}FDG (1.5 mCi,[67] 395.9 MBq,[71] 370 MBq[66]); two studies used a weight-based dose (2.516-5.2 MBq/kg[70] and 2 MBq/kg[64]); two studies reported a dose range (370-444 MBq[65] and 370-555 MBq[68]); and one study did not report on dosing.[69] The time between ^{18}FDG injection and PET scan was 50 minutes[66]; 60 minutes[64,65,67,70]; 45 minutes,[69] and ranged between 45-60 minutes.[68,71] Patients fasted for four hours,[67,70] six hours,[64-66] and overnight.[71] Three of these studies measured a maximum glucose levels of 135 mg/Dl,[65] 140 mg/dL,[70] and 150 mg%[66] before administration of ^{18}FDG-PET. Methods of interpretation were qualitative in five studies[64,65,68,69,71] and both qualitative and quantitative in two studies.[66,70] Scans were interpreted qualitatively using visual analysis in all studies.[64-66,68-71] Both studies[66,70] used SUV values for the quantitative interpretation of the PET images with one study reporting the criterion for abnormality as an SUV > 2.5 g/mL.[66]

Comparisons

Comparisons for which data were considered for meta-analysis are summarized in Table 16. Pooled data were obtained to evaluate the accuracy of ^{18}FDG-PET for the primary diagnosis and staging of kidney cancer. Individual study data are summarized in Appendix D.

Table 16. Summary of comparisons considered for meta-analyses of the accuracy of ^{18}FDG-PET for kidney cancer

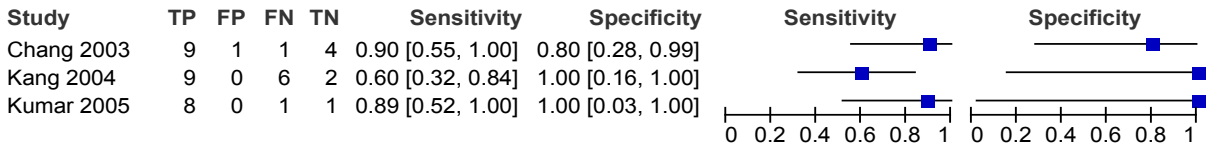
Indication	Studies	Design	Type of PET	Reference standard	Meta-analysis
Primary diagnosis and staging	Aide 2003[64]	P	FDG-PET	Histology/biopsy or clinical followup	1. FDG-PET vs. any reference standard (R studies) [66,69,70] 2. FDG-PET vs. histology/biopsy or clinical followup (R studies) [69,70]
	Chang 2003[66]	R	FDG-PET	Histology/biopsy	
	Kang 2004[69]	R	FDG-PET	Histology/biopsy or clinical followup	
	Kumar 2005[70]	R	FDG-PET	Histology/biopsy or clinical followup	
Staging and recurrences	Majhail 2003[71]	R	FDG-PET	Histology/biopsy	No
Primary diagnosis	Ak 2005[65]	P	FDG-PET	Histology/biopsy	No
Restaging	Jadvar 2003[68]	R	FDG-PET	Histology/biopsy or clinical followup	No
Staging	Dilhuydy 2006[67]	P	FDG-PET	Histology/biopsy or clinical followup	No

FDG= fluorodeoxyglucose; P = prospective; PET=positron emission tomography; R = retrospective; vs.=versus

1. ^{18}FDG-PET for the primary diagnosis and staging of kidney cancer

Reference standard: any; retrospective studies. A meta-analyses of retrospective studies was conducted to evaluate the accuracy of ^{18}FDG-PET for the primary diagnosis and staging of kidney cancer. Three retrospective studies[66,69,70] totaling 42 participants compared ^{18}FDG-PET versus any reference standard for the primary diagnosis and staging of kidney cancer. Individual 2x2 table results are presented in Figure 37. Sensitivity values ranged from 60%[69] and 90%.[66] Specificity ranged from 80%[66] and 100%.[69,70]

Figure 37. Results from 2x2 tables of individual retrospective studies of 18FDG-PET versus any reference standard for the primary diagnosis and staging of kidney cancer



We found that[18]FDG-PET had a pooled positive LR of 3.95 (95% CI 1.14, 13.73) and a pooled negative LR of 0.30 (95% CI = 0.12, 0.79) to accurately help in the diagnosis and staging of kidney cancer (Figures 38 and 39). Both the positive and negative LRs were statistically significant and the results were fairly homogeneous across the studies. Therefore, [18]FDG-PET seems to be helpful in the primary diagnosis and detection of staging of kidney cancer.

Figure 38. Meta-analysis of the positive LR of [18]FDG-PET versus any reference standard for the primary diagnosis and staging of kidney cancer (retrospective studies)

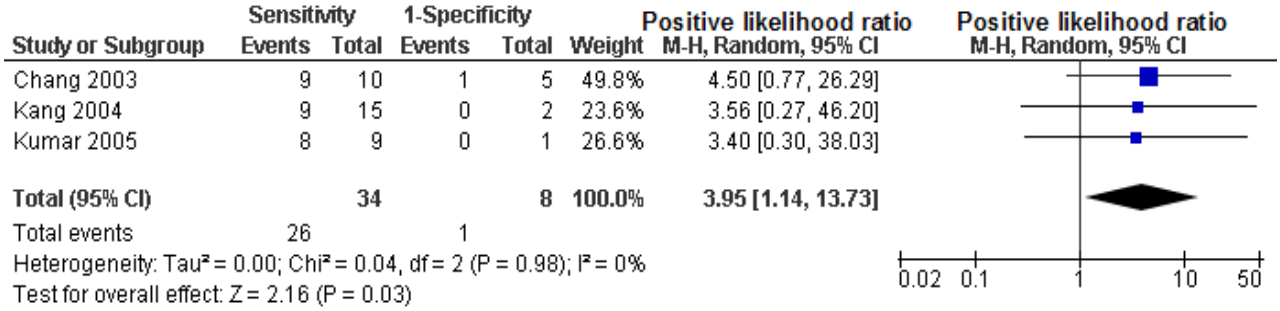


Figure 39. Meta-analysis of the negative LR of [18]FDG-PET versus any reference standard for the primary diagnosis and staging of kidney cancer (retrospective studies)

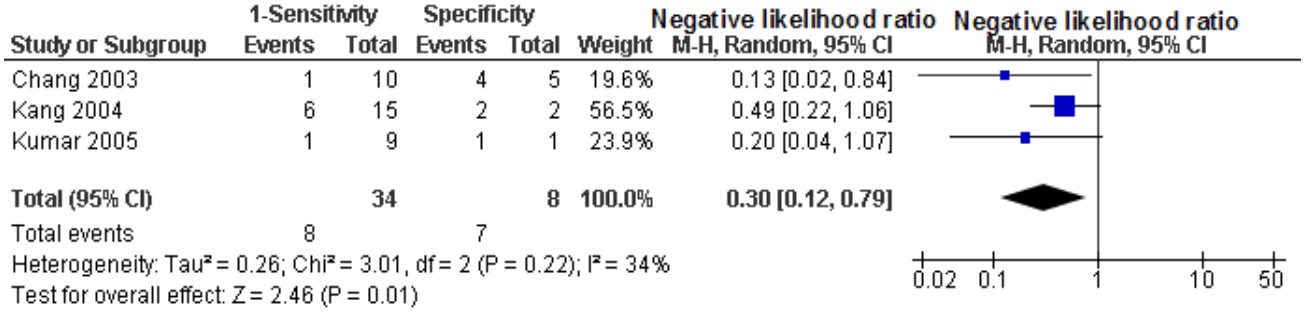
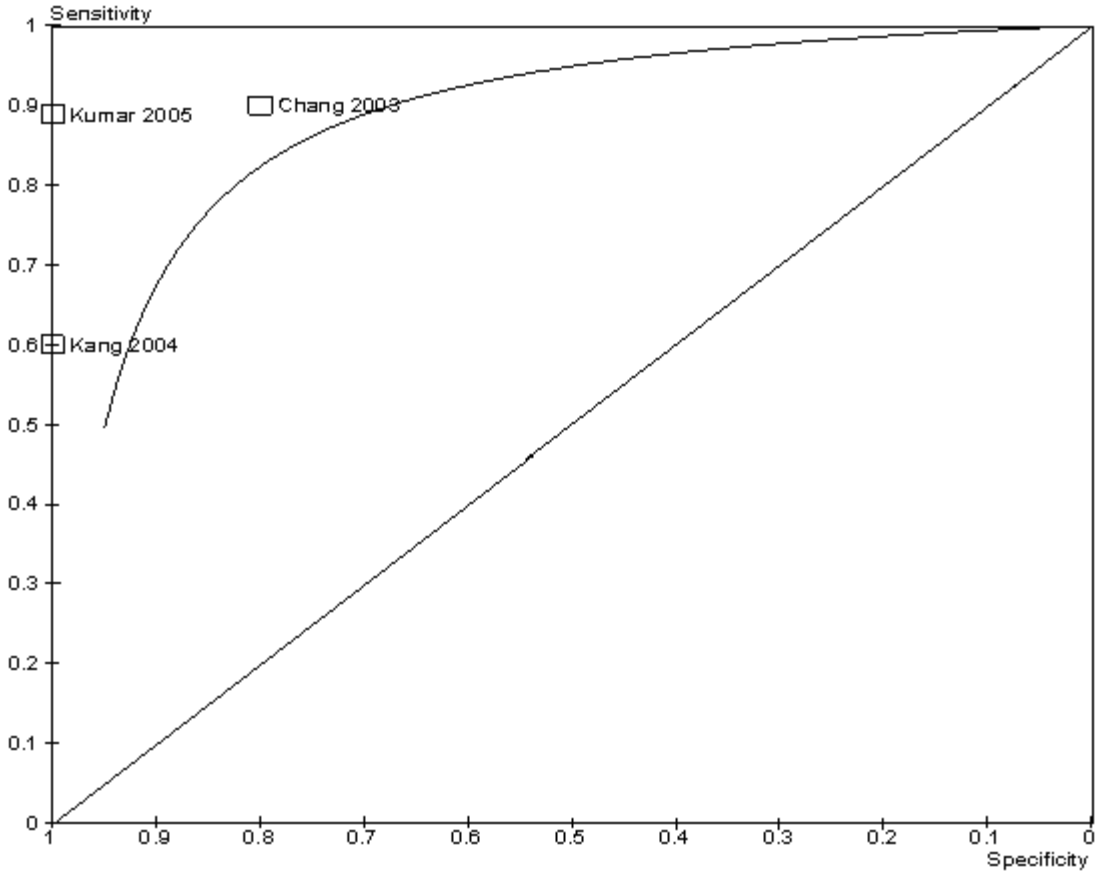


Figure 40 shows the estimates of sensitivity and 1-specificity plotted in ROC space for [18]FDG-PET versus any reference standard for the primary diagnosis and staging of kidney cancer based on retrospective studies.

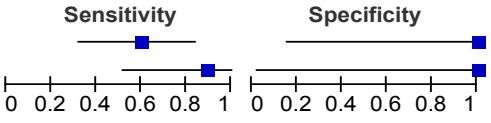
Figure 40. Summary ROC plot of ^{18}FDG-PET versus any reference standard for the primary diagnosis and staging of kidney cancer (retrospective studies)



Reference standard: histology/biopsy or clinical followup; retrospective studies. Two retrospective studies[69,70] totaling 27 participants provided data for a subgroup analysis of the accuracy of ^{18}FDG-PET when histology/biopsy or clinical followup were used as the reference standard to for the primary diagnosis and staging of kidney cancer. Individual 2x2 table results are presented in Figure 41. Sensitivity values in individual studies were 60%%[69] and 89%.[70] Specificity was 100% in both studies.

Figure 41. Results from 2x2 tables of individual retrospective studies of 18FDG-PET versus histology/biopsy or clinical followup for the primary diagnosis and staging of kidney cancer

Study	TP	FP	FN	TN	Sensitivity	Specificity
Kang 2004	9	0	6	2	0.60 [0.32, 0.84]	1.00 [0.16, 1.00]
Kumar 2005	8	0	1	1	0.89 [0.52, 1.00]	1.00 [0.03, 1.00]



We found that when only histology/biopsy were considered as reference standard, ^{18}FDG-PET had a pooled positive LR of 3.48 (95% CI 0.60, 20.15) and a pooled negative LR of 0.42 (95% CI = 0.21, 0.84) t to accurately help in the diagnosis and staging of kidney cancer (Figures 42 and 43). The positive LR was not statistically significant and therefore, ^{18}FDG-PET does not seem to be helpful to rule in a primary diagnosis or identify the staging of the disease. The negative LR was statistically significant and homogeneous across the studies and therefore, it can be said that ^{18}FDG-PET may be useful to rule out a diagnosis of kidney cancer.

Figure 42. Meta-analysis of the positive LR of ^{18}FDG-PET versus histology/biopsy or clinical followup for the primary diagnosis and staging of kidney cancer (retrospective studies)

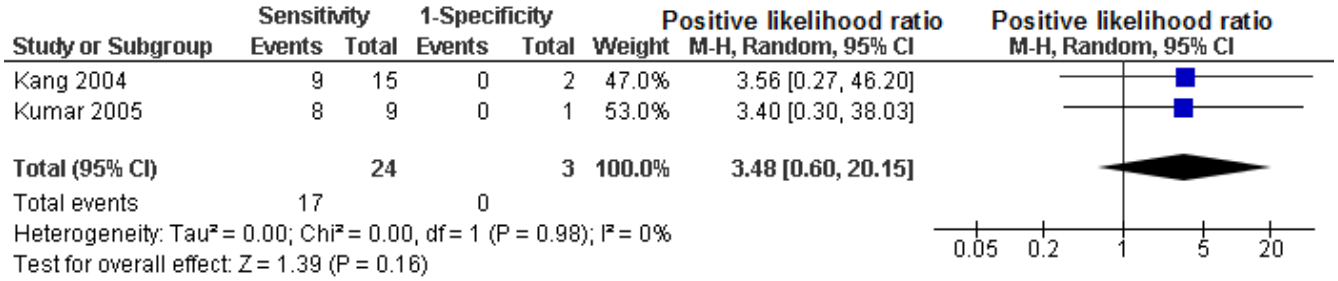


Figure 43. Meta-analysis of the negative LR of ^{18}FDG-PET versus histology/biopsy or clinical followup for the primary diagnosis and staging of kidney cancer (retrospective studies)

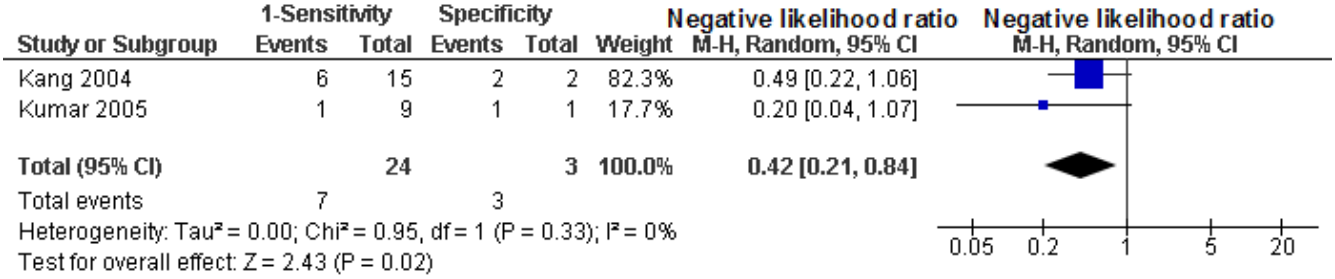
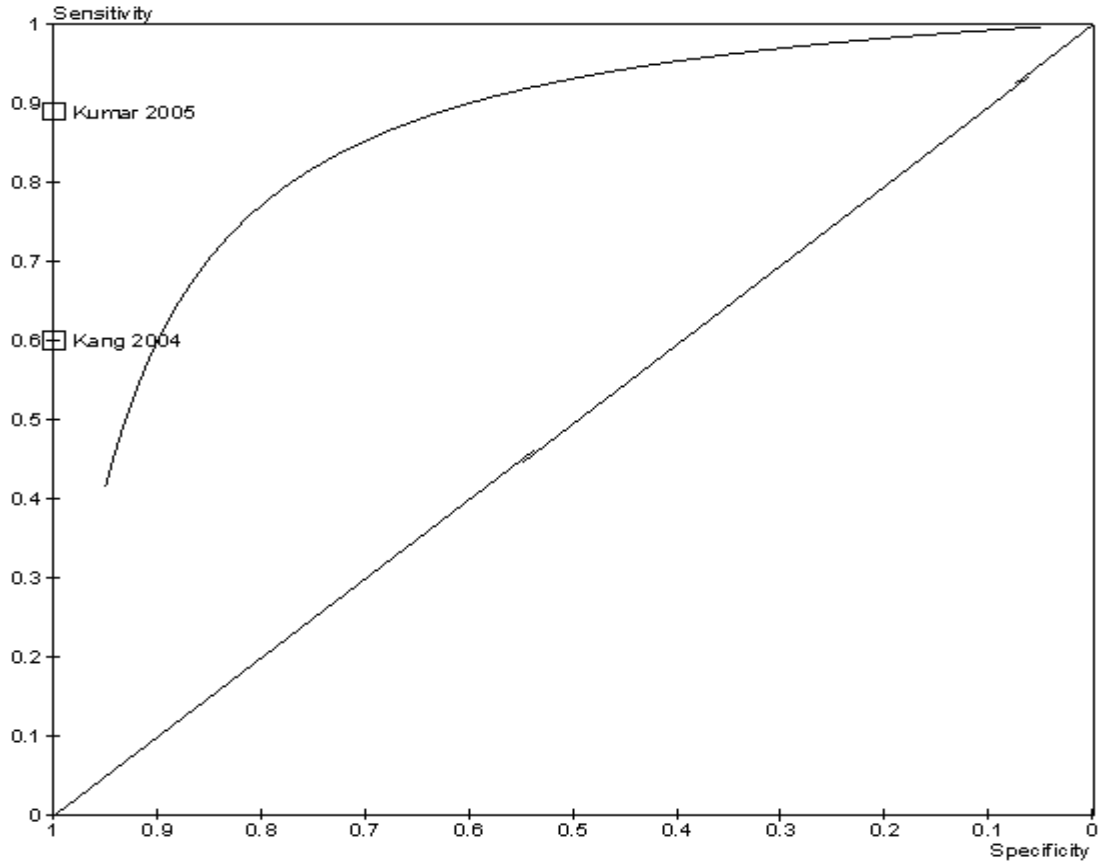


Figure 44 shows the estimates of sensitivity and 1-specificity plotted in ROC space for ^{18}FDG-PET versus histology/biopsy or clinical followup for the primary diagnosis and staging of kidney cancer based on retrospective studies.

Figure 44 Summary ROC plot of ^{18}FDG-PET versus histology/biopsy or clinical followup for the primary diagnosis and staging of kidney cancer (retrospective studies)



Summary of the results

Meta-analyses were calculated to evaluate the accuracy of ^{18}FDG-PET for the diagnosis and staging of kidney cancer (Table 17). When ^{18}FDG-PET was compared against any reference standard, prospective studies reported a statistically significant result for the positive LR that was not confirmed by the analysis of retrospective studies. The pooled negative LRs were similar across both prospective and retrospective studies and they indicated that ^{18}FDG-PET may be useful for the exclusion of a diagnosis of kidney cancer or for the exclusion of particular stages of the disease.

Table 17. Results of meta-analyses of the accuracy of ^{18}FDG-PET for kidney cancer

PET Purpose	Type of PET	Reference standard	Design	Studies	N	Effect estimate M-H, Random, 95% CI
Primary diagnosis and staging	FDG-PET	Any reference standard	P	3	42	PLR=3.95 [1.14, 13.73]
						NLR=0.30 [0.12, 0.79]
			R	2	27	PLR=3.48 [0.60, 20.15]
						NLR=0.42 [0.21, 0.84]

95% CI=95% confidence interval; FDG= fluorodeoxyglucose; M-H = Mantel Hantzel; NLR=negative likelihood ratio; P=prospective; PET=positron emission tomography; PLR=positive likelihood ratio; R=retrospective

4.3.2. Diagnostic thinking impact of ^{18}FDG-PET and ^{18}FDG-PET/CT on physician decision making with respect to diagnosis and management strategy for patients with kidney cancer

Three studies[67,69,70] evaluated the use of ^{18}FDG-PET on patient management and diagnostic work-up of renal cell carcinomas (RCC). The studies considered patients with suspected but undiagnosed primary RCCs, and patients with recurrent or metastatic disease. The imaging by ^{18}FDG-PET was therefore used for both initial diagnostic and staging purposes, as well as for restaging. The impact of ^{18}FDG-PET imaging regarding patient management and diagnostic work-up were both considered.

Dilhuydy *et al*[67] investigated the treatment decision impact of ^{18}FDG-PET imaging on the restaging and management of patients suffering from RCC with metastatic disease. Participants included 24 patients who underwent a total of 26 PET scans. In the overall sample of 24 patients, there were of five changes (21%) to the management strategy. Evaluation of the changes to clinical management was subdivided by the type of assessment the patients were undergoing. There were 20 ^{18}FDG-PET scans in patients to assess limited or solitary tumor sites. Of these, the treatment plan was modified after ^{18}FDG-PET in only three patients (15%). Additionally, five ^{18}FDG-PET scans were performed in patients who appeared to have had a complete response to treatment. Of these, two scans were positive for ^{18}FDG uptake, prompting a change in therapeutic management. Thus, the impact of the ^{18}FDG-PET imaging appeared to be greater in the assessment of patients thought to have complete response following treatment. However, the number of patients in this group was very small, so this result should be interpreted with caution. The five changes resulting from the ^{18}FDG-PET imaging were: from observation to surgery (n=2) or immunotherapy (n=2), and from surgery to immunotherapy (n=1).

The authors concluded that positive ^{18}FDG-PET images may lead to modification of the treatment decisions made; however negative ^{18}FDG-PET results should not alter the treatment planning. Particular value of ^{18}FDG-PET imaging was found in the identification of distant metastatic sites, justifying the addition of complementary treatment in addition to surgery.

This retrospective study was determined to be of moderate quality. The choice and administration of the independent reference standard were well reported. Additionally, equivocal results were reported, and there was satisfactory explanation for withdrawals. However, given the retrospective nature of the study, interpretation of the reference standard was not blinded, which may have introduced review bias. Furthermore, there was an incomplete description of the spectrum of included patients and the inclusion criteria, making it difficult to rule out selection bias. There was more than one reference test, which may have introduced verification bias.

Kang *et al*[69] evaluated the accuracy of ^{18}FDG-PET imaging on a mixed population of patients undergoing initial diagnosis and staging or restaging of RCC. The subsequent impact on treatment decisions and diagnostic workup was assessed. This was a retrospective review of 66 consecutive patients who underwent ^{18}FDG-PET scans. The sample included two types of patients: those with suspicion of primary RCC who had not undergone nephrectomy (n=17, 17 scans); and for restaging of patients with RCC who had undergone nephrectomy (n=54, 73 scans). The treatment plan was revised in 12 cases (13 %) of the total 90 scans in this study. There was minor impact on the additional diagnostic work-up in one case in which the ^{18}FDG-PET scan led to the order for an abdominal MRI to confirm the presence of a primary RCC. Changes made in treatment plans included two cases in which surgery was indicated as a result of ^{18}FDG-PET imaging. Additionally, in nine cases the ^{18}FDG-PET analyses lead to reinterpretation of conventional imaging. Within the subgroup of 17 patients with no history of nephrectomy, two were accurately identified as having benign cysts by ^{18}FDG-PET, however, 6/15 (40%) disease positive individuals were not captured by ^{18}FDG-PET imaging, yielding to a lower sensitivity than conventional CT imaging. Of the patients with a history of disease who had undergone nephrectomy, ^{18}FDG-PET detected 64% of all soft tissue metastasis and 79% of bone metastasis. For 87 of the 90 ^{18}FDG-PET studies in patients, there was at least one associated conventional image available (e.g., CT scan). When compared to the associated conventional images, ^{18}FDG-PET studies showed a lack of sensitivity for detection of metastatic lesions. ^{18}FDG-PET imaging failed to identify all lesions detected by conventional

imaging in 39 scans (45%). However, ^{18}FDG-PET images did identify previously unknown lesions in 11 scans (13%).

The prognostic value of ^{18}FDG-PET imaging was assessed by following the progression of metastatic lesions present on ^{18}FDG-PET imaging prior to immunotherapy. Of 31 lesions which progressed, 25 (81%) had been positively identified on the initial ^{18}FDG-PET scan. There were 42 lesions that remained stable, of which only 28 (67%) had been positive on the initial ^{18}FDG-PET scan.

Overall, the authors concluded that although ^{18}FDG-PET imaging was more specific than conventional imaging, its use was limited by its low sensitivity for detecting RCC. It was thought that ^{18}FDG-PET imaging holds value as a complementary tool, particularly in suspicious or equivocal cases.

This retrospective study was assessed as being of moderate quality. The spectrum of patients and selection criteria, the choice and administration of the independent reference standard, and intermediate test results were all well reported. Additionally, all cases were verified by a reference standard and there were no withdrawals. There was inadequate reporting on some aspects, including detail about the execution of the ^{18}FDG-PET scan and reference tests. Due to the retrospective design of the study the reference standard was not blindly interpreted, thus leading to the possibility of review bias. There was no one reference standard; rather a combination of methods was used (histological or clinical followup), which may have introduced verification bias in the validation of true disease status.

Kumar *et al*[70] retrospectively evaluated the impact of ^{18}FDG-PET imaging on a mixed population of patients with suspected or known RCC who were undergoing assessment for diagnosis and staging of their disease. The impact on subsequent treatment management was assessed. Twenty-four patients who underwent ^{18}FDG-PET imaging were included in this analysis. In the 24 patients, a total of 28 solid renal masses were assessed. There were 10 patients with primary renal tumours and 14 metastatic renal tumors. ^{18}FDG-PET results led to changes in 3 of the 10 patients with primary tumors (30%). These changes included avoidance of surgery in the case of a mass determined to be benign, proceeding with surgery in a case where lung metastasis was ruled out, and cancellation of surgery due to detection of unsuspected bone metastases. There were no changes in treatment management reported for the 14 metastatic renal tumors imaged by ^{18}FDG-PET.

The authors concluded that ^{18}FDG-PET was useful as a complementary modality to CT scans for staging and treatment management of primary malignant renal tumors, as well as for characterization of renal masses resulting from metastases of other primary cancers. They identify that the study was limited by the population, as the included cases had known renal masses previously detected by conventional imaging by CT scan or MRI.

This retrospective study was assessed as being of moderate quality. Methodological strengths included: a clear description of the selection criteria and spectrum of included patients, appropriate choice of reference standard. Additionally, intermediate results reported and there were no withdrawals. There was inadequate reporting of some aspects, including detail about the execution of the ^{18}FDG-PET scan and reference tests. As only patients with known renal masses were included, the generalizability of the study may be limited. The interpretation of the index and reference tests was not reported to be blinded, thus introducing the possibility of review bias. Finally, it is crucial to not that not only was there was no single reference standard, but PET imaging also formed a part of the reference standard in some instances. This methodological flaw may have introduced verification bias in the validation of the true disease status.

Table 18 provides a summary of the main findings and the types of bias that affected the evidence on the diagnostic thinking impact of ^{18}FDG-PET and ^{18}FDG-PET/CT on kidney cancer.

Table 18. Main findings and types of bias that affected the evidence on the diagnostic thinking impact of ^{18}FDG-PET and ^{18}FDG-PET/CT for kidney cancer

Study	Results of FDG-PET imaging on Patient Diagnosis and Treatment	Types of Bias
Dilhuydy 2006[67] Study type: Retrospective	**Management decision:** Treatment and diagnostic testing impact Management strategy changed 5 / 24 (21%) Treatment instead of monitoring strategy changed (n=4): Received surgery (n=2) or immunotherapy (n=2) Type treatment altered (n=1) (surgery instead of immunotherapy) Management changed in 2 / 5 patients assessed as "complete response" to prior treatment by conventional CT + bone scans	Spectrum Bias (unclear) Selection Bias (unclear) Verification Bias (+ 1 RS) Review Bias (PET, unblinded; RS, unclear)
Kang 2004[69]	**Management decision:** Treatment and diagnostic testing impact 66 patients received 90 PET scans Management strategy changed in 12 / 90 (13%) Recurrences identified lead to surgery (n=2) (Treatment); Additional diagnostic by MRI ordered (n=1) (Diagnostic Imaging); Reinterpretation of previous imaging (n=9) (Diagnostic Imaging) **Prognostic value** for immunotherapy: Accuracy of metastatic lesion detection by PET assessed: 81% of PET positive lesions progressed vs. 67% of PET negative lesions	Verification Bias (>+1 RS) Review Bias (PET, unblinded; RS, unclear if blinded)

Table 18. Main findings and types of bias that affected the evidence on the diagnostic thinking impact of ^{18}FDG-PET and ^{18}FDG-PET/CT for kidney cancer (cont')

Study	Results of FDG-PET imaging on Patient Diagnosis and Treatment	Types of Bias
Kumar 2005[70]	**Management decision:** Treatment Treatment strategy changed for 3 / 10 (30%) primary renal tumor cases. No changes were mentioned in the 14 cases of renal cancer metastasis. Thus, overall 3/24 cases changed (13%): -Identified to have a benign mass, and surgery avoided (n = 1) -Unsuspected bone metastasis, radical surgery cancelled (n = 1) -Ruled out lung metastasis, surgery proceeded (n = 1)	Verification Bias (>+1 RS) (PET, unclear if blinded; RS, unblinded)

CT=computer tomography; FDG=Fluorodeoxyglucose F18; mo=months; MRI=magnetic resonance imaging; PET=positron emission tomography; RS=reference standard;vs.=versus

5. Ovarian Cancer

5.1. Background

Ovarian cancer is both the fifth most common malignancy and the fifth leading cause of cancer mortality in American women. It also leads to more deaths than any other gynecological malignancy.[150] In the United States, an estimated 21,650 new cases will be diagnosed and 15,520 women with die due to ovarian cancer in 2008.[133] The highest incidence rates of ovarian cancer occur in the United States, Europe and Israel, whereas the lowest numbers occur in Japan and developing countries. When women emigrate from low-incidence countries to high-incidence countries, rates of ovarian cancer gradually rise to numbers similar to those of native-born women. Caucasian women experience higher incidence rates than African American or Asian American women.[150]

Between 1996 and 2004, the 5-year survival rate for women with ovarian cancer in the United States was 45.5%.[133] Poor outcomes are associated with the lack of effective methods for prevention and early detection. If caught early, survival rates improve dramatically, to approximately 95%.[151] For 80 to 90% of women, diagnosis occurs after 40 years of age and less than 1% occurs before 20 years of age.[150] The median age at first diagnosis is 62 years.[133]

The most significant risk factor for ovarian cancer is family history.[150] Estimates suggest that one in 800 women carry the mutated cancer gene.[151] Women who are nulliparas or are infertile are at an increased risk, as are women who undergo prolonged fertility treatment. Abortions do not appear to significantly alter risk; however, lactation slightly reduces risk. Late menopause, history of pelvic inflammatory disease, polycytic ovary syndrome and endometriosis are associated with increased risk of ovarian cancer. Individuals with Lynch syndrome are also at risk.[150] Bilateral removal of the ovaries reduces risk,[151] but cancer still develops in two to 10% of cases. Tubal ligation and hysterectomy can reduce the risk of ovarian cancer by 67%. The effect appears to last for 20 to 25 years after surgery.[150]

Approximately 90% of ovarian cancers are derived from the epithelial cells of the ovaries.[150] Of epithelial ovarian neoplasms, 10 to 20% tend to develop into borderline or low malignant potential tumors. Epithelial tumors are divided into five categories: serous tumors, mucinous tumors, endometrioid tumors, clear-cell tumors and Brenner tumors are cells similar in appearance to urothelial cells. Mixed forms of tumor cells where there is a second or third cell type in addition to

the main tumor cell are possible.[152] Nonepithelial tumors include: sex cord-stromal, germ-cell and indeterminate tumors.[150]

Before proceeding with treatment, the extent of disease must be determined. Ovarian cancer is classified into four stages. In the first stage, disease is limited to ovaries. Classification is subdivided further into: Ia—one ovary involved; Ib—both ovaries or; Ic—ruptured capsule, surface tumor or positive washings. In the second stage of disease, cancer spreads to the pelvis. In IIa—the uterus and one or more tubes are involved; IIb—tumors spread to other pelvic tissue; and IIc—positive washings and ascities. The third stage of ovarian cancer involves tumor progression into the abdomen and/or regional lymph nodes. Metastases to the peritoneal are: microscopic in IIIa; macroscopic, but less than 2cm in IIIb; and macroscopic and greater than 2cm in IIIc. Finally, the fourth stage involves distant metastases outside peritoneal cavity.[153]At the time of diagnosis approximately three quarters of patients present with advanced disease.[151]

Two techniques are used in screening for ovarian cancer and neither has shown an ability to reduce morbidity or mortality. These are measuring for serum tumor marker cancer antigen 125 (CA-125), and transvaginal ultrasonography (TVUS), both of which tend to fail to identify ovarian cancer at an earlier, potentially curable stage. Unlike cervical cancer, there has been no success in identifying precancerous lesions, which can be identified through screening techniques. The link between current epidemiological, biological and pathological data in not fully understood and there is a lack of animal models. Moreover, the disease is virulent and frequently diagnosed only in the advanced stage of disease.[151]

The diagnostic agility of ^{18}FDG-PET has been investigated for the use in women with ovarian cancer. ^{18}FDG-PET combined with ultrasonography and MRI is considered the choice method for the imaging assessment. Accuracy of imaging is increased by adding ^{18}FDG-PET to CT. Although ^{18}FDG-PET has shown the ability to identify macroscopic disease when other methods are negative, it is still limited in detecting microscopic disease. When evaluating patients with elevated serum tumor markers, ^{18}FDG-PET has demonstrated greater sensitivity. Additionally, ^{18}FDG-PET may be capable of detecting early, small regions of relapse when other tests do not detect disease.[144]

Treatment for ovarian cancer typically involves surgery, the extent of which depends on the stage of disease. Total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, peritoneal biopsies are required. Consideration for preserving fertility may be necessary for younger patients with less advanced disease. For women with stage Ia/b, surgery alone should be adequate to

treat the disease, however patients with stage Ic/IIb may also require adjuvant chemotherapy. For more developed stages of disease additional surgical goals include cytoreduction aiming at leaving no residual disease. Chemotherapy is also required, and typically incorporates a platinum-based regime.[153]A second surgery to determine if further therapy in required may be performed.[144]

5.2. Importance of Key Questions in the Clinical Management of Ovarian Cancer

The diagnostic work-up currently used for the characterization of ovarian lesions includes gynaecological examination and TVUS. It has been reported that TVUS is not accurate enough to guarantee a precise differential diagnosis, due to the fact that benign and malignant ovarian lesions may present similar morphological characteristics. Measurement of specific serum tumor markers such as CA-125 is often used to detect recurrences, however, this does not allow localizing the recurrence or differentiating between localized and diffuse disease. Furthermore, nonrecurrent conditions like infections will often produce the elevation of CA-125 titers. Conventional imaging modalities such as MRI and helical CT with contrast enhancement are often used in conjunction with CA-125 to detect recurrences. However, detection of recurrences in small peritoneal lesions or differentiation of peritoneal abnormalities can be challenging. Early detection of recurrence in ovarian cancer may allow different therapeutic interventions that could improve outcomes and increase the chances of prolonged remission and survival. There is a need to evaluate the evidence on the use of ^{18}FDG-PET in differentiating malignant from benign disease, staging and grading malignant disease, differentiating recurrent disease from therapy-induced changes and monitoring response to therapy in ovarian cancer.

5.3. Results

Twenty-four studies[63,72-90,126-128,130] provided evidence on the use of ^{18}FDG-PET or ^{18}FDG-PET/CT for ovarian cancer. Twenty studies[63,72-90] evaluated the diagnostic accuracy of ^{18}FDG-PET or ^{18}FDG-PET/CT, five studies[75,89,126-128] reported on the diagnostic thinking impact of ^{18}FDG-PET/CT, and one study[130] evaluated the effects of ^{18}FDG-PET as part of a management strategy on patient centered outcomes. There were no economic evaluations on the use of ^{18}FDG-PET or ^{18}FDG-PET/CT for ovarian cancer. Characteristics of the populations, conditions of ^{18}FDG-PET administration, interpretation of results and methodological quality of the studies are summarized in appendices D to J.

5.3.1. Diagnostic accuracy of ^{18}FDG-PET and ^{18}FDG-PET/CT in ovarian cancer

Characteristics of the studies

Twenty studies (fourteen prospective, [63,72,74-76,78,79,81,82,84,85,87,88,90] six retrospective[73,77,80,83,86,89]) evaluated the diagnostic accuracy of ^{18}FDG-PET[63,77,79,81,84,88,90] or ^{18}FDG-PET/CT[72-76,78,80,82,83,85-87,89] on ovarian cancer. Twelve studies used ^{18}FDG-PET to assess recurrences,[72,73,75,77,78,80-83,86,88,89] two for primary diagnosis,[79,85] two for initial staging,[76,90] two for restaging purposes,[84,87] one primary diagnosis and initial staging,[74] and one initial staging and assessing recurrences. The studies contained a total of 871 patients with sample sizes ranging from 13 to 101. The participant ages ranged from 17 to 89 years. ^{18}FDG-PET was compared to a reference standard that varied across the studies. In ten studies the reference standard was exclusively histology/biopsy,[72-74,76,79,83-85,87,90] in nine studies the reference standard was either histology/biopsy or clinical follow-up,[75,77,78,80-82,86,88,89] and one study used histology/biopsy or conventional imaging as the reference standard.[63] Seven studies reported the mean time between last treatment and ^{18}FDG-PET as ≥ 6 months,[72,73] > 6 months,[77] ≤ 3 months,[83] 3.6 months,[80] 30 days,[84] and 29 days.[87] Six studies used a fixed dose of ^{18}FDG-PET of 350 MBq[78] or 370 MBq, [79,81,82,87,90] five studies used a weight-based dose of 6.5 MBq/kg,[76] 5.5 MBq/kg,[74] 5.2 MBq/kg,[84] 0.22 mCi/kg,[75,83] and six studies reported dose ranges varying between 260 to 666 MBq.[63,77,80,85,86,89] When reported, the time between injection and PET scan ranged from 45 to 90 minutes. Patients fasted for four hours,[63,72,73,75,83] six hour,[74,77,80,86]1903}[76,81,82,84,87-89] or twelve hours,[79,90] and one study[78] did not indicate fasting. Thirteen studies[72,73,75,77,78,80-84,86,87,89] measured glucose levels before administration of ^{18}FDG-PET; the maximum glucose levels allowed were normal levels,[78,80,82] 200 mg/dL,[72,73,83,86,89] 140 mg/dL,[81,87] and 7.5 mmol/L.[77] Methods of interpretation of the images were qualitative in nine studies[72,73,77,80,81,85-87,89] and both qualitative and quantitative in seven studies.[74,75,78,79,82,84,90] Scans were interpreted qualitatively using visual analysis in all studies. SUV values were reported in five studies for the interpretation of the PET images. The criterion for abnormality was SUV > 3 g/mL[74,75,87,88] or > 2.5 g/mL.[78]

Comparisons

Comparisons for which data were considered for meta-analysis are summarized in Table 19. Pooled data were obtained to evaluate the accuracy of ^{18}FDG-PET and ^{18}FDG-PET/CT for assessing recurrences of ovarian cancer. Individual study data are summarized in Appendix D.

Table 19. Summary of comparisons considered for meta-analyses of the accuracy of ^{18}FDG-PET and ^{18}FDG-PET/CT for ovarian cancer

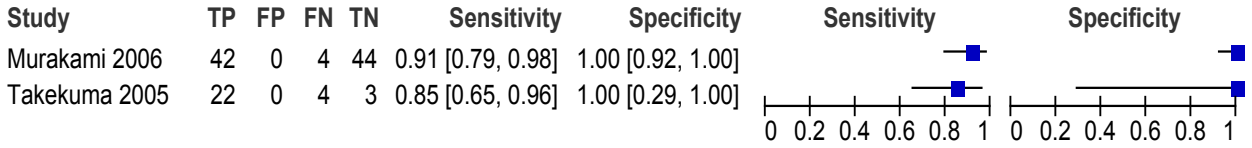
Indication	Studies	Design	Type of PET	Reference standard	Meta-analysis
Primary diagnosis and staging	Castellucci 2007[74]	P	FDG-PET/CT	Histology/biopsy	No
Staging and recurrences	Grisaru 2004[63]	P	FDG-PET	Histology/biopsy or clinical followup	No
Primary diagnosis	Kawahara 2004[79]	P	FDG-PET	Histology/biopsy	No
	Risum 2007[85]	P	FDG-PET/CT	Histology/biopsy	
Recurrences	Bristow 2003[72]	P	FDG-PET/CT	Histology/biopsy	1. FDG-PET vs.histology/biopsy or clinical followup (P studies) (P studies) [81,88] 2. FDG-PET/CT vs. any reference standard (P studies)[72,75,78,82] 3. FDG-PET/CT vs. histology/biopsy or clinical followup (P studies)[75,78,82] 4. FDG-PET/CT vs. any reference standard (R studies) [73,80,83,86,89] 5. FDG-PET/CT vs. histology/biopsy or clinical followup (R studies) [80,86,89] 6. FDG-PET/CT vs. histology/biopsy (R studies) [73,83]
	Bristow 2005[73]	R	FDG-PET/CT	Histology/biopsy	
	Chung 2007[75]	P	FDG-PET/CT	Histology/biopsy or clinical followup	
	Garcia-Velloso 2007[77]	R	FDG-PET	Histology/biopsy or clinical followup	
	Hauth 2005[78]	P	FDG-PET/CT	Histology/biopsy or clinical followup	
	Kim 2007[80]	R	FDG-PET/CT	Histology/biopsy or clinical followup	
	Murakami 2006[81]	P	FDG-PET	Histology/biopsy or clinical followup	
	Nanni 2005[82]	P	FDG-PET/CT	Histology/biopsy or clinical followup	
	Pannu 2004[83]	R	FDG-PET/CT	Histology/biopsy	
	Sebastian 2008[86]	R	FDG-PET/CT	Histology/biopsy or clinical followup	
	Takekuma 2005[88]	P	FDG-PET	Histology/biopsy or clinical followup	
	Thrall 2007[89]	R	FDG-PET/CT	Histology/biopsy or clinical followup	
Restaging	Picchio 2003[84]	P	FDG-PET	Histology/biopsy	No
	Sironi 2004[87]	P	FDG-PET/CT	Histology/biopsy	
Staging	Drieskens 2003[76]	P	FDG-PET/CT	Histology/biopsy	No
	Yoshida 2004[90]	P	FDG-PET	Histology/biopsy	

CT=computer tomographyl; FDG= fluorodeoxyglucose; P=prospective; PET=positron emission tomography; R=retrospective; vs.=versus

1. ^{18}FDG-PET for recurrences of ovarian cancer

Reference standard: histology/biopsy or clinical followup; prospective studies. Two prospective studies[81,88] totaling 119 participants provided data for a meta-analysis of the accuracy of ^{18}FDG-PET versus histology/biopsy or clinical follow up to detect recurrences of ovarian cancer. Individual 2x2 table results are presented in Figure 45. Sensitivity values were 91%[81] and 85%,[88] and specificity was 100%.

Figure 45. Results from 2x2 tables of individual prospective studies of ^{18}FDG-PET versus histology/biopsy or clinical follow up to detect recurrences of ovarian cancer



We found that ^{18}FDG-PET had a pooled positive LR of 22.4 (95% CI 1.64, 305.38) and a pooled negative LR of 0.13 (95% CI = 0.06, 0.29) to accurately detect recurrences of ovarian cancer (Figures 46 and 47). Both the positive and negative LRs were statistically significant and therefore, ^{18}FDG-PET seems to be helpful for identifying recurrences of the disease. There was moderate heterogeneity in the positive LR ($p = 0.17$; $I^2 = 47$ percent) across the studies.

Figure 46. Meta-analysis of the positive LR of ^{18}FDG-PET versus histology/biopsy or clinical followup to detect recurrences of ovarian cancer (prospective studies)

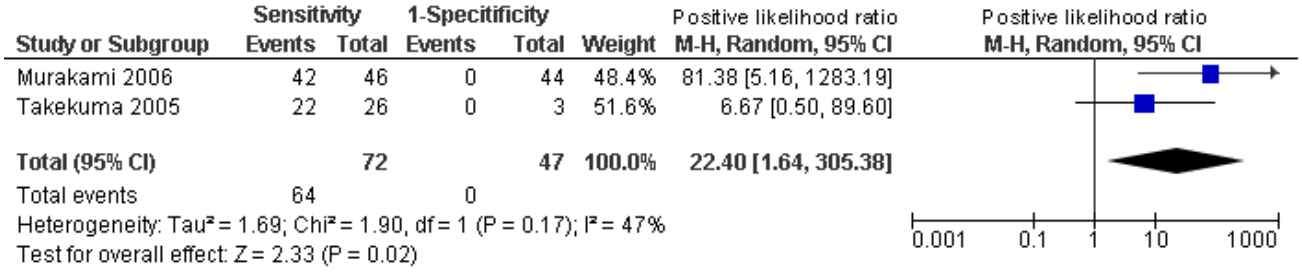


Figure 47. Meta-analysis of the negative LR of ^{18}FDG-PET versus histology/biopsy or clinical followup to detect recurrences of ovarian cancer (prospective studies)

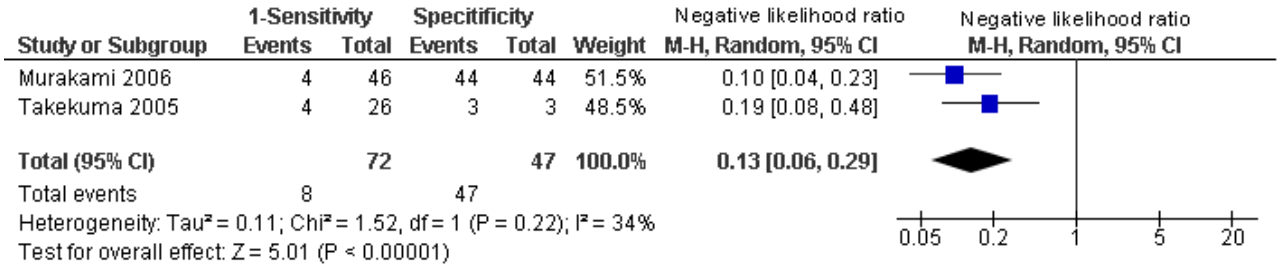
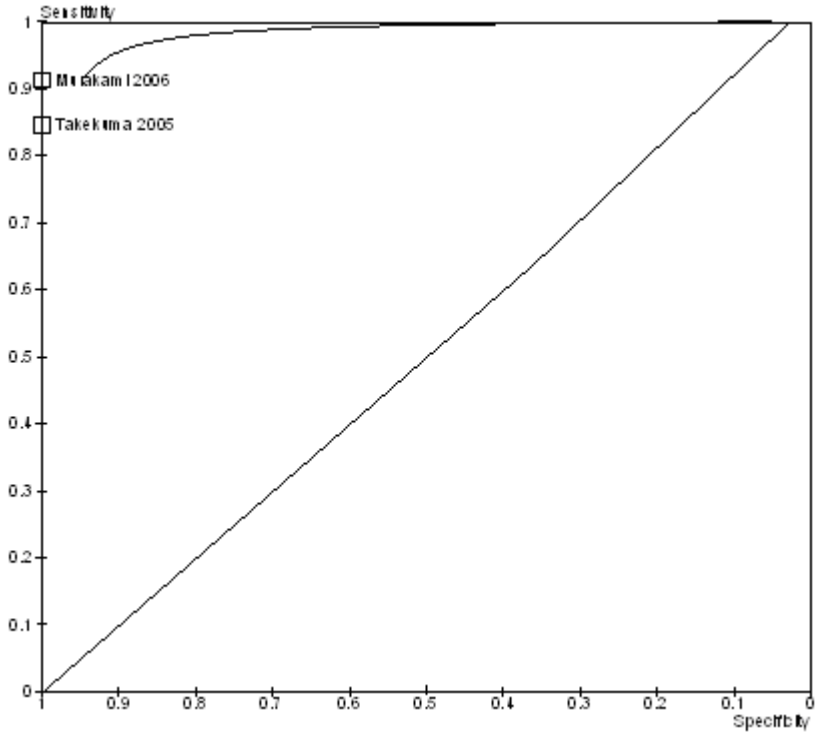


Figure 48 shows the estimates of sensitivity and 1-specificity plotted in ROC space for ^{18}FDG-PET versus histology/biopsy or clinical followup to detect recurrences of ovarian cancer based on prospective studies.

Figure 48. Summary ROC plot of ^{18}FDG-PET versus histology/biopsy or clinical followup to detect recurrences of ovarian cancer (prospective studies)

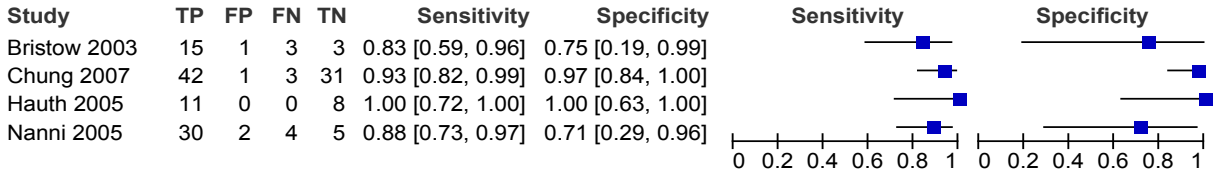


2. ^{18}FDG-PET/CT for recurrences of ovarian cancer

Reference standard: any; prospective studies. Four prospective studies[72,75,78,82] totaling 159 participants provided data for a meta-analysis of the accuracy of ^{18}FDG-PET/CT versus any

reference standard to detect recurrences of ovarian cancer. Individual 2x2 table results are presented in Figure 49. Sensitivity ranged from 83%[72] to 100%.[78] Specificity ranged from 71%[82] to 100%.[78]

Figure 49. Results from 2x2 tables of individual prospective studies of ^{18}FDG-PET/CT versus any reference standard to detect recurrences of ovarian cancer



We found that ^{18}FDG-PET/CT had a pooled positive LR of 6.97 (95% CI 1.64, 25) and a pooled negative LR of 0.12 (95% CI = 0.06, 0.26) to accurately detect recurrences of ovarian cancer (Figures 50 and 51). Both the positive and negative LRs were statistically significant and therefore, ^{18}FDG-PET/CT seems to be helpful for identifying recurrences of the disease. There was moderate heterogeneity in the positive LR ($p = 0.10$; $I^2 = 52$ percent) across the studies.

Figure 50. Meta-analysis of the positive LR of ^{18}FDG-PET/CT versus any reference standard to detect recurrences of ovarian cancer (prospective studies)

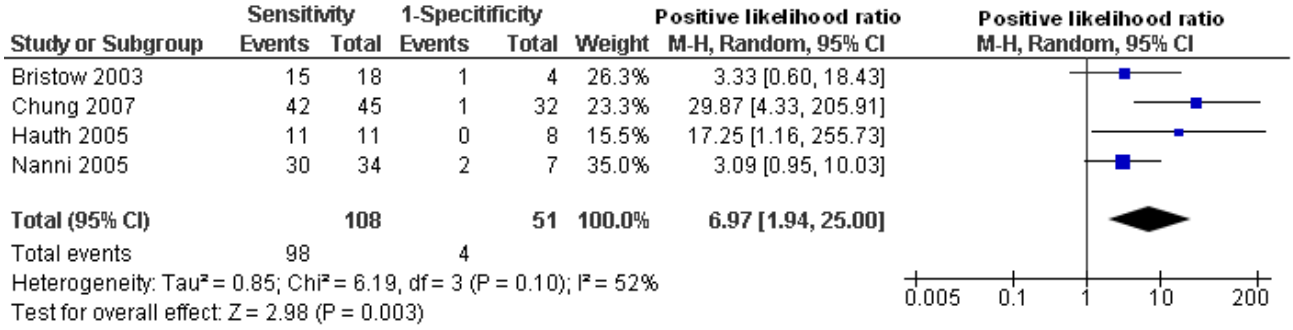


Figure 51. Meta-analysis of the negative LR of ^{18}FDG-PET/CT versus any reference standard to detect recurrences of ovarian cancer (prospective studies)

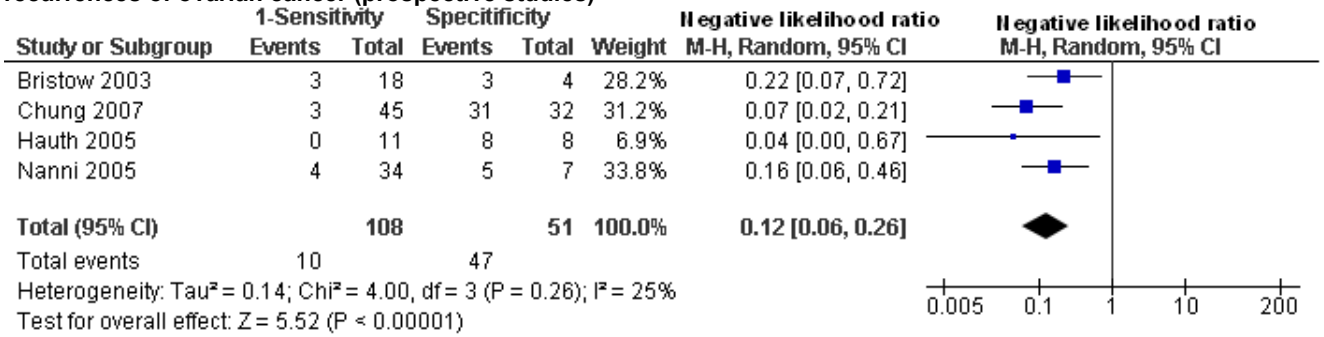
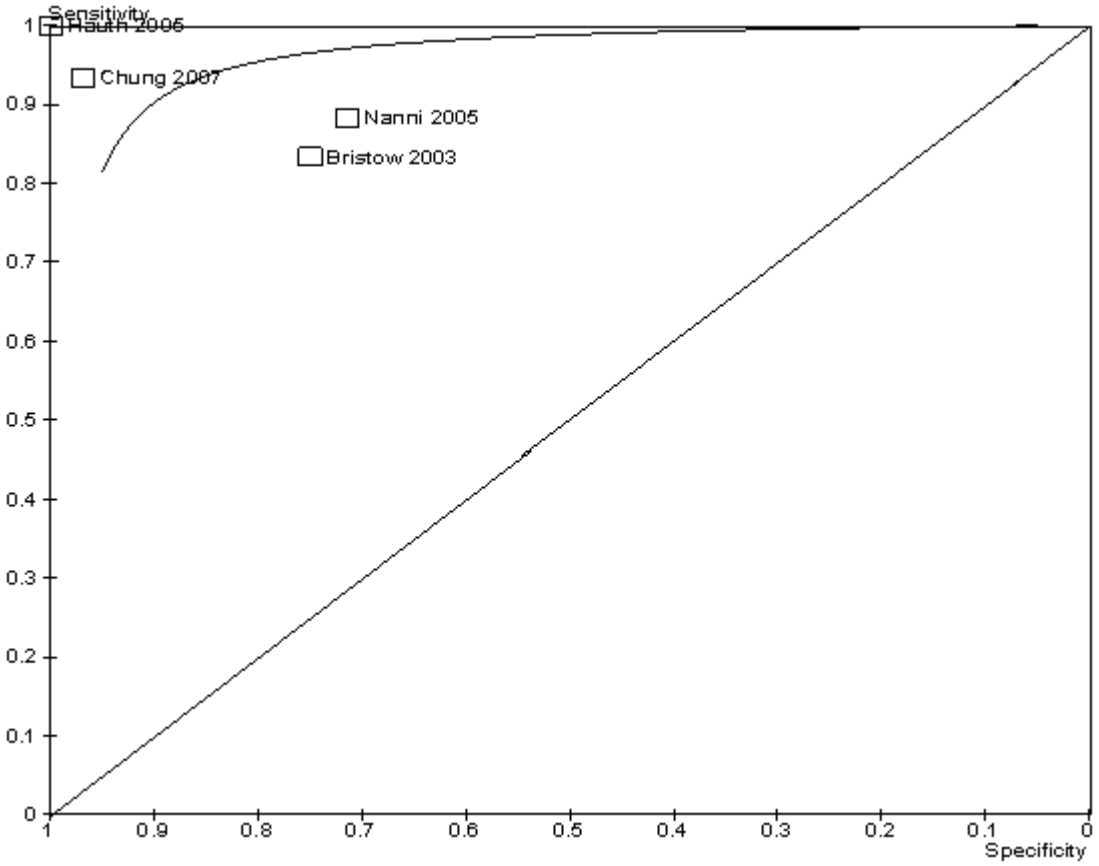


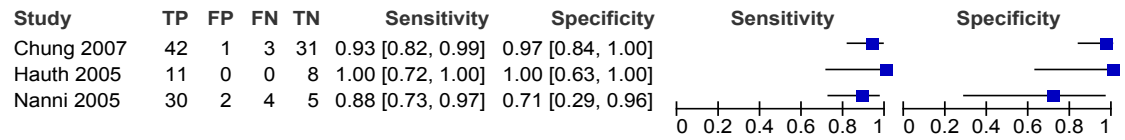
Figure 52 shows the estimates of sensitivity and 1-specificity plotted in ROC space for ^{18}FDG-PET/CT versus any reference standard to detect recurrences of ovarian cancer based on prospective studies.

Figure 52. Summary ROC plot of ^{18}FDG-PET/CT versus any reference standard to detect recurrences of ovarian cancer (prospective studies)



Reference standard: histology/biopsy or clinical followup, prospective studies (subgroup analysis). Three prospective studies[75,78,82] totaling 137 participants provided data for a subgroup analysis of the diagnostic accuracy of ^{18}FDG-PET/CT when histology/biopsy or clinical followup were used as the reference standard to detect recurrences of ovarian cancer. Individual 2x2 table results are presented in Figure 53. Sensitivity values ranged from 88%[82] to 100%.[78] Specificity values ranged from 71%[82] to 100%.[78]

Figure 53. Results from 2x2 tables of individual prospective studies of ^{18}FDG-PET/CT versus histology/biopsy or clinical followup for detecting recurrences of ovarian cancer (subgroup analysis)



We found that when only histology/biopsy were considered as reference standard, ^{18}FDG-PET/CT had a pooled positive LR of 9.84 (95% CI 1.64, 59.15) and a pooled negative LR of 0.10 (95% CI = 0.05, 0.22) to accurately detect recurrences of ovarian cancer (Figures 54 and 55). Both the positive and negative LRs were statistically significant and therefore, ^{18}FDG-PET/CT seems to be helpful for identifying recurrences of the disease. The positive LR was moderately heterogeneous (p=0.06, I^2 = 64 percent) but the negative LRs was homogeneous across the studies.

Figure 54. Meta-analysis of the positive LR of ^{18}FDG-PET/CT versus histology/biopsy or clinical followup for detecting recurrences of ovarian cancer (prospective studies)

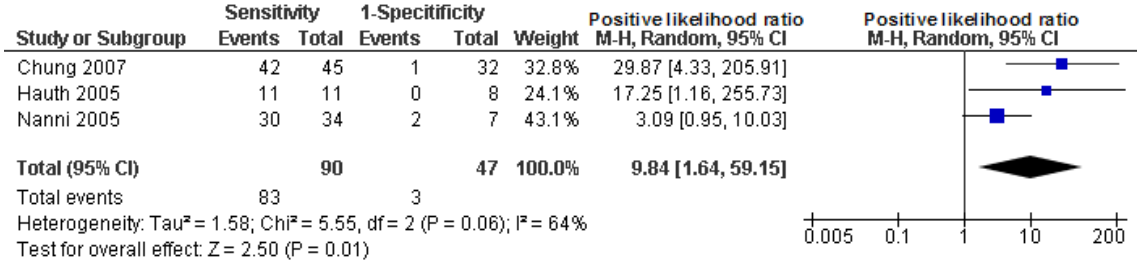


Figure 55. Meta-analysis of the negative LR of ^{18}FDG-PET/CT versus histology/biopsy or clinical followup for detecting recurrences of ovarian cancer (prospective studies)

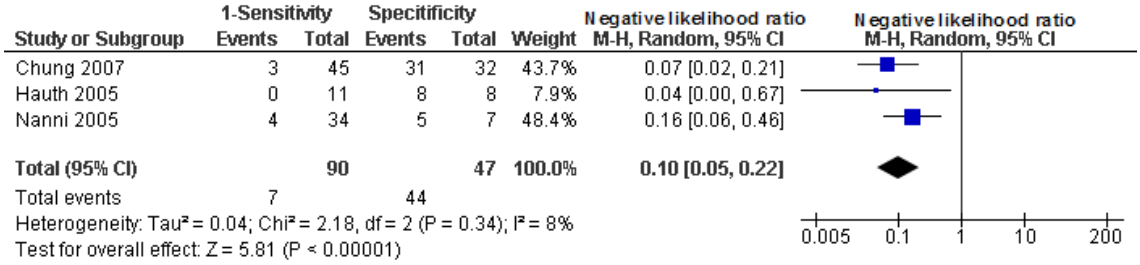
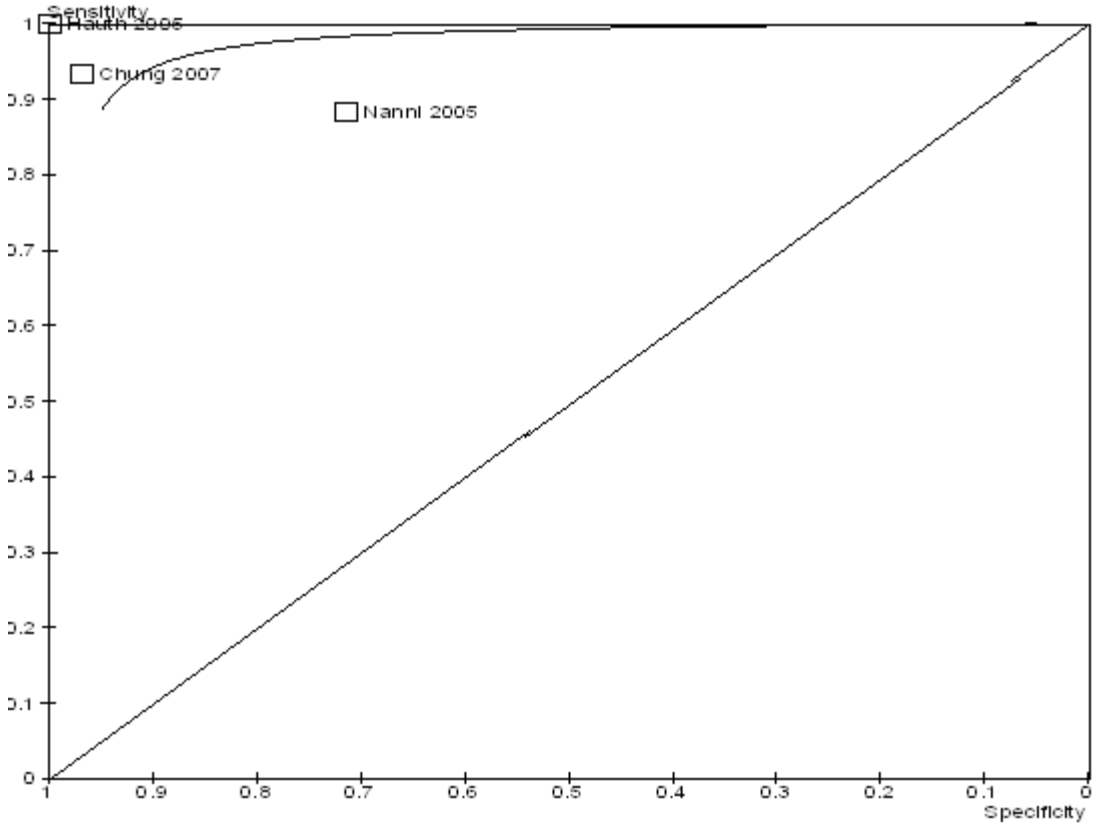


Figure 56 shows the estimates of sensitivity and 1-specificity plotted in ROC space for ^{18}FDG-PET/CT versus histology/biopsy or clinical followup to detect recurrences of ovarian cancer based on prospective studies.

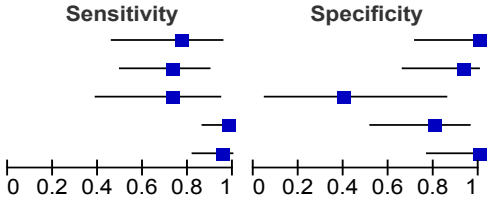
Figure 56. Summary ROC plot of ^{18}FDG-PET versus histology/biopsy or clinical followup to detect recurrences of ovarian cancer (prospective studies)



Reference standard: any; retrospective studies. Separate meta-analyses were conducted for retrospective studies. Five retrospective studies[73,80,83,86,89] totaling 180 participants provided data for a meta-analysis of the accuracy of ^{18}FDG-PET/CT versus any reference standard to detect recurrences of ovarian cancer. Individual 2x2 table results are presented in Figure 57. Sensitivity ranged from 73%[80,83] to 97%.[86] Specificity ranged from 40%[83] to 100%.[73,89]

Figure 57. Results from 2x2 tables of individual retrospective studies of ^{18}FDG-PET/CT versus any reference standard to detect recurrences of ovarian cancer

Study	TP	FP	FN	TN	Sensitivity	Specificity
Bristow 2005	10	0	3	11	0.77 [0.46, 0.95]	1.00 [0.72, 1.00]
Kim 2007	16	1	6	13	0.73 [0.50, 0.89]	0.93 [0.66, 1.00]
Pannu 2004	8	3	3	2	0.73 [0.39, 0.94]	0.40 [0.05, 0.85]
Sebastian 2008	37	3	1	12	0.97 [0.86, 1.00]	0.80 [0.52, 0.96]
Thrall 2007	35	0	2	14	0.95 [0.82, 0.99]	1.00 [0.77, 1.00]



Based on the analysis of retrospective studies, we found that ^{18}FDG-PET/CT had a pooled positive LR of 6.02 (95% CI 1.40, 25.91) and a pooled negative LR of 0.19 (95% CI = 0.08, 0.45) to accurately detect recurrences of ovarian cancer (Figures 58 and 59). The positive and negative LRs were statistically significant and therefore, ^{18}FDG-PET/CT seems to be helpful for identifying recurrences of the disease. However, both the positive ($p = 0.001$; $I^2 = 78$ percent) and the negative ($p = 0.02$; $I^2 = 66$ percent) LRs were highly heterogeneous across the studies precluding firm conclusions based on these results.

Figure 58. Meta-analysis of the positive LR of ^{18}FDG-PET/CT versus any reference standard to detect recurrences of ovarian cancer (retrospective studies)

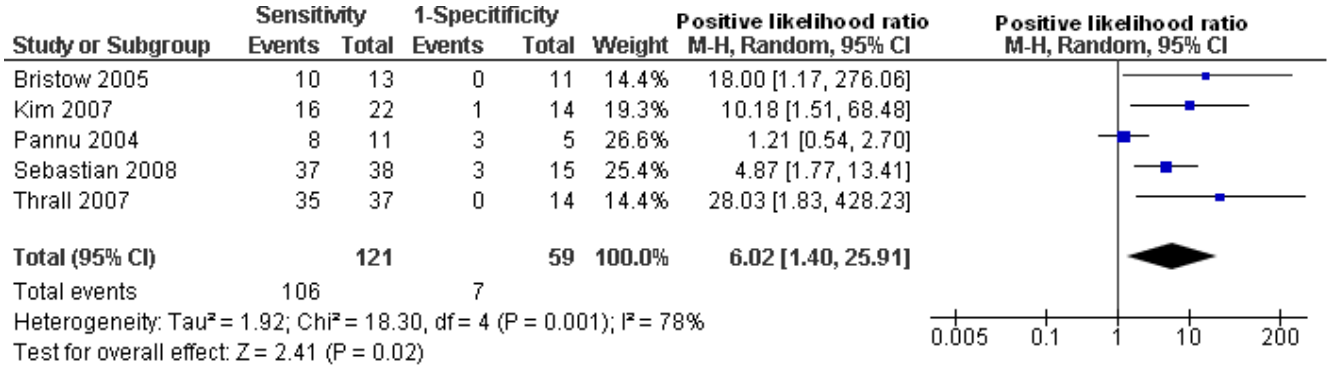


Figure 59. Meta-analysis of the negative LR of ^{18}FDG-PET/CT versus any reference standard to detect recurrences of ovarian cancer (retrospective studies)

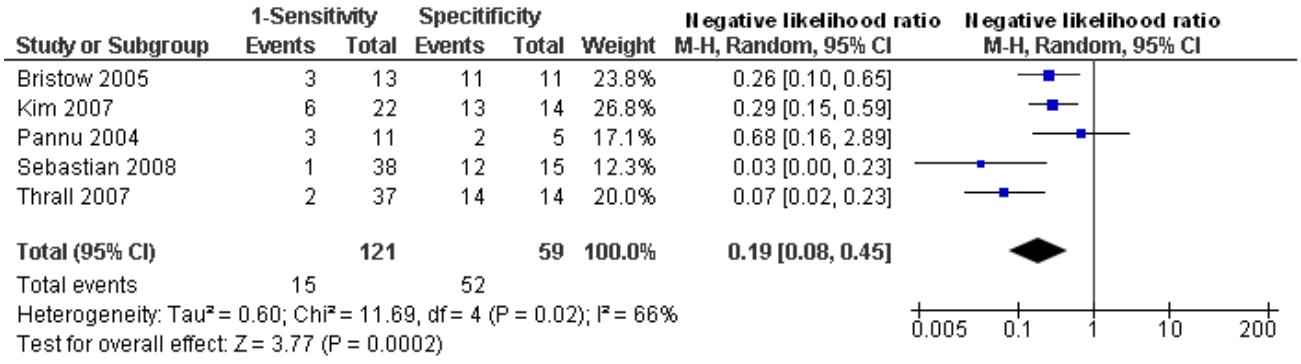
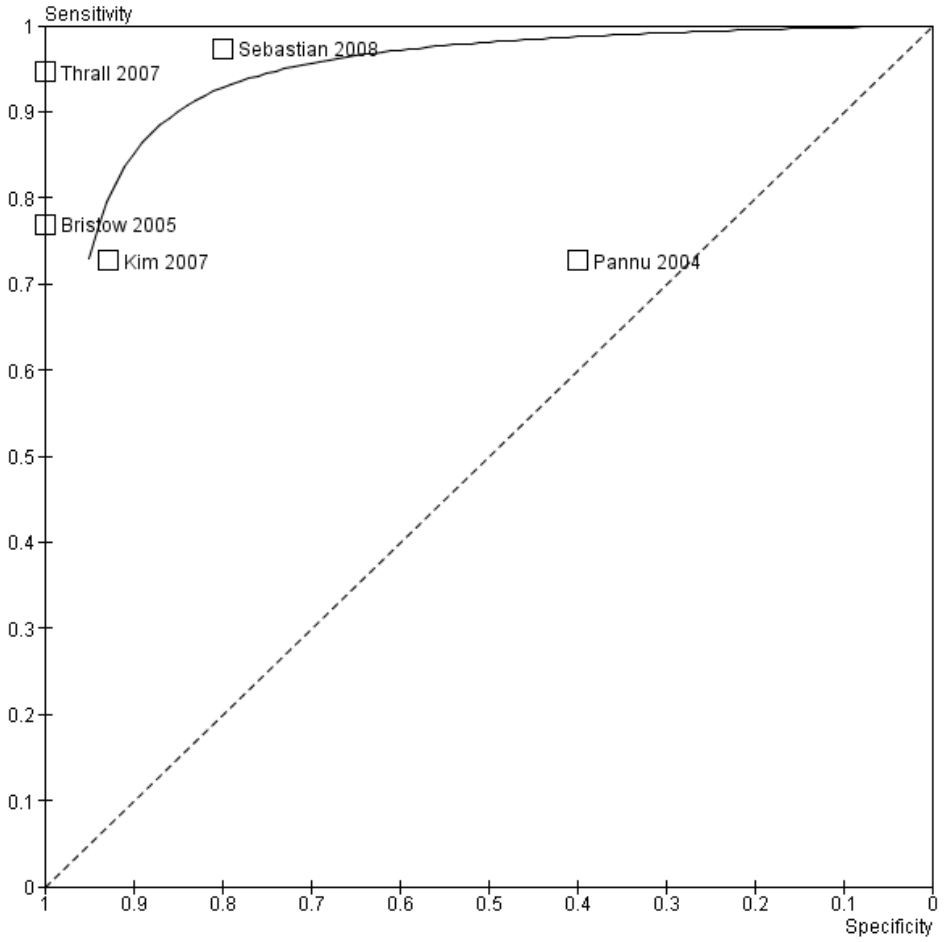


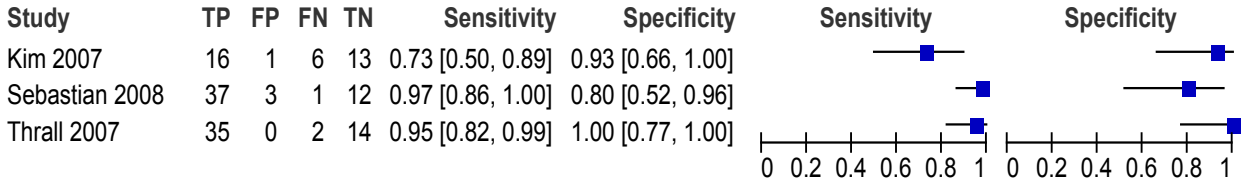
Figure 60 shows the estimates of sensitivity and 1-specificity plotted in ROC space for ^{18}FDG-PET/CT versus any reference standard to detect recurrences of ovarian cancer based on retrospective studies.

Figure 60. Summary ROC plot of ^{18}FDG-PET versus any reference standard to detect recurrences of ovarian cancer (retrospective studies)



Reference standard: histology/biopsy or clinical followup, retrospective studies (subgroup analysis). Three retrospective studies[80,86,89] totaling 140 participants provided data for a subgroup analysis of the diagnostic accuracy of ^{18}FDG-PET/CT when histology/biopsy or clinical followup were used as the reference standard to detect recurrences of ovarian cancer. Individual 2x2 table results are presented in Figure 61. Sensitivity values ranged from 73%[80] to 97%.[86] Specificity values ranged from 80% [86] to 100%.[89]

Figure 61. Results from 2x2 tables of individual retrospective studies of ^{18}FDG-PET/CT versus histology/biopsy or clinical followup to detect recurrences of ovarian cancer (subgroup analysis)



We found that when only histology/biopsy or clinical followup were considered as reference standard in retrospective studies, ^{18}FDG-PET/CT had a pooled positive LR of 6.68 (95% CI 2.86, 15.64) and a pooled negative LR of 0.10 (95% CI = 0.02, 0.44) to accurately detect recurrences of ovarian cancer (Figures 62 and 63). The positive and negative LRs were statistically significant and therefore, ^{18}FDG-PET/CT seems to be helpful for identifying recurrences of the disease. The positive LR was homogeneous across the studies, but the negative LR was heterogeneous across the studies ($p = 0.01$; $I^2 = 77$ percent).

Figure 62. Meta-analysis of the positive LR of ^{18}FDG-PET/CT versus histology/biopsy or clinical followup to detect recurrences of ovarian cancer (retrospective studies)

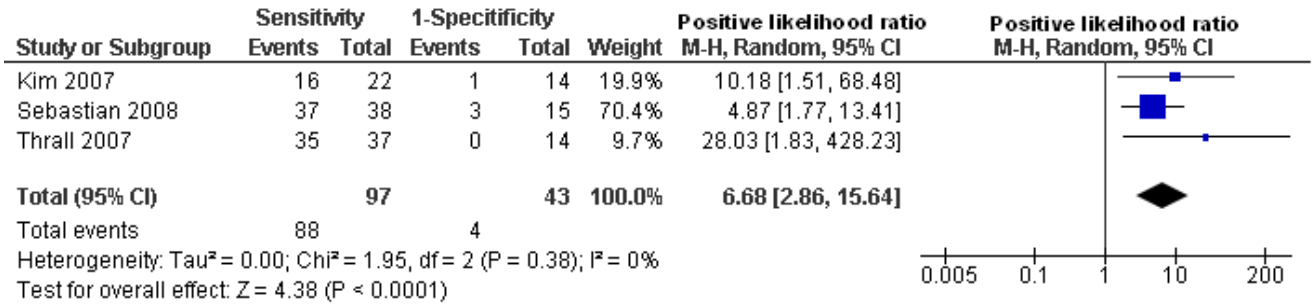


Figure 63. Meta-analysis of the negative LR of ^{18}FDG-PET/CT versus histology/biopsy or clinical followup to detect recurrences of ovarian cancer (retrospective studies)

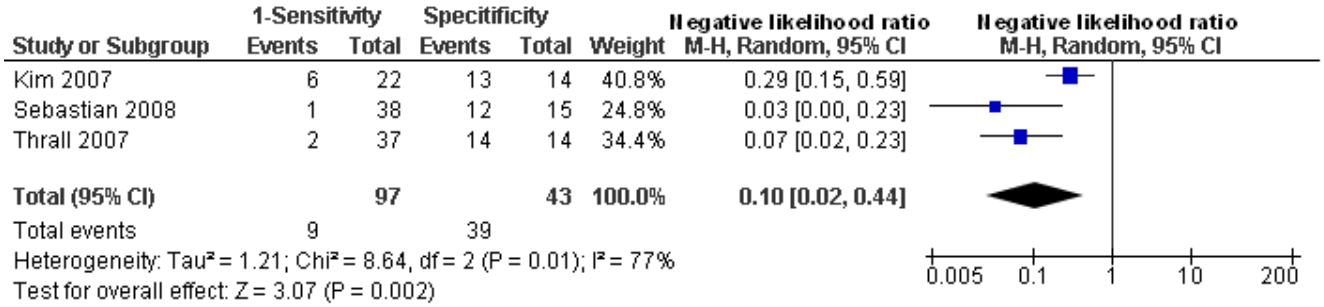
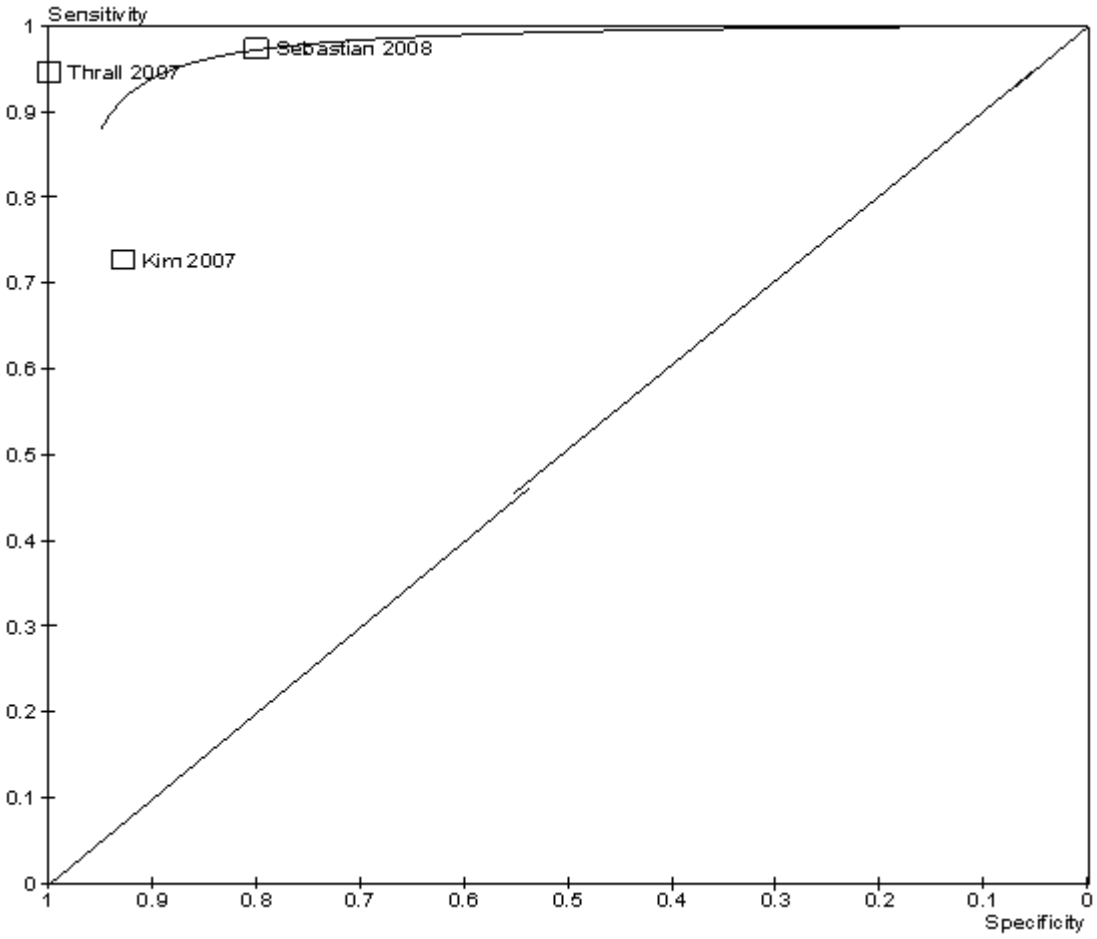


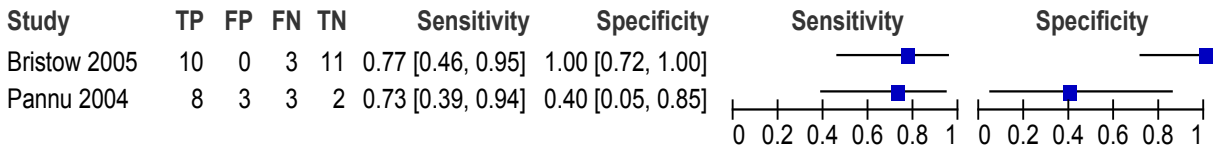
Figure 64 shows the estimates of sensitivity and 1-specificity plotted in ROC space for ^{18}FDG-PET/CT versus histology/biopsy or clinical followup to detect recurrences of ovarian cancer based on retrospective studies.

Figure 64. Summary ROC plot of ^{18}FDG-PET versus histology/biopsy or clinical followup to detect recurrences of ovarian cancer (retrospective studies)



Reference standard: histology/biopsy, retrospective studies (subgroup analysis). Two retrospective studies[73,83] totaling 40 participants provided data for a subgroup analysis of the diagnostic accuracy of ^{18}FDG-PET/CT when only histology/biopsy was used as the reference standard to detect recurrences of ovarian cancer. Individual 2x2 table results are presented in Figure 65. Sensitivity values were 73%[83] and 77%.[73] Specificity values were 40%[83] and 100%.[73]

Figure 65. Results from 2x2 tables of individual retrospective studies of ^{18}FDG-PET/CT versus histology/biopsy or clinical followup to detect recurrences of ovarian cancer (subgroup analysis)



We found that when only histology/biopsy was considered as the reference standard in retrospective studies, ^{18}FDG-PET/CT had a pooled positive LR of 3.97 (95% CI 0.09, 167.47) and a pooled negative LR of 0.36 (95% CI = 0.15, 0.86) to accurately detect recurrences of the disease (Figures 66 and 67). Only the negative LR was statistically significant. The positive LR was not statistically significant and quite heterogeneous across the studies ($p = 0.008$; $I^2 = 86$ percent), precluding any reliable interpretation from the results.

Figure 66. Meta-analysis of the positive LR of ^{18}FDG-PET/CT versus histology/biopsy to detect recurrences of ovarian cancer (retrospective studies)

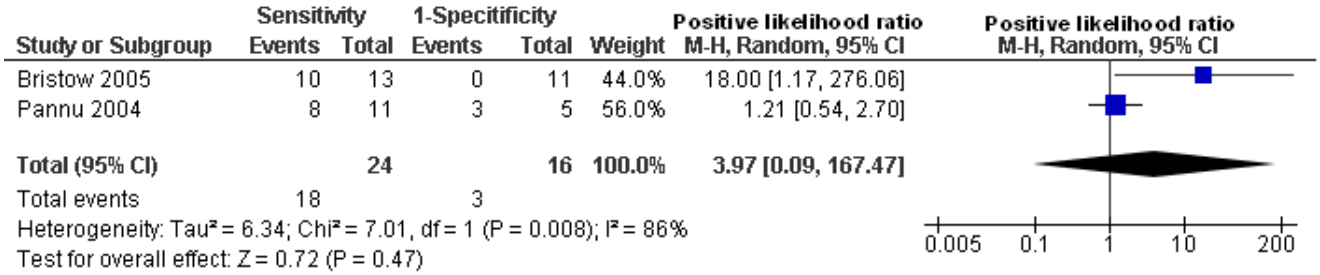


Figure 67. Meta-analysis of the negative LR of ^{18}FDG-PET/CT versus histology/biopsy to detect recurrences of ovarian cancer (retrospective studies)

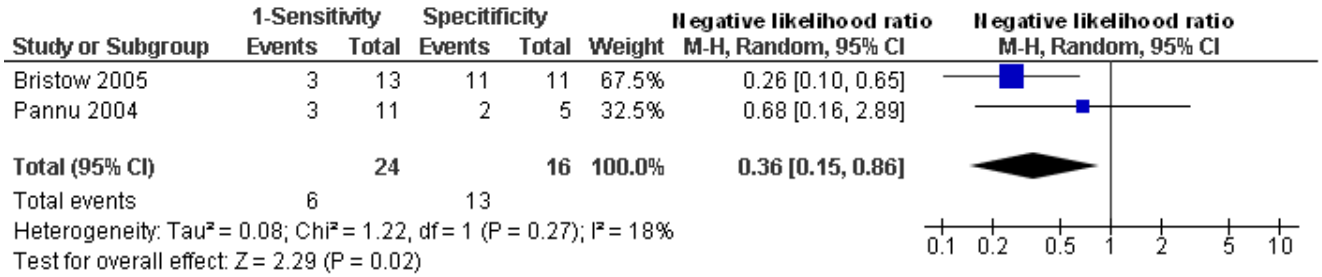
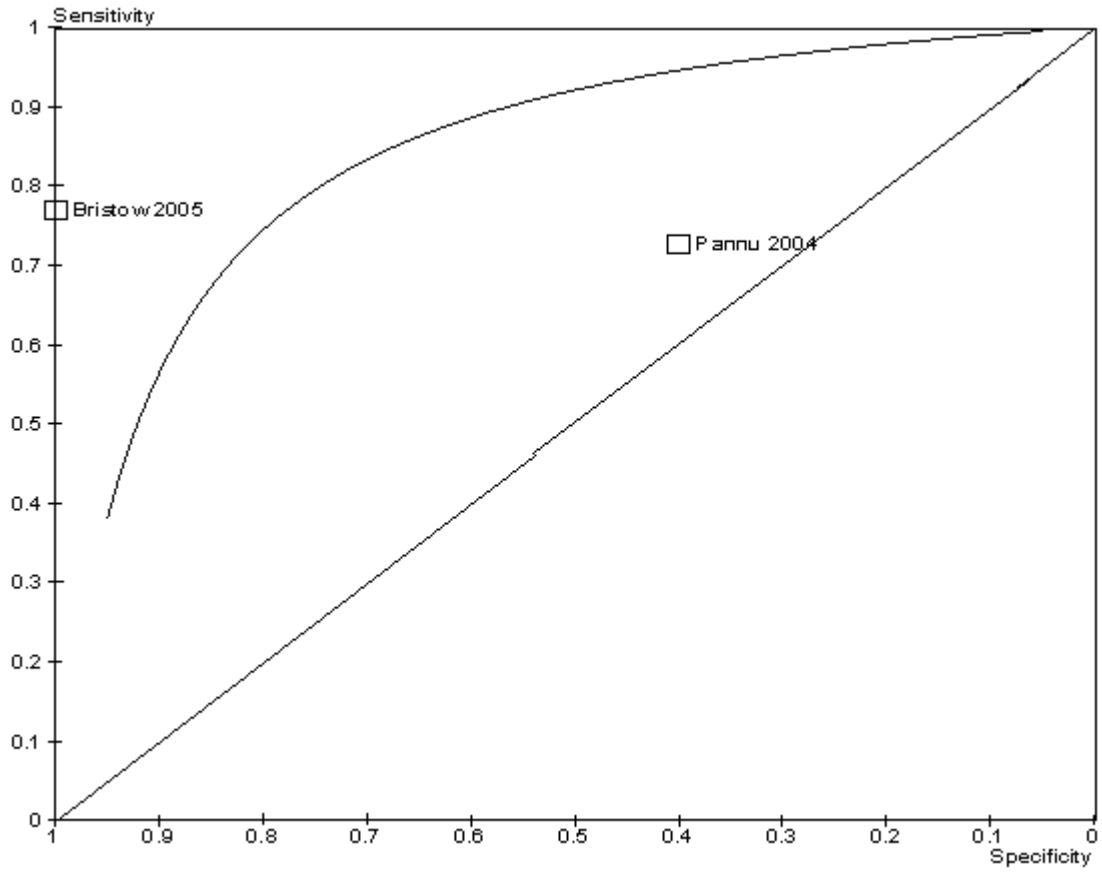


Figure 68 shows the estimates of sensitivity and 1-specificity plotted in ROC space for ^{18}FDG-PET/CT versus histology/biopsy to detect recurrences of ovarian cancer based on retrospective studies.

Figure 68. Summary ROC plot of ^{18}FDG-PET versus histology/biopsy to detect recurrences of ovarian cancer (retrospective studies)



Summary of the results

Meta-analyses were calculated to evaluate the accuracy of ^{18}FDG-PET and ^{18}FDG-PET/CT in detecting recurrences of ovarian cancer (Table 20). The largest estimate of the positive LR was obtained for ^{18}FDG-PET when compared to histology/biopsy or clinical followup in prospective studies (positive LR=22.40). The confidence interval indicates that more data should be collected before any definite conclusions can be drawn regarding this parameter. The smallest estimate of the negative LR was obtained for ^{18}FDG-PET/CT compared to histology/biopsy or clinical followup in both prospective and retrospective studies (negative LR=0.10).

Table 20. Results of meta-analyses of the accuracy of ^{18}FDG-PET and ^{18}FDG-PET/CT for ovarian cancer

PET Purpose	Type of PET	Reference standard	Design	Studies	N	Effect estimate M-H, Random, 95% CI
Recurrences	FDG-PET	Histology/biopsy or clinical followup	P	2	119	PLR=22.40 [1.64, 305.38]
						NLR=0.13 [0.06, 0.29]
	FDG-PET/CT	Any reference standard	P	4	159	PLR=6.97 [1.94, 25.00]
						NLR=0.12 [0.06, 0.26]
		Histology/biopsy or clinical followup		3	137	PLR=9.84 [1.64, 59.15]
						NLR=0.10 [0.05, 0.22]
		Any reference standard	R	5	180	PLR=6.02 [1.40, 25.91]
						NLR=0.19 [0.08, 0.45]
		Histology/biopsy or clinical followup		3	140	PLR=6.68 [2.86, 15.64]
						NLR=0.10 [0.02, 0.44]
		Histology/biopsy		2	40	PLR=3.97 [0.09, 167.47]
						NLR=0.36 [0.15, 0.86]

95% CI=95% confidence interval; FDG= fluorodeoxyglucose; M-H = Mantel Hantzel; NLR=negative likelihood ratio; P=prospective; PET=positron emission tomography; PLR=positive likelihood ratio; R=retrospective

5.3.2. Diagnostic thinking impact of ^{18}FDG-PET and ^{18}FDG-PET/CT on physician decision making with respect to diagnosis and management strategy for patients with ovarian cancer

All five studies[75,89,126-128] considered fused or integrated ^{18}FDG-PET/CT imaging to assess for recurrence in patients previously diagnosed with ovarian cancer. The included studies assessed the impact of ^{18}FDG-PET/CT imaging both on the management of patients suspected of suffering a recurrence of cancer, and on the surveillance for recurrences in patients' following treatment for their primary cancer.

Chung *et al*[75] evaluated the accuracy of integrated ^{18}FDG-PET/CT imaging on diagnosis of suspected recurrences of ovarian cancer and whether the results altered either treatment decisions or additional diagnostic testing regimes for the participants.

This prospective study enrolled 77 women with suspected cancer recurrence. ^{18}FDG-PET/CT impacted either the diagnostic followup or the treatment plan in 19 cases (25%). The majority of changes (11/19) occurred in cases with a positive ^{18}FDG-PET/CT scan and no other clinical indicators of tumor recurrence. These 11 patients had normal CA-125 and no clinical symptoms, but were identified to have recurrent lesions based on ^{18}FDG-PET/CT. The treatment plan was thus changed from observation to a regime of chemotherapy. There were an additional eight patients whose CA-125 levels were elevated but who were shown to have only physiological or inflammatory ^{18}FDG uptake. The need for additional diagnostic procedures was therefore eliminated, and the patients were followed by normal observation. Overall, ^{18}FDG-PET/CT was determined to have high impact on patient care.

The authors concluded that the use of ^{18}FDG-PET/CT is a sensitive surveillance method to identify cervical cancer recurrences and that it allows for the optimization and customization of an appropriate treatment plan.

This prospective study was assessed being of moderate quality. The spectrum of patients that were included and the details of the selection criteria, as well as the choice and administration of the reference standard were well described. There was also a good description of the ^{18}FDG-PET/CT procedure and intermediate test results. There was inadequate reporting on some aspects, notably of the time delay between the ^{18}FDG-PET/CT scan and the reference verification of disease status, the lack of detail of the reference test procedure, and the unblinded interpretation of the final reference standard. The interpretation of the final reference with knowledge of the ^{18}FDG-PET/CT results introduces the possibility of backward review bias. Additionally, because the disease status of patients was not verified by one reference standard, there is the possibility of verification bias. A further limitation identified by the authors was the strict inclusion criteria employed to maintain a homogenous study group. This may have lead to a selection bias in the included patients. In practice, the population would be more varied which may impact the ^{18}FDG-PET/CT performance. Furthermore, as regards management change it was not stated whether the management change was documented to be a correct change by either biopsy or follow-up confirmation. This is particularly concerning in the case of patients having a normal CA-125, but a positive PET who were subsequently treated with chemotherapy.

In the second study, Mangili *et al*[126] evaluated the impact of ^{18}FDG-PET/CT imaging on the management decisions for patients suspected to have ovarian cancer recurrence. Data from a chart review of 32 patients who underwent ^{18}FDG-PET/CT scans were used in this study. All patients had previously undergone surgery and chemotherapy for ovarian cancer. The suspicion of recurrence was based on any of a number of followup measures, including elevated serum CA-125 or abnormalities on an annual chest X-ray or abdominal ultrasound. The impact on patient management was assessed retrospectively in a blinded fashion. All pertinent information (e.g., diagnosis, staging, previous treatment of primary tumor, followup including CA-125 values and imaging studies, and the detailed CT report) from the patient charts was collected and distributed to two teams of oncologists that completed a "pre^{18}FDG-PET/CT" questionnaire regarding the clinical management based on the history. Where there was discrepancy between the respective plans of the two teams, they were asked to come to a consensus regarding patient management. The ^{18}FDG-PET/CT scans

were then distributed with the coded patient information and in a different sequence than the "pre^{18}FDG-PET/CT" charts. Both teams came to a "post^{18}FDG-PET/CT" consensus on the most appropriate course of clinical management. There were changes to the treatment plans for 14 patients (44 %) upon addition of the ^{18}FDG-PET/CT images to the patient information. The treatment modality was altered for eight patients, including being scheduled for switches between chemotherapy and surgery or vice versa (n=4), undergoing further instrumental examination (e.g., CT) rather than diagnostic surgery (n=1), or chemotherapy rather than diagnostic surgery (n=3). Pre^{18}FDG-PET/CT, seven patients were designated to the observation approach, however, post^{18}FDG-PET/CT, this decision was changed for six of the patients. Of these, two underwent further diagnostic procedures, while four underwent changes to their treatment plans to undergo chemotherapy (n=1) or surgery (n=3). Thus, for seven patients (22%), the ^{18}FDG-PET/CT imaging facilitated a change in management from either further invasive diagnostics or a "watch and see" approach to a definitive treatment plan. There was an increase in the overall number of patients undergoing chemotherapy (10/32 to 16/32) as a result of the discovery of more disseminated disease based on the ^{18}FDG-PET/CT images.

The authors concluded that ^{18}FDG-PET/CT imaging for detection of ovarian cancer recurrence demonstrates a higher level of accuracy then conventional contrast enhanced CT. The authors suggested that use of integrated ^{18}FDG-PET/CT with a fully diagnostic CT could replace the current approach of using multiple imaging modalities from a number of sessions to restage ovarian cancer recurrences.

This retrospective chart review was determined to be of moderate quality. The spectrum of included patients, choice and administration of the reference standard and the inclusion of intermediate test results were well reported. Additionally, all cases were verified by a reference standard which was interpreted without knowledge of the ^{18}FDG-PET/CT results. There was also satisfactory description provided for withdrawals. There was inadequate reporting on some aspects, including the inclusion criteria, and the lack of blinded interpretation of the ^{18}FDG-PET/CT imaging, which may have resulted in forward review bias. The period of time between the administration of the ^{18}FDG-PET/CT scan and the reference standard was unclear, and there was not one standard reference test used to verify disease status; rather a combination of methods were used (histological or clinical followup), which may have introduced verification bias.

Simcock *et al*[127] investigated the treatment decision impact of integrated ^{18} -PET/CT imaging on the restaging and management of recurrent ovarian cancer in a population of 61 patients. Of the 61 women, 56 had sufficient followup data to be included in the analysis (median total followup: 21.6 months). Collectively, these patients had undergone 66 ^{18}FDG-PET/CT scans; the majority of women (86%) had one scan.

The disease state immediately prior to each of the 66 ^{18}FDG-PET/CT scans were described as follows: "uncertain" (n=30), "suspected local recurrence" (n=15), "suspected systemic disease" (n=14), and "surveillance with no evidence of disease" (n=7). The impact of the ^{18}FDG-PET/CT imaging on the patient management plans was "high" for 32 patients (57%) who received a total of 33 ^{18}FDG-PET/CT scans. There were also minor changes in the care of an additional 29 patients. Of the 32 high-impact management changes, 20 occurred in patients who were not assigned a disease state using conventional assessment. As there were 30 patients in this "uncertain" category following their conventional staging, two-thirds of the patients were diagnosed following the ^{18}FDG-PET/CT. The ^{18}FDG-PET/CT facilitated changes ranging from altering an active treatment approach to observation (n=6), or from observation to treatment by radiation, chemotherapy or surgery (n=7). Thus, in 13 patients (23%) the results of the ^{18}FDG-PET/CT determined whether or not they received treatment. Other high-impact modality changes included switching from surgery to chemotherapy (n=6), chemotherapy to radiation or a combination of therapies (n=4), biopsy to chemotherapy or surgery (n=4), radiation to chemotherapy or enlargement of radiation target fields (n=1), and switching from a combination of therapies to radiation or chemotherapy alone (n=2).

Additionally, prognostic outcomes were reported. The survival of patients was analyzed according to their ^{18}FDG-PET/CT determined disease status (systemic, localized, or no disease/equivocal). While there was no significant difference in overall survival among the three groups, there was significantly lower survival in patients with ^{18}FDG-PET/CT designated systemic disease versus the combined ^{18}FDG-PET/CT designated localized and no disease/equivocal patient survival.

The authors concluded that the use of ^{18}FDG-PET/CT in monitoring of patients with recurrent or suspected recurrent ovarian cancer significantly modifies the assessment of cancer state. They also concluded that ^{18}FDG-PET/CT alters management in a substantial proportion of patients.

This prospective study was determined to be of moderate quality. The selection criteria, choice and execution of the reference standard, and intermediate test results were well reported.

Additionally, all cases were verified by a reference standard, and there was satisfactory explanation for withdrawals. However, there was inadequate reporting on some aspects, notably of whether or not the spectrum of patients was representative of typical clinical practice which raises the possibility of selection bias. In addition, the lack of blinded interpretation of either the ^{18}FDG-PET/CT scans or the reference standards may have introduced review bias to the interpretation of results. Furthermore, there was no clear period of time between the administration of the ^{18}FDG-PET/CT scan and the reference standard, and there was no standard reference test; rather, a combination of methods was used (histological or clinical followup). This variation in validation of the diagnosis may have lead to verification bias

Soussan *et al*[128] investigated the impact of integrated ^{18}FDG-PET/CT on treatment decision for the management of possible recurrent ovarian cancer. This prospective study enrolled 29 outpatients who underwent ^{18}FDG-PET/CT scans under the suspicion of recurrence. All patients had previously undergone surgical and chemotherapy. Two questionnaires were completed by the treating oncologists to determine the impact of ^{18}FDG-PET/CT on management decisions; the first was completed following the independent CT scan but prior to the ^{18}FDG-PET/CT scan, and the second was completed upon receipt of the ^{18}FDG-PET/CT data. Followup data were also collected from the referring oncologists.

The final therapeutic decision was changed based on the results of the ^{18}FDG-PET/CT for 10 patients (34%). The modality of therapy for the patient changed in three cases (e.g., chemotherapy to chemotherapy plus surgery); for six patients there was a change in plan from an approach of observation to treatment. One patient was switched from a plan of chemotherapy to observation. There was major modification in the assessment of disease distribution in 15 patients (52%); of these, 11 were found to have more advanced disease, and four were found to have more limited disease. A minor change in distribution was found in one patient. Of these patients, nine had their treatment plan altered as a result.

The authors concluded that the use of ^{18}FDG-PET/CT in evaluating patients with suspicion of recurrent ovarian cancer significantly modifies treatment decisions. The impact is particularly important for the management of cases which were determined to be positive by ^{18}FDG-PET/CT despite being assessed as negative by CT alone.

This prospective study was determined to be of reliable quality. The choice and execution of the reference standard, description of the ^{18}FDG-PET/CT interpretation, and inclusion of intermediate

test results were well reported. Additionally, all cases were verified by a reference standard, and there was satisfactory accounting for all participants enrolled. However, there was inadequate reporting on some aspects, including whether or not the spectrum of patients was representative of typical clinical practice, which raises the possibility of selection bias. The selection criteria for eligibility in the study were not reported in detail. The reference standard used to verify disease included a number of measures, which varied between patients, thus leading to potential verification bias. It was unclear whether the interpretation of either the ^{18}FDG-PET/CT or the reference standard was blinded. There may have been review bias due to the reference standard being interpreted without blinding post-^{18}FDG-PET/CT scan which may have influenced interpretation.

Thrall *et al*[89] retrospectively investigated the treatment decision impact for 39 patients who underwent integrated ^{18}FDG-PET/CT scans. All patients had confirmed ovarian cancer; the majority (69%) having been assessed as having stage III. All patients had undergone cytoreductive surgery and platinum-based chemotherapy. The analysis of possible recurrences included a total of 59 ^{18}FDG-PET/CT scans. Indications for undergoing ^{18}FDG-PET/CT imaging ranged from a routine component with no clinical or imaging abnormalities (n=4 scans) to abnormalities such as elevated serum CA-125 (n=24), clinical symptoms of recurrence (n=9), abnormal CT scan (n=14), as well as for assessment of treatment response (n=8). Twenty-five patients had one ^{18}FDG-PET/CT scans, 10 patients had two ^{18}FDG-PET/CT scans, two patients had either three or four scans.

During the followup period, 33 patients (84.6%) had a cancer recurrence. For 22 (66.7%), ^{18}FDG-PET/CT correctly identified recurrences in 18 of the 24 scans. The correct determination of recurrence was associated with subsequent clinical management decisions. Overall, ^{18}FDG-PET/CT imaging resulted in changes to the treatment plans of 14 patients (36%) with known disease recurrence. In four (29%) ^{18}FDG-PET/CT imaging identified distant metastases, prompting a change from treatment with curative intent to palliative care. Changes in diagnostic work-up prompted by the use of ^{18}FDG-PET/CT imaging, and included imaging of four patients with no other evidence to suggest recurrence who would have otherwise undergone second-look surgery. Additionally, of the eight ^{18}FDG-PET/CT scans completed in five patients to assess treatment response, there was one case of nonresponsive progressive disease was correctly identified by ^{18}FDG-PET/CT, one patient had stable disease, and three were responsive to treatment. None of these patients had clearly identifiable disease by conventional CT imaging at baseline.

The authors concluded that the use of ^{18}FDG-PET/CT is most valuable in assessment of patients with rising CA-125 levels despite negative or equivocal CT scans. They found ^{18}FDG-PET/CT to be useful in optimal selection of patients for planning of appropriate surgery and radiation therapy.

This retrospective study was determined to be of reliable quality. The spectrum of participants and their selection criteria were clearly the defined. In addition, the choice and execution of the reference standard, the description of the ^{18}FDG-PET/CT imaging procedure and reporting intermediate test results were well detailed. However, due to the retrospective nature of the study, there was no blinded interpretation of either the ^{18}FDG-PET/CT scans or the reference standards. The reference standard used to verify disease status consisted of a combination of methods (histological, clinical followup, surgical findings), which raises concerns about the possibility of verification bias.

5.3.3. ^{18}FDG-PET and ^{18}FDG-PET/CT as part of a management strategy in ovarian cancer

Kim *et al*[130] retrospectively assessed the value of ^{18}FDG-PET compared to second-look laparotomy (SLL) in the prognosis and detection of recurrences in patients with advanced ovarian carcinoma following primary chemotherapy. The study population consisted of 55 patients aged 25 to 78 years of age (mean age: 49.2, SD = 12.1) with ovarian cancer, primarily of mainly stages III (49%) and IV (44%). All patients were treated with a regime of chemotherapy, following which they were divided into two groups for followup. One group (n=30) underwent SLL while the second (n=25) underwent ^{18}FDG-PET imaging during the followup period. The ^{18}FDG-PET was performed a median of 6.8 months after in the initial laparotomy and visually interpreted by consensus of two nuclear physicians. Quantitative assessment by calculation of SUV values were determined to decide on malignancy status. The median length of followup for both groups was 35 months, and disease recurrence was verified by a variety of methods, including histology, physical exam, additional imaging, and CA-125 levels. The prognostic indicators investigated were the progression free interval, the disease free interval and the incidence of disease recurrence.

Overall, there was evidence of recurrence of ovarian cancer in 37 patients (67%). In the ^{18}FDG-PET group there were 17 cases with recurrent cancer, 13 of which (76%) were detected by ^{18}FDG-PET. The proportion of the remaining 20 cases detected by SLL was not specified. There were no significant differences in prognostic indicators between the two groups. When the progression-free

interval was compared between the two groups overall, there was not a significant difference in the duration of the disease free period. The same was true for the disease-free interval for subset of patients found to be negative or positive for recurrent disease in either the ^{18}FDG-PET or SLL group.

The authors concluded that neither SLL nor ^{18}FDG-PET is clearly advantageous for indicating disease prognosis and that ^{18}FDG-PET can be used to substitute followup modality for patients with ovarian cancer.

Overall, this study was determined to be of low quality. The retrospective nature of the prognostic indicator portion of the research, and the lack of a definitive method for determination of an ^{18}FDG-uptake positive lesion were some areas of concern. As there was no clear definition of a positive lesion, the study was subject to threshold bias in varied interpretation between assessors. Additionally, there was no uniform reference standard administered to the participants, introducing t the possibility of verification bias in the interpretation of the results. Outcomes were adequately described and there was appropriate description of the general characteristics and accounting for numbers of the included participants. Detailed inclusion criteria are lacking, which makes it difficult to rule out the potential for selection bias in the choice of participants enrolled in the study.

Table 21 provides a summary of the main findings and the types of bias that affected the evidence on the diagnostic thinking impact and effect on patient-centered outcomes of ^{18}FDG-PET and ^{18}FDG-PET/CT for ovarian cancer

Table 21. Main findings and types of bias that affected the evidence on the diagnostic thinking impact and effect on patient-centered outcomes of ^{18}FDG-PET and ^{18}FDG-PET/CT for ovarian cancer

Study	Results of FDG-PET imaging on Patient Diagnosis, Treatment and Outcomes	Types of Bias
Chung 2007[75] Study type: Prospective	**Management decision:** Treatment and diagnostic imaging Impact Management strategy changed 19 / 77 cases (24.7%) 11 cases without clinical symptoms or abnormal CA-125 were changed from observation to chemotherapy. (Treatment) 8 cases with elevated CA-125 had negative PET/CT, so additional diagnostic tests were cancelled. (Diagnostics)	Disease progression bias (unclear) Verification bias (>1 RS) Review bias (RS, unclear if blinded)
Kim 2004[130] Study type: Retrospective	**Patient Centered Outcomes and Prognosis:** Progression-free interval: PET: 28.8m (SD 12.7 m) for 25 cases; SLL: 30.6 m (SD 13.7 m) for 30 cases Disease free interval in Pts with negative test results: PET: 40.5 m (SD 11.6 m); SLL: 48.6 m (SD 12.1 m) Disease free interval in Pts with positive test results: PET: 23.7 m (SD 5.3 m); SLL: 26.2 m (SD 6.7 m)	Selection bias (unclear) Review bias (RS, unclear if blinded)
Mangili 2007[126] Study type: Retrospective	**Management decision:** Treatment and diagnostic imaging Impact Management strategy changed 14 / 32 cases (44%) Changed from observation to treatment or further diagnostics (n=6) Changed to surgery (n=3) Underwent further diagnostic examination (n=2) Changed to chemotherapy (n=1) Treatment modality changed (n=8) Surgery to chemotherapy (n=3) Diagnostic surgery to chemotherapy (n=3) Chemotherapy to surgery (n=1) Chemotherapy to additional diagnostic examination (n=1)	Selection bias (unclear) Disease progression bias (unclear) Verification bias (>1 RS) Review bias (RS, unclear if blinded)
Simcock 2006[127] Study type: Prospective	**Management decision:** Treatment 32 cases high impact of PET/CT on management (57%) 20/32 of high impact changes in patients with "uncertain disease" based on conventional diagnostics Observation changed to treatment (n=7) Active treatment changed to observation (n=6) Surgery changed to chemotherapy (n=6) Biopsy changed to treatment (e.g., chemotherapy) (n=4) Changed between various other treatment modalities (n=8) (e.g., radiation, chemotherapy, surgery) Changed from treatment to biopsy (n=1) Minor impact of PET/CT on management 29 / 32 (43%)	Spectrum bias (possible) Selection bias (unclear) Disease progression bias (lengthy interval) Verification bias (>1 RS) Review bias (RS unblinded)
Soussan 2008[128] Study type: Prospective	**Management decision:** Treatment 16 cases were diagnosis altered by PET (52%) Upstaged (n=11); downstaged (n=4); different disease distribution (n=1) Management strategy changed 10 / 29 (34%) Changed from observation to chemotherapy (n=6) Additional treatment modality added to care plan (n=2) Changed from chemotherapy to observation (n=1)	Spectrum bias (possible) Selection bias (unclear) Review bias (RS, not blinded)
Thrall M 2007[89] Study type: Retrospective	**Management decision:** Treatment and diagnostic imaging Impact Assisted treatment planning of known recurrences 14 / 39 (36%) Changed from treatment to palliative (n=4) Assisted with treatment modality plan (n=10) In cases with no clinical symptoms and normal CA-125, 3 recurrences identified by PET (8% of population) Negative PET allowed cancellation of SSL in 4 surveillance cases	Disease progression bias (lengthy interval) Verification bias (>1 RS) Review bias (RS, not blinded)

CA-125 = cancer antigen 125; CT=computer tomography; FDG=Fluorodeoxyglucose F18; mo=months; PET=positron emission tomography; RS=reference standard; SLL = second-look laparotomy

Pancreatic Cancer

6.1. Background

In 2008 there will be an estimated 37,680 new cases of pancreatic cancer and an estimated 34,290 deaths from the same disease.[133] In 2006 pancreatic cancer was the fourth leading cause of cancer deaths in the United States with a survival rate of four percent yet it only contributes two percent of the overall new cancer cases each year.[154] The majority of cases occur in people over the age of 50 with the median age of diagnosis being 72 years. Caucasians show an older median age of diagnosis (72 years) than African-Americans (68 years).[133] Improvements in the disease management of other cancers have been unrepeated with pancreatic cancer due to the inability to employ effective screening measures. This is largely because there are no tumor markers that can be screened at an early stage of disease.[155]

The only two risk factors consistently associated with pancreatic cancer are age and cigarette smoking with smoking correlated with 25-29% of pancreatic cancers.[156] In some cases a genetic risk may be present, such as hereditary pancreatitis or familial atypical multiple-mole melanoma.[156] Diets high in fruits and vegetables have been noted as exhibiting a protective role against pancreatic cancer.[156]

Pancreatic cancers are staged using both the TNM classification, and by clinical assessment (i.e. respectable, locally advanced, or metastatic).[155] Assignment of the disease stage is typically determined by a combination of history and physical examination, coupled with CT imaging. In patients deemed to be at high risk for metastasis or for whom the staging is indeterminate, the diagnosis is confirmed by fine needle aspiration or laparoscopy.

The majority of pancreatic cancers are diagnosed at a late stage of disease hampering efforts to provide curative therapy. Early symptoms may include weight loss, jaundice, pain, anorexia, dark urine, nausea, vomiting, and weakness.[154] The majority of cancers are palliative at diagnosis, however up to 20% of patients present with surgically resectable disease.[156] Obstructive jaundice that is painless has been traditionally associated with resectable disease.[154] For those patients optimally staged and who have surgery, only 20% are expected to survive to 5 years.[156] Chemotherapy is wholly ineffective in treating metastatic disease and has only limited palliative benefit.[156] Surgical resection remains the only treatment that is potentially curative.[154]

Diagnosing pancreatic cancer at an earlier stage is thus critical to providing curative therapy to an increased number of patients. Research focused on the molecular aspects of the disease has noted common genetic changes in pancreatic cancer cells and indicates a use for these changes in developing future screening and treatment technologies.[155] Ultrasonography is often the first diagnostic test performed when patients present with suspected disease with a sensitivity of 95% in tumors > 3cm.[157] Sensitivity decreases with smaller tumors.[157] Conventional CT is also appropriate for initial imaging; however dual-phase helical CT scans have the highest sensitivity (98%) in detecting pancreatic malignancies and metastases.[154] Early studies have indicated that combined ^{18}FDG-PET without contrast enhancement does not provide additional benefit compared to other diagnostic imaging techniques in the diagnosis of pancreatic cancer.[157]

6.2. Importance of Key Questions in the Clinical Management of Pancreatic Cancer

The high mortality rates of pancreatic cancer are associated to the lack of specificity of symptoms that lead to late presentations at the time of diagnosis, the aggressive nature of the disease, and the limitations of current diagnostic procedures. Accurate staging, particularly identification of distant metastases, appears of paramount importance to properly select patients who are the most likely to benefit from surgery. Currently, dynamic CT or endoscopic pancreatocholangiography are used in the diagnosis of patients with suspected pancreatic cancer. Mass-forming pancreatitis occurs when the pancreatitis-associated inflammation affects a portion of the pancreas, creating the appearance of a mass on imaging tests. Chronic pancreatitis is a risk factor for pancreatic cancer, so mass-forming pancreatitis is frequently found in those patients with suspected pancreatic cancer. Differential diagnosis between pancreatic cancer and pancreatitis is a commonly encountered problem with imaging modalities. Another problem of CT scan is related to monitoring the treatment response. Pancreatic cancer usually presents cancer cells sparsely scattered in active desmoplastic background and frequently invades major organs including celiac trunk or superior mesenteric vessels with small primary mass. These characteristics of pancreatic cancer make it difficult to determine tumor response with chemotherapy or chemoradiotherapy. Other recent technological advances for the diagnosis of pancreatic cancer include magnetic resonance cholangiopancreatography (MRCP) which is useful for the noninvasive demonstration of the morphologic contours of the pancreatic duct. However, this tool cannot always detect tumor

progression, especially when the tumor is not large enough to be identified accurately, and it is difficult to know the biological activity of the tumor with this method.

6.3. Results

Eighteen studies[91-107,158] provided evidence on the use of ^{18}FDG-PET or ^{18}FDG-PET/CT for pancreatic cancer. Seventeen[91-107] evaluated the diagnostic accuracy of ^{18}FDG-PET or ^{18}FDG-PET/CT, and five studies reported on the diagnostic thinking impact of ^{18}FDG-PET[91,101,103,105] and ^{18}FDG-PET/CT.[95] One study[91] evaluated the effects of ^{18}FDG-PET as part of a management strategy on patient centered outcomes. Finally, one study[95] conducted an economic evaluation on the use of ^{18}FDG-PET/CT for pancreatic cancer. Characteristics of the populations, conditions of ^{18}FDG-PET administration, interpretation of results and methodological quality of the studies are summarized in appendices D to J.

6.3.1. Diagnostic accuracy of ^{18}FDG-PET and ^{18}FDG-PET/CT in pancreatic cancer

Characteristics of the studies

Seventeen studies (fourteen prospective,[91,93-98,100-106] three retrospective[92,99,107]) evaluated the diagnostic accuracy of ^{18}FDG-PET[91,92,94,97-107] and ^{18}FDG-PET/CT[95,96] or both[93] on pancreatic cancer. ^{18}FDG-PET was used for primary diagnosis in five studies,[94,99,100,102,106] for initial staging in two studies,[101,107] for assessing recurrence in one study,[104] and for both primary diagnosis and staging in six studies.[91,92,97,98,103,105] Two studies used ^{18}FDG-PET/CT for both diagnosis and staging,[95,96] while one study used ^{18}FDG-PET and ^{18}FDG-PET/CT for diagnosis, staging and re-staging.[93] The studies contained a total of 1051 patients with sample sizes ranging from 15 to 112. The participant ages ranged from 21 to 93 years. One study reported the distribution by stage of cancer: CS I = 6%, CS II = 23%, CS III = 65% and CS IV = 6%.[104] ^{18}FDG-PET was compared to a reference standard that varied across the studies. In fifteen studies the reference standard was either histology/biopsy or clinical follow-up.[91-101,103-106] Two studies established the final diagnosis of all patients using histology/biopsy.[102,107] One study reported the mean time between last treatment and ^{18}FDG-PET as 12 months.[104] Seven studies used a fixed dose of ^{18}FDG (5 MCi,[107] 120 MBq,[94] 200 MBq,[98] 370 MBq,[91] 400 MBq,[97,102] 444 MBq[105]). Seven studies used a weight based dose (3 MBq/kg,[100,101] 3.7 MBq/kg,[98] 4 MBq/kg,[93] 5 MBq/kg[96,103,104]). Three studies reported a dose range for ^{18}FDG: 200-220 MBq,[106] 260-370 MBq,[92] 350–450 MBq.[95] The time between injection and PET

scan was 20 minutes,[97] 35-50 minutes,[102] 60 minutes,[91,93-95,98,100,101,105-107] 60-90 minutes,[96] 60-120 minutes,[92] and 90 minutes.[103,104] Patients fasted for the following durations: four hours,[91,95,107] five hours,[98,100] six hours,[93,97,101,106] eight hours,[103,104] twelve hours,[94] and overnight.[92,105] Eight studies[92,93,96,97,100,103-105] measured glucose levels before administration of ^{18}FDG-PET; the maximum glucose level that was allowed was 10 mmol/L,[97] 110 mg/Dl,[96,103,104] 120 mg/Dl,[105] and 200 mg/Dl.[93,100] Methods of interpretation of the images were qualitative in three studies[93,95,101] and both qualitative and quantitative in fourteen.[91,92,94,96-100,102-107] Scans were interpreted qualitatively using visual analysis. [91-98,100-107] Seven studies reported using SUV, where the criterion for abnormality was SUV > 2.5 g/Ml,[92,105] SUV > 3 g/Ml,[98,102] SUV > 3.5 g/Ml.[96,100,103]

Comparisons

Comparisons for which data were considered for meta-analysis are summarized in Table 22. Pooled data were obtained to evaluate the accuracy of ^{18}FDG-PET for both primary diagnosis and staging purposes, and for primary diagnosis purposes separately. Pooled data were also obtained to evaluate the accuracy of ^{18}FDG-PET/CT for both the primary diagnosis and staging of pancreatic cancer. Individual data are summarized in Appendix D.

Table 22. Summary of comparisons considered for meta-analyses of the accuracy of ^{18}FDG-PET and ^{18}FDG-PET/CT for pancreatic cancer

Indication	Studies	Design	Type of PET	Reference standard	Meta-analysis
Primary diagnosis and staging	Bang 2006[91]	P	FDG-PET	Histology/biopsy or clinical followup	1. FDG-PET vs. histology/biopsy or clinical followup (P studies) [91,93,96-98,103,105]
	Borbath 2005[92]	R	FDG-PET	Histology/biopsy or clinical followup	
	Heinrich 2005[95]	P	FDG-PET/CT	Histology/biopsy or clinical followup	
	Lemke 2004[96]	P	FDG-PET and FDG-PET/CT	Histology/biopsy or clinical followup	2. FDG-PET/CT v vs. histology/biopsy or clinical followup (P studies) [93,95,96]
	Lytras 2005[97]	P	FDG-PET	Histology/biopsy or clinical followup	
	Maemura 2006[98]	P	FDG-PET	Histology/biopsy or clinical followup	
	Ruf 2006[103]	P	FDG-PET	Histology/biopsy or clinical followup	
	Sperti 2007[105]	P	FDG-PET	Histology/biopsy or clinical followup	
	Casneuf 2007[93]	P	FDG-PET and FDG-PET/CT	Histology/biopsy or clinical followup	

Table 22. Summary of comparisons considered for meta-analyses of the accuracy of ^{18}FDG-PET and ^{18}FDG-PET/CT for pancreatic cancer (cont')

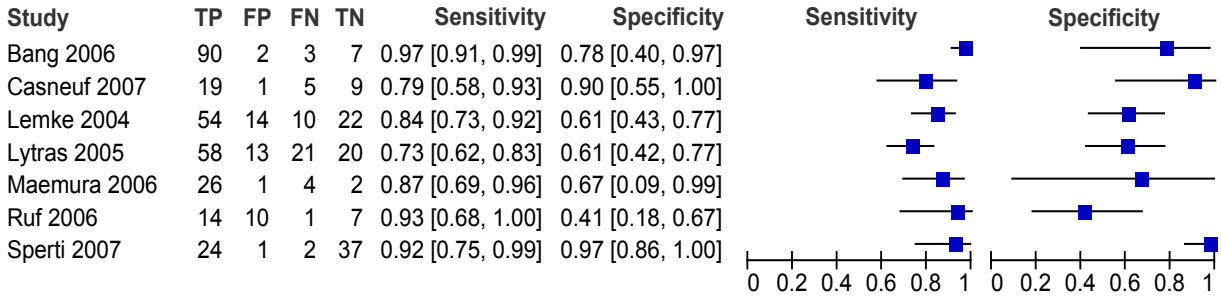
Indication	Studies	Design	Type of PET	Reference standard	Meta-analysis
Primary diagnosis	Giorgi 2004[94]	P	FDG-PET	Histology/biopsy or clinical followup	1. FDG-PET vs. all comparators (P studies) [94,100,102,106]
	Mansour 2006[99]	R	FDG-PET	Histology/biopsy or clinical followup	
	Nishiyama 2005[100]	P	FDG-PET	Histology/biopsy or clinical followup	2. FDG-PET vs. histology/biopsy or clinical followup (P studies) [94,100,106]
	Rasmussen 2004[102]	P	FDG-PET	Histology/biopsy	
	van Kouwen 2005[106]	P	FDG-PET	Histology/biopsy or clinical followup	
Recurrences	Ruf 2005[104]	P	FDG-PET	Histology/biopsy or clinical followup	No
Staging	Nishiyama 2005[101]	P	FDG-PET	Histology/biopsy or clinical followup	No
	Wakabayashi 2008[107]	R	FDG-PET	Histology/biopsy	

FDG= fluorodeoxyglucose; P = P; PET=positron emission tomography; R = retrospective

1. ^{18}FDG-PET for the primary diagnosis and staging of pancreatic cancer

Reference standard: histology/biopsy or clinical followup; prospective studies. Seven prospective studies[91,93,96-98,103,105] totaling 479 participants provided data for a meta-analysis of the diagnostic accuracy of ^{18}FDG-PET versus histology/biopsy or clinical followup for the diagnosis and staging of pancreatic cancer. Individual 2x2 table results are presented in Figure 69. Sensitivity values ranged from 73%[97] to 97%.[91] Specificity ranged from 41% [103] to 97%.[105]

Figure 69. Results from 2x2 tables of individual prospective studies of ^{18}FDG-PET versus histology/biopsy or clinical followup for the primary diagnosis and staging of pancreatic cancer



We found that, ^{18}FDG-PET had a pooled positive LR of 2.77 (95% CI 1.62, 4.73) and a pooled negative LR of 0.19 (95% CI = 0.10, 0.34) to accurately diagnose and identify the stage of pancreatic cancer (Figures 70 and 71). There was considerable heterogeneity in the positive (p = 0.003; I^2 = 70 percent) and negative (p = 0.004, I^2 = 68 percent) LRs across the studies, suggesting

considerable difficulties in drawing conclusions about the overall accuracy of ^{18}FDG-PET based on the pooled estimates.

Figure 70. Meta-analysis of the positive LR of ^{18}FDG-PET versus histology/biopsy or clinical followup for the primary diagnosis and staging of pancreatic cancer (prospective studies)

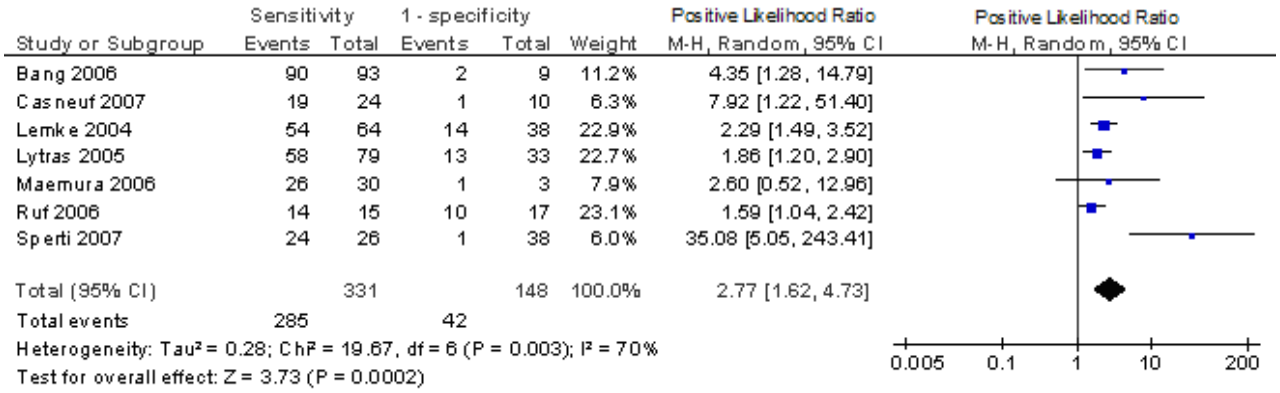


Figure 71. Meta-analysis of the negative LR of 18FDG-PET versus histology/biopsy or clinical followup for the primary diagnosis and staging of pancreatic cancer (prospective studies)

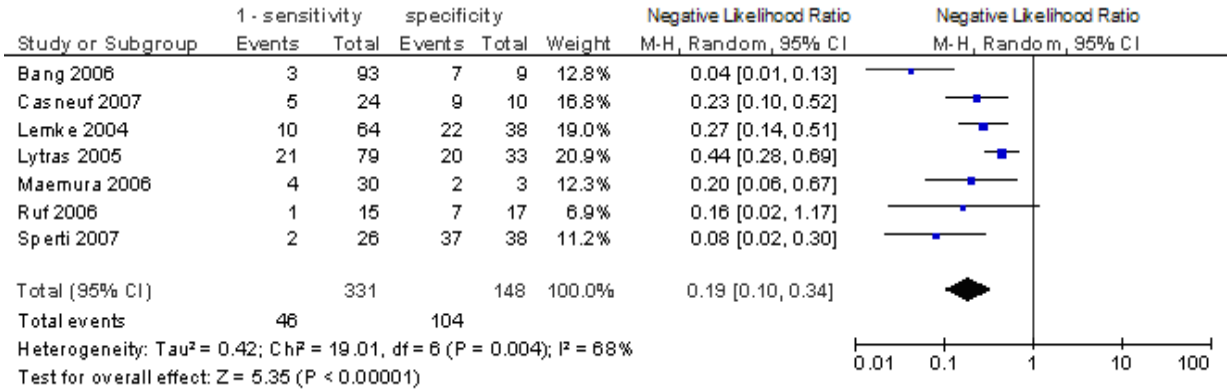
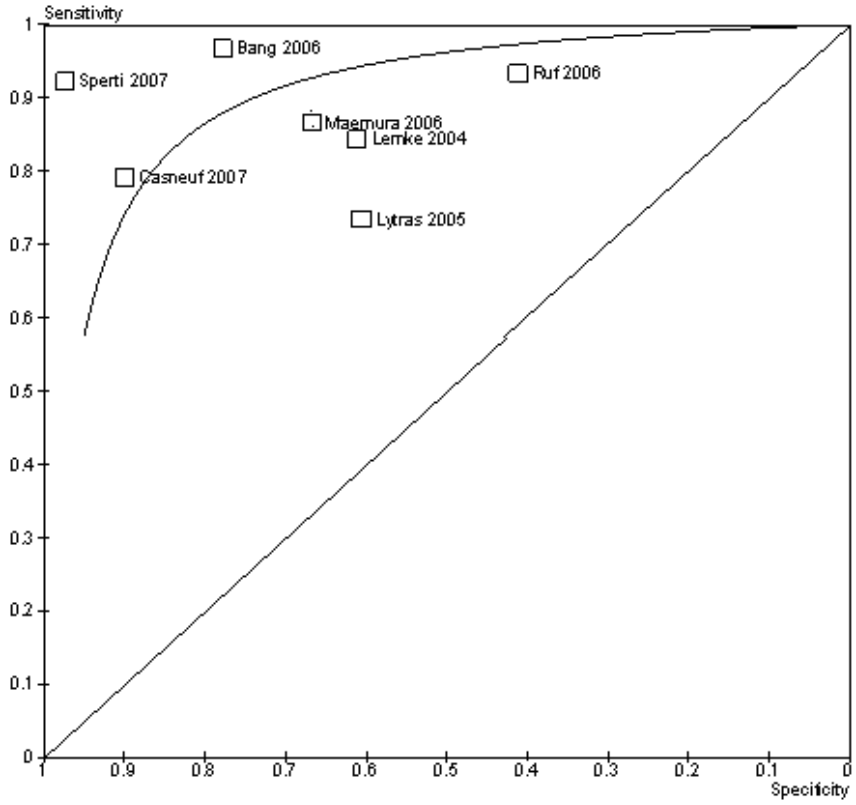


Figure 72 shows the estimates of sensitivity and 1-specificity plotted in ROC space for ^{18}FDG-PET versus histology/biopsy or clinical followup for the primary diagnosis and staging of pancreatic cancer based on prospective studies.

Figure 72. Summary ROC plot of ^{18}FDG-PET versus histology/biopsy or clinical followup for the primary diagnosis and staging of pancreatic cancer (prospective studies)

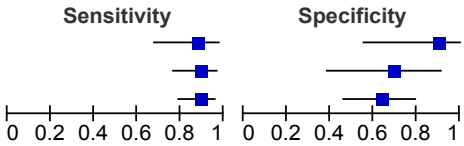


2. ^{18}FDG-PET/CT for the primary diagnosis and staging of pancreatic cancer

Reference standard: histology/biopsy or clinical followup; prospective studies. Three prospective studies[93,95,96] totaling 193 participants provided data for a meta-analysis of the diagnostic accuracy of ^{18}FDG-PET/CT versus histology/biopsy or clinical followup for the diagnosis and staging of pancreatic cancer. Individual 2x2 table results are presented in Figure 73. Sensitivity value was 89% in all the individual studies. Specificity ranged from 64%[96] to 90%.[93]

Figure 73. Results from 2x2 tables of individual prospective studies of ^{18}FDG-PET/CT versus histology/biopsy or clinical followup for the primary diagnosis and staging of pancreatic cancer

Study	TP	FP	FN	TN	Sensitivity	Specificity
Casneuf 2007	21	1	3	9	0.88 [0.68, 0.97]	0.90 [0.55, 1.00]
Heinrich 2005	41	4	5	9	0.89 [0.76, 0.96]	0.69 [0.39, 0.91]
Lemke 2004	57	13	7	23	0.89 [0.79, 0.95]	0.64 [0.46, 0.79]



We found that ^{18}FDG-PET/CT had a pooled positive LR of 2.69 (95% CI = 1.84, 3.94) and a pooled negative LR of 0.16 (95% CI = 0.10, 0.26) to accurately diagnose and identify the stage of the disease (Figures 74 and 75). Both positive and negative LRs were homogeneous across the studies.

Figure 74. Meta-analysis of the positive LR of ^{18}FDG-PET/CT versus histology/biopsy or clinical followup for the primary diagnosis and staging of pancreatic cancer (prospective studies)

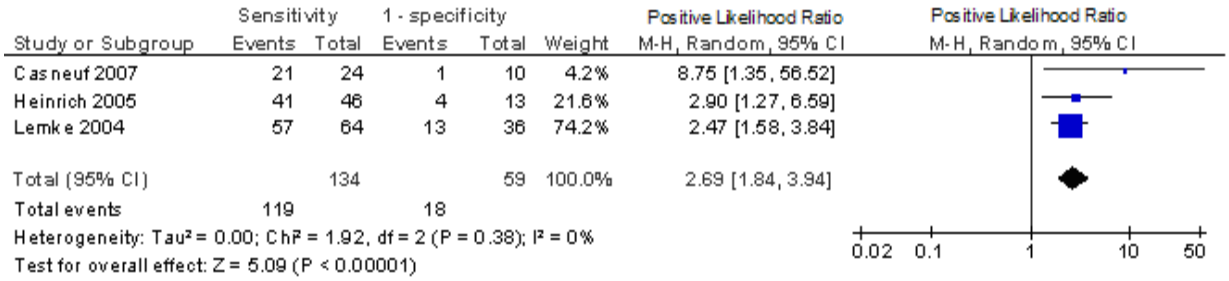


Figure 75. Meta-analysis of the negative LR of ^{18}FDG-PET/CT versus histology/biopsy or clinical followup for the primary diagnosis and staging of pancreatic cancer (prospective studies)

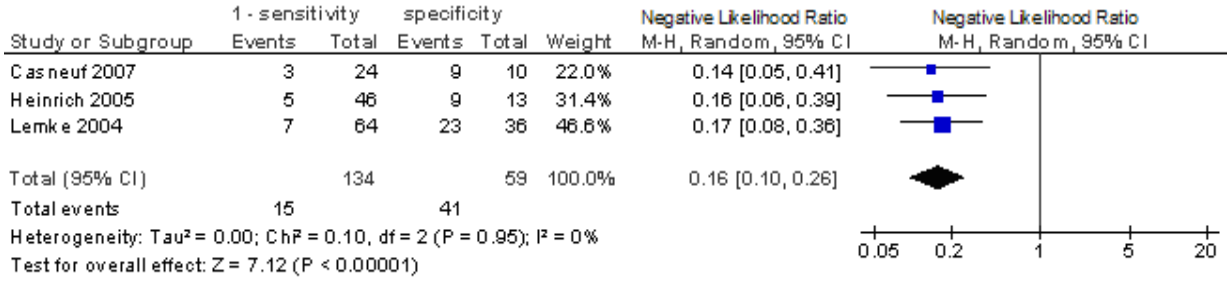
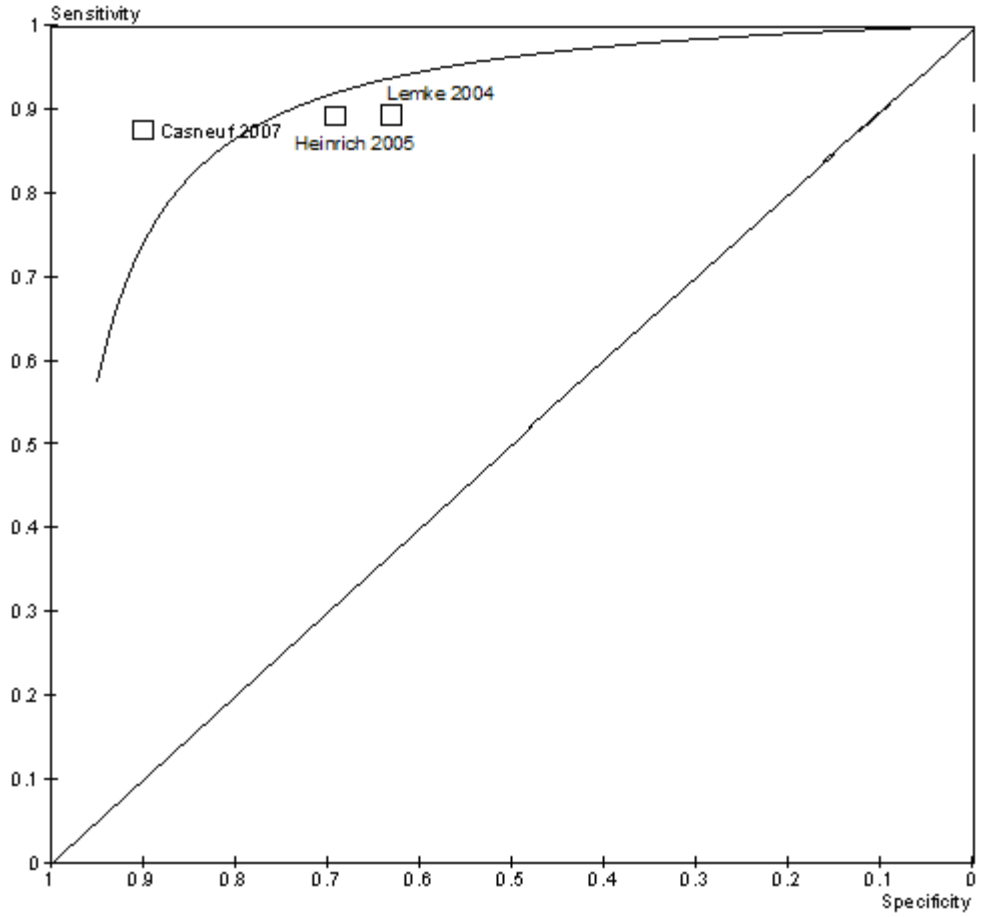


Figure 76 shows the estimates of sensitivity and 1-specificity plotted in ROC space for ^{18}FDG-PET/CT versus histology/biopsy or clinical followup for the primary diagnosis and staging of pancreatic cancer, based on prospective studies

Figure 76. Summary ROC plot of ^{18}FDG-PET/CT versus histology/biopsy or clinical followup for the primary diagnosis and staging of pancreatic cancer (prospective studies)

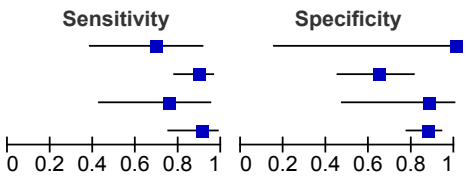


3. ^{18}FDG-PET for the primary diagnosis of pancreatic cancer

Reference standard: any; prospective studies. Four prospective studies[94,100,102,106] totaling 230 participants provided data for a meta-analysis of the diagnostic accuracy of ^{18}FDG-PET compared to a variety of reference standards for the primary diagnosis of pancreatic cancer. Individual 2x2 table results are presented in Figure 77. Sensitivity values ranged from 69%[94] to 91%.[106] Specificity ranged from 65%[100] to 100%.[94]

Figure 77. Results from 2x2 tables of individual prospective studies of ^{18}FDG-PET versus any reference standard for the primary diagnosis of pancreatic cancer

Study	TP	FP	FN	TN	Sensitivity	Specificity
Giorgi 2004	9	0	4	2	0.69 [0.39, 0.91]	1.00 [0.16, 1.00]
Nishiyama 2005	49	11	6	20	0.89 [0.78, 0.96]	0.65 [0.45, 0.81]
Rasmussen 2004	9	1	3	7	0.75 [0.43, 0.95]	0.88 [0.47, 1.00]
van Kouwen 2005	29	10	3	67	0.91 [0.75, 0.98]	0.87 [0.77, 0.94]



We found that, when all the reference standards were considered, ^{18}FDG-PET had a pooled positive LR of 4.28 (95% CI = 2.07, 8.86) and a pooled negative LR of 0.21 (95% CI = 0.12, 0.40) to accurately diagnose the disease (Figures 78 and 79). There was moderate heterogeneity in the positive ($p = 0.07$; $I^2 = 58$ percent) and negative ($p = 0.16$, $I^2 = 42$ percent) LRs across the studies, suggesting some difficulties in drawing conclusions about the overall accuracy of ^{18}FDG-PET based on the pooled results.

Figure 78. Meta-analysis of the positive LR of 18FDG-PET versus any reference standard for the primary diagnosis of pancreatic cancer (prospective studies)

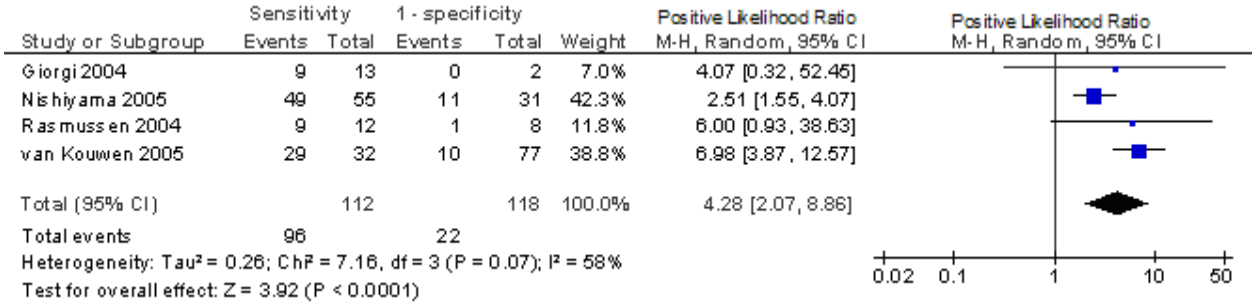


Figure 79. Meta-analysis of the negative LR of ^{18}FDG-PET versus any reference standard for the primary diagnosis of pancreatic cancer (prospective studies)

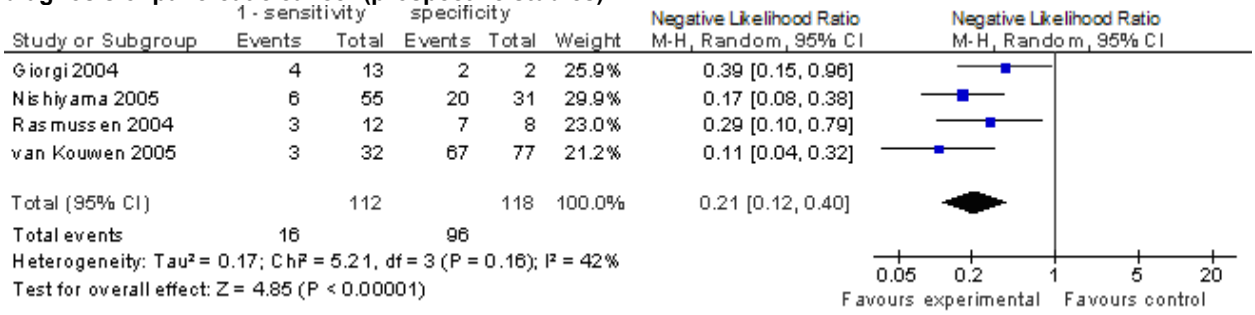
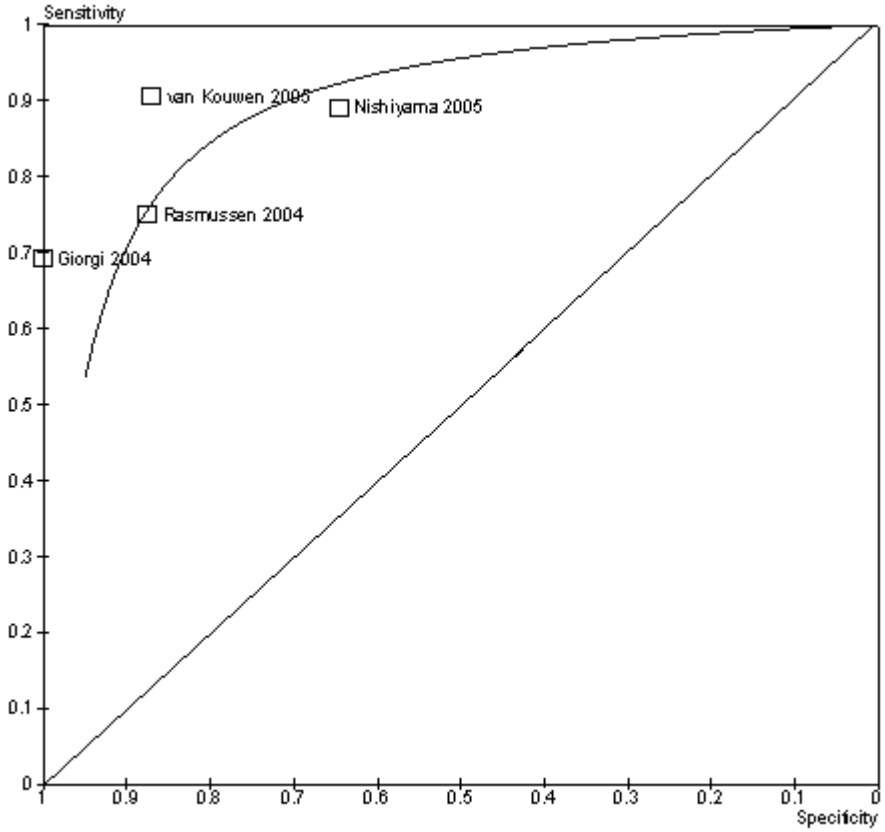


Figure 80 shows the estimates of sensitivity and 1-specificity plotted in ROC space for ^{18}FDG-PET versus all the reference standards for the primary diagnosis of pancreatic cancer, based on prospective studies.

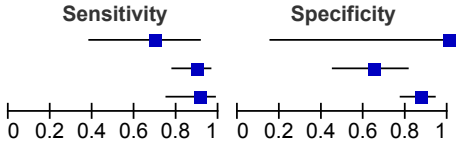
Figure 80. Summary ROC plot of ^{18}FDG-PET versus any reference standard for the primary diagnosis of pancreatic cancer (prospective studies)



Reference standard: histology/biopsy or clinical followup, prospective studies (subgroup analysis). Three prospective studies[94,100,106] totaling 210 participants provided data for a subgroup analysis of the diagnostic accuracy of ^{18}FDG-PET when only histology/biopsy or clinical followup was used as the reference standard for the primary diagnosis of pancreatic cancer. Individual 2x2 table results are presented in Figure 81. Sensitivity values ranged from 69%[94] to 91%.[106] Specificity ranged from 41% [103] to 97%.[105]

Figure 81. Results from 2x2 tables of individual prospective studies of ^{18}FDG-PET versus histology/biopsy or clinical followup for the primary diagnosis of pancreatic cancer

Study	TP	FP	FN	TN	Sensitivity	Specificity
Giorgi 2004	9	0	4	2	0.69 [0.39, 0.91]	1.00 [0.16, 1.00]
Nishiyama 2005	49	11	6	20	0.89 [0.78, 0.96]	0.65 [0.45, 0.81]
van Kouwen 2005	29	10	3	67	0.91 [0.75, 0.98]	0.87 [0.77, 0.94]



When ^{18}FDG-PET was compared to histology/biopsy or clinical followup for the primary diagnosis of pancreatic cancer, the pooled positive LR was 4.11 (95% confidence interval [CI] 1.74,

9.70) and the pooled negative LR was 0.9 (95% CI = 0.09, 0.44) (Figures 82 and 83). There was considerable heterogeneity in the positive (p = 0.03; I^2 = 71 percent) and negative (p = 0.09, I^2 = 58 percent) LRs across the studies, suggesting considerable difficulties in drawing conclusions about the overall accuracy of ^{18}FDG-PET based on the pooled results.

Figure 82. Meta-analysis of the positive LR of ^{18}FDG-PET versus histology/biopsy or clinical followup for the primary diagnosis of pancreatic cancer (prospective studies)

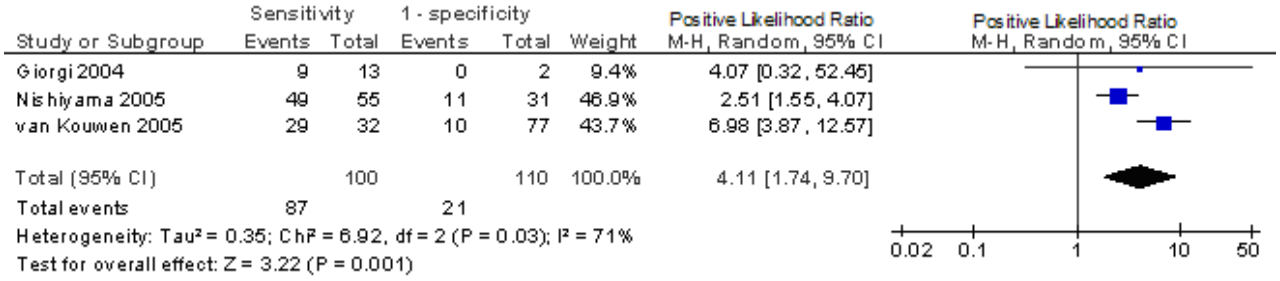


Figure 83. Meta-analysis of the negative LR of ^{18}FDG-PET versus histology/biopsy or clinical followup for the primary diagnosis of pancreatic cancer (prospective studies)

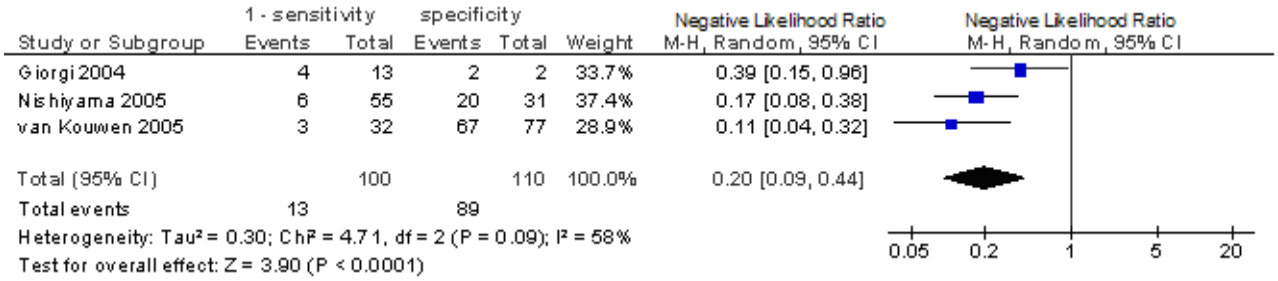
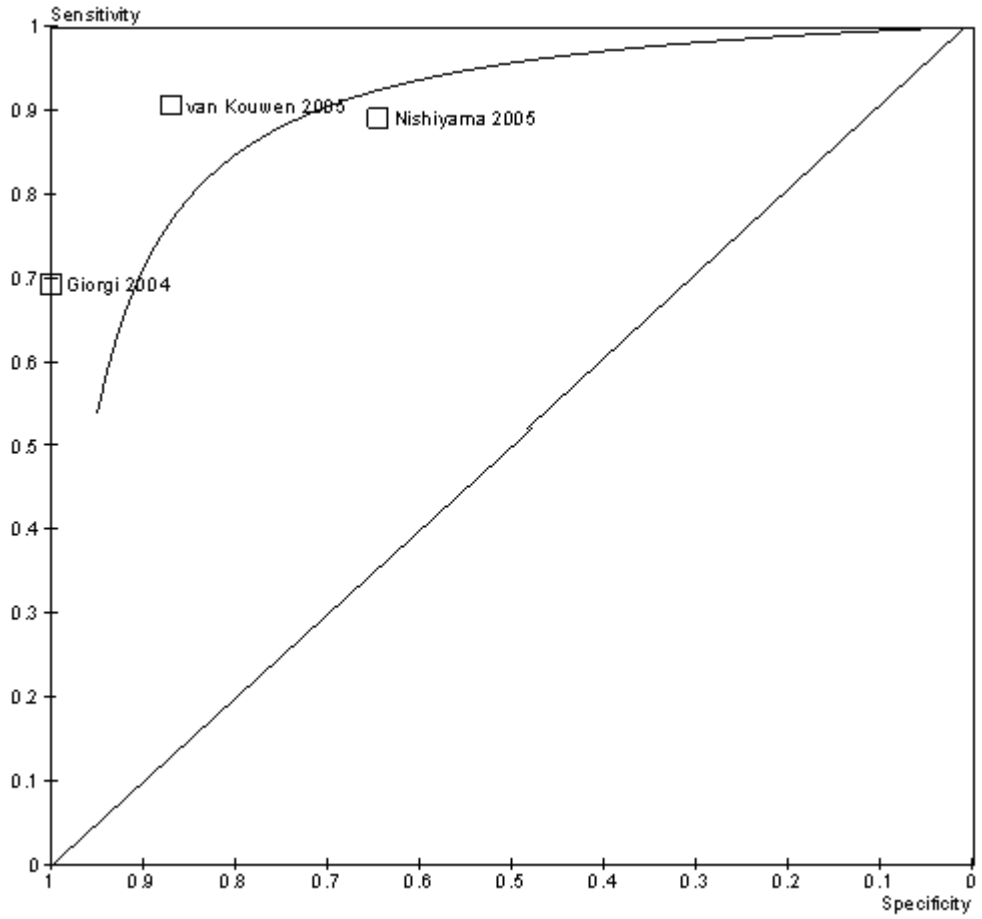


Figure 84 shows the estimates of sensitivity and 1-specificity plotted in ROC space for ^{18}FDG-PET versus histology/biopsy or clinical followup for the primary diagnosis of pancreatic cancer

Figure 84 Summary ROC plot of ^{18}FDG-PET versus histology/biopsy or clinical followup for the primary diagnosis of pancreatic cancer (prospective studies)



Summary of the results

Meta-analyses were calculated to evaluate the accuracy of ^{18}FDG-PET and ^{18}FDG-PET/CT for both the primary diagnosis and staging of pancreatic cancer. The pooled LRs suggest that, compared to ^{18}FDG-PET/CT, ^{18}FDG-PET is slightly superior in its ability to accurately diagnose and identify the initial stage of the disease (Table 23). However, the values are relatively low. The observed heterogeneity indicates considerable uncertainty in these estimates. Pooled LRs were calculated for ^{18}FDG-PET for primary diagnosis purposes separately. When ^{18}FDG-PET was evaluated for primary diagnosis purposes only, the positive likelihood radio was slightly better for ruling in the disease, but the negative LR remained almost the same. Evidence on the use of ^{18}FDG-PET for recurrences and staging is derived from individual study data and therefore, firm conclusions about the utility of ^{18}FDG-PET for these indications cannot be made.

Table 23. Results of meta-analyses of the accuracy of ^{18}FDG-PET and ^{18}FDG-PET/CT for pancreatic cancer

PET Purpose	Type of PET	Reference standard	Design	Studies	N	Effect estimate M-H, Random, 95% CI
Primary diagnosis/staging	FDG-PET	Histology/biopsy or clinical followup	P	7	479	PLR=2.77 [1.62, 4.73]
						NLR=0.19 [0.10, 0.34]`
	FDG-PET/CT			3	193	PLR=2.69 [1.84, 3.94]
						NLR=0.16 [0.10, 0.26]
Primary diagnosis	FDG-PET	Any reference standard	P	4	230	PLR=4.28 [2.07, 8.86]
						NLR=0.21 [0.12, 0.40]
		Histology/biopsy or clinical followup		3	210	PLR=4.11 [1.74, 9.70]
						NLR=0.20 [0.09, 0.44]

95% CI=95% confidence interval; FDG= fluorodeoxyglucose; M-H = Mantel Hantzel; NLR=negative likelihood ratio; P=prospective; PET=positron emission tomography; PLR=positive likelihood ratio

6.3.2. Diagnostic thinking impact of ^{18}FDG-PET and ^{18}FDG-PET/CT on physician decision making with respect to diagnosis and management strategy for patients with pancreatic cancer

Bang *et al*[91] evaluated the clinical impact of using ^{18}FDG-PET on the diagnosis and staging of pancreatic cancer, and on monitoring tumor response to chemoradiation. One hundred and two patients undergoing evaluation for suspected primary pancreatic cancer were prospectively enrolled in this study. There were 93 patients confirmed to have pancreatic cancer who were assessed specifically for the diagnostic thinking impact of ^{18}FDG-PET. Among the 93 patients diagnosed with pancreatic cancer, ^{18}FDG-PET findings led to a change in the pre-treatment staging in 25 patients (27%). Additionally, in 20 patients, the treatment management was altered by changing the respectability status. The majority of changes (17/20) were due to the identification of previously unsuspected metastases, and resulted in the cancellation of previously planned surgical resection. Of particular note, 8/17 of the newly identified metastases were sites in the liver and had not been detected by the initial dynamic CT scan. Three cases previously considered un-resectable were downstaged and suggested be treatable by ^{18}FDG-PET. These findings were subsequently confirmed by biopsy.

The authors concluded that ^{18}FDG-PET sensitive and specific imaging modality which would be a good adjunct to conventional imaging techniques. They noted that the ^{18}FDG-PET was particularly sensitive in the detection of small unsuspected hepatic lesions relative to conventional imaging by CT scan or ultrasonography. ^{18}FDG-PET was useful in the reassessment of conventionally staged tumors and critical treatment decisions regarding resectability were amended with the additional information obtained which allowed for the cancellation of unnecessary surgeries.

This prospective study was determined to be of moderate quality. Methodological strengths included: a clear description of the selection criteria, as well as sufficient description of the choice of the standard, blinded interpretation of the index test, accounting for all participants and intermediate test results. Weaknesses included partial description of the spectrum of patients included in the study, as well as an incomplete description of the execution of the index test or reference standards and lack of clarity about the period between the execution of ^{18}FDG-PET/CT and the reference standard. These weaknesses could have led to spectrum and disease progression bias. Additionally, there was more than one standard used for verification of the true disease status, which may have introduced verification bias. Of particular concern is the fact that the physicians interpreting the results of the reference standard was not described as blinded to the results of the ^{18}FDG-PET/CT, possibly introducing review bias.

Heinrich *et al*[95] investigated the treatment decision impact of integrated ^{18}FDG-PET/CT on the diagnosis and staging of pancreatic cancer. Fifty-nine consecutive patients with focal lesions in the pancreas were prospectively enrolled in this study.

Of the 37 patients who were judged to have resectable pancreatic cancer, treatment management changed in six patients (16%) as a result of ^{18}FDG-PET/CT findings. In addition, of the 46 patients who were found by the reference standard to have malignant pancreatic lesions, ^{18}FDG-PET/CT findings changed oncological management in 15 patients (33%). ^{18}FDG-PET/CT resulted in changes to significantly more treatment decisions compared to standard staging (9/46 cases; 20% [p=0.03]). ^{18}FDG-PET/CT also identified 17 benign lesions. Although the detection of these lesions did not impact treatment, scan results occasionally prompted further diagnostic evaluation, including biopsies. In addition, ^{18}FDG-PET/CT improved detection of distant metastases; these were diagnosed in 13 patients, of which five were *solely* identified by ^{18}FDG-PET/CT findings. In two patients, cancer was found by ^{18}FDG-PET/CT only and had not been previously identified on physical examination. As a result of this detection, the surgical treatment was changed for both patients.

The authors concluded that ^{18}FDG-PET/CT significantly changed the overall management of patients with pancreatic cancer in comparison with standard staging. Based on their clinical and economic evaluation, the authors stated that preoperative staging use of ^{18}FDG-PET/CT is beneficial and may advance standard staging.

This prospective study consecutively enrolled patients and was determined to be of moderate quality. The methodological strengths of this study include: a short period between the ^{18}FDG-PET/CT and reference standard, as well as sufficient description of the choice of the standard, the execution of the index test, accounting for all participants and intermediate test results. However, the execution of the reference standard, spectrum of patients included in the study, and selection criteria were not described in adequate detail. Thus, both spectrum bias and selection bias may have affected the results of this study. Furthermore, patients did not all receive the same reference standard, which may have introduced verification bias. Of particular concern is the fact that the physicians interpreting the results of the reference standard were not blinded to the results of the ^{18}FDG-PET/CT, and blinding of the ^{18}FDG-PET/CT interpretation was not clearly reported. The authors report a further limitation of their study, to be the limited followup at the time of analysis. However, this is unlikely to affect the diagnostic accuracy of ^{18}FDG-PET/CT, since the majority of patients had verification of disease by histopathology and only a minority by clinical followup.

Nishiyama *et al*[101] examined the impact of ^{18}FDG-PET used in the diagnosis and staging of pancreatic cancer on treatment decisions. Forty-two consecutive patients with histopathologically confirmed pancreatic cancer and no previous treatment were prospectively enrolled. ^{18}FDG-PET had an impact on treatment management in five of 42 patients (12%). Three patients were altered from curative to palliative treatment, while two other patients were changed from palliative to curative treatment.

The authors recommended routine ^{18}FDG-PET for preoperative staging of patients with potentially resectable pancreatic cancer. This could result in a marked increased detection of metastases. However, the authors also stated the CT and ^{18}FDG-PET have a complementary role in the identification of distant metastases and that ^{18}FDG-PET alone does not provide sufficient information for staging. This article was written prior to readily available access to integrated ^{18}FDG-PET/CT scanners, and the authors speculated that such hybrid scanners will increase detection and localization by overcoming the challenges associated with separate ^{18}FDG-PET and CT analysis.

This prospective study consecutively enrolled patients and was assessed to be of high quality. Components that were well addressed included description of the spectrum of patients, choice of reference standard, details of the execution of index test and reference standard, and clear reporting of all participants and test results. In addition, the time interval between the index and reference

standard was judged to be sufficiently brief to avoid significant change in patients' conditions. Although all patients received verification of their disease status by a reference test, they did not all receive the same standard, introducing the possibility of verification bias. The index test was interpreted without knowledge of the result of the reference standard, but the interpretation of the reference standard was unblinded. An additional weakness was the limited description of the selection criteria, raising uncertainty as to what these criteria were and how they were applied and the possibility of selection bias.

Ruf *et al*[103] evaluated the treatment decision influence of ^{18}FDG-PET/MRI fusion on the diagnosis and staging of pancreatic cancer. The study prospectively enrolled 32 adult patients suspected of having a pancreatic mass. In eight of 32 patients (25%), topographical assignment and interpretation of ^{18}FDG-PET foci was improved through fusion of ^{18}FDG-PET and MRI images. However, image fusion only resulted in a change of treatment in one patient, for whom surgery was expanded to that for curative intent. The remaining seven patients did not have a change in treatment as a result of ^{18}FDG-PET/MRI image fusion due to: inoperability (n=2), other medical reasons (n=1), other metastases being present in other regions therefore preventing curative surgery (n=2) and image fusion having no influence on the palliative surgical setting chosen (n=2).

The authors concluded the ^{18}FDG-PET/MRI improved assignment of foci but had only minimal therapeutic consequences. This was mainly attributed to the small number of patients in which multiple lesions prevented curative treatment. It is plausible that a larger treatment impact would be evident in patients with small, resectable primaries and only peripancreatic lymph node manifestations.

This prospective study was assessed to be of moderate quality. Many elements of the study were well described, including the selection criteria, choice of reference standard, as well as the period between, and execution of, the index test and reference standard. In addition, intermediate test results and study withdrawals were reported. However, the spectrum of patients included in the study was not sufficiently documented, as it was unclear from where patients were recruited or referred. Therefore, it is possible that spectrum bias may have occurred. Also, both the index and reference standard tests were interpreted in an unblinded manner, thereby increasing the risk of review bias in this study.

A final study by Sperti *et al*[105] investigated the treatment decision impact of integrated ^{18}FDG-PET on the diagnosis of pancreatic cancer. A prospective population of 71 patients with suspected

intraductal papillary mucinous neoplasms (IPMN) of the pancreas underwent ^{18}FDG-PET scans. Of the 71 patients enrolled, 64 had ^{18}FDG-PET scans available and were included in the analysis. The treatment plan was substantially altered in 44 of 64 patients (69%) with suspected pancreatic cancer. Positive ^{18}FDG-PET results impacted treatment decisions in 10 patients; seven (11%) underwent surgical resection, two patients with hepatic metastases not evident in CT avoided laparotomy, and one patient underwent resection of a borderline IPMN associated with unsuspected colon cancer. Negative ^{18}FDG-PET results prompted changes in treatment management in 34 patients; ^{18}FDG-PET suggested followup in 19 patients (30%) and more limited resection in 15 patients (23%), where six patients had a more conservative resection and nine patients avoided splenectomy.

The authors concluded that ^{18}FDG-PET is superior to conventional imaging techniques in its ability to select patients with pancreatic IPMN for surgical intervention or followup. This is particularly true for asymptomatic patients.

This prospective study was assessed to be of high quality. The spectrum of patients is representative of those who would receive this test in practice, and the choice of reference standard is both appropriate and independent of the index test. There was good reporting of the execution of the index and reference tests, any intermediate test results and study withdrawals. Notably, both the index test and reference standard were interpreted in a blinded manner. Although all patients received a reference standard, this reference was not the same for all patients, as some patients received histological verification of disease, and others clinical followup. Therefore, verification bias may have affected the results of this study. The main weaknesses of the study were lack of clarity on the duration between index and reference tests, and only partial description of the selection criteria.

6.3.3. ^{18}FDG-PET as part of a management strategy in pancreatic cancer

Bang *et al*[91] additionally examined using ^{18}FDG-PET to monitor patient response to concurrent chemoradiation. The characteristics of the study population and quality have been discussed in detail in the section above. The outcomes of a subset of 15 / 93 patients diagnosed with pancreatic cancer who were followed with pre- and post-treatment imaging were included in this analysis. The remaining 78 / 93 patients did not receive concurrent chemoradiation for reasons not specified. ^{18}FDG-PET was compared to dynamic CT scans, serial serum CA19-9 measurements, and a clinical benefit score determined by a series of quantitative and qualitative measurements (intensity of pain,

analgesic use, Karnofsky performance scale and body weight). The authors evaluated whether treatment response could be determined by follow-up CT and ^{18}FDG-PET assessments in all patients, and correlated the patient's response status with the time to disease progression. Response was judged as complete response if disease sites disappeared and a partial response if lesions were reduced in size (CT scan) or ^{18}FDG uptake (^{18}FDG-PET).

There were no patients judged to be "responders" based on the CT scan results, however five cases judged to be "responders" by ^{18}FDG-PET. The time to disease progression was significantly longer in the ^{18}FDG-PET "responders" group as compared to the ^{18}FDG-PET "non-responders." The mean time to progression in the "responders" was 399 d (95% CI, 282-526) versus 233 d (95% CI, 181-235) in the "non-responders." As there were no responders based on the dynamic CT, no similar data was available for this imaging modality. The clinical benefit score and serial changes in CA19-9 did not correlate significantly with the results of either imaging modality.

The authors concluded that ^{18}FDG-PET is more accurate that dynamic CT scan for determining treatment response to concurrent chemoradiotherapy. Neither clinical benefit score, nor serum CA19-9 measurements were found to predict treatment response. While not discussed by the authors, it should be noted that while the overall study population was large, there was only a small number of patients (n=15) included in this analysis of ^{18}FDG-PET impact on management strategy relating patient-centered outcomes.

6.3.4. Cost-effectiveness of ^{18}FDG-PET/CT for pancreatic cancer

Heinrich *et al*[95] examined cost savings with use of ^{18}FDG-PET/CT in addition to routine diagnostic procedures to determine staging and eligibility for surgery among patients with presumed resectable pancreatic cancer. The authors conducted a secondary analysis of patient data that had been collected as part of a phase II clinical trial evaluating neoadjuvant chemotherapy for resectable pancreatic cancer. The sample included 59 patients who had a focal pancreatic lesion or suspected pancreatic cancer and had undergone ^{18}FDG-PET/CT. Accuracy data for the diagnostic tests were derived from the trial data; diagnosis was confirmed through intraoperative findings and results of histology or biopsy. Cost data were obtained from the hospital accounting department. A cost-benefit analysis considering direct costs during the staging and peri-operative period was conducted from a hospital perspective. Among the 59 patients, ^{18}FDG-PET/CT detected metastasis in five patients who were then deemed ineligible for surgery. This resulted in cost savings of US$1,066 per

patient. Cost savings were higher (US$2,844 per patient) with selective use of ^{18}FDG-PET/CT among patients identified as surgical candidates through standard, routine staging procedures. Results of sensitivity analyses for shorter length of stay, type of fine-needle aspiration, and surgical confirmation of metastasis were consistent in demonstrating cost savings. The study was based on Swiss data and practice patterns, however, the authors suggested that results may be generalizable to other centers in Europe and the United States. The authors presented results and conclusions within the stated objectives and given data. The primary and sensitivity analyses were restricted to a limited number of costs and outcomes.

Table 24 provides a summary of the main findings and the types of bias that affected the evidence on the diagnostic thinking impact, effect on patient-centered outcomes of ^{18}FDG-PET and ^{18}FDG-PET/CT and economic outcomes for pancreatic cancer

Table 24 Main findings and types of bias that affected the evidence on the diagnostic thinking impact, effect on patient-centered outcomes and economic outcomes of ^{18}FDG-PET and ^{18}FDG-PET/CT for pancreatic cancer

Study	Results of FDG-PET imaging on Patient Diagnosis, Treatment and Outcomes	Types of Bias
Bang 2006[91] Study type: Prospective	Treatment strategy and staging was impacted for 25 / 93 cases (27%): -Upstaged: 20 / 25 changes -Downstaged: 5 / 25 changes Treatment modality changed in 20 / 25 cases (80%): -Upstaged and deemed to be unresectable: 17 / 20 -Downstaged and deemed to be resectable: 3 / 20 Previously unidentified distant metastases were found in the 17 cases determined to be unresectable	Spectrum bias (unclear) Verification bias (>1 RS)
Heinrich 2005[95] Study type: Prospective	**Management decision**: Treatment and diagnostic testing impact Treatment strategy changed for 6 / 37 patients (16%) judged to have resectable cancer. -Distant metastasis detected by PET/CT only (n = 5) -Simultaneous cancer found and led to change in surgery (n = 2, one with curative intent, one palliative) PET/CT enabled minimally invasive histological assessment by exact anatomic delineation of lesions. Detected benign lesions in 17 patients, 10 of which were not identified by conventional CT. Some lesions required further diagnostic evaluation and no change in treatment made **Economic evaluation** Alternatives compared: a) Standard, routine staging; b) FDG-PET/CT + standard staging PET/CT identified metastasis & avoided surgery in 5 / 59 patients. Total net savings from PET/CT: $62,912 ($1,066 per patient). Total net savings for patients eligible for surgery after routine staging: $105,262 ($2,844 per patient)	Spectrum bias (unclear) Selection bias (unclear) Verification bias (>1 RS) Review bias (PET, unclear; RS, unblinded)

Table 24 Main findings and types of bias that affected the evidence on the diagnostic thinking impact, effect on patient-centered outcomes and economic outcomes of ^{18}FDG-PET and ^{18}FDG-PET/CT for pancreatic cancer (cont')

Study	Results of FDG-PET imaging on Patient Diagnosis, Treatment and Outcomes	Types of Bias
Nishiyama 2005[101] Study type: Prospective	**Management decision:** Treatment Treatment management impacted in 5 / 42 patients (12%) Changed from curative to palliative treatment (n=3); Changed from palliative to curative treatment (n=2)	Selection bias (unclear) Verification bias (> 1 RS) Review bias (RS, unclear if blinded)
Ruf 2006[103] Study type: Prospective	**Management decision:** Treatment and diagnostic testing impact Interpretation of PET foci improved through fusion of PET/MRI images 8 / 32 patients (25%), Image fusion resulted in a change of treatment in only 1 patient (surgery was expanded to curative)	Spectrum bias (unclear) Verification bias (>1 RS) Review Bias (PET and RS unblinded)
Sperti 2007[105] Study type: Prospective	**Management decision:** Treatment Treatment plans were altered in 44 / 64 patients (69%) Positive PET results impacted treatment in 10 patients, Negative PET results impacted management in 34 patients	Selection bias (unclear) Disease progression bias (unclear) Verification bias (>1 RS)

CT=computer tomography; FDG=Fluorodeoxyglucose F18; mo=months; MRI=magnetic resonance imaging; PET=positron emission tomography; RS=reference standard

7. Prostate Cancer

7.1. Background

Cancer of the prostate is the most common cancer in men.[159] In developed countries, prostate cancer is the second most frequently diagnosed cancer and the third most common cause of death from cancer in men. In 2004, the incidence of invasive prostate cancer was 145.3 per 100,000 with a death rate of 25.4 per 100,000.[160] It is estimated that 186,320 new cases will be diagnosed in the United States in 2008[133] and there will be 28,660 attributable deaths.[133] African American men have mortality rates that are more than twice the rates observed in other racial and ethnic groups in the United States.[161]

Risk factors for prostate cancer include family history of prostate cancer, dietary fat (low-fat diets high in rye or soy consumption are thought to be protective), sexual behaviour, alcohol consumption and exposure to ultraviolet radiation.[162] Evidence concerning associations with amount of physical exercise, diets high in the antioxidant lycopene, and other micro-nutrients and vitamins are suggestive but inconclusive.[162,163]

Diagnosis of prostate cancer begins with the assessment of general health and co-morbities.[159] Prostate cancer screening is controversial because of the lack of definitive evidence of benefit.[164] The digital rectal examination (DRE) was the test traditionally used for prostate cancer screening; however, two other procedures, transrectal ultrasound (TRUS) imaging and serum prostate-specific antigen (PSA) concentrations, are also now used. Rectal examination is inexpensive, relatively noninvasive, and nonmorbid and can be taught to nonprofessional health workers; however, its effectiveness depends on the skill and experience of the examiner.

Imaging procedures have been suggested as possible screening modalities for prostate cancer. Prostatic imaging is possible by ultrasound, computed tomography, and magnetic resonance imaging. Each modality has relative merits and disadvantages for distinguishing different features of prostate cancer.

Widespread adoption of the PSA test in the United States represented a major improvement in the management of prostate cancer. This test, which measures the amount of PSA protein in the blood (often elevated in patients with prostate cancer)[161] is still the best marker, despite efforts to find other markers for early detection, and although no specific cut-off point for normal PSA has been defined.[162] However, this screening method is known to overdiagnose,[159,161] and the effect of

early detection and treatment on mortality is not fully understood because of the long natural history of prostate cancer and the inherent delay in measurable treatment effects.[162] Bone scintigrapy may be performed if bone metastases are suspected clinically by the Gleason score or PSA level.[159]

The most common grading system used in the United States is the Gleason grading system.[165] Biopsy material is needed to assess the Gleason score. The system uses a summary score between 2 and 10 (10 being the most aggressive) of the two most common patterns tumor growth in a biopsy specimen (one for >50% of the growth and one for the majority of the remaining tumor growth), which are each given a score of 1 to 5 (5 being the most aggressive).[162] The summary score reflects the addition of these two scores, with a higher score being indicative of more disordered growth and aggressive cancer.

Two other systems are in common use for the staging of prostate cancer. The Jewett system (stages A through D)[166] and a revised TNM system that employs the same broad T stage categories as the Jewett system but includes subcategories of T stage, such as a stage to describe patients diagnosed through PSA screening. This revised TNM system is clinically useful and more precisely stratifies newly diagnosed patients.[167]

Local staging (T stage) is evaluated by DRE.[159,162] Pelvic imaging using MRI or CT is performed before radical treatment when Partin tables (probabilities of disease extension and progression) indicate >15% risk of nodal involvement.[159]

Rigorous evaluation of any prostate cancer screening modality is desirable because the natural history of the disease is variable, and appropriate treatment is not clearly defined.[164] Clinical practice guidelines on the management of clinically localized prostate cancer demonstrate major differences in their specific recommendations,[168] and there is no general consensus as to what constitutes best treatment for localized disease.[159] Little high-quality evidence is available to guide decisions regarding the comparative effectiveness and harms of treatments for clinically localized prostate cancer, especially in men with PSA-detected disease.[169]

Radical prostatectomy (removal of the entire prostate and (potential) removal of nearby lymph nodes),[163] radiotherapy[162] and hormone therapy (androgen supression or bicalutamide monotherapy)[159] are the main treatments for locally advanced prostate cancer. Cryosurgery is a second surgical technique under development that involves destruction of prostate cancer cells by intermittent freezing of the prostate tissue with cryoprobes, followed by thawing. It is less well

established than standard prostatectomy, and long-term outcomes are not as well established as with prostatectomy or radiation therapy.[170]

Improvements in brachytherapy have made it an effective radiotherapy for early-stage prostate cancer. Advances in hormonal therapy for prostate cancer have included the development of gonadotropin-releasing hormone (GnRH) agonists, which inhibit the ability of the pituitary gland to stimulate the testes to make testosterone. Additional approaches include bilateral orchiectomy, estrogen therapy, antiandrogens, ketoconazole, and aminoglutethimide.[164] Advances have also been made in chemotherapy for advanced prostate cancer.[161] There is high-quality evidence from one RCT in favor of surgery over watchful waiting with palliative intent for nonhigh grade localized prostate cancer.[171] Data from RCTs indicate that men with Gleason scores of 8 to 10 were likely to have evidence of biochemical recurrence, regardless of whether treatment was radical prostatectomy alone or was combined with androgen deprivation. High-dose electron beam radiation therapy (EBRT) was more effective than conventional-dose EBRT in controlling biochemical failure in both low-risk disease and higher-risk disease.[169]

7.2. Importance of Key Questions in the Clinical Management of Prostate Cancer

Tumor grading of prostate cancer is a fundamental determinant of disease biology and prognosis. Implementation of an accurate noninvasive imaging technique to detect recurrent and metastatic prostate cancer is critical for the effective management of these patients. Current imaging tests in prostate cancer include ultrasound (US), CT, MRI, and In-111 capromab pendetide scan. There are still controversies regarding the value of ^{18}FDG-PET to identify local recurrences, metastases or nodal and soft tissue lesions. ^{18}FDG-PET imaging in prostate cancer can be problematic because ^{18}FDG tracer undergoes renal excretion with subsequent accumulation in the urinary bladder, causing image artifacts in the lower pelvis. The close proximity of excreted ^{18}FDG to sites of potential local recurrence (i.e., the prostate bed and adjacent lymph nodes) complicates the interpretation of ^{18}FDG-PET images of the pelvis. Furthermore, ^{18}FDG accumulation in the primary prostate cancer is generally low, and may overlap with the uptake in benign prostatic hyperplasia (BPH) and uptake in the normal gland. It is important to evaluate the utility of ^{18}FDG-PET in patients with suspected or known prostate cancer, and the impact on management and patient outcomes.

7.3. Results

Four studies[108-111] provided evidence on the use of ^{18}FDG-PET or ^{18}FDG-PET/CT for prostate cancer. All of them evaluated the diagnostic accuracy of ^{18}FDG-PET or ^{18}FDG-PET/CT. None of the studies reported on the diagnostic thinking impact of ^{18}FDG-PET or ^{18}FDG-PET/CT or evaluated the impact of ^{18}FDG-PET or ^{18}FDG-PET/CT as part of a management strategy on patient-centered outcomes. There were no economic evaluations on the use of ^{18}FDG-PET and ^{18}FDG-PET/CT for prostate cancer. Characteristics of the populations, conditions of ^{18}FDG-PET administration, interpretation of results and methodological quality of the studies are summarized in appendices D to J.

7.3.1. Diagnostic accuracy of ^{18}FDG-PET and ^{18}FDG-PET/CT in prostate cancer

Characteristics of the studies

Four studies (two prospective,[109,110] two retrospective[108,111]) evaluated the diagnostic accuracy of ^{18}FDG-PET[108-111] and ^{18}FDG-PET/CT[111] on prostate cancer. ^{18}FDG-PET was used for initial staging in one study,[108] for assessment of recurrences in one study,[110] and for both staging and recurrence purposes in two studies.[109,111] One study also used ^{18}FDG-PET/CT for both staging and assessment of recurrences.[111] The studies contained a total of 173 patients with sample sizes ranging from 12 to 91. The participant ages ranged from 49 to 81 years. One study reported the distribution by stage of cancer: T1N0M0 = 54%, T2N0M0 = 46%.[108] ^{18}FDG-PET was compared to a reference standard that varied across the studies. In two studies the reference standard was either histology/biopsy or clinical follow-up,[109,111] while the reference standard in one study was either histology/biopsy or CT/bone scintigraphy.[110] One study established the final diagnosis of all patients using histology/biopsy.[108] Three studies reported the mean time between last treatment and ^{18}FDG-PET as 6 months[109] and 43.2 months[111] and 3.2 years.[108] Three studies used a fixed dose of ^{18}FDG (10 MCi[108] and 555 MBq[110,111]); one study reported a dose range of 370–555 MBq.[109] The time between injection and PET scan was 30-45 minutes,[108] 45-60 minutes,[109,111] and 40-90 minutes.[110] Patients fasted for four hours.[108-110] One study[110] measured glucose levels before administration of ^{18}FDG-PET; the maximum glucose level that was allowed was not reported. Methods of interpretation of the images were qualitative in three studies[108-110] and both qualitative and quantitative in the remaining study.[111] Scans were interpreted qualitatively using visual analysis.[108-111] One study[111] reported using SUV but the criterion for abnormality was not reported.

Comparisons

No pooled data were obtained to evaluate the accuracy of ^{18}FDG-PET for prostate cancer for any of the clinical indications considered: staging, recurrences, considered together or separately. Comparisons for which data were considered for meta-analysis were summarized in Table 25. Individual data are summarized in Appendix D.

Table 25 Summary of comparisons considered for meta-analyses of the accuracy of ^{18}FDG-PET for prostate cancer

Indication	Studies	Design	Type of PET	Reference standard	Meta-analysis
Staging and recurrences	Jadvar 2003[109]	P	FDG-PET	Histology/biopsy or clinical followup	No
	Schoder 2005[111]	R	FDG-PET and FDG-PET/CT	Histology/biopsy or clinical followup	
Recurrences	Oyama 2003[110]	P	FDG-PET	Histology/biopsy, CT, bone scintigraphy	No
Staging	Chang 2003[108]	R	FDG-PET	Histology/biopsy	No

FDG= fluorodeoxyglucose; P = prospective; PET=positron emission tomography; R = retrospective

8. Small-Cell Lung Cancer

8.1. Background

The leading cause of cancer death world wide is lung cancer.[172] Every year 15% of new lung cancer diagnoses are classified as small cell lung cancer (SCLC) , which accounts for up to 25% of lung cancer deaths. In the United States there were an estimated 213,380 new cases of lung cancer diagnosed (all types) and 160,390 deaths in 2007.[173] Rates peaked in 1986 with 17.36% of new cancers diagnosed as SCLC. In the early 1970s 72.37% of those diagnosed with SCLC occurred in male patients. This male predominance disappeared over time until the male to female ratio of patients diagnosed with SCLC reached 1:1 in 2002.[174]

Approximately 95% of all cases are due to cigarette smoking, although environmental factors may also play a role. Decreasing incidence and mortality rates may be related to the declining number of smokers[173] (in the United States, 36% of population smoked in 1950 compared to 20% of population in 1990)[174] and the development of low-tar filters.[173] Additionally, smoking during treatment tends to shorten patient survival times. The risk of all types of lung cancer can be decreased by smoking cessation.[175]

SCLC is difficult to treat due to its rapid growth, quick development of widespread metastasis and its initial dramatic response to treatment; however, the majority of patients die from recurrent disease.[174] It is possible to obtain long-term survival with cure in some patients treated with chemotherapy, but less than 5% survive five years.[175] Disease usually reoccurs at the primary site in the lung or lymph nodes. Factors that improve prognosis are: small tumor size, no lymph node involvement and possibility of lobectomy.[176] Dyspnea, persistent cough and hemoptysis are the most common presenting symptoms and postobstructive pneumonia may also occur. Common sites of metastases include bone, liver, lymph nodes, central nervous system, adrenal glands, subcutaneous tissue and pleura. Disease that has metastasized can produce pain, headache, malaise, seizures, fatigue anorexia and weight loss.[173] Extent of disease, performance status, gender and age are the strongest clinical prognostic factors.[175]

Traditionally staging of SCLC uses a system developed by the Veterans Administration Lung Cancer Study Group (VALCSG). There are two stages. Limited-stage disease (LD) is defined as disease confined to one hemithorax with the tumor encompassed in one radiation port. Approximately 30% of patients are staged with LD at diagnosis.[173] Half of these patients achieve

remission compared to the 20 to 40 % of patients with extensive-stage disease.[175] Extensive-stage disease (ED) is any cancer that does not fit into the LD category, and represents patients with more disseminated disease.[173] Generally, ED patients have a poorer prognosis and palliative chemotherapy and radiation treatment aims to provide relief of symptoms with minimal toxicity.[175] TNM classifications are not typically used in SCLC as they require surgery to confirm accuracy and SCLC patients are frequently poor candidates for surgery. The International Association for the Study of Lung Cancer have proposed TNM groupings for the clinical staging of SCLC, since such systems have shown to be a good tool for prediction outcome.[177]

Establishing a diagnosis of SCLC is a multi-step process that includes a detailed history, physical examination and testing involving a complete blood count, electrolyte panel and histology or cytology.[173] Contrast-enhanced CT scan of the chest and abdomen, bone scan, and CT scan or MRI of the brain are also performed.[118]

Specimens for cytological evaluation can be obtained through patient expectoration, bronchoscopic techniques and fine-needle aspiration. Transthoracic needle aspiration is typically safe method, although it may cause pneumothorax and intrapulmonary hemorrhage on occasion. It is considered to be cost-effective and can be performed in the outpatient setting. Samples adequate enough for histological confirmation can be obtained in 40 to 75% of patients.[178] Centrally located endobronchial lesions and atypical carcinoids can be mistaken for small-cell carcinoma by cytology. Older methods of staging such as bone marrow aspiration and biopsy are no longer performed.[173] Bronchoscopy, respiratory function tests and other examinations may be used prior to surgery in order to assess potential risks.[176]

For the initial staging and followup evaluation, PET is a widely used tool. PET has been used for the assessment of single pulmonary nodules and for the evaluation of the mediastinum in patients with nonSCLC. Initial studies suggest that the ^{18}FDG tracer is avidly absorbed by SCLC tumors and that staging evaluation with ^{18}FDG-PET may be an effectively accompany conventional staging methods.[118]

When treating SCLC the control of symptoms and improvements to patient quality of life should be considered.[175] As a primary treatment, surgery was abandoned in the early 1970s[172] as radiotherapy showed to be as effective in maintaining local control and patients were frequently not suitable for resection.[176] In patients with LD, combination regimens of chemo and radiotherapy achieve better responses and longer survival than single agents.[173] Dosing schedules of chemo and

radiotherapy may be concurrent, sequential or alternating.[172] Patients diagnosed with ED receive chemotherapy as their mainstay treatment. Patient response rate is high, at 60 to 80%, but the median survival time is only 8 to 10 months.[173] Palliative radiotherapy may be provided to patients with relapsed ED to help control symptoms.[175] If surgery is planned, it must be a part of a multidisciplinary approach and chemotherapy should still be considered the primary treatment.[176]

8.2. Importance of Key Questions in the Clinical Management of Small-Cell Lung Cancer

SCLC has a very aggressive biological behavior. Exact staging of SCLS has an important impact on survival and treatment decisions. The primary role of diagnostic imaging in SCLC is to accurately distinguish between LD and ED. Patients with LD are often offered concomitant chemotherapy and radiotherapy, whereas chemotherapy alone is the standard treatment of patients with ED. Thus, accurate staging is pivotal to reserve the combined modality treatment to those patients who actually might benefit from it.

Chest radiography, thorax and upper abdomen CT scan, MRI, thoracoscopy, bone scans, and bone marrow biopsy are routinely used for staging. However, the use of these diagnostic procedures may result in difficulties identifying tumor tissue in some settings (e.g., in normal-sized lymph nodes). Furthermore, anatomic imaging modalities are mostly used to evaluate a given region of the body rather than the entire body and therefore, it is likely that metastases outside the imaging field are not diagnosed. In contrast to the dependence primarily on anatomic imaging features, ^{18}FDG-PET depends on the metabolic characteristics of a tissue for the detection of disease. As ^{18}FDG preferentially accumulates in viable tumor cells and not in fibrotic or necrotic tissue, a change in ^{18}FDG-uptake on PET scan might be a better parameter for monitoring the response and it might be able to assess response before structural changes occur.

8.3. Results

Ten studies[112-121] provided evidence on the use of ^{18}FDG-PET or ^{18}FDG-PET/CT for small-cell lung cancer. All of them evaluated the diagnostic accuracy of ^{18}FDG-PET or ^{18}FDG-PET/CT. Three studies[112,113,117] reported on the diagnostic thinking impact of ^{18}FDG-PET and one of them[117] also evaluated the impact of ^{18}FDG-PET/CT. None of the studies evaluated the impact of ^{18}FDG-PET or ^{18}FDG-PET/CT as part of a management strategy on patient-centered outcomes. There were no economic evaluations on the use of ^{18}FDG-PET or ^{18}FDG-PET/CT for SCLC. Characteristics of the

populations, conditions of ^{18}FDG-PET administration, interpretation of results and methodological quality of the studies are summarized in appendices D to J.

8.3.1. Diagnostic accuracy of ^{18}FDG-PET and ^{18}FDG-PET/CT in small-cell lung cancer

Characteristics of the studies

Ten studies (six prospective, [113-118] four retrospective[112,119-121]) evaluated the diagnostic accuracy of ^{18}FDG-PET on small cell lung cancer. Seven studies used ^{18}FDG-PET for initial staging[113,114,116,118-121] and three used ^{18}FDG-PET for both initial staging and restaging.[112,115,117] The studies contained a total of 471 patients with sample sizes ranging from 21 to 120. The participant ages ranged from 33 to 90 years. ^{18}FDG-PET was compared to a reference standard that varied across the studies. In four studies the reference standard was either histology/biopsy or clinical follow-up,[112,113,117,120] three studies used clinical follow-up and conventional imaging.[115,119,121] One study established the final diagnosis by histology/biopsy and conventional imaging,[114] one study used histology/biopsy,[116] and one study used conventional imaging.[118] Two studies reported the median time between last treatment and ^{18}FDG-PET as 207 days[120] and 4 days;[119] one reported the time as greater two weeks.[118] Five studies used a fixed dose of ^{18}FDG (400MBq,[115,116] 370MBq,[120] 300MBq,[119] and 15MCi[118]); three studies used a dose range (300-400MBq,[117] 10-15MCi,[113] and 15-20MCi[121]); one study used a weight-based dose (5MBq/kg[114]); and one study did not report on dosing.[112] The time between ^{18}FDG injection and PET scan was 50 minutes,[113] 60 minutes,[116,118-120] a median of 84 minutes,[115] 90 minutes,[114] and two studies reported ranges (45-60 minutes[121] and 50-60 minutes[117]). In nine studies patient fasting was reported between four and twelve hours,[112-120] with five of these studies measuring a maximum glucose levels before administration of ^{18}FDG-PET (4.6 mmol/L,[115] 4.7 mmol/L,[116] 6 mmol/L,[114] and 150 mg/dL.[113,118] Methods of interpretation were qualitative in four studies[114,116,118,119] and both qualitative and quantitative in four studies.[112,113,115,120] Scans were interpreted qualitatively using visual analysis in all eight studies. One study[112] used a marker of lesions > 10 mm in transverse diameter for quantitative interpretation of the PET images.

Comparisons

Comparisons for which data were considered for direct meta-analysis are summarized in Table 26. Statistical pooling was considered to evaluate the accuracy of ^{18}FDG-PET and ^{18}FDG-PET/CT

for the primary diagnosis and staging of kidney cancer. Individual study data are summarized in Appendix D.

Table 26. Summary of comparisons considered for meta-analyses of the accuracy of ^{18}FDG-PET for SCLC

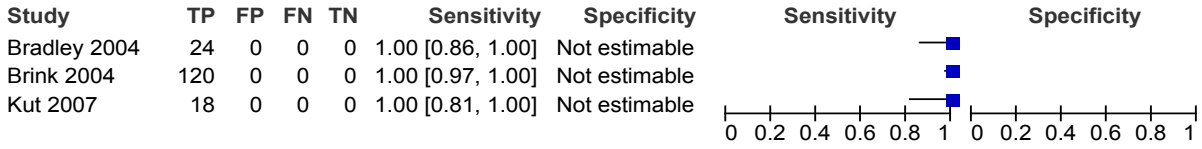
Indication	Studies	Design	Type of PET	Reference standard	Meta-analysis
Staging and restaging	Blum 2004[112]	R	FDG-PET	Histology/biopsy or clinical followup	No
	Fischer 2006[115]	P	FDG-PET/CT	Clinical followup	
	Kamel 2003[117]	P	FDG-PET and FDG-PET/CT	Histology/biopsy or clinical followup	
Staging	Bradley 2004[113]	P	FDG-PET	Histology/biopsy or clinical followup	1. FDG-PET vs. all comparators (P studies) [113,114,118] 2. FDG-PET or FDG-PET/CT vs. all comparators (R studies) [119,121]
	Brink 2004[114]	P	FDG-PET	Histology/biopsy or conventional staging	
	Fischer 2007[116]	P	FDG-PET and FDG-PET/CT	Histology/biopsy	
	Kut 2007[118]	P	FDG-PET	Conventional staging	
	Niho 2007[119]	R	FDG-PET and FDG-PET/CT	Clinical followup or conventional staging	
	Pandit 2003[120]	R	FDG-PET	Histology/biopsy or clinical followup	
	Vinjamuri 2008[121]	R	FDG-PET and FDG-PET/CT	Clinical followup	

FDG= fluorodeoxyglucose; P = prospective; PET=positron emission tomography; R = retrospective; vs.=versus

1. ^{18}FDG-PET for the staging of SCLC

Reference standard: any; prospective studies. Three prospective studies[113,114,118] totaling 162 participants provided data to analyze the accuracy of ^{18}FDG-PET versus any reference standard for identifying the staging of SCLC. Individual 2x2 table results are presented in Figure 85. Sensitivity value in the three studies was 100%. The studies did not provide data to calculate specificity and therefore, pooled estimates of the positive and negative LRs were not obtained.

Figure 85. Results from 2x2 tables of individual prospective studies of ^{18}FDG-PET versus any reference standard for the staging of SCLC

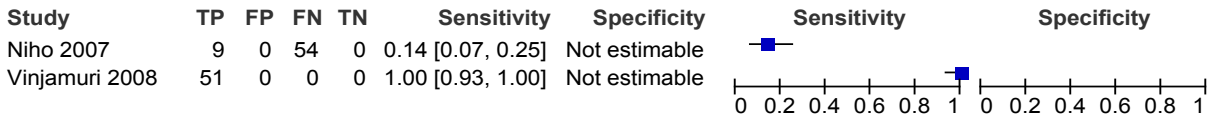


2. ^{18}FDG-PET/CT for the staging of SCLC

Reference standard: any; retrospective studies. Two retrospective studies[119,121] totaling 114 participants provided data to analyze the accuracy of ^{18}FDG-PET/CT versus any reference standard

for identifying the staging of SCLC. Individual 2x2 table results are presented in Figure 86. Sensitivity values reported in the studies were 14%[119] and 100%.[121] The studies did not provide data to calculate specificity and therefore, pooled estimates of the positive and negative LRs were not obtained.

Figure 86. Results from 2x2 tables of individual retrospective studies of ^{18}FDG-PET/CT versus any reference standard for the staging of SCLC (retrospective studies)



Summary of the results

Only limited conclusions can be drawn regarding the utility of ^{18}FDG-PET or ^{18}FDG-PET/CT for the staging of SCLC. No pooled data of the positive and negative LRs were obtained. Information about the specificity of the test is not available from the studies included in this analysis.

8.3.2. Diagnostic thinking impact of ^{18}FDG-PET and ^{18}FDG-PET/CT on physician decision making with respect to diagnosis and management strategy for patients with small cell lung cancer

Three studies reported on the diagnostic thinking impact of ^{18}FDG-PET. Blum *et al*[112] evaluated the treatment decision impact of ^{18}FDG-PET on staging and restaging patients with SCLC. Thirty-six consecutive outpatients who had undergone 47 ^{18}FDG-PET scans were retrospectively enrolled in this study. Of the 36 patients, 15 underwent ^{18}FDG-PET for staging, 25 for re-staging, and four patients for staging and re-staging. The treatment plan was considerably altered for 17 (43%) of all cases. Seven of the 15 (47%) patients who underwent ^{18}FDG-PET for initial staging had changes to their treatment plans due to upstaging in their disease identified by ^{18}FDG-PET. Five of these patients had their management altered from radical concurrent chemoradiotherapy to palliative chemotherapy alone or the later addition of palliative radiotherapy. The remaining two patients had their radiotherapy target volume changed to include additional disease shown by ^{18}FDG-PET. In addition, 10 of the 25 patients (40%) who underwent ^{18}FDG-PET for restaging had their treatment plans changed. Five of these patients were upstaged based on ^{18}FDG-PET and therefore had prophylactic cranial irradiation (PCI) omitted (n=3) or changed from chemotherapy to observation alone (n=2). Three patients were downstaged and went on to have PCI. An additional two patients

were reported to have changes in their treatment plan, yet the nature of this change in management was not specifically stated.

Prognostic outcomes were also reported in the study. Patients who achieved a completed metabolic response on ^{18}FDG-PET had a median time to progression of 13.7 months, compared to 9.7 months for patients who did not achieve a complete response. In addition, of the 16 patients with an incomplete response, five were still alive with a median followup of 19 months. It is possible that salvage treatments had a favorable impact on patients found to have residual disease by ^{18}FDG-PET.

The authors concluded that structural imaging, such as CT, might inaccurately assess the extent of disease and that ^{18}FDG-PET can be used in conjunction with conventional imaging to significantly improve staging. In this manner, use of ^{18}FDG-PET can ensure that patients get the most appropriate management.

The study reviewed consecutive patients and was assessed to be of moderate quality. The spectrum of included patients, the choice of reference standard, any intermediate results and withdrawals were well reported. Although all patients received a reference standard, the reference standards were not the same across all patients, as some received histological confirmation of disease and others were followed up clinically. The multiple methods used to validate disease status may have lead to verification bias. In addition, the selection criteria and execution of the index and reference tests were only partially described and the duration between the index and reference tests was unclear. The results of the index test were interpreted in an unblinded manner and the blinding of the reference test interpretation was unclear, making this study vulnerable to review bias. This bias was identified by the study authors, yet they believed this to have only a minor impact on the diagnostic performance of ^{18}FDG-PET, since many structural imaging abnormalities were still reported as negative and further sites of disease were identified without structural imaging correlates. Finally, the results from this study are limited by their retrospective nature, an additional limitation which was acknowledged by the authors.

Bradley *et al*[113] evaluated the treatment decision impact of ^{18}FDG-PET on the staging of SCLC. A prospective sample of 25 outpatients with newly diagnosed, untreated, histologically or cytologically confirmed SCLC underwent ^{18}FDG-PET scans Of the 25 patients enrolled in the study, 24 were included in the analysis and one patient withdrew from the study. ^{18}FDG-PET scans contributed to a major change in the diagnosis of seven patients (29%), all of whom were upstaged. An unsuspected primary tumor or regional nodal metastasis was identified by ^{18}FDG-PET in seven

patients (29%), six of whom had nodes that were not enlarged by CT criteria but showed ^{18}FDG uptake on PET. This resulted to a significant alteration to the radiation therapy portal, such that the ^{18}FDG-PET -positive/CT-negative nodes were included in the high-dose region for each of these patients. Further, the addition of ^{18}FDG-PET identified two patients (8%) with extensive-stage disease, who were thought to have limited-stage SCLC based on conventional staging.

The authors concluded that ^{18}FDG-PET has high sensitivity and appears to be of value for staging and treatment planning in patients presumed to have limited-stage SCLC.

This study was determined to be of high quality. The selection criteria, choice of the reference standard, intermediate test results and study withdrawals were well reported. In addition, the reference standard was independent of the index test and all the tests were conducted within a sufficiently brief time period. However, there was inadequate reporting of the recruitment of patients and the execution of the index and reference tests. Since cases were not all verified using the same reference standard, there is risk of verification bias. Although the reference standard was interpreted blinded to the results of the ^{18}FDG-PET, the results of references tests were used in the interpretation of the ^{18}FDG-PET scans, which raised the possibility of review bias. A further limitation identified by the authors was the strict inclusion criteria, such that patients with questionable equivocal findings for metastasis on bone scintigraphy or CT were not enrolled. In practice, the patient population would likely be more varied, potentially impacting the performance of ^{18}FDG-PET.

Kamel *et al*[117] investigated the treatment decision impact of ^{18}FDG-PET and integrated ^{18}FDG-PET/CT on staging and restaging in patients with SCLC. Forty-five consecutive outpatients who underwent ^{18}FDG-PET imaging were retrospectively enrolled in the study, of which 24 patients were referred for ^{18}FDG-PET for initial staging, 20 patients for restaging and two patients for both staging and re-staging. No description regarding the interpretation of the scans was provided. Of the 45 patients enrolled, 42 were included in the analysis and three patients were excluded due to incomplete data. The treatment management was considerably altered in 12 of 42 patients (29%). Nine of the 24 patients (37%) with ^{18}FDG-PET for initial staging had a change in treatment. Three patients were given palliative chemotherapy, and one patient was given curative surgery since ^{18}FDG-PET findings excluded mediastinal involvement and distant metastases. Five patients had a change in radiation field (n=3) or radiation volume (n=2). Therefore, of the patients who received ^{18}FDG-PET for initial staging, three were upstaged, one was downstaged and five patients had minor changes to their diagnosis which influenced their treatment plan. Three of the 20 patients (15%) with

^{18}FDG-PET for restaging after therapy had a change in treatment management; one patient had chemotherapy reinstituted, while chemotherapy was discontinued in two patients. Four patients had a change in diagnosis, including the three patients with changes in regard to chemotherapy and one patient with a false negative from ^{18}FDG-PET. Three additional patients were identified as having progressive disease by ^{18}FDG-PET and therefore had a minor change to their diagnosis that did not impact their treatment.

The authors concluded that ^{18}FDG-PET imaging has the potential of improving the outcomes of combined chemoradiotherapy by preventing futile treatment of patients with distant metastases or advanced locoregional disease not identified by conventional imaging. In addition, ^{18}FDG-PET may optimize radiation treatment for patients with limited-stage disease through its accurate definition of radiation field and volume.

This retrospective study reviewed consecutive patients and was assessed to be of high quality. The spectrum of included patients, the execution of the index test, intermediate results and study withdrawals were well reported. In addition, patients received an appropriate reference standard, which was consistent across all patients. Although there was blinded interpretation of the reference standard, the index test was interpreted with knowledge of the results of the standard, introducing risk of review bias. Other weaknesses of this study included only partial description of the selection criteria, raising the possibility that the results are not generalizable to other patient populations. In addition, disease progression bias cannot be ruled out as there was lack of clarity with regard to the time between the diagnostic tests. Finally, results were not presented separately for ^{18}FDG-PET and ^{18}FDG-PET/CT. Although this study may be vulnerable to several biases, the vast majority of the quality components were adequately addressed.

Table 26 provides a summary of the main findings and the types of bias that affected the evidence on ^{18}FDG-PET as part of a management strategy in SCLC cancer

Table 26 Main findings and types of bias that affected the evidence on the diagnostic thinking impact of ^{18}FDG-PET and ^{18}FDG-PET/CT for SCLC cancer

Study	Results of FDG-PET imaging on Patient Diagnosis and Treatment	Types of Bias
Blum 2004[112] Study type: Retrospective	**Management decision:** Treatment Treatment plans altered for 17 / 36 patients (43%) overall Initial staging: 7 / 15 plans changed (all upstage) Radical concurrent chemotherapy to palliative therapy (n=5) Radiotherapy target volume increased (n=2) Restaging: 10 / 25 plans changed (3 upstage, 5 downstage, 2 ND). PCI in patients with positive CT but negative FDG uptake (n=3) PCI omitted in cases that did not have complete response (n=3) Observation in cases with no FDG uptake, but positive CT (n=2) **Prognostic outcomes:** Complete metabolic responders on PET had a longer median time to progression (13.7 mo vs. 9.7 mo).	Selection bias (unclear) Disease progression bias (unclear) Verification bias (>1 RD) Review bias (PET unblinded; RD, unclear)
Bradley 2004[113] Study type: Prospective	**Management decision:** Treatment Major change in diagnosis of 7 / 25 patients (29%); all upstaged. Unsuspected primary tumor identified in 6 patients (not detected by CT), lead to significant change to radiation therapy portal. Identification of 2 patients with extensive-stage disease, who were diagnosed as limited-stage SCLC by conventional staging.	Spectrum bias (unclear) Selection bias (unclear) Verification Bias (>1 RD) Review bias (RD, unclear if blinded)
Kamel 2003[117] Study type: Retrospective	**Management decision:** Treatment Treatment altered in 12 / 42 patients (29%) overall. Initial staging: 9 / 24 changes in management. Upstaged & palliative chemotherapy (n=3); downstaged and curative resection (n=1); minor change to diagnosis & altered radiation field (n=5). Restaging after therapy, 3 / 20 changes in management: chemotherapy reinstituted (n=1); discontinued (n=2)	Selection bias (unclear) Disease progression bias Review bias (PET and RD unblinded)

CT=computer tomography; FDG=Fluorodeoxyglucose F18; mo=months; PET=positron emission tomography; RS=reference standard; vs=versus

9. Testicular Cancer

9.1. Background

Testicular cancer is characterized by malignant cells in one or both testicles. The majority (95%) of testicular neoplasms are germ cell tumors ([GCTs] the cells that become spermatazoa) with other neoplasms, such as sex-chord stromal tumors and lymphomas, occurring only rarely.[179] GCTs, which are characterized by the acquisition of extra copies of chromosome 12p (most commonly through the isochromosome i12p),[179,180] are broadly separated into two groups: seminomas and nonseminomas, each comprising approximately 50% of cases.[179] Seminomas originate from the sperm-producing germ cells of testes and may be one of three types: classic, anaplastic, or spermatocytic. Nonseminomas are also a germ cell tumors but appear very different histologically. Types of nonseminomas include choriocarcinoma, embryonal carcinoma, teratoma, and yolk sac tumors. Testicular tumors may contain both seminoma and nonseminoma cells.[181]

Testicular cancer is the most common cancer in men between the ages of 15 and 35 years, accounting for one to two percent of all neoplasms in men.[182] In 2004, the incidence of invasive testicular cancer was 5.2 per 100,000 and the attributable death rate 0.2 per 100,000 (measures adjusted by age to the 2000 United States standard population).[160] National cancer statistics estimate that there will be 8, 090 new cases and 380 deaths in 2008.[133] Testicular cancer occurs most often in men between the ages of 20 and 39.[181]

Risk factors for testicular cancer include cryptorchidism (undescended testicle), congenital abnormalities of the testicles, penis, or kidneys, as well as those with inguinal hernia, history of testicular cancer, family history of testicular cancer,[180-182] tobacco use and Caucasian race.[181,182] There is no clear or consistent evidence of an association between diet or trauma and testicular cancer.[182]

Testicular changes symptomatic of GCT are usually found during self-examination, after testicular trauma or by a sex partner.[182] Signs and symptoms of testicular cancer include acute pain in the testicle or scrotum, dull ache in the scrotum or abdomen, scrotal heaviness, and firmness of the testicle. A physical examination must include palpation of the testes and be accompanied by blood tests that measure the levels of tumor markers[180] such as alpha-fetoprotein (AFP), beta-human chorionic gonadotropin (ß-HCG), and lactate dehydrogenase (LDH). Higher than normal levels of these markers may suggest the presence of a testicular tumor, even if it is too small to be detected by

physical exams or imaging tests.[181] Scrotal ultrasonography will determine whether a suspected mass is intra- or extratesticular. Intratesticular masses are presumed to be cancerous until proven otherwise.[182] Final diagnosis is by radical orchiectomy (surgical removal of the testicle through an incision in the groin). PET scans are not recommended outside clinical trials as part of routine staging procedures because the procedure has not conclusively demonstrated improved sensitivity of staging compared with CT scanning alone.[180]

After testicular cancer is diagnosed, a patient should receive CT of the abdomen and pelvis to detect metastasis to the retroperitoneal lymph nodes and chest radiography.[182] Patients with neurologic symptoms may receive CT or MRI of the brain.[182]

Testicular cancer is categorized using the TNMS system. Staging is determined based on how much the primary tumor has spread to tissues surrounding the testicles, on extent of spread to regional lymph nodes, on metastasis to other organs, and on serum levels of proteins produced by certain types of testicular cancer.[182]

With overall cure rates of more than 95% (80% for metastatic disease), testicular GCT are considered the model for curable cancer.[179] Nonseminomas tend to grow and spread more quickly; seminomas are more sensitive to radiation. As a result, treatment options differ slightly depending on the characterization of the cancer. If the tumor contains both seminoma and nonseminoma cells, it is treated as a nonseminoma.[181]

The primary treatment for all testicular tumors is radical inguinal orchiectomy.[180,182] Almost all seminomas are curable with orchiectomy with or without radiation, and only occasionally do these cancers require chemotherapy.[179] Nonseminomatous GCTs are less sensitive to radiation and, when metastatic, frequently require both chemotherapy and surgery.[179] A surveillance strategy is an option for patients with stage I seminomas,[180] radiation therapy for seminomas stage I and IIa, and lymph node dissection for stage I and II nonseminoma.[182] Though limited data exist to guide the choice of high-dose (2-3 cycles of etoposide and carboplatin with or without cyclophosphamide or ifosfamide) or conventional-dose chemotherapy for initial salvage treatment,[179] chemotherapy is a treatment option for seminoma stage II and III and all stage II nonseminoma.[182]

Multiple studies have demonstrated the importance of resecting residual masses following first-line of salvage chemotherapy for nonseminoma GCTs.[179] Postchemotherapy surgical resection of seminoma is technically more difficult and carries a higher morbidity due to the desmoplastic

reaction frequently induced by treatment.[179] PET scan can be used to guide surgical decisions in this setting.[179]

9.2. Importance of Key Questions in the Clinical Management of Testicular Cancer

The role of ^{18}FDG-PET in the diagnosis, staging and followup of germ cell tumors is still a matter of debate and there is a need to define optimal indications of ^{18}FDG-PET in testicular cancer. ^{18}FDG-PET may have a role in distinguishing between benign and malignant tissue by characterizing the metabolic activity of the tissue rather than the anatomical size only. ^{18}FDG-PET may also offer the potential to detect residual malignancy after primary curative therapy for testicular cancer. For many solid tumors the early detection of recurrent or residual disease may not confer a clinical benefit to patients, because further curative treatment options may not be available. However, residual or recurrent germ cell malignancy can be cured by further treatment and hence ^{18}FDG-PET may have an important clinical role for patients with such tumors. Existing imaging methods, such as CT scan, chest X-ray and tumor marker evaluation with AFP and β-HCG may be insufficient to identify absent, residual or recurrent disease. Identification of these characteristics may influence subsequent patient management policy

9.3. Results

Four studies[122-125] provided evidence on the use of ^{18}FDG-PET or ^{18}FDG-PET/CT for testicular cancer. All the four studies[122-125] evaluated the diagnostic accuracy of ^{18}FDG-PET or ^{18}FDG-PET/CT, one study[124] reported on the diagnostic thinking impact of ^{18}FDG-PET. None of the studies evaluated the effects of ^{18}FDG-PET or ^{18}FDG-PET/CT as part of a management strategy on patient centered outcomes. There were no economic evaluations on the use of ^{18}FDG-PET or ^{18}FDG-PET/CT for testicular cancer. Characteristics of the populations, conditions of ^{18}FDG-PET administration, interpretation of results and methodological quality of the studies are summarized in appendices D to J.

9.3.1. Diagnostic accuracy of ^{18}FDG-PET and ^{18}FDG-PET/CT in testicular cancer

Characteristics of the studies

Four studies (three prospective,[122,123,125] one retrospective[124]) evaluated the diagnostic accuracy of ^{18}FDG-PET on testicular cancer. One study used ^{18}FDG-PET for initial staging,[125] one for restaging purposes,[122] and two to assess recurrences.[123,124] The studies contained a total of 135 patients with

sample sizes ranging from 15 to 54. The participant ages ranged from 20 to 62 years. Two studies reported the distribution by clinical stage of cancer. One included patients at CS I (20%), CS II (47%) and CS III (33%);[124] the other included patients at CS IIb (10%), CS IIc (70%) and CS III (20%) %.[123] ^{18}FDG-PET was compared to a reference standard that varied across the studies. In two studies the reference standard was either histology/biopsy or clinical follow-up.[122,125] One study established the final diagnosis of all patients using histology/biopsy[123] and one study used clinical follow-up for final diagnosis.[124] Two studies reported the median time between last treatment and ^{18}FDG-PET as 29 days[123] and 45 days;[124] one reported the time since last treatment as 4 to 12 weeks.[122] All studies used a fixed dose of ^{18}FDG, which ranged from 320 MBq to 400 MBq. When reported, the time between injection and PET scan was 45 minutes.[122,125] Patients fasted for four hours[122,123] to six hours.[124,125] Two studies[122,123] measured glucose levels before administration of ^{18}FDG-PET; the maximum glucose level that was allowed was normal levels. Methods of interpretation of the images were qualitative in three studies[122,124,125] and both qualitative and quantitative in one.[123] Scans were interpreted qualitatively using visual analysis in all studies. SUV values were reported in one study[123] for interpretation of the PET images. The criterion for abnormality was SUV > 2 g/mL.

Comparisons

No pooled data were obtained to evaluate the accuracy of ^{18}FDG-PET for testicular cancer for any of the clinical indications considered (i.e., staging, recurrences, and restaging). Comparisons for which data were considered for statistical pooling are summarized in Table 27. Individual data are summarized in Appendix D.

Table 27. Summary of comparisons considered for meta-analyses of the accuracy of ^{18}FDG-PET for testicular cancer

Indication	Studies	Design	Type of PET	Reference standard	Meta-analysis
Staging	Lassen 2003[125]	P	FDG-PET	Histology/biopsy or clinical followup	No
Recurrences	Hinz 2008[123]	P	FDG-PET	Histology/biopsy	No
	Karapetis 2003[124]	R	FDG-PET	Clinical followup	No
Restaging	Becherer 2005[122]	P	FDG-PET	Histology/biopsy or clinical followup	No

FDG= fluorodeoxyglucose; P = prospective; PET=positron emission tomography; R = retrospective

9.3.2. Diagnostic thinking impact of ^{18}FDG-PET on physician decision making with respect to diagnosis and management strategy for patients with testicular cancer

One study[124] reported on the diagnostic thinking impact of ^{18}FDG-PET. The study by Karapetis *et al*[124] examined the treatment decision impact of ^{18}FDG-PET imaging on assessing the recurrence of testicular cancer. A series of 15 patients with metastatic or extragonadal germ cell tumors, who had undergone ^{18}FDG-PET scanning were retrospectively enrolled. The treatment plan was altered in only one patient on the basis of the ^{18}FDG-PET scan; management was changed from observation to surgical excision of residual mass. Normal ^{18}FDG-PET scans provided confirmation in four patients with small residual masses, however, did not alter their subsequent treatment. Seven patients had more than one ^{18}FDG-PET scan. The subsequent ^{18}FDG-PET scans supported, but did not change, treatment management plans.

The authors concluded that ^{18}FDG-PET scanning did not have a discernable impact on treatment decisions for the majority of patients. However, ^{18}FDG-PET often provided support for management decisions made on the basis of the results of other clinical assessments. The authors recommended that ^{18}FDG-PET scans should be arranged with a clear aim in patient management and should not be interpreted in isolation of other assessments.

This study was assessed to be of moderate quality. The spectrum of patients included was representative of patients who would receive the test in practice, a reference standard was applied to the whole sample and was independent of the index test, and all patients and test results were accounted for. However, both the choice of reference standard and time period between tests was unclear. The selection criteria were only partially described, raising the possibility of selection bias. The authors acknowledge the risk of selection bias that is inherent to this study, particularly relevant given the retrospective nature of data collection. In addition, patients did not all receive the same reference standard test, and the execution of the index and reference tests was not described sufficiently. Although the index test was blindly interpreted, the reference standard was interpreted using the results of the index, which may have introduced review bias.

Table 28 provides a summary of the main findings and the types of bias that affected the evidence on the diagnostic thinking impact of ^{18}FDG-PET and ^{18}FDG-PET/CT on testicular cancer

Table 28. Main findings and types of bias that affected the evidence on the diagnostic thinking impact of ^{18}FDG-PET and ^{18}FDG-PET/CT for testicular cancer

Study	Results of FDG-PET imaging on Patient Diagnosis and Treatment	Types of Bias
Karapetis 2003[124] Study type: Retrospective	**Management decision:** Treatment Management plan altered in only 1 / 15 patients (7%), Changed from observation to surgical excisions of residual Confirmation of small residual masses in 4 / 15, subsequent treatment not altered	Selection bias (unclear) Disease progression bias (unclear) Verification bias (>1 rRS) Review bias (RS unblinded)

FDG=Fluorodeoxyglucose F18; PET=positron emission tomography; RS=reference standard

Abbreviations

Abbreviation	Description
^{18}FDG	18F-fluorodeoxyglucose
95% CI	95% confidence interval
AC	carbon-11 acetate
AD	adenocarcinoma
AFP	alpha-fetoprotein
AHRQ	Agency for Healthcare Research and Quality
ASC	adenosquamous carcinoma
ß-HCG	beta-human chorionic gonadotropin
BCG	Bacillus Clamette-Geurin
BEP	bleomycin, etoposide, and platinum
BMI	body mass index
BPH	benign prostatic hyperplasia
CA-125	cancer antigen 125
CCRT	concurrent chemotherapy and radiotherapy
CEA	carcinoembryonic antigen
CHEC	Consensus on Health Economic Criteria
CIN	cervical intraepithelial neoplasia
CMS	Center for Medicaid and Medicare Services
COI	conflict of interest
CP	chronic pancreatitis
CS	clinical stage
CT	computer tomography
D	days
DM	diabetes mellitus
DRE	digital rectal examination
EBRT	electron beam radiation therapy
ECOG	Eastern Cooperative Oncology Group
ED	extensive-disease
ERCP	endoscopic retrograde cholangiopancreatography
EPC	Evidence-based Practice Centers
EUS	endoscopic ultrasound
F-FMISO	18F-fluoromisonidazole
FIGO	Federation Internationale de Gynecologie et d'Obstetrique
FNA	fine needle aspiration
FOV	field of view
GBM	glioblastoma multiforme
GCT	germ cell tumors
GLUT	glucose transport proteins
GnRH	gonadotropin-releasing hormone
H	hours
HPV	human papilloma virus
HR	hazard ratio
ILN	Inguinal lymph node
IPMN	intraductal papillary mucinous neoplasms
IQR	interquartile range
IV	intravenous
LD	limited-disease
LDH	lactate dehydrogenase
LD	lymph nodes
LR	likelihood ratio
MAX	maximum
MET	carbon-11 methionine
M-H	Mantel-Hantzel
MIN	minutes
MLN	mediastinal lymph node

MRCP	magnetic resonance cholangiopancreatography
MO	months
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
NA	not applicable
ND	not described
NLR	negative likelihood ratio
OSEM	ordered subset expectation maximization
PALN	para-aortic lymph node
PCI	prophylactic cranial irradiation
PET	positron emission tomography
PLN	pelvic lymph node
PLR	positive likelihood ratio
PO	oral
PSA	prostate-specific antigen
PTC	percutaneous transhepatic cholangiography
QUADAS	Quality Assessment of Studies of Diagnostic Accuracy
RCC	renal cell carcinoma
RCT	randomized controlled trial
RH-PLND	radical hysterectomy + pelvic lymphadenectomy
RI	retention index
RMI	risk of malignancy index
ROC	receiver operating characteristic
ROI	region of interest
RT	radiotherapy
SCC-Ag	squamous cell carcinoma antigen
SCLC	small-cell lung cancer
SD	standard deviation
SEC	seconds
SIGN	Scottish Intercollegiate Guidelines Network
SLL	second-look laparotomy
SLN	supraclavicular lymph node
SROC	summary receiver operating characteristic
SUV	standardized uptake value
TA	technology assessment
TNMS	tumor, node, metastasis staging
TRUS	transrectal ultrasound
TUR	transurethral resection
TVUS	transvaginal ultrasonography
UICC	Union International Contre le Cancer
US	Ultrasound
VALCSG	Veterans Administration Lung Cancer Study Group
VATAP	Veterans Affairs Technology Assessment Program
WK	weeks
WHO	World Health Organization
YR	years

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