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SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA

Criteria for appropriate use of FDG-PET in lung cancer

ORIentamenti 6

Osservatorio regionale per l'innovazione

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List of abbreviations

AIOM	Associazione italiana oncologia medica
ASSR	Agenzia sanitaria e sociale regionale
BAC	bronchioloalveolar cancer
CDSR	Cochrane database of systematic reviews
CCT	controlled clinical trial
CENTRAL	Central register of controlled trials - The Cochrane Library
CRD	Centre for reviews and dissemination
CT	computed tomography
CTV	clinical target volume
DARE	Database of Abstracts of Reviews of Effects
ESMO	European society of medical oncology
FDG	fluorodeoxyglucose
FN	false negatives
FP	false positives
LR	likelihood ration
MA	meta-analysis
MRI	magnetic resonance imaging
NICE	National institute of clinical excellence
NSCLC	non-small cell lung cancer
PET	positron emission tomography
PS	primary study
RCT	randomized controlled trial
RER	Regione Emilia-Romagna
RT	radiotherapy
SIGN	Scottish Intercollegiate Guidelines Network
SCLC	small cell lung cancer
SPN	solitary pulmonary nodule
SR	systematic review
SUV	standardized uptake value
TN	true negatives
TP	true positives

Sintesi dei risultati

Criteri per l'uso appropriato della tomografia ad emissione di positroni con FDG (FDG-PET) nel tumore del polmone

Il gruppo di lavoro ha esaminato e valutato il ruolo diagnostico della FDG-PET nelle seguenti indicazioni cliniche:

- caratterizzazione dei noduli polmonari solitari di dimensione ≥1 cm -
  Appropriato (livello di evidenza: moderato)
- stadiazione dei pazienti con tumore del polmone non a piccole cellule (NSCLC) -
  Appropriato (livello di evidenza: moderato)
- stadiazione dei pazienti con tumore bronchiolo alveolare (BAC) -
  Inappropriato per mancanza di ruolo diagnostico della FDG-PET
- stadiazione dei pazienti con tumore del polmone a piccole cellule (SCLC) -
  Incerto (livello di evidenza: molto basso)
- definizione del *target volume* nel trattamento radiante a intento curativo dei pazienti con tumore al polmone -
  Incerto (livello di evidenza: molto basso)
- valutazione durante il trattamento della risposta precoce alla terapia neo-adiuvante nei pazienti trattati per tumore del polmone non a piccole cellule (NSCLC) -
  Inappropriato per mancanza di ruolo diagnostico della FDG-PET
- valutazione durante il trattamento della risposta precoce alla terapia sistemica nei pazienti trattati per tumore del polmone a piccole cellule (SCLC) -
  Inappropriato per mancanza di ruolo diagnostico della FDG-PET
- valutazione al termine del trattamento della risposta alla terapia neo-adiuvante nei pazienti trattati per tumore del polmone non a piccole cellule (NSCLC) -
  Incerto (livello di evidenza: molto basso)
- valutazione al termine del trattamento della risposta alla terapia sistemica nei pazienti trattati per tumore del polmone a piccole cellule (SCLC) -
  Inappropriato per mancanza di ruolo diagnostico della FDG-PET
- *follow up* dei pazienti trattati per tumore al polmone (NSCLC) con nessun sospetto di recidiva -
  Inappropriato per mancanza di ruolo diagnostico della FDG-PET
- diagnosi e stadiazione di recidiva loco-regionale in pazienti trattati per tumore del polmone non a piccole cellule (NSCLC) -
  Incerto (livello di evidenza: molto basso)

CARATTERIZZAZIONE DEI NODULI POLMONARI SOLITARI DI DIMENSIONE ≥1 CM - APPROPRIATO

Il *panel* ha concordato alla prima votazione nel giudicare appropriato l'uso della FDG-PET per caratterizzare i noduli polmonari singoli identificati alla TAC. Vi sono infatti parecchi dati a supporto di questa indicazione e il livello di evidenza è stato giudicato moderato per una specificità della FDG-PET migliore rispetto ai test diagnostici di confronto (TC con mezzo di contrasto e RM con mezzo di contrasto). Tutti gli esiti clinici sono stati giudicati critici dai panelisti.

STADIAZIONE DEI PAZIENTI CON TUMORE DEL POLMONE NON A PICCOLE CELLULE - NSCLC - APPROPRIATO

Il *panel* ha concordato alla prima votazione nel giudicare appropriato l'uso della FDG-PET come esame di secondo livello nella stadiazione dei pazienti con tumore del polmone non a piccole cellule. Il livello di evidenza a sostegno di questa indicazione è risultato essere moderato per una buona *performance* diagnostica della FDG-PET nell'identificare il coinvolgimento del mediastino o le metastasi a distanza non individuate dalla TC. Evitare un intervento chirurgico non efficace (conseguenza per i veri positivi) è stato considerato importante mentre il rischio di essere sottoposti a un intervento inutile (conseguenza per il falsi negativi) così come quello di non essere sottoposti a un intervento potenzialmente curativo (conseguenza per i falsi positivi) sono entrambi stati giudicati critici dal *panel*, con un voto mediano rispettivamente di 8 e 7, confermando la necessità di una accurata e scrupolosa stadiazione pre-trattamento.

STADIAZIONE DEI PAZIENTI CON TUMORE BRONCHIOLO ALVEOLARE - BAC - INAPPROPRIATO

Due studi hanno valutato il ruolo della FDG-PET/TC nel differenziare il tumore bronchiolo alveolare dai sottotipi di tumore del polmone non a piccole cellule. Non è stato reperito alcuno studio sullo staging del BAC. Il *panel* ha stabilito che non vi sia un ruolo diagnostico della FDG-PET nella stadiazione dei pazienti con BAC e ha unanimemente giudicato questa indicazione inappropriata.

STADIAZIONE DEI PAZIENTI CON TUMORE DEL POLMONE A PICCOLE CELLULE - SCLC - INCERTO

I dati disponibili sull'accuratezza della FDG-PET nel discriminare la malattia limitata da quella estesa nei pazienti con tumore del polmone a piccole cellule sono pochi e il livello di evidenza è stato giudicato molto basso. La limitata differenza nel beneficio offerto dalle opzioni terapeutiche disponibili ha indotto il *panel* ad assegnare un basso punteggio agli esiti clinici: conseguenze per veri e falsi positivi trattati con sola chemioterapia sono stati votati non importanti (voto mediano 3), mentre le conseguenze per i veri e falsi negativi trattati con chemio/radioterapia combinata sono stati votati importanti (voto mediano 4). Entrambe le votazioni sull'appropriatezza hanno registrato un disaccordo con punteggi assegnati sia all'area dell'inappropriato sia dell'incerto. L'utilizzo della FDG-PET nella stadiazione dei pazienti con SCLC è risultato pertanto incerto per disaccordo.

DEFINIZIONE DEL *TARGET VOLUME* NEL TRATTAMENTO RADIANTE A INTENTO CURATIVO DEI PAZIENTI CON TUMORE AL POLMONE - INCERTO

In nessuna delle due votazioni sull'appropriatezza il *panel* ha raggiunto un accordo nel giudicare l'utilizzo della FDG-PET nella definizione del *target volume*, con punteggi che ricadevano sia nell'area dell'inappropriato sia dell'incerto (prima votazione: punteggio mediano 3,5 - *range* 2-5; seconda votazione punteggio mediano 4.5 - *range* 2-6). L'utilizzo della FDG-PET in questa indicazione è risultato pertanto incerto per disaccordo.

VALUTAZIONE DURANTE IL TRATTAMENTO DELLA RISPOSTA PRECOCE ALLA TERAPIA NEO-ADIUVANTE NEI PAZIENTI TRATTATI PER TUMORE DEL POLMONE NON A PICCOLE CELLULE - NSCLC - INAPPROPRIATO

L'accuratezza diagnostica della FDG-PET nel valutare, durante il trattamento, la risposta precoce alla terapia neoadiuvante nei pazienti trattati per tumore non a piccole cellule è stata poco studiata e il livello di evidenza è risultato molto basso. Poiché il trattamento chemioterapico è breve e non vi è spazio per una valutazione della risposta precoce al trattamento, il *panel* ha concordato che non vi è un ruolo diagnostico per la FDG-PET nella valutazione precoce della risposta al trattamento e ha unanimemente giudicato inappropriato questo utilizzo della FDG-PET.

VALUTAZIONE DURANTE IL TRATTAMENTO DELLA RISPOSTA PRECOCE ALLA TERAPIA SISTEMICA NEI PAZIENTI TRATTATI PER TUMORE DEL POLMONE A PICCOLE CELLULE - SCLC - INAPPROPRIATO

Un solo studio con pochi pazienti ha indagato l'accuratezza diagnostica della FDG-PET nella valutazione, durante il trattamento, della risposta precoce alla terapia dei pazienti trattati per tumore del polmone a piccole cellule. Poiché il trattamento chemioterapico è breve e non vi è spazio per una valutazione della risposta precoce al trattamento, il *panel* ha concordato che non vi è un ruolo diagnostico per la FDG-PET nella valutazione precoce della risposta al trattamento e ha unanimemente giudicato inappropriato questo utilizzo della FDG-PET.

VALUTAZIONE AL TERMINE DEL TRATTAMENTO DELLA RISPOSTA ALLA TERAPIA NEO-ADIUVANTE NEI PAZIENTI TRATTATI PER TUMORE DEL POLMONE NON A PICCOLE CELLULE - NSCLC - INCERTO

Anche se una buona risposta alla terapia neoadiuvante potrebbe influenzare, in pazienti selezionati, la successiva scelta tra le opzioni terapeutiche, gli esiti clinici per i pazienti non sono stati considerati molto importanti dal *panel*: le conseguenze per i falsi *responders* e i falsi *non responders* sono state giudicate non importanti (punteggio mediano 3), mentre le conseguenze per i veri *responders/non responders* sono state giudicate importanti con punteggio mediano rispettivamente di 5 e 4. Il livello di evidenza per l'accuratezza diagnostica della FDG-PET nel valutare la risposta al trattamento di pazienti trattati per NSCLC è stato giudicato molto basso a causa della eterogeneità delle

stime sia di sensibilità che di specificità. Questo utilizzo della FDG-PET è risultato incerto per disaccordo, in quanto il *panel* non ha raggiunto un accordo in entrambe le votazioni, con punteggi assegnati sia nell'area dell'inappropriato sia dell'incerto.

VALUTAZIONE AL TERMINE DEL TRATTAMENTO DELLA RISPOSTA ALLA TERAPIA SISTEMICA NEI PAZIENTI TRATTATI PER TUMORE DEL POLMONE A PICCOLE CELLULE - SCLC - INAPPROPRIATO

Un solo studio con pochi pazienti ha valutato la *performance* diagnostica della FDG-PET nella valutazione della risposta alla terapia sistemica al termine del trattamento nei pazienti con tumore del polmone a piccolo cellule. Il livello di evidenza è pertanto risultato molto basso. Il *panel* ha tuttavia concordato che non vi è un ruolo diagnostico per la FDG-PET nella valutazione della risposta al trattamento per SCLC e ha unanimemente giudicato inappropriato questo utilizzo della FDG-PET.

FOLLOW UP DEI PAZIENTI TRATTATI PER TUMORE AL POLMONE - NSCLC - CON NESSUN SOSPETTO DI RECIDIVA - INAPPROPRIATO

È stato reperito un solo studio sull'accuratezza diagnostica della FDG-PET nel *follow up* dei pazienti trattati per tumore al polmone e con nessun sospetto di recidiva. Il livello di evidenza è stato quindi giudicato molto basso. Il *panel* ha concordato sulla mancanza di un ruolo diagnostico per la FDG-PET in questa indicazione, che è stata unanimemente giudicata inappropriata.

DIAGNOSI E STADIAZIONE DI RECIDIVA LOCO-REGIONALE IN PAZIENTI TRATTATI PER TUMORE DEL POLMONE NON A PICCOLE CELLULE - NSCLC - INCERTO

L'accuratezza diagnostica della FDG-PET nella caratterizzazione di recidiva loco-regionale è stata valutata da pochi studi e su pochi pazienti. Il livello di evidenza è risultato molto basso. Gli esiti clinici per i pazienti sono stati giudicati critici dal *panel*: voto mediano 8 (*range* 2-8) per le conseguenze per pazienti erroneamente diagnosticati con recidiva, voto mediano 7 (*range* 2-9) per i tre rimanenti esiti (conseguenze per veri positivi e per veri e falsi negativi). È stato registrato un leggero disaccordo in entrambe le votazioni sull'appropriatezza tra giudizi di appropriato e giudizi di incerto (voto mediano 7), pertanto l'utilizzo della FDG-PET nella diagnosi e stadiazione di sospetta recidiva loco-regionale in pazienti già trattati per NSCLC è risultato incerto per disaccordo.

Summary of results

Criteria for the appropriate use of positron emission tomography with FDG (FDG-PET) in lung cancer

The panel examined and assessed the role of FDG-PET for the following clinical indications:

- characterization of solitary pulmonary nodules ≥1 cm -
  Appropriate (level of evidence: moderate)
- staging of patients with non-small cell lung cancer (NSCLC) -
  Appropriate (level of evidence: moderate)
- staging of patients with bronchioloalveolar cancer (BAC) -
  Inappropriate for lack of diagnostic role of FDG-PET
- staging of patients with small cell lung cancer (SCLC) -
  Uncertain (level of evidence: very low)
- target volume definition of radiation treatment with curative intent in patients treated for lung cancer -
  Uncertain (level of evidence: very low)
- during-treatment evaluation of early response to neo-adjuvant therapy in patients treated for non-small cell lung cancer (NSCLC) -
  Inappropriate for lack of diagnostic role of FDG-PET
- during-treatment evaluation of early response to neo-adjuvant therapy in patients treated for small cell lung cancer (SCLC) -
  Inappropriate for lack of diagnostic role of FDG-PET
- end of treatment evaluation of response to neo-adjuvant therapy in patients treated for non-small cell lung cancer (NSCLC) -
  Uncertain (level of evidence: very low)
- end of treatment evaluation of response to systemic therapy in patients treated for small cell lung cancer (SCLC) -
  Inappropriate for lack of diagnostic role of FDG-PET
- follow up of patients treated for lung cancer (NSCLC) with no suspicion of recurrence - Inappropriate for lack of diagnostic role of FDG-PET
- diagnosis and staging of suspected loco-regional recurrence in patients treated for non-small cell lung cancer (NSCLC) -
  Uncertain (level of evidence: very low)

CHARACTERIZATION OF SOLITARY PULMONARY NODULES ≥1 CM - APPROPRIATE

The panel agreed during the first voting round that the use of FDG-PET to characterize solitary pulmonary nodules (SPNs) identified by CT is appropriate. There is in fact a large body of evidence supporting this indication and the level of evidence has been judged moderate, with FDG-PET showing a slightly better specificity than comparators (dynamic contrast-enhanced CT and dynamic contrast-enhanced MRI). All the clinical outcomes were judged critical by the panelists.

STAGING OF PATIENTS WITH NON-SMALL CELL LUNG CANCER - NSCLC - APPROPRIATE

The panel agreed at the first voting round that the use of FDG-PET as an add on test in NSCLC staging is appropriate. The level of evidence supporting this indication is moderate with FDG-PET performing well in identifying mediastinal involvement or distant metastases missed by CT.

While avoiding unnecessary surgery (consequences for true positives) has been considered important, undergoing futile surgery (consequences for false negatives) or not undergoing a potentially curative radical surgery (consequences for false positives) have been considered critical outcomes with median scores of 8 and 7 respectively, confirming the need for thorough and accurate pre-treatment staging.

STAGING OF PATIENTS WITH BRONCHIOLOALVEOLAR CANCER - BAC - INAPPROPRIATE

Two studies have assessed the role of PET/CT in differentiating BAC from other NSCLC subtypes and no study was found on staging of BAC. The panel established that there is no diagnostic role of FDG-PET in staging of patients with BAC and unanimously agreed to judge its use as inappropriate.

STAGING OF PATIENTS WITH SMALL CELL LUNG CANCER - SCLC - UNCERTAIN

The available data on FDG-PET accuracy in discriminating limited from extended SCLC are sparse and the level of evidence was considered very low. The limited difference in gain offered by the therapeutic options available led the panel to give low scores for clinical outcomes: consequences for true and false positive treated with just chemotherapy were voted not important (median score 3), while consequences for true and false negative receiving combined chemo/radiotherapy were voted important (median score 4). Both voting rounds on appropriateness registered a disagreement among panelists with ratings falling in both the inappropriate and uncertain regions. The use of FDG-PET in staging SCLC resulted therefore uncertain due to disagreement.

TARGET VOLUME DEFINITION OF RADIATION TREATMENT WITH CURATIVE INTENT IN PATIENTS TREATED FOR LUNG CANCER - UNCERTAIN

In neither of the two voting rounds the panel reached an agreement on the appropriateness of FDG-PET in Target Volume definition with votes falling between the inappropriate and uncertain regions (first round: median score 3.5 with range 2-5; second round: median score 4.5 with range 2-6). The use of FDG-PET resulted therefore uncertain due to disagreement.

DURING-TREATMENT EVALUATION OF EARLY RESPONSE TO NEO-ADJUVANT THERAPY IN PATIENTS TREATED FOR NON-SMALL CELL LUNG CANCER - NSCLC - INAPPROPRIATE

The diagnostic accuracy of FDG-PET in evaluating early response, during treatment, to neo-adjuvant therapy in patients treated for NSCLC has been poorly studied and level of evidence is very low. Due to the brevity of the neo-adjuvant treatment, the panel agreed in the lack of diagnostic role of FDG-PET in this clinical situation, and unanimously decided to judge this use of FDG-PET inappropriate.

DURING-TREATMENT EVALUATION OF EARLY RESPONSE TO SYSTEMIC THERAPY IN PATIENTS TREATED FOR SMALL CELL LUNG CANCER - SCLC - INAPPROPRIATE

Only one study with very few patients evaluated diagnostic performance of FDG-PET in the early response, during treatment, to therapy in patients treated for SCLC. The level of evidence is therefore very low. Due to the brevity of the treatment, the panel agreed in the lack of diagnostic role of FDG-PET in this clinical situation, and unanimously decided to judge this use of FDG-PET inappropriate.

END OF TREATMENT EVALUATION OF RESPONSE TO NEO-ADJUVANT IN PATIENTS TREATED FOR NON-SMALL CELL LUNG CANCER - NSCLC - UNCERTAIN

Although a good response to neo-adjuvant therapy could influence subsequent choice of therapeutic options for selected patients, patient-important outcomes were not considered very important by the panel, with consequences for false responders and false non responders rated as not important (median score 3) and consequences for true responders/non responders rated important (median score 5 and 4 respectively). Level of evidence for FDG-PET diagnostic accuracy in evaluating end of treatment response to therapy in patients treated for NSCLC was judged very low due to heterogeneity of estimates for both sensitivity and specificity. This use of FDG-PET resulted uncertain due to disagreement as the panel did not reach an agreement in both voting rounds, with ratings falling in both the inappropriate and uncertain regions.

END OF TREATMENT EVALUATION OF RESPONSE TO SYSTEMIC THERAPY IN PATIENTS TREATED FOR SMALL CELL LUNG CANCER - SCLC - INAPPROPRIATE

Only one study with very few patients evaluated diagnostic accuracy of FDG-PET in the end of treatment evaluation of patients' response to systemic therapy for SCLC. The level of evidence is therefore very low. Due to the lack of diagnostic role of FDG-PET in this clinical situation, the panel unanimously decided to judge this use of FDG-PET inappropriate.

FOLLOW UP OF PATIENTS TREATED FOR LUNG CANCER - NSCLC - WITH NO SUSPICION OF RECURRENCE - INAPPROPRIATE

Only one study evaluating diagnostic accuracy of FDG-PET in follow up of patients treated for lung cancer with no suspicion of recurrence was retrieved. The level of evidence was therefore judged very low. The panel agreed on the lack of diagnostic role for FDG-PET in this indication, which was unanimously judged inappropriate.

DIAGNOSIS AND STAGING OF SUSPECTED LOCO-REGIONAL RECURRENCE IN PATIENTS TREATED FOR NON-SMALL CELL LUNG CANCER - NSCLC - UNCERTAIN

Diagnostic accuracy of FDG-PET in the characterization of loco-regional recurrence has been evaluated by few studies and in relatively few patients. The level of evidence was therefore judged very low. Patient-important outcomes were voted critical by the panel, with consequences for patients wrongly diagnosed for recurrence scoring 8 (median, range 2-8) and consequences for true positives and true and false negatives scoring 7 (median, range 2-9 for all three outcomes). There was a slight disagreement among panelists voting uncertain and appropriate in both rounds (median score 7) and the use of FDG-PET in the diagnosis and staging of suspected loco-regional recurrence in patients treated for NSCLC resulted uncertain due to disagreement.

Foreword

The Regional Observatory for Innovation (Osservatorio regionale per l'innovazione - ORI) is a research unit within the Regional Health and Social Agency of Emilia-Romagna, Italy (Agenzia sanitaria e sociale regionale - ASSR), which supports the Local Authority and its individual health care organizations in governing the adoption of health technologies.

The Dossiers are developed by multidisciplinary working groups representative of the regional professional networks. Conclusions are made on both adoption of the technology and on necessary research projects.

The work leading to the development of the present Dossier on the criteria of appropriate use of FDG-PET in lung cancer has been carried out between November 2010 and February 2011.

All members of the panel have completed and signed a declaration of conflict of interests and further details of these are available on request.

This Dossier was also reviewed in draft form by independent and external expert referees and their comments are reported in full at the end of the document.

To synthesize and present the evidence base, the logic and principles of the GRADE approach were applied and the consensus process was based on the RAND/UCLA Appropriateness Method.

This Dossier is published in 2012 and will be considered for review in five years. Any update in the interim period will be noted on the ASSR website
http://asr.regione.emilia-romagna.it

1. Introduction and objectives

PET imaging is a non invasive nuclear medicine examination based on the detection of metabolic abnormalities of disease processes through the use of short-lived radiopharmaceuticals.

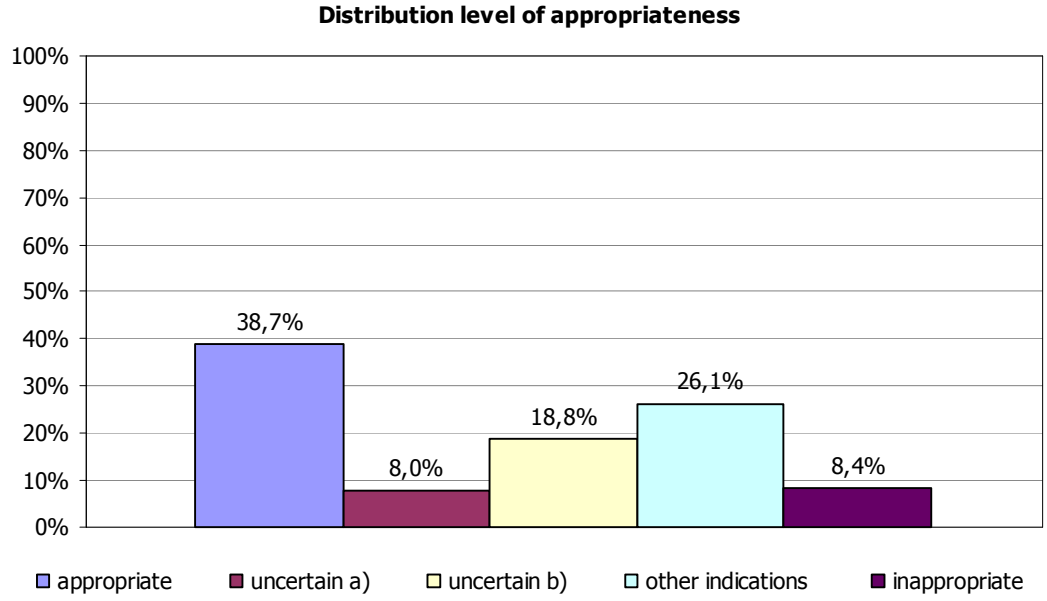
Since its introduction in the Emilia-Romagna Regional Health Service, the ASSR has been committed to promote and support regional research programs aimed at assessing clinical indications for FDG-PET and supporting programming policies.

The first research program, conducted with a multidisciplinary panel of regional experts, resulted in the publication in 2003 of the first regional report on the appropriate use of FDG-PET in 16 types of tumor, for a total of 47 clinical indications. The results of this first report were used to carry out a first clinical audit on the use of FDG-PET in the only PET centre present in the region in 2002. Of the 452 FDG-PET scans, consecutively registered and analyzed between January and July 2002, about one third (38.7%) turned out to be to be appropriate, while 26.1% were inappropriate (*Graph 1*).

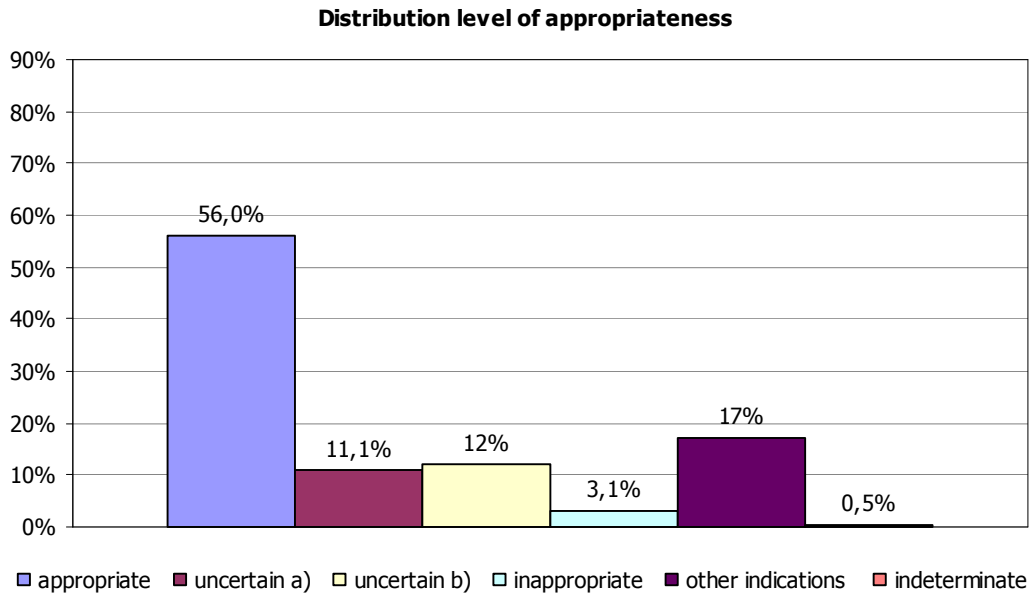
Following the increase in number of FDG-PET scanners (from 1 to 6) an update of the 2003 report was commissioned to a second regional panel and published in 2007. The second report addressed the role of FDG-PET in 18 types of cancer for a total of 65 clinical indications, and a second clinical audit was carried out in the 6 regional FDG-PET centers. From the 600 consecutive FDG-PET exams analyzed, 56% resulted to be appropriate, 23.4% fell in the uncertain categories and just over 3% were inappropriate (*Graph 2*). While appropriate use had substantially increased since the previous clinical audit (and inappropriateness had also quite considerably decreased), the increase from around 8 to 17% of use of FDG-PET in clinical indications not included in the report suggested that the evaluation had not been sufficiently comprehensive of most clinical and diagnostic questions addressed in clinical practice.

The present update of the criteria for appropriate use of FDG-PET in oncology, which involves a much larger multidisciplinary panel of regional experts, is a research project financed by a national research program of the Ministry of Health. The project proposes a new methodology for the definition of clinical questions, covering most clinical situations occurring in routine practice, for the evaluation of the available evidence on FDG-PET diagnostic accuracy and for the development of criteria of appropriate clinical use. The critical appraisal of the available literature would be also directed at the identification of main research gaps, in order to set a list of high priority research questions that could be addressed by a future research program. With currently 8 authorized PET scanners in the Emilia-Romagna region, a further aim of this project is to explore whether and to what extent criteria of appropriate use can be used for the programming of policies and services' activities.

Graph 1. Clinical audit 2002 - appropriate use of FDG-PET (452 FDG-PET scans)



Graph 2. Clinical audit 2006 - appropriate use of FDG-PET (588 FDG-PET scans)



1.1. Use of FDG-PET in lung cancer: objectives

This work is part of a wider research program covering the use of FDG-PET in a total of 20 types of cancer.

The objective of the present report was to define criteria for appropriate use of FDG-PET for patients with lung cancer.

The criteria reported in this document are to be intended as guidance for programs of clinical governance aimed at:

- supporting clinicians on the use of FDG-PET in lung cancer;
- post hoc analyses of appropriate use of FDG-PET;
- contributing to the planning of the regional health service.

The purpose of this report is not to produce clinical recommendations for the use of FDG-PET in lung cancer.

1.2. Context

Incidence of lung cancer

Crude incidence rate of lung cancer in Emilia-Romagna Region in 2004 (RER 2009) was 122.8 per 100 000 male inhabitants per year and 34.0 per 100 000 female inhabitants per year.

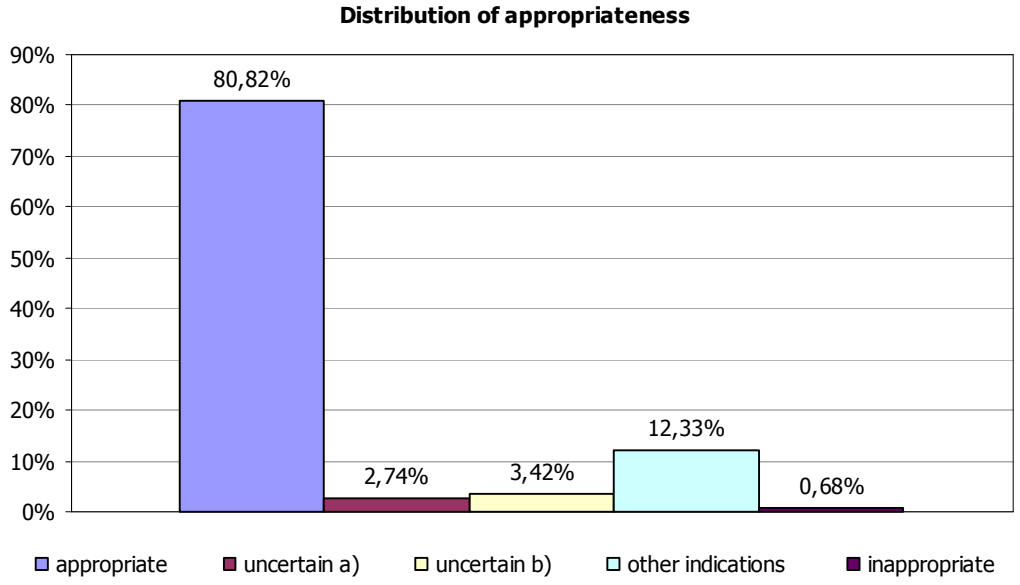
Prevalence of lung cancer

Cumulative 10 years prevalence estimates of lung cancer in Emilia-Romagna Region at 1/1/2005 (RER 2009) was 199.2 per 100 000 male inhabitants, corresponding to 4 019 cases in Emilia-Romagna region, and 63.3 per 100 000 female inhabitants, corresponding to 1 351 cases.

In the regional audit carried out in 2002 audit, FDG-PET scans requested for patients with lung cancer represented 23.5% of the total sample included (106 out of 452), with 58% of requests considered appropriate, while 25% fell in the uncertain-b and 17% in the inappropriate categories.

In the 2007 audit, following the criteria update in 2006, FDG-PET scans for lung cancer represented 24.8% of the total sample and 86.98% fell in the appropriate and uncertain category, with only one inappropriate request *(Graph 3*). The remaining 12.33% of requests fell into the "other indications" category.

Graph 3. Clinical audit 2006 - appropriate use of FDG-PET in lung cancer



2. Methods

A panel of 20 experts, comprising nuclear physicians, radiologists, radiotherapists, surgeons, oncologists, pneumologists, haematologists and health directors working in health trusts and teaching hospital of Emilia-Romagna was convened to discuss and agree on the methodology for a research program aimed at defining the criteria for appropriate use of FDG-PET in lung cancer.

At the first meeting the group decided upon the following issues:

- clinical questions to be addressed;
- systematic review of literature;
- grading of level of evidence;
- voting process;
- definition of criteria of appropriateness.

2.1. Clinical questions to be addressed

On the basis of the clinical pathway of patients with non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) (*Figure 2.1 and 2.2, respectively*), shared by most international clinical practice guidelines, the panel examined and assessed the role of FDG-PET for 11 clinical indications (*Table 2.1*).

Table 2.1. Clinical indications selected by the panel

• Characterization of solitary pulmonary nodules ≥1 cm
• Staging of patients with non-small cell lung cancer (NSCLC)
• Staging of patients with bronchioloalveolar cancer (BAC)
• Staging of patients with primary small cell lung cancer (SCLC)
• Target volume definition of radiation treatment with curative intent in patients treated for lung cancer
• During-treatment evaluation of response to neo-adjuvant therapy in patients treated for lung cancer - NSCLC
• During-treatment evaluation of response to systemic therapy in patients treated for lung cancer - SCLC
• End of treatment evaluation of response to neo-adjuvant therapy in patients treated for lung cancer - NSCLC
• End of treatment evaluation of response to systemic therapy in patients treated for lung cancer - SCLC
• Follow up of patients treated for lung cancer with no suspicion of recurrence - NSCLC
• Diagnosis and staging of suspected loco-regional recurrence in patients treated for lung cancer - NSCLC

Figure 2.1. Clinical pathway for NSCLC

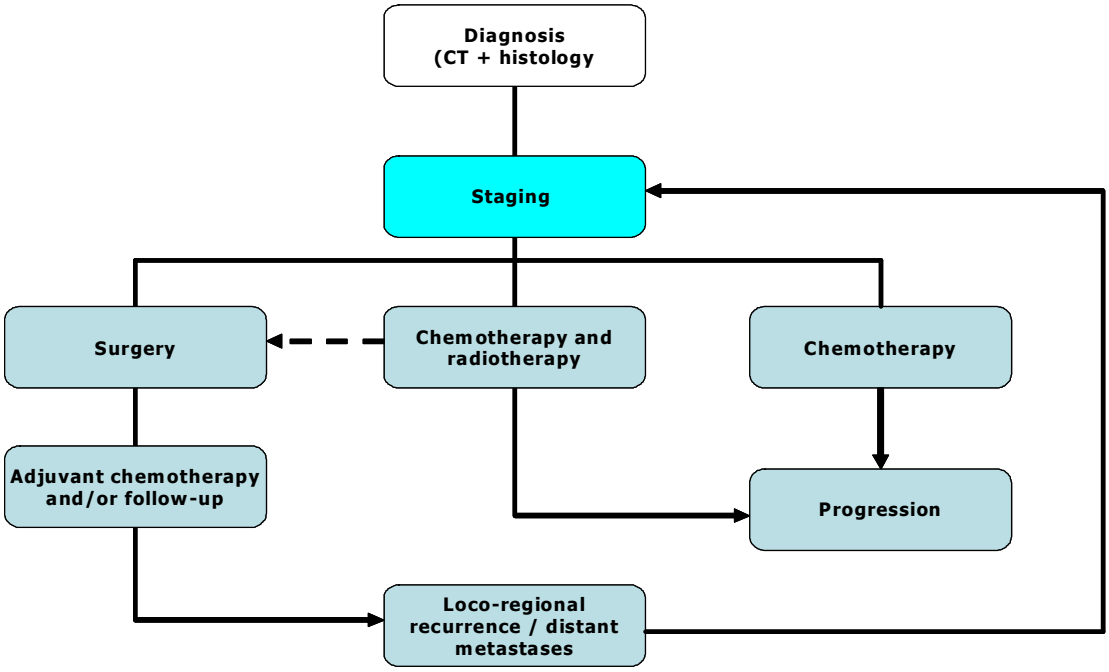
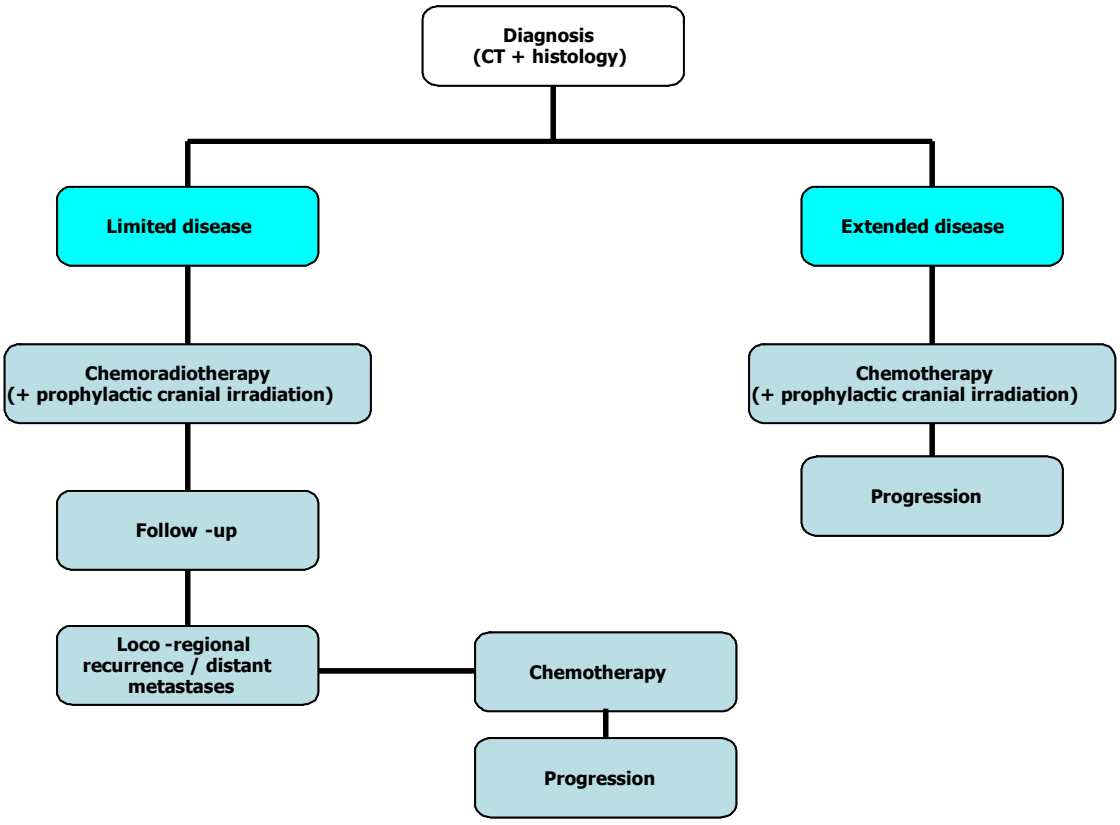


Figure 2.2. Clinical pathway for SCLC

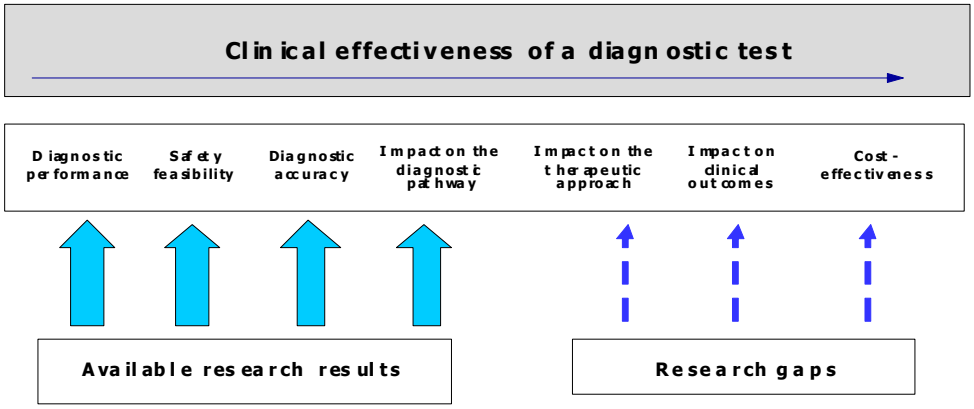


The starting point for the development of answerable "research questions", based on the PICO structure (patient intervention comparator outcome), has been the broad definition of appropriateness of a diagnostic test, which implies:

- an initial diagnosis and the therapeutic approach following the initial diagnosis;
- the capacity of the new test (i.e. FDG-PET) to modify the initial diagnosis (or stage of the disease);
- the subsequent change in the therapeutic approach;
- the clinical benefit expected from the change in the therapeutic approach endorsed by test results.

As for the previously published reports, the evidence profile necessary to comprehensively assess and evaluate the role of a diagnostic test was defined and is represented in Figure 2.3.

Figure 2.3. Evidence profile for a diagnostic test



The persistent gap in research evaluating the impact on therapeutic approach, clinical outcomes and costs, that is common to most diagnostic tests, was acknowledged and answerable clinical questions were developed as follows.

To build the PICOs on FDG-PET's clinical appropriateness, participants were identified as patients in one of the clinical situations selected by the panel (*Table 2.1*).

Potentials for change in patient's management following test results was stated in the rationale supporting the diagnostic role of FDG-PET and were backed up by either evidence from studies on change in management or by the pre-test probability calculated from the raw data extracted from the studies on diagnostic accuracy, representing the expected percentage of change of approach over the whole patients population.

The intervention was either FDG-PET or FDG-PET/CT with a specific role within the diagnostic pathway and with a pre-defined position in relation to the comparator (replacement, triage, add on) as defined by Bossuyt 2006. The comparator was identified as the currently used or existing test for the diagnostic role under consideration.

Diagnostic accuracy (sensitivity and specificity) of FDG-PET was identified as the outcome conveying the test's capacity to modify the initial diagnosis.

As randomized clinical trials providing robust data on clinical effectiveness of diagnostic tests are very difficult to perform, and seldom found by systematic literature search, we decided to adopt the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach to evaluate benefits expected from the change in the therapeutic approach endorsed by the test's results (Schünemann 2008). This approach suggests to state clinical consequences for patients testing positive (true and false positive) and for patients testing negative (true and false negative). Data of effectiveness related to important clinical outcomes are replaced by judgements of experts and panelists are asked to assign a score from 1 to 9 stating the level of importance of patient outcomes as the result of being a true or false positive or a true or false negative. The balance or trade-off between the presumed benefits and the presumed harms, together with the quality of evidence on diagnostic accuracy, are used by panel members to judge the level of appropriateness of a test.

2.2. Systematic review of literature

Search methods for the identification of the studies

The following databases were searched for the period between January 2006 - date of the literature search for the precedent update - and September 2010:

- Cochrane Database of Systematic Reviews (CDSR - The Cochrane Library);
- Database of Abstracts of Reviews of Effects (DARE - Centre for Reviews and Dissemination);
- Health Technology Assessment Database (HTA Database - Centre for Reviews and Dissemination);
- Cochrane Central Register of Controlled Trials (CENTRAL - The Cochrane Library);
- National Library of Medicine's Medline database (PubMed);
- Elsevier's Embase.

Language restrictions: English, Italian, French and Spanish.

Reference lists of identified articles were checked for additional references.

Full details of search terms used are given in Appendix 2.

Selection criteria

Type of studies	systematic reviews, RCTs, CCTs, cross-sectional diagnostic studies, prospective or retrospective cohort studies, case series of at least 10 patients
Participants	patients with lung cancer
Intervention	FDG-PET or FDG-PET/CT
Reference standard	histology or clinical follow up (for diagnostic accuracy studies)
Comparator	any other imaging technique

Outcomes	sensitivity, specificity, LR, accuracy in Clinical Target Volume (CTV) definition, metabolic/tumor response, quality of life, adverse events, time to recurrence, local, loco-regional and distant recurrence, disease free survival, disease survival, overall survival

Assessment of methodological quality of studies

The following criteria have been used for the quality assessment of different study designs.

Systematic reviews criteria drawn from the AMSTAR checklist (Shea 2007)

Diagnostic cross sectional studies
criteria drawn from the QUADAS checklist (Whiting 2003)

Randomized controlled trials
criteria suggested by the Cochrane Handbook (Higgins 2009)

Case control studies and cohort studies
criteria drawn from the New Castle-Ottawa checklist[1]

Case series: no standardized checklist has been published for the assessment of methodological quality of case series; the following two criteria have been used: prospective vs retrospective recruitment; consecutive recruitment

Data collection and analysis

One review author assessed all abstracts of potentially relevant articles against the study inclusion criteria, analyzed all articles acquired in full text and assessed methodological quality for risk of bias addressing selection bias and blind interpretation of results of index and verification tests.

Data were extracted related to study design, study population, intervention, comparator, reference standard and outcomes, and pre-test probabilities were calculated. Data extracted are reported in single study tables of evidence and summarized in synoptic tables (*Appendix 2*).

Data synthesis

The following data were extracted from the included studies and provided to the panel:

- median of the pre-test probability to have the initial diagnosis modified (for example to have distant metastasis) or to be in a specific clinical situation (for example histopathologic response to chemotherapy);
- estimates of diagnostic accuracy (sensitivity and specificity) of FDG-PET and comparator.

[1] http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

When available from meta-analyses, diagnostic accuracy pooled estimates and clinical outcomes pooled estimates were reported.

When no pooled estimates were given, the median values with ranges were calculated and test for heterogeneity was carried out with the Cochran's chi square heterogeneity test (Meta-Disc Version 1.4). When heterogeneity was found ($p<0.1$), only the range of estimates (minimum and maximum values) were given.

With systematic reviews/meta-analyses and primary studies available, if patients included in primary studies published after systematic reviews or meta-analyses added up to a number smaller than the patients included in the systematic reviews/meta-analyses, results from primary studies were analyzed only for consistency.

With systematic reviews/meta-analyses and primary studies available, if patients included in primary studies published after systematic reviews/meta-analyses added up to a number greater than the patients included in the systematic reviews/meta-analyses, estimates of all studies have been pooled and re-calculated and heterogeneity of diagnostic estimates of FDG-PET tested.

2.3. Level of evidence

Randomized controlled trials, cross sectional or cohort studies in patients with diagnostic uncertainty and direct comparison of test results with an appropriate reference standard were considered of high quality, but their quality was downgraded if any of the following situations occurred (Guyatt 2008):

- study limitations (retrospective or non consecutive recruitment of patients, selection and spectrum bias, verification bias, lack of concealment, large losses to follow up, lack of blinding in results reading for index and reference test);
- inconsistency of results (heterogeneity or variability in results; unexplained inconsistency in sensitivity, specificity);
- indirectness of results (if important differences exist between the population included in the studies and the population of interest, or between the chosen comparator and routine practice testing);
- imprecision of results (if results come from sparse data, i.e. from few studies - less than two studies - or an overall small number of patients - less than 200).

Although we used the GRADE criteria for assessing quality of studies, we did not adopt its scale for rating quality of evidence, but opted for the following classification of levels of evidence:

high	no risk of bias or important study limitations, consistent results from several studies and a large number of patients
moderate	some study limitations, possible risk of bias, consistent results from several studies and a large number of patients

low	presence of bias, inconsistency and heterogeneity of results for one estimate of diagnostic accuracy (either sensitivity or specificity), results coming from several studies and a large number of patients
very low	presence of bias, sparse data or inconsistency and heterogeneity of results for both estimates of diagnostic accuracy (sensitivity and specificity).

2.4. Voting process

The panel met twice to discuss and vote on the use of FDG-PET in lung cancer. Each member of the panel, except for the methodologists, voted each clinical question individually. When voting the level of appropriateness, panelists were asked to take into consideration:

- the role of FDG-PET in the diagnostic-therapeutic pathway of patients;
- the change in management brought in by the introduction of FDG-PET and the effectiveness of the therapeutic approach following FDG-PET results;
- the proportion of patients who would have the initial diagnosis changed by FDG-PET;
- the level of evidence for the diagnostic accuracy of FDG-PET;
- the impact on clinical outcomes resulting from the therapeutic course of action determined by FDG-PET results;
- the balance between benefits and risks resulting from acting on FDG-PET results.

Voting forms

For each clinical question panelists were presented with a voting form (*Appendix 1*) containing the following background information:

- clinical rationale in support of the use of FDG-PET;
- clinical effectiveness of therapeutic approach resulting from test results;
- suggested role of FDG-PET in diagnostic pathway;
- pre-test probability as a surrogate for change in management or evidence from studies on change in management when available;
- estimates of diagnostic accuracy for FDG-PET and comparator;
- level of evidence;
- a matrix reporting presumed clinical outcomes for patients testing true and false positive or negative;
- estimates of impact on clinical outcomes - when available - and level of evidence.

All the above data and information were discussed and approved by the panel during the first meeting and before proceeding to the vote.

Each panelist voted the level of importance of the clinical outcomes, i.e. the importance for patients of the consequences from resulting true or false negative or true or false positive. Scores from 1 to 3 deemed the consequence and resulting outcomes as "not important", from 4 to 6 as "important" and from 7 to 9 as "critical".

When in presence of high, moderate or low level of evidence for diagnostic accuracy, a matrix of "natural frequencies" (Gigerenzer 2007) reporting absolute numbers for true and false positive and negative results per 100 patients was given, using the pre-test probability estimates as prevalence and the estimates of sensitivity and specificity obtained from the systematic review process.

After viewing all the above information, panelists were asked to place a vote on appropriateness (1 to 3 for "inappropriate", 4 to 6 for "uncertain" and 7 to 9 for "appropriate").

Voting procedure

During the first round, panelists voted the importance of the clinical outcomes and, during the second round, median scores were presented to the panel.

Two rounds of votes were requested for the judgment of appropriateness and results were analyzed using the RAND/UCLA Appropriateness Method,[2] which allows to measure both the rating on appropriateness and the level of agreement or disagreement among the panelists' rating.

Results from the first round of voting were presented to the panel at the second meeting, which served the purpose to discuss disagreements and unresolved judgement.

At the end of the two rounds of votes the use of FDG-PET for a specific clinical indication was judged as appropriate when, after discarding one extreme high and one extreme low rating, all remaining ratings fell within the 7-9 score region. The use of FDG-PET was judged as inappropriate when, after discarding one extreme high and one extreme low rating, all remaining ratings fell within the 1-3 score region. Finally the use of FDG-PET was judged as uncertain when, after discarding one extreme high and one extreme low rating, all remaining ratings fell within the 4-6 score region or when no agreement was reached after the second round of voting.

Results from the voting rounds are reported for each clinical question addressed by the panels.

2.5. Definition of criteria of appropriateness

To assign a level of appropriateness to the use of FDG-PET, the working group agreed on the following definitions of appropriate, uncertain and inappropriate use. A fourth category (indeterminate) was added to take into account clinical indications considered relevant by the panel, but for which no research results are available.

2 http://www.rand.org/pubs/monograph_reports/MR1269.html

APPROPRIATE

Clinical indications for which there is a rationale for change in management related to a patient-important clinical outcome, there is a high or moderate level of evidence for good diagnostic accuracy of PET and the presumed benefit - resulting from the test results - is greater than the presumed harm.

UNCERTAIN

Clinical indications for which there is a rationale for change in management related to a patient-important clinical outcome, but there is a low or very low level of evidence for diagnostic accuracy of FDG-PET and balance between harms and benefit is unclear.

INAPPROPRIATE

- Clinical indications for which there is NO rationale for change in management related to a patient-important clinical outcome

or

- Clinical indications for which there is a rationale for change in management related to a patient-important clinical outcome, there is a high or moderate level of evidence on poor diagnostic accuracy of FDG-PET and/or the presumed harm - resulting from the test results - is greater than the presumed benefit.

INDETERMINATE

Clinical indications for which there is a rationale for change in management related to a patient-important clinical outcome, but there are no data on diagnostic accuracy of FDG-PET.

Clinical indications for which the panel does not reach an agreement on level of appropriateness after two rounds of voting also fall in the UNCERTAIN category.

3. Systematic review of literature

3.1. Overall results

Full methods and results of the systematic review of literature are reported in Appendix 2.

The initial search identified 2 079 records; 1 917 were excluded as they did not meet the inclusion criteria or were duplicates. Full text was acquired for the remaining potentially eligible 162 records, from which 48 studies were excluded on the basis of inclusion criteria. One hundred and fourteen studies were finally included.

The study selection process is summarized in the PRISMA flow diagram (Moher 2009; see *Figure 1* in *Appendix 2*), while Tables 3.1 and 3.2 report number and type of studies for each clinical question and endpoint, as well as results of previous 2007 report (Liberati 2007 - *Dossier 157*).

All retrieved studies evaluated diagnostic accuracy of FDG-PET, and no studies evaluating the impact of FDG-PET on clinical outcomes were found.

Table 3.1. Number of included studies for questions and endpoints

Clinical question / Endpoint	Diagnosis of SPN	Staging (including BAC)	Curative intent RT field definition	Early response to therapy (during treatment)	Response to therapy (end of treatment)	Follow up	Detection and re-staging of suspected recurrence
Diagnostic accuracy	System. reviews: 2 Primary studies: 34	System. reviews: 3 Primary studies: 48	System. reviews: 1 Primary studies: 13	System. reviews: 2 Primary studies: 1	System. reviews: 2 Primary studies: 3	System. reviews: 0 Primary studies: 1	System. reviews: 0 Primary studies: 3
Impact on clinical outcomes	System. reviews: 0 Primary studies: 0	System. reviews: 0 Primary studies: 0	System. reviews: 0 Primary studies: 0	System. reviews: 0 Primary studies: 0	System. reviews: 0 Primary studies: 0	System. reviews: 0 Primary studies: 0	System. reviews: 0 Primary studies: 0
Dossier 157/2007 (Liberati 2007)	Appropriate	Appropriate	Appropriate	Not considered	Uncertain B	Not considered	Appropriate

Table 3.2. SCLC - Number of included studies for questions and endpoints

Clinical question / Endpoint	Staging	Curative intent RT field definition	Early response to therapy (during treatment)	Response to therapy (end of treatment)	Follow up	Detection and re-staging of suspected recurrence
Diagnostic accuracy	Systematic reviews: 1 Primary studies: 1	Systematic reviews: 0 Primary studies: 1	Systematic reviews: 0 Primary studies: 1	Systematic reviews: 0 Primary studies: 1	Systematic reviews: 0 Primary studies: 0	Systematic reviews: 0 Primary studies: 0
Impact on clinical outcomes	Systematic reviews: 0 Primary studies: 0	Systematic reviews: 0 Primary studies: 0	Systematic reviews: 0 Primary studies: 0	Systematic reviews: 0 Primary studies: 0	Systematic reviews: 0 Primary studies: 0	Systematic reviews: 0 Primary studies: 0
Dossier 157/2007 (Liberati 2007)	Uncertain A	Not considered	Not considered	Uncertain A	Not considered	Not considered

4. Characterization of solitary pulmonary nodules ≥1 cm

Rationale

Solitary pulmonary nodules (SPNs) are defined as lesions up to 3 cm in size. Because of the widespread use of CT in the investigation of respiratory symptoms, the SPN is a frequent incidental finding. The prevalence of SPNs in lung cancer screening studies ranges between 8% to 51% and the prevalence of malignancy in patients with SPNs between 1.1% to 12% (Wahidi 2007). The prevalence of malignancy in SPNs increases in proportion with size (from 0-1% for nodules <5 mm to 64-82% for nodules >20 mm) and varies according to edge characteristics (20-30% smooth edge nodules; 33-100% nodules with irregular, lobulated, or spiculated borders) and morphology (7-9% solid nodules; 59-73% pure ground-glass opacities) (Wahidi 2007). Recent guidelines recommend use of FDG-PET as an add on test for patients with solitary pulmonary nodules (AIOM 2009; SIGN 2005; NICE 2005).

Diagnostic role of FDG-PET

FDG-PET is a candidate test to characterize SPNs identified by CT.

Treatment effectiveness

Surgery is the cornerstone of early stage non-small cell lung cancer treatment. Five-year survival of stage I patients is over 50% (73% in stage IA, 58% in stage IB), with much room for improvement with systemic adjuvant approaches in stages II and III (ESMO 2010a).

Pre-test probability and change in management

The median pre-test probability of malignancy of solitary pulmonary nodule is 64.7% (range 27.2-86.0%) from FDG-PET studies included in Cronin 2008a and from following primary studies: Alkhawaldeh 2010; Baram 2008; Bryant 2006; Chang 2010; Christensen 2006; Chun 2009; Degirmenci 2008; Ferran 2006; Fletcher 2008; Grgic 2010; Hashimoto 2006; Hau 2008; Hsieh 2008; Huang 2010; Jeong 2008; Kagna 2009; Kaira 2009; Khalaf 2008; Kim 2007; Kim 2008; Kim 2009; Lu 2007; Mori 2008; Nunez 2007; Ohba 2009a; Ohba 2009b; Ohno 2008a; Pauls 2008; Suga 2009; Tian 2008; Tsunezuka 2007; Tsushima 2008; Yamamoto 2008a; Yi 2006.

Research question: FDG-PET as add on

Has FDG-PET sufficient accuracy for characterizing malignant SPN?

4.1. Systematic review of literature: results

Results from update of systematic review of literature from January 2006

Only studies on diagnostic accuracy were retrieved.

Systematic reviews

Two systematic reviews have been retrieved (Cronin 2008a, 2008b; Ung 2007); both assessed the diagnostic accuracy of FDG-PET for the diagnosis of malignancy in patients with solitary pulmonary nodule. The methodological quality was judged as high for Cronin 2008a, 2008b and low for Ung 2007 (*Table 4.1*). Eighteen out of 20 studies from Cronin 2008a, 2008b (2 studies without available data) included patients with nodules greater than 5 mm. The systematic review by Cronin (2008a, 2008b) reported problems in the verification test in 13 out of 22 studies and problems in blinding of interpretation of test results in 12 out of 22 studies.

Table 4.1. Results from systematic reviews on diagnosis of SPN with FDG-PET

Reference	Cronin 2008a, 2008b	Ung 2007
Update to	December 2005	June 2006
Number of studies	22 primary studies	2 systematic reviews and 7 primary studies
Number of patients	2 867 CT: 1 093 MRI: 284 TC-99M- depreotide SPECT: 421 FDG-PET: 1 069 (912 with available data; median 37, range 13-116)	SPN: 1 909 patients from one review (in the other review the number of patients is not reported) 497 patients from 6 prospective studies (in 1 study the number of patients is not reported)
FDG-PET	sensitivity: pooled 95% (95% CI 93-98%); statistical heterogeneity specificity: pooled 82% (95% CI 77-88%); statistical heterogeneity	Pooled estimates were not calculated: only descriptive results Primary studies sensitivity: range 79-100% specificity: range 40-90% Systematic reviews sensitivity: pooled 96% (SE = 1%) median 97% specificity: pooled 78% (SE = 3%) median 78%
Comparator	Dynamic contrast-enhanced CT: sensitivity: pooled 93% (95% CI 88-97%) statistical heterogeneity specificity: pooled 76% (95% CI 68-97%) statistical heterogeneity Dynamic contrast-enhanced MRI sensitivity: pooled 94% (95% CI 91-97%) statistical heterogeneity specificity: pooled 79% (95% CI 73-86%) statistical heterogeneity TC-99M- depreotide SPECT sensitivity: pooled 95% (95% CI 93-97%) statistical heterogeneity specificity: pooled 82% (95% CI 77-88%) statistical heterogeneity	Gamma Camera FDG-PET sensitivity: mean 92% (SE = 4%) specificity: mean 86% (SE = 4%)
Reference standard	histopathology (percutaneous or surgical biopsy, surgical resection) for more than 50% of patients	histology followed by CT or additional imaging, follow up biopsy

Primary studies

Thirty-four studies evaluating diagnostic accuracy of FDG-PET for the diagnosis of malignancy in patients with SPN published after the above reported SRs were included (*Table 4.2*).

Twenty-one studies reported on FDG-PET/CT and 13 FDG-PET. Twenty-seven studies included patients with any kind of indeterminate SPN and 7 studies included patients selected for size, morphology or other features of SPN (2 SPN smaller than 2 cm, 2 SPN with non-solid components/ground glass opacity, 2 SUV max lower than 2.5, 1 with a priori positive FDG-PET). Nine studies tested also one or two comparators (6 CT, 2 MRI, 1 TC-99M- depreotide SPECT). The reference standard applied was histopathology in all studies, with any kind of follow up (ranging from 6 months up to three years) in 23 studies. The median pre-test probability of malignancy was 57.1% (range 27.2-86.1%); in the group of studies with patients with any kind of SPN it was 66.4% (range 27.2-86.1%); in the group of studies with selected patients it was 48.1% (range 29.1-55.3%).

As the number of patient included in studies published after the systematic review added up to a smaller number than that of patients included in the systematic reviews and results of primary studies were consistent with those of the systematic reviews, the latter's pooled estimates for patients with SPN were chosen (Cronin 2008a, 2008b).

Table 4.2. Results from primary studies on diagnosis of SPN with FDG-PET

References	Alkhawaldeh 2010; Baram 2008; Bryant 2006; Chang 2010; Christensen 2006; Chun 2009; Degirmenci 2008; Ferran 2006; Fletcher 2008; Grgic 2010; Hashimoto 2006; Hau 2008; Hsieh 2008; Huang 2010; Jeong 2008; Kagna 2009; Kaira 2009; Khalaf 2008; Kim 2007; Kim 2008; Kim 2009; Lu 2007; Mori 2008; Nunez 2007; Ohba 2009a; Ohba 2009b; Ohno 2008a; Pauls 2008; Suga 2009; Tian 2008; Tsunezuka 2007; Tsushima 2008; Yamamoto 2008a; Yi 2006
Number of studies	34
Number of patients	4 222 (median 102, range 15-585) 3 873 (studies with any kind of SPN) 549 (studies with selected patients)
FDG-PET/PET-CT	All studies sensitivity: median 90.7% (range 46.1-100%) specificity: median 76% (range 17-93%) Studies with any kind of SPN sensitivity: median 91.7% (range 50-100%) specificity: median 76% (range 17-88%) Studies with selected patients sensitivity: median 78% (range 46.1-100%) specificity: median 74.6% (range 63-93%)
Comparator	CT (6 studies, 663 patients, all types of SPN) sensitivity: median 90.6% (range 81-100%) specificity: median 50.8% (range 29-93%) DW MRI (2 studies, 214 patients, with any kind of SPN) sensitivity range 70-73% specificity range 96-97% TC-99M- depreotide SPECT (1 study, 29 patients, with any kind of SPN) sensitivity 85% specificity 88%
Reference standard	histopathology with or without follow up

Comments of ASSR reviewers

A remarkable number of patients has been studied to assess the diagnostic accuracy of FDG-PET - and other diagnostic tools - in detecting malignant SNP. All diagnostic tools have similar high sensitivity and lower specificity, but a great variability in the estimates is noticed. This heterogeneity can be explained by the different populations studied (source and criteria of inclusion of patients, i.e. with a different spectrum of SPNs included).

Diagnostic accuracy estimates

FDG-PET sensitivity: pooled 95% (95% CI 93-98%)
FDG-PET specificity: pooled 82% (95% CI 77-88%)

Comparator:

Dynamic contrast-enhanced CT:	sensitivity: pooled 93% (95% CI 88-97%)
	specificity: pooled 76% (95% CI 68-97%)
Dynamic contrast-enhanced MRI:	sensitivity: pooled 94% (95% CI 91-97%)
	specificity: pooled 79% (95% CI 73-86%)

LEVEL OF EVIDENCE: MODERATE

4.2. Clinical outcomes

To evaluate the balance between benefits and risks, the panel agreed to consider the presumed patient-important outcomes reported below (*Table 4.3*), and voted on the level of importance.

All the outcomes achieved scores which placed them in the "critical" category but no studies investigating the impact of FDG-PET on the above clinical outcomes were found.

The following matrix of "natural frequencies" was provided (*Table 4.4*).

Table 4.3. Patient-important clinical outcomes and median scores of importance

Patient-important outcomes	Median score (range)
Consequences of test for patients with malignant SPN	
• True positives - patients correctly diagnosed for malignancy, proceed to curative surgery, in order to improve survival	8 (6-9)
• False negatives - patients incorrectly diagnosed as not having cancer, delay diagnosis and curative surgery, with possible impact on survival	7 (7-9)
Consequences of test for patients with non malignant SPN	
• True negatives - patients correctly diagnosed as not having cancer end clinical investigation pathway	7 (6-8)
• False positives - patients incorrectly diagnosed for malignancy proceed to unnecessary surgical intervention, with possible serious harm	8 (6-9)

Table 4.4. "Natural frequencies" of patients assessed for SPN malignancy

		N of patients out of 100 submitted to the exam (pre-test probability range: 27.2-86%)	
		According to FDG-PET	**According to multirow CT**
Patients with malignant SPN	True positives	26 - 82	25 - 80
	False negatives	1 - 4	2 -6
Patients with non malignant SPN	True negatives	60 -11	55 -11
	False positives	13 - 3	18 -3
		100	100

4.3. Voting results

During the first voting round the panel unanimously agreed to judge the use of FDG-PET in this indication as appropriate (median score 8, range 7-9).

FINAL RATING FOR THE USE OF FDG-PET FOR CHARACTERIZATION OF SPN:

APPROPRIATE

4.4. Conclusions

The panel agreed during the first voting round that the use of FDG-PET to characterize SPNs identified by CT is appropriate. There is in fact a large body of evidence supporting this indication and the level of evidence has been judged moderate, with FDG-PET showing a slightly better specificity than comparators (dynamic contrast-enhanced CT and dynamic contrast-enhanced MRI). All the clinical outcomes were judged critical by the panelists.

5. Staging of patients with non-small cell lung cancer - NSCLC

Rationale

Staging is the assessment of the extent of disease and is performed for prognostic and therapeutic purposes. The selection of patients for radical treatment (surgery, radical chemotherapy/radiotherapy) requires an investigation pathway directed towards as much diagnostic and staging information as possible (SIGN 2005; BTS 2010). CT is the initial imaging modality of choice for diagnosis and staging of lung cancer, and serves as a tool for triage that determines the most appropriate further investigation. Involvement of the mediastinal lymph nodes and metastatic disease should be thoroughly investigated and evaluated, before excluding patients from radical treatment. Recent guidelines recommend use of FDG-PET as an add on test for patients with negative or unclear results (BTS 2010; ESMO 2010a; SIGN 2005; NICE 2005).

Diagnostic role of FDG-PET

To further investigate patients with negative or unclear results for mediastinal lymph node involvement or metastatic disease, in order to either direct patients to confirmatory biopsies of lesions or to radical treatment.

Treatment effectiveness

Surgery is the most recommended treatment for early stage NSCLC (AIOM 2009; BTS 2010; ACCP 2007) and five-year survival of stage I patients is over 50% (73% in stage IA, 58% in stage IB), with much room for improvement with systemic adjuvant approaches in stages II and III (ESMO 2010a). In patients with unresectable stage III or stage IV disease chemotherapy and/or following or concurrent radiotherapy is the standard of care.

Pre-test probability and change in management

The median pre-test probability of mediastinal lymph node metastases is 33.5% (range 15-78%; data from Ung 2007), while the median pre-test probability of distant metastasis, extracted from only one study, is resulted to be 6% (Ung 2007).

One RCT - cited in Ung 2007 - found that addition of FDG-PET to conventional workup led to a 20% absolute reduction in futile thoracotomies. This results was not confirmed by other two RCTs which found no reduction (Ung 2007).

Research question: FDG-PET as add on

Has FDG-PET sufficient sensitivity and specificity to identify mediastinal lymph nodes involvement or distant metastasis in patients with negative or unclear conventional imaging results?

5.1. Systematic review of literature: results

Results from update of systematic review of literature from Januray 2006

Only studies assessing the diagnostic accuracy of FDG-PET were identified.

Systematic reviews

Three systematic reviews were identified (Alongi 2006; Schimmer 2006; Ung 2007). All assessed the diagnostic accuracy of FDG-PET for mediastinal staging in patient (*Table 5.1*). One review reported the diagnostic accuracy of FDG-PET for distant metastases staging (Ung 2007) (*Table 5.2*). The methodological quality was judged as moderate for Alongi 2006 and very low for Schimmer 2006 and Ung 2007.

Table 5.1. Results from systematic reviews on mediastinal lymph node staging with FDG-PET

Reference	Alongi 2006	Schimmer 2006	Ung 2007
Update to	December 2005	2005	2005
Number of studies	13	28 studies (3 systematic reviews and 25 primary studies)	3 systematic reviews and 22 prospective observational studies
Number of patients	674	reported only for single studies	reported only for single studies
FDG-PET	sensitivity: 83% (95% CI 75-91%) specificity: pooled 87% (95% CI 80-95%)	descriptive results "FDG-PET in clinical staging can prevent unnecessary invasive procedures in a significant number of cases"	descriptive results of previous systematic reviews (the most recent Gould 2003 - cited in Dossier 157)
Comparator	CT sensitivity: pooled 68% (95% CI 58-79%) specificity: 76% (95% CI 67-86%)	mediastinoscopy (4 studies) descriptive results "In patients with positive FDG-PET scan mediastinoscopy still remains the definitive method for exact lymph node staging"	not reported
Reference standard	histology by axillary lymph node dissection or biopsy	not reported	not reported

Table 5.2. Results from systematic reviews on staging for distant metastases with FDG-PET

Reference	Ung 2007
Update to	1996-2005
Number of studies	2 systematic reviews
Number of patients	not reported
FDG-PET	results from one systematic review (published in 2005)* sensitivity: pooled 93% specificity: pooled 96%
Comparator	not reported
Reference standard	not reported
Notes	* not known if brain metastasis were considered

Primary studies

Thirty-six studies (3 826 patients) evaluating diagnostic accuracy of FDG-PET for mediastinal lymph node staging published after the above reported SRs were included (Al Sarraf 2008a; Al Sarraf 2008b; An 2008; Bernasconi 2006; Bille 2009; Carnochan 2009; Cerfolio 2007a; Chen 2010; Craanen 2007; De Wever 2007b; Hellwig 2007; Jeon 2010; Kaira 2007; Kasai 2010; Kelly 2006; Kim 2006; Lee 2007; Lee 2008; Liu 2009; Melek 2008; Nambu 2010; Nishiyama 2008; Nomori 2008; Nosotti 2008; Perigaud 2009; Plathow 2008; Quaia 2008; Rodriguez Fernandez 2007; Sanli 2009; Shinya 2009; Tournoy 2007; Ventura 2010; Yamamoto 2008b; Yang 2008; Yang 2010; Yi 2007). Diagnostic accuracy estimates from the primary studies have been assessed just for consistency with estimates of systematic reviews and a median sensitivity of 77% (range 25-100%) and a median specificity of 89% (range 18-100%) were calculated. Both estimates fall within the confidence intervals pooled from systematic reviews.

Thirteen studies (3 402 patients) evaluating diagnostic accuracy of FDG-PET in the distant metastases staging published after the above reported systematic reviews were included (Chen 2010; De Wever 2007a; De Wever 2007b; Kelly 2006; Lee 2009; Liu 2010; Min 2009; Nosotti 2008; Ohno 2007; Ohno 2008b; Song 2008; Takenaka 2009; Yi 2007). Seven of them studied all types of distant metastases (2 studies also brain metastases) and 5 of them bone metastases. Diagnostic accuracy estimates have been compared only for consistency with results of systematic reviews and a median sensitivity of 94% (range 48-100%) and a median specificity of 98% (range 74-100%) were calculated.

Diagnostic estimates from Alongi 2006 systematic review for mediastinal lymph node staging and from Ung 2007 for distant metastases staging were chosen (*Table 5.3*).

Table 5.3. Diagnostic accuracy of FDG-PET for mediastinal lymph node staging and for distant metastases staging

Diagnostic accuracy	mediastinal lymph node staging	distant metastases staging
FDG-PET	sensitivity: pooled 83% (95% CI 75-91%) specificity: pooled 87% (95% CI 80-95%)	sensitivity: pooled 93% specificity: pooled 96%
Comparator	CT sensitivity: 68% (95% CI 58-79%) specificity: 76% (95% CI 67-86%)	none
References	Alongi 2006	Ung 2007

Comments of ASSR reviewer

A large number of patients has been studied to assess the diagnostic accuracy of FDG-PET in the staging of patients with NSCLC. Systematic reviews and the more recent primary studies report consistent high estimates for sensitivity and specificity both for mediastinal lymph node metastases and distant metastases. For mediastinal lymph node staging FDG-PET shows better diagnostic accuracy estimates than CT.

Diagnostic accuracy estimates

Mediastinal lymph node staging

FDG-PET sensitivity: (pooled) 83%
FDG-PET specificity: (pooled) 87%

CT sensitivity: (pooled) 68%
CT specificity: (pooled) 76%

Distant metastases staging

FDG-PET sensitivity: (pooled) 93%
FDG-PET specificity: (pooled) 96%

LEVEL OF EVIDENCE: MODERATE

5.2. Clinical outcomes

To evaluate the balance between benefits and risks, the panel agreed to consider the presumed patient-important outcomes reported below (*Table 5.4*), and voted on the level of importance.

All but one clinical outcomes were rated critical with the highest score assigned to the risk of undergoing a futile surgery in patients resulting false negatives for mediastinal involvement or distant metastases. Being correctly diagnosed for mediastinal involvement or distant metastasis and undergoing a confirmatory biopsy was scored "important".

No evidence on the impact of FDG-PET on such important clinical outcomes was identified.

The following matrix of "natural frequencies" for mediastinal involvement was provided (*Table 5.5*).

Table 5.4. Patient-important clinical outcomes and median scores of importance

Patient-important outcomes	**Median score (range)**
Consequences of test for patients with mediastinal lymph nodes involvement or with distant metastasis	
• True positives - patients correctly diagnosed for mediastinal involvement or distant metastasis, proceed to confirmatory biopsy in order to establish best therapeutic plan	6 (4-9)
• False negatives - patients incorrectly diagnosed as not having mediastinal involvement or distant metastasis proceed to, possibly futile, radical surgery	8 (7-9)
Consequences of test for patients with no mediastinal lymph nodes involvement or distant metastasis	
• True negatives - patients correctly diagnosed as not having mediastinal involvement or distant metastasis proceed to curative radical surgery	7 (5-9)
• False positives - patients incorrectly diagnosed as having mediastinal involvement or distant metastasis proceed to confirmatory biopsy	7 (3-9)

Table 5.5. "Natural frequencies" for mediastinal involvement

		N of patients out of 100 submitted to the exam	
		According to FDG-PET	**According to multirow CT**
Patients with mediastinal involvement	True positives	28	23
	False negatives	6	11
Patients with non malignant SPN	True negatives	57	50
	False positives	9	16
		100	100

5.3. Voting results

During the first voting round the panel unanimously judged the use of FDG-PET in this indication appropriate (median score 7, range 7-8).

FINAL RATING FOR THE USE OF FDG-PET FOR STAGING OF PRIMARY NSCLC:

APPROPRIATE

5.4. Conclusions

The panel agreed at the first voting round that the use of FDG-PET as an add on test in NSCLC staging is appropriate. The level of evidence supporting this indication is moderate with FDG-PET performing well in identifying mediastinal involvement or distant metastases missed by CT. While avoiding unnecessary surgery (consequences for true positives) has been considered important, undergoing futile surgery (consequences for false negatives) or not undergoing a potentially curative radical surgery (consequences for false positives) have been considered critical outcomes with median scores of 8 and 7 respectively, confirming the need for thorough and accurate pre-treatment staging.

6. Staging of patients with bronchioloalveolar cancer - BAC

Rationale

Bronchioloalveolar carcinoma (BAC) has been recently reclassified as essentially adenocarcinoma-in-situ. True BAC is diagnosed with a complete resection, allowing full lesion examination to rule out extended disease. Pre-operative diagnosis is based on appropriate radiology (pure localized "ground glass" lesions) and in some cases consistent pathology (BTS 2010). Recent guidelines warn against the high rate of false negative findings of malignancy on FDG-PET scans for patients with known or suspected lung cancer (ACCP 2007).

Diagnostic role of FDG-PET

The panel unanimously agreed that there is no diagnostic role of FDG-PET in the staging of patients with BAC.

Treatment effectiveness

Surgery represents the standard treatment in early stage disease. Patients with resected BAC have prolonged survival and a lower recurrence rate after surgical resection than those with other subtypes of NSCLC (ACCP 2007).

6.1. Systematic review of literature: results

Results from update of systematic review of literature from January 2006

Only studies on diagnostic accuracy were identified and retrieved.

Systematic reviews

No systematic reviews have been identified.

Primary studies

No primary study was found on staging of BAC. Two primary studies have been retrieved (Balogova 2010; Sun 2009) assessing the accuracy of FDG-PET/CT in differentiating BAC from other histological NSCLC subtypes. These studies aimed at evaluating the role of PET for diagnosis, rather than staging, BAC.

Comments of ASSR reviewer

No primary study was found on staging of BAC. Only two primary studies have been retrieved assessing the role of PET for diagnosis.

Diagnostic accuracy estimates

Unavailable for staging due to absence of data. Unavailable for diagnosis due to sparse data.

LEVEL OF EVIDENCE: VERY LOW

6.2. Clinical outcomes

As the panel agreed on absence of diagnostic role of FDG-PET in staging of patients with BAC, no patient-important outcomes have been proposed and voted.

6.3. Voting results

Due to the lack of diagnostic role of FDG-PET the panel agreed not to follow the full voting procedure and unanimously agreed to judge the use of FDG-PET in this clinical indication as inappropriate.

FINAL RATING FOR THE USE OF FDG-PET FOR BAC STAGING: INAPPROPRIATE

6.4. Conclusions

Two studies have assessed the role of PET/CT in differentiating BAC from other NSCLC subtypes and no study was found on staging of BAC. The panel established that there is no diagnostic role of FDG-PET in staging of patients with BAC and unanimously agreed to judge its use as inappropriate.

7. Staging of patients with small cell lung cancer - SCLC

Rationale

The role of surgery for the treatment of SCLC is considered inappropriate due to poor overall survival. In general patients should be treated with a combination of chemotherapy and radiotherapy (BTS 2010). Pre-treatment staging is necessary to differentiate between limited disease - eligible for concurrent chemotherapy and radiotherapy - and extended disease, generally treated with chemotherapy alone (BTS 2010; ESMO 2010).

Diagnostic role of FDG-PET

To further investigate patients with negative or unclear results for metastatic disease, to decide on therapeutic approach (chemotherapy or combined chemo/radiotherapy).

Treatment effectiveness

Clinical trials have reported better 5 year-survival rate (between 20 and 25%) in patients randomized to concurrent chemo-radiotherapy compared to patients treated with sequential chemo-radiotherapy (BTS 2010; ESMO 2010).

The prognosis for extensive disease is poor with a median survival of 10 months and a 2-year survival rate of 10%. Long term survivors are extremely rare (ESMO 2010).

Pre-test probability and change in management

Pre-test probability of limited disease is 33% (Fischer 2007).

Research question: FDG-PET as add on

Has FDG-PET sufficient sensitivity and specificity to identify distant metastasis in patients with negative or unclear conventional imaging results?

7.1. Systematic review of literature: results

Results from update of systematic review of literature from January 2006

Only studies assessing FDG-PET accuracy were retrieved.

Systematic reviews

One systematic review (*Table 7.1*) was retrieved (Samson 2007). The review assessed different aspects on SCLC management and included six studies (277 patients) assessing the role of FDG-PET in SCLC staging (primarily to differentiate limited from extensive disease).

Table 7.1. Results from systematic reviews on diagnosis of SCLC with FDG-PET

Reference	Samson 2007
Update to	March 2005
Number of studies	6
Number of patients	277
FDG-PET	Descriptive data only "Six studies suggest that, except for brain metastases, PET added to conventional staging is more sensitive in detecting disease. However, there is so much uncertainty about the execution and interpretation of the reference standard in all of these studies that confidence is quite low in estimates of diagnostic and staging accuracy. The frequency of incorrect changes in stage attributable to PET is unknown because of incomplete reporting".

Primary studies

One study (*Table 7.2*) evaluating FDG-PET accuracy for pre-treatment staging of patients with SCLC was retrieved and analyzed (Fischer 2007). It is a prospective study comparing concordance between FDG-PET, FDG-PET/CT and standard staging. The study is biased by partial verification.

Table 7.2. Primary study on diagnostic accuracy of FDG-PET in the staging of SCLC

Reference	Fischer 2007
Number of patients	29
FDG-PET/PET-CT	FDG-PET sensitivity: 93% specificity: 83% FDG-PET/CT sensitivity: 93% specificity: 100%
Comparator	standard staging (CT, bone scintigraphy + bone biopsy) sensitivity: 79% specificity: 100%
Reference standard	histology and follow up

Comments of ASSR reviewer

The studies suggest that, except for brain metastases, FDG-PET added to conventional imaging is more sensitive in detecting disease. However, the quality of studies is low and there is a consistent uncertainty about execution and interpretation of the reference standard; for this reason confidence in estimates of diagnostic and staging accuracy is very low.

Diagnostic accuracy estimates

Not available due to sparse data.

LEVEL OF EVIDENCE: VERY LOW

7.2. Clinical outcomes

To evaluate the balance between benefits and risks, the panel agreed to consider the presumed patient-important outcomes reported below (*Table 7.3*), and voted on the level of importance.

Table 7.3. Patient-important clinical outcomes and median scores of importance

Patient-important outcomes	Median score (range)
Consequences of test for patients with extended disease - SCLC	
• True positives - patients correctly diagnosed for extended disease proceed to palliative systemic treatment	3 (1-8)
• False negatives - patients incorrectly diagnosed for limited disease undergo combined chemotherapy and concurrent radiotherapy, with no gain on survival	4 (3-6)
Consequences of test for patients with limited disease - SCLC	
• True negatives - patients correctly diagnosed for limited disease proceed to combined chemotherapy and concurrent radiotherapy, to improve their survival	4 (2-8)
• False positives - patients incorrectly diagnosed for extended disease do not receive combined chemo-radiotherapy with possible loss in survival	3 (2-5)

All patient-important outcomes received quite low median scores, probably due to the limited gain offered by one therapeutic option compared to the other. The panel considered the situation of being (truly or falsely) negative at FDG-PET examination and receiving combined chemo-therapy as important for patients, whilst judged not important the condition of resulting (truly or falsely) positive and being treated only with chemotherapy.

Because of the scarcity of data, a matrix of "natural frequencies" of distant metastases has not been provided.

7.3. Voting results

During both first and second round of voting, the panel did not reach an agreement on the appropriateness of FDG-PET in SCLC staging with votes falling between the inappropriate and uncertain regions (first round median score 3, range 2-4; second round: median score 4, range 3-6). The use of FDG-PET in staging SCLC resulted uncertain due to disagreement.

FINAL RATING FOR THE USE OF FDG-PET FOR STAGING OF SCLC: UNCERTAIN

7.4. Conclusions

The available data on FDG-PET accuracy in discriminating limited from extended SCLC are sparse and the level of evidence was considered very low. The limited difference in gain offered by the therapeutic options available led the panel to give low scores for clinical outcomes: consequences for true and false positive treated with just chemotherapy were voted not important (median score 3), while consequences for true and false negative receiving combined chemo/radiotherapy were voted important (median score 4). Both voting rounds on appropriateness registered a disagreement among panelists with ratings falling in both the inappropriate and uncertain regions. The use of FDG-PET in staging SCLC resulted therefore uncertain due to disagreement.

8. Target volume definition of curative radiation treatment in patients with lung cancer

Rationale

Radical radiation treatment is recommended for patients with unresectable NSCLC disease and concurrent chemo/radiation therapy is recommended for patients with limited SCLC.

Post-operative radiotherapy has no indication in patients with a negative resection margin (R0) whilst its role in patients with positive resection margin (R1) is still unknown (BTS 2010).

The main limitation of radiotherapy is related to radiation-induced lung toxicity. Knowledge of risk of radiotherapy is essential and a combination of parameters is generally used to guide the plan of radiation treatment (BTS 2010).

Diagnostic role of FDG-PET

FDG-PET imaging could be an additional parameter to be used when planning treatment delivery, in order to decrease risk of severe lung acute and late toxicity.

Treatment effectiveness

Three dimensional treatment planning is recommended for patients undergoing radical thoracic radiotherapy. There are evidence suggesting that radical radiotherapy in patients with NSCLC, when compared to radical surgery, performs well for overall survival, though not so well for loco-regional control and disease-free survival (ESMO 2010, SIGN 2005). Patients with limited SCLC disease are potentially curable and clinical trials have reported better 5 year-survival rate (between 20% and 25%) in patients randomized to concurrent chemo-radiotherapy compared to patients treated with sequential chemo-radiotherapy (BTS 2010, ESMO 2010).

Pre-test probability and change in management

Few available data show a trend in decrease of GTV.

Research question: FDG-PET in addition to CT

Does adding FDG-PET imaging improve the precision of target volume definition?

8.1. Systematic review of literature: results

Results from update of systematic review of literature from January 2006

Only data on diagnostic accuracy of FDG-PET were retrieved.

Systematic reviews

One systematic review assessing the role of FDG-PET in tumor volume definition in radiotherapy treatment planning in NSCLC was included (van Baardwijk 2006). Methodological quality was judged as low (*Table 8.1*).

Table 8.1. Results from systematic review on diagnostic accuracy of FDG-PET in the field definition of curative RT

Reference	van Baardwijk 2006
Update to	August 2005
Number of studies	8
Number of patients	304
Results	Descriptive data only "Mostly a decrease in target volume was noticed, with a change of about 20-25%, when adding PET information for radiotherapy planning. Main causes for increase in target volume are large primary tumors and inclusion of nodal disease. Major cause for decrease in target volume was the ability of PET to exclude atelectasis." In NSCLC, FDG-PET/CT has a high diagnostic accuracy for detecting mediastinal lymph nodes and adding FDG-PET information for radiation treatment planning will lead to modified plans. In a clinical study, it was shown that it was safe to only irradiate FDG-PET positive mediastinal lymph nodes. 1 study: a significant lower average maximum dose for the spinal cord was found for the FDG-PET-CT plans compared to the CT plans.
Reference standard	histopathology of lymph nodes (1 study)
Notes	* GTV = gross target volume

Primary studies

Thirteen study (Boursot 2009; Ceresoli 2007; Devic 2010; Faria 2008; Grills 2007; Hanna 2010; Hong 2007; Lewandowska 2006; MacManus 2007; Nestle 2007; Spratt 2010; Videtic 2008; Yap 2010), not included in the SR by van Baardwijk 2006, were found (*Table 8.2*). Ten of them studied the change in the contouring of GTV for RT comparing FDG-PET results with CT results. The other three studies investigated other parameters of RT field definition (GTV Ratio, change in the nodal target, accuracy of registration of the CT components).

Only one simulation study evaluating FDG-PET radiation planning of mediastinal lymph nodes in patients with limited SCLC was found (Van Loon 2008), which studied FDG-PET and CT images of 21 patients. It is an exploratory phase I trial and no conclusions can be drawn.

Table 8.2. Results from primary studies on diagnostic accuracy of FDG-PET in the field definition of curative RT

Reference	Boursot 2009; Ceresoli 2007; Devic 2010; Faria 2008; Grills 2007; Hanna 2010; Hong 2007; Lewandowska 2006; MacManus 2007; Nestle 2007; Spratt 2010; Van Loon 2008; Videtic 2008; Yap 2010
Number of studies	14 (13 NSCLC; 1 SCLC)
Number of patients	355 NSCLC; median 20 (range 10-87) 21 SCLC
Results	The 10 studies dealing with change in the contouring of GTV show a trend in decrease of GTV, both in terms of percentage of patients with decrease of GTV and of mean reduction of GTV. Summary estimates cannot be provided due to the different parameters adopted by the studies. The only study evaluating radiation planning in SCLC patients reported change in 5 patients (resulting in both increase and decrease in the number of involved nodal areas), but no significant difference in GTV, lung and esophageal parameters between FDG-PET and CT based plans.
Notes	* GTV = gross target volume

Comments of ASSR reviewer

According to the systematic review and the primary studies published after its update, the use of FDG-PET/CT resulted in changes of target volumes in comparison with CT alone. In particular a decrease of GTV is observed as an overall trend. Nevertheless there are no data on decrease in toxicity nor on longer term clinical outcomes, and it is not possible to ascertain whether FDG-PET-based changes in target volume represent better pathological tumor coverage than CT-based volume delineation.

Diagnostic accuracy estimates

Not available.

LEVEL OF EVIDENCE: VERY LOW

8.2. Clinical outcomes

To evaluate the balance between benefits and risks, the panel agreed to consider the presumed patient-important outcomes reported below (*Table 8.3*), and voted on the level of importance.

The panel considered all consequences as important for patients.

Because of the lack of data on accuracy, it was not possible to provide a matrix of "natural frequencies".

Table 8.3. Patient-important clinical outcomes and median scores of importance

Patient-important outcomes	**Median score (range)**
Consequences of test for patients with large target volume	
• True positives - correct increase in target volume	5 (3-9)
• False negatives - incorrect decrease in target volume	6 (3-9)
Consequences of test for patients with small target volume	
• True negatives - correct decrease in target volume	6 (3-9)
• False positives - incorrect increase in target volume	6 (3-9)

8.3. Voting results

In neither of the two voting rounds the panel reached an agreement on the appropriateness of FDG-PET in target volume definition with votes falling between the inappropriate and uncertain regions (first round: median score 3.5, range 2-5, second round: median score 4.5, range 2-6). The use of FDG-PET resulted therefore uncertain due to disagreement.

FINAL RATING FOR THE USE OF FDG-PET FOR TARGET VOLUME DEFINITION IN PATIENTS WITH LUNG CANCER:

UNCERTAIN

8.4. Conclusions

The available literature on FDG-PET's accuracy in delineation of target volume consists mainly of simulation studies with no data on actual coverage of pathological tumor. Level of evidence was very low, while patient-important outcomes have all been voted important by panelists. In both voting rounds there was disagreement on level of appropriateness with votes falling between inappropriateness and uncertainty (first round: median score 3.5 with range 2-5; second round: median score 4.5 with range 2-6). The use of FDG-PET in target volume definition resulted therefore uncertain due to disagreement.

9. During-treatment evaluation of early response to neo-adjuvant therapy in patients treated for non-small cell lung cancer - NSCLC

Rationale

According to the most recent guidelines (AIOM 2009, BTS 2010, ACCP 2007), surgical resection remains the standard of care for fit for surgery patients with early (0, I, II) NSCLC; in these patients pre-surgical (neo-adjuvant) chemo and/or radiotherapy is not recommended.

Selected patients with locally advanced (stage IIIA) cancer can be eligible for surgery, but the role of neo-adjuvant therapy for them is still debated.

Diagnostic role of FDG-PET

The panel agreed that there is no diagnostic role of FDG-PET in the during-treatment evaluation of response to therapy, due to the brevity of the treatment itself.

Treatment effectiveness

The evidence on the effectiveness of pre-operative chemotherapy in NSCLC is still controversial.

Pre-test probability and change in management

The pre-test probability of histopathologic response of primary tumour after pre-operative chemotherapy appears to be 26% (data from a single primary study: Aukema 2010).

9.1. Systematic review of literature: results

Results from update of systematic review of literature from January 2006

Two systematic reviews, none of which provided data on diagnostic accuracy of FDG-PET, and one primary study were retrieved.

Systematic reviews

Two systematic reviews (de Geus-Oei 2007, Rebollo-Aguirre 2010) assessing the accuracy of FDG-PET or FDG-PET/CT in predicting histological response to therapy during treatment have been retrieved, each including 9 studies. The accuracy of FDG-PET in assessing the patient's response during treatment was examined only by the same unique study analyzed by both the reviews (Hoekstra 2005) - the remaining considering patients' response at the end of treatment. The study assessing the during-treatment response included 47 patients treated with neo-adjuvant chemotherapy of which only 25 underwent surgery; however study results do not include data on accuracy of FDG-PET in predicting histological response to therapy.

Primary studies

Only one small study (Aukema 2010) was retrieved (*Table 9.1*), assessing diagnostic accuracy of FDG-PET/CT for early prediction of pathological response to pre-operative chemotherapy (with erlotinib) in 23 patients with stage I-III resectable NSCLC (mean age 63 years). FDG-PET/CT was performed at baseline and within 7 days of initiation of treatment (median time: 6 days) and all patients underwent surgery (lobectomy and regional lymph node dissection). The pre-test probability of histological response to treatment was 26%.

Table 9.1. Results on diagnostic accuracy of FDG-PET in evaluating response during neo-adjuvant chemotherapy

Reference	Aukema 2010
Number of studies	1
Number of patients	23
FDG-PET	sensitivity: 66.7% specificity: 88.2%
Comparator	none
Reference standard	histopathologic confirmation following surgery

Comments of ASSR reviewer

Considering the paucity of data on accuracy of FDG-PET and FDG-PET/CT in assessing the response during neo-adjuvant and adjuvant treatment in NSCLC patients it is impossible to draw any conclusion.

Diagnostic accuracy estimates

Not available due to sparse data.

LEVEL OF EVIDENCE: VERY LOW

9.2. Clinical outcomes

As the panel agreed on lack of diagnostic role of FDG-PET in the evaluation of early response to neo-adjuvant therapy during treatment in patients treated for NSCLC no patient-important outcomes have been proposed and voted.

9.3. Voting results

The panel decided not to carry out the full voting procedure and unanimously agreed to judge the use of FDG-PET in the evaluation of patients' early response to neo-adjuvant therapy for NSCLC as inappropriate.

FINAL RATING FOR THE USE OF FDG-PET FOR DURING-TREATMENT EVALUATION OF RESPONSE TO NEO-ADJUVANT THERAPY IN PATIENTS TREATED FOR NSCLC:

INAPPROPRIATE

9.4. Conclusions

The diagnostic accuracy of FDG-PET in evaluating early response, during treatment, to neo-adjuvant therapy in patients treated for non-small cell lung cancer has been poorly studied and the level of evidence is very low. Due to the brevity of the neo-adjuvant treatment, the panel agreed in the lack of diagnostic role of FDG-PET in this clinical situation, and unanimously decided to judge this use of FDG-PET inappropriate

10. During-treatment evaluation of early response to systemic therapy in patients treated for small cell lung cancer - SCLC

Rationale

Patients with limited disease are treated with a combination chemotherapy and radiotherapy, while patients with extended disease are treated with only chemotherapy (BTS 2010; ESMO 2010). Response to treatment is mainly used for prognosis.

Diagnostic role of FDG-PET

The panel agreed that there is no diagnostic role of FDG-PET in the during-treatment evaluation of response to therapy, due to the brevity of the treatment itself.

Treatment effectiveness

A survival benefit was demonstrated for patients treated with second-line chemotherapy in a small randomized study (n = 141) (ESMO 2010). Candidates for second-line chemotherapy should be selected on the basis of response to first-line therapy, time interval since the discontinuation of first-line therapy, residual toxicity to first-line therapy and performance status (ESMO 2010).

Pre-test probability and change in management

The pre-test probability of complete or partial response at the end of treatment is around 90% (Fischer 2006).

10.1. Systematic review of literature: results

Results from update of systematic review of literature from January 2006

Systematic reviews

No systematic reviews were identified.

Primary studies

One primary study on 20 patients was identified and retrieved (Fischer 2006). The study evaluates the performance of CT and FDG-PET/CT in assessing early and final response to treatment in SCLC patients. Both tests were performed before initiation of treatment, after one or two cycles of chemotherapy and at the end of therapy. No reference standard test was performed but the analysis focused on correlation between FDG-PET/CT and CT (*Table 10.1*).

Table 10.1. Diagnostic accuracy of FDG-PET/CT in assessing response to treatment

Reference	Fischer 2006
Number of patients	20
FDG-PET/CT **Comparator**	Only narrative data on the two test agreements: "At response evaluation after one cycle of chemotherapy major disagreement (responder versus non responder) between PET and CT in predicting final response was seen in 1 of 12 patients. At final response evaluation major disagreement between PET, PET/CT and CT was seen in 2 of 19 patients (11%)"
Reference standard	no reference standard performed

Comments of ASSR reviewer

Considering the paucity of data on accuracy of FDG-PET and FDG-PET/CT in assessing early response during chemo/radiotherapy in SCLC patients it is impossible to draw any conclusion.

Diagnostic accuracy estimates

Not available due to sparse data.

LEVEL OF EVIDENCE: VERY LOW

10.2. Clinical outcomes

As the panel agreed on lack of diagnostic role of FDG-PET in the evaluation of early response to neo-adjuvant therapy during treatment in patients treated for SCLC no patient-important outcomes have been proposed and voted.

10.3. Voting results

The panel decided not to carry out the full voting procedure and unanimously agreed to judge the use of FDG-PET in the evaluation of patients' early response to neo-adjuvant therapy for SCLC as inappropriate.

FINAL RATING FOR THE USE OF FDG-PET FOR DURING-TREATMENT EVALUATION OF RESPONSE TO SYSTEMIC THERAPY IN PATIENTS TREATED FOR SCLC:

INAPPROPRIATE

10.4. Conclusions

We identified one small study assessing the performance of PET on treatment response to therapy in people with SCLC. The level of evidence is therefore very low. Due to the brevity of the treatment, the panel agreed in the lack of diagnostic role of FDG-PET in this clinical situation, and unanimously decided to judge this use of FDG-PET inappropriate.

11. End of treatment evaluation of response to neo-adjuvant therapy in patients treated for non-small cell lung cancer - NSCLC

Rationale

In patients with unresectable stage III or stage IV disease who can tolerate the treatment, chemotherapy and/or following or concurrent radiotherapy is the standard of care. Selected patients with locally advanced (stage IIIA) cancer can be considered for surgery, especially those with a good response to systemic therapy. The role of neo-adjuvant therapy is nevertheless still on debate. While response to treatment is mainly used for prognosis, in selected patients it could influence subsequent therapeutic options.

Diagnostic role of FDG-PET

To identify patients with a good response to curative (for stage III and IV NSCLC) or neo-adjuvant (for stage IIIA NSCLC) treatment, to decide on subsequent therapeutic approach.

Treatment effectiveness

The evidence on the effectiveness of pre-operative chemotherapy in NSCLC is still controversial and routine neo-adjuvant treatment for locally advanced NCSLC is not recommended.

Systemic and radiation therapy are the only therapeutic options for unresectable early stage (I and II), locally advanced (stage III) and metastatic (stage IV) NSCLC. In patients with locally advanced NSCLC, concurrent chemo-radiotherapy performed better than sequential chemo-radiotherapy in term of 3-yr survival rates (24.8% and 18.2%, respectively, Auperin 2010).

Pre-test probability and change in management

According to two studies, the range of pre-test probability of persistent viable malignant cells after neo-adjuvant treatment is between 30% and 50% (Stigt 2009, Eschmann 2007).

Research question: FDG-PET as add on

What is the diagnostic accuracy of FDG-PET in evaluating response to treatment of patients treated for NSCLC and with unclear results from conventional imaging?

11.1. Systematic review of literature: results

Results from update of systematic review of literature from January 2006

Studies retrieved evaluating diagnostic accuracy of FDG-PET include two systematic reviews and three further primary studies.

Systematic reviews

Two systematic reviews (de Geus-Oei 2007, Rebollo-Aguirre 2010) assessing the accuracy of FDG-PET or FDG-PET/CT were identified and retrieved; both included 9 studies, one of which was common to both reviews and evaluated early (after 1 cycle) response to neo-adjuvant chemotherapy (*Table 11.1*).

The review by de Geus-Oei included 9 studies on neo-adjuvant therapy; treatment consisted in chemotherapy (2 studies), radiotherapy (1 study) or both (6 studies). All studies were on FDG-PET. The sensitivity of FDG-PET in detecting pathological tumor response ranged from 81 to 97%, while specificity ranged from 64 to 100%. Methodological quality of the review was judged as very low.

The review by Rebollo-Aguirre included 9 studies and estimated accuracy of FDG-PET (7 studies) or FDG-PET/CT (2 studies) both on primary tumor and lymph nodes re-staging. A meta-analysis of data on accuracy in lymph nodes re-staging (7/9 studies) was performed whilst heterogeneity did not allow a pooled estimate of accuracy for primary tumor re-staging after induction therapy. The authors report that studies were of moderate to low quality. Methodological quality of the review was judged moderate.

Table 11.1. Results from systematic reviews on response to neo-adjuvant/adjuvant therapy at the end of treatment (de Geus-Oei, Rebollo-Aguire)

Reference	de Geus-Oei 2007	Rebollo-Aguire 2010
Update to	July 2006	1999 - August 2006
Number of studies	9	9
Number of patients	not reported	367
FDG-PET/PET-CT	prediction of histopathologic response of the primary tumor re-staging: no meta-analysis performed accuracy: 83-96% sensitivity: median 88% (range 80-97%) specificity: median 80% (range 64-100%)	prediction of histopathologic response of the primary tumor re-staging (no meta-analysis performed due to heterogeneity among studies) sensitivity: range 80-100% specificity: range 0-100% PPV: 42.9-100% NPV: 0-100% prediction of histopathologic mediastinal lymph node re-staging sensitivity: pooled 63.8% (95% CI 53.3-73.5%) specificity: pooled 85.3% (95% CI 80.4-89.4%)
Comparators	CT data not reported; however PET is found to be a "better" predictor of histopathologic response in 5 out of 9 studies	CT data not reported
Reference standard	histopathology	histopathology

Primary studies

Literature search retrieved three additional studies that weren't included in the above-mentioned systematic reviews (Cerfolio 2007b, Eschmann 2007, Stigt 2009, *Table 11.2*) and that evaluated FDG-PET (1 study) or FDG-PET/CT (2 studies) for assessment of response after completion of neo-adjuvant chemotherapy (1 study) or chemo-radiotherapy (2 studies). All studies included stage III patients (only Cerfolio et al 2007b included also 4/109 patients in stage II) and evaluated also another comparator (1 CT and 2 EUS-FNA). The reference standard applied was histopathology in all studies.

Table 11.2. Results from primary studies on assessment with FDG-PET of therapy response after neo-adjuvant therapy at the end of treatment

Reference	Cerfolio 2007b, Eschmann 2007, Stigt 2009
Number of studies	3
Number of patients	207 (median: 70, range: 28-109)
FDG-PET/PET-CT	prediction of histopathologic response of the primary tumor re-staging sensitivity: median 85% (range 14-94.6%) specificity: median 80% (range 70-100%) prediction of histopathologic response of lymph nodes re-staging sensitivity: median 77% (range 0-80%) specificity: median 68% (range 68-92%)
Comparator	EUS-FNA (1 study) sensitivity: 50% specificity: 100% CT (1 study) data not reported
Reference standard	histopathology

Comments of ASSR reviewer

In assessing FDG-PET's diagnostic accuracy in evaluating response to neo-adjuvant therapy, the best source of evidence comes from the review of Rebollo-Aguirre and for this reason sensitivity and specificity estimates are drawn from it. Estimates of FDG-PET accuracy for evaluation of primary tumor response are very heterogeneous, and only ranges are given, while estimates for lymph node re-staging are slightly less heterogeneous, showing relatively low performance of FDG-PET.

Diagnostic accuracy estimates

Histopathologic response of the primary tumor re-staging
- FDG-PET sensitivity: (heterogeneous) range 80-100%
- FDG-PET specificity: (heterogeneous) range 0-100%

Histopathologic mediastinal lymph node re-staging
- FDG-PET sensitivity: pooled 63.8% (95% CI 53.3-73.5%)
- FDG-PET specificity: pooled 85.3% (95% CI 80.4-89.4%)

Data on comparator tests not available.

LEVEL OF EVIDENCE: VERY LOW

11.2. Clinical outcomes

To evaluate the balance between benefits and risks, the panel agreed to consider the presumed patient-important outcomes reported below (*Table 11.3*), and voted on the level of importance.

Table 11.3. Patient-important clinical outcomes and median scores of importance

Patient-important outcomes	Median score (range)
Patients not responding to neo-adjuvant therapy	
• True non responders - patients correctly identified as non responders change from curative treatment to palliative treatment	4 (3-8)
• False responders - patients incorrectly identified as responders undergo curative - possibly surgical - treatment, which will not impact on their survival	3 (2-8)
Patients responding to neo-adjuvant therapy	
• True responders - patients correctly identified as having a good response to therapy can undergo curative surgical treatment, which might improve survival	5 (2-8)
• False non responders - patients incorrectly identified as non responders proceed to palliative treatment, with no gain in survival	3 (3-9)

The panel considered consequences for patients wrongly diagnosed (false responders and false non responders) as not important, while consequences for correct classification of response were judged important.

Because of the heterogeneity of estimates for accuracy, it was not possible to provide a matrix of "natural frequencies".

11.3. Voting results

Both voting rounds registered a slight disagreement with ratings falling in the inappropriate and uncertain regions. Median scores were was 3.5 in the first vote (range 3-6) and 4 in the second vote (range 2-6). Appropriateness was therefore rated uncertain due to disagreement.

FINAL RATING FOR THE USE OF FDG-PET FOR THE EVALUATION OF RESPONSE TO NEO-ADJUVANT THERAPY AT THE END OF TREATMENT IN PATIENTS TREATED FOR NSCLC:

UNCERTAIN

11.4. Conclusions

Although a good response to neo-adjuvant therapy could influence subsequent choice of therapeutic options for selected patients, patient-important outcomes were not considered very important by the panel, with consequences for false responders and false non responders rated as not important (median score 3) and consequences for true responders/non responders rated important (median score 5 and 4 respectively). Level of evidence for FDG-PET diagnostic accuracy in evaluating end of treatment response to therapy in patients treated for NSCLC was judged very low due to heterogeneity of estimates for both sensitivity and specificity. This use of FDG-PET resulted uncertain due to disagreement as the panel did not reach an agreement in both voting rounds, with ratings falling in both the inappropriate and uncertain regions.

12. End of treatment evaluation of response to systemic therapy in patients treated for small cell lung cancer - SCLC

Rationale

Patients with limited disease are treated with a combination of chemotherapy and radiotherapy, while patients with extended disease are treated only with chemotherapy (BTS 2010; ESMO 2010). Response to treatment is mainly used for prognosis.

Diagnostic role of FDG-PET

The panel agreed on the lack of diagnostic role of FDG-PET in the end of treatment evaluation of response to therapy in patients treated for SCLC.

Treatment effectiveness

Patients with limited disease are potentially curable and clinical trials have reported a 5 year-survival rate between 20% and 25% in patients treated with concurrent chemo-radiotherapy (BTS 2010; ESMO 2010). The prognosis of extensive disease is poor with a median survival of 10 months and a 2-year survival rate of 10%. Long term survivors are extremely rare (ESMO 2010).

A survival benefit was demonstrated for patients treated with second-line chemotherapy in a small randomized study (n = 141) (ESMO 2010). Candidates for second-line chemotherapy should be selected on the basis of a number of parameters, including response to first-line therapy, time interval since the discontinuation of first-line therapy, residual toxicity to first-line therapy and performance status (ESMO 2010).

Pre-test probability and change in management

The pre-test probability of complete or partial response at the end of treatment is around 90% (Fischer 2006).

12.1. Systematic review of literature: results

Results from update of systematic review of literature from January 2006

Systematic reviews

No systematic reviews were retrieved.

Primary studies

One primary study on 20 patients was retrieved (Fischer 2006, *Table 12.1*). The study evaluates the performance of CT and FDG-PET/CT in assessing early and final response to chemotherapy treatment in SCLC patients. Both tests were performed before initiation of treatment, after one or two cycles of chemotherapy and at the end of therapy. No reference standard test was performed but the analysis focused on correlation between FDG-PET/CT and CT results.

Table 12.1. Diagnostic accuracy of FDG-PET/CT in assessing response to treatment

Reference	Fischer 2006
Number of patients	20
FDG-PET/CT	Only narrative data:
Comparator	"At response evaluation after one cycle of chemotherapy major disagreement (responder versus non responder) between PET and CT in predicting final response was seen in 1 of 12 patients. At final response evaluation major disagreement between PET, PET/CT and CT was seen in 2 of 19 patients (11%)"
Reference standard	No reference standard performed

Comments of ASSR reviewer

Considering the paucity of data on accuracy of FDG-PET and FDG-PET/CT in assessing the response at the end of chemo/radiotherapy in SCLC patients it is impossible to draw any conclusion.

Diagnostic accuracy estimates

Not available due to sparse data.

LEVEL OF EVIDENCE: VERY LOW

12.2. Clinical outcomes

As the panel agreed on the lack of diagnostic role of FDG-PET in the evaluation, at the end of treatment, of response to therapy in patients treated for SCLC no patient-important outcomes have been proposed and voted.

12.3. Voting results

The panel decided not to carry out the full voting procedure and unanimously agreed to judge the use of FDG-PET in the end of treatment evaluation of patients' response to therapy for SCLC as inappropriate.

FINAL RATING FOR THE USE OF FDG-PET FOR THE EVALUATION OF RESPONSE TO SYSTEMIC THERAPY AT THE END OF TREATMENT IN PATIENTS TREATED FOR SCLC:

INAPPROPRIATE

12.4. Conclusions

Only one study with very few patients assessed diagnostic accuracy of FDG-PET in the end of treatment evaluation of patients' response to chemotherapy for SCLC. The level of evidence is therefore very low. Due to the lack of diagnostic role of FDG-PET in this clinical situation, the panel unanimously decided to judge this use of FDG-PET inappropriate.

13. Follow up of patients treated for lung cancer - NSCLC - with no suspicion of recurrence

Rationale

No guideline recommends an active follow up with imaging tests, other than CT, in asymptomatic patients (ESMO 2010, NCCN 2011, BTS 2010).

The post-treatment management of patients with early stage and locally advanced (non-metastatic) NSCLC is controversial as evidence on a better prognosis correlated to earlier diagnosis and treatment of recurrence is still lacking (ESMO 2010).

Diagnostic role of FDG-PET

There is no diagnostic role for FDG-PET in the follow up of patient treated for lung cancer.

Treatment effectiveness

Presently, there is no evidence that an earlier diagnosis of recurrence followed by an early treatment is related to an improved survival.

Pre-test probability and change in management

Reported recurrence rates after complete resection range from 30% to 75% depending on the final pathologic stage (Takenaka 2010).

13.1. Systematic review of literature: results

Results from update of systematic review of literature from January 2006

Only two primary studies were included.

Systematic reviews

No systematic reviews have been retrieved.

Primary studies

Two primary studies evaluating accuracy of FDG-PET/CT in follow up were retrieved (Takenaka 2010, Onishi 2010). As patients of Takenaka 2010 are included in the Onishi 2010 study, only data from the latter have been considered (*Table 13.1*). The study included 121 consecutive patients with pathologically and surgically confirmed NSCLC who underwent a complete surgical resection and were followed up by FDG-PET/CT and standard radiological examinations (brain MRI, chest, abdominal, neck CT, bone scintigraphy) every 6 months for more than 12 months after surgery. At the end of the study 26/121 patients (21.5%) had recurrent disease. FDG-PET/CT images were evaluated qualitatively with a 5-point visual scoring system (from 1: definitively absent to 5: definitely present) and quantitatively (cut off value of SUV max 2.5).

Table 13.1. Results from studies on diagnostic accuracy of FDG-PET in the follow up of asymptomatic patients after surgery

Reference	Onishi 2010
Number of studies	1
Number of patients	121
FDG-PET/CT	including brain metastases (visual assessment) sensitivity: 80.8% specificity: 76.8% including brain metastases (visual + quantitative assessment) sensitivity: 73.1% specificity: 87.4% excluding brain metastases (visual assessment) sensitivity: 84% specificity: 76.8% excluding brain metastases (visual assessment + quantitative) sensitivity: 76% specificity: 87.4%
Comparator	standard radiological examinations including brain metastases sensitivity: 73.1% specificity: 73.7% excluding brain metastases sensitivity: 72% specificity: 73.7%
Reference standard	histology and clinical-radiological follow up every 6 months for at least 24 months

Comments of ASSR reviewer

Only one study was found with few patients. It is not possible to draw any conclusion about the accuracy of FDG-PET/CT in the follow up of asymptomatic patients.

Diagnostic accuracy estimates

Estimates not available due to sparse data.

LEVEL OF EVIDENCE: VERY LOW

13.2. Clinical outcomes

As the panel agreed on lack of diagnostic role of FDG-PET in the follow up of patients treated for lung cancer no patient-important outcomes have been proposed and voted.

13.3. Voting results

The panel decided not to carry out the full voting procedure and unanimously agreed to judge the use of FDG-PET in the follow up of patients treated for lung cancer as inappropriate.

FINAL RATING FOR THE USE OF FDG-PET FOR THE FOLLOW UP OF PATIENTS TREATED FOR NSCLC:

INAPPROPRIATE

13.4. Conclusions

As only one study evaluating the diagnostic accuracy of FDG-PET in follow up of patients treated for lung cancer, the level of evidence was judged very low. The panel agreed on the lack of diagnostic role for FDG-PET in this indication, which was unanimously judged inappropriate.

14. Diagnosis and staging of suspected loco-regional recurrence in patients treated for lung cancer - NSCLC

Rationale

Although advancements in early diagnosis and treatment have been made in the hope of improving survival recurrence remains a major obstacle to achieving a complete cure for NSCLC patients. Reported recurrence rates after complete resection ranges from 30% to 75% depending on the final pathologic stage (Takenaka 2010).

While progressive disease is treated with palliative types of treatments, solitary lesions occurring in the contralateral lung should be considered as secondary primary lesions and treated with curative intention if tumors are potentially curable (ESMO 2010).

Diagnostic role of FDG-PET

To characterize unclear lesions appearing after radical treatment, in order to identify a local recurrence eligible for radical treatment.

Treatment effectiveness

Evidence on impact of earlier treatment of recurrence on clinical outcomes is lacking, but treatment of solitary lesions is recommended (ESMO 2010, BTS 2010).

Pre-test probability and change in management

The range of pre-test probability of loco-regional recurrence in patients with suspected recurrence of NSCLC is between 68.2% and 75.3% (Hellwig 2006, Isobe 2009). Evidence from 2 studies evaluating change in management following FDG-PET exams (Hicks 2001, Nakamoto 2008) shows a change ranging between 17 and 63% - with the start of a new therapeutic program.

Research question: FDG-PET as add on

Is FDG-PET sufficiently specific to characterize malignant solitary lesions in patients with unclear results from conventional imaging?

14.1. Systematic review of literature: results

Results from update of systematic review of literature from January 2006

Systematic reviews

None identified.

Primary studies

Three studies (Hellwig 2006, Isobe 2009, Nakamoto 2008), for a total of 125 patients, have been retrieved. They assessed the accuracy of FDG-PET/CT (Nakamoto 2008) or FDG-PET (Hellwig 2006, Isobe 2009) in detecting suspected recurrence in patients after surgical therapy of lung cancer (*Table 14.1*).

Table 14.1. Primary studies on diagnostic accuracy of FDG-PET in patients with suspected recurrence after surgery

Reference	Helliwig 2006	Isobe 2009	Nakamoto 2008
Number of patients	62	22	41
FDG-PET/CT	sensitivity: 93% specificity: 89%	sensitivity: 93% specificity: 86%	sensitivity: 87% specificity: 50%
Comparator	none	none	CT sensitivity: 77% specificity: 70%
Reference standard	histopathologic confirmation and clinical follow up	histopathologic confirmation and clinical follow up	histopathologic confirmation and clinical follow up

Comments of ASSR reviewer

Only three studies were found with few patients. It is not possible to draw any conclusion about the accuracy of FDG-PET/CT in patients with suspected recurrence after surgery.

Diagnostic accuracy estimates

Not available due to sparse data.

LEVEL OF EVIDENCE: VERY LOW

14.2. Clinical outcomes

To evaluate the balance between benefits and risks, the panel agreed to consider the presumed patient-important outcomes reported below (*Table 14.2*), and voted on the level of importance.

The panel considered all four patient-important outcomes critical.

Because of the heterogeneity of estimates for accuracy, it was not possible to provide a matrix of "natural frequencies".

Table 14.2. Patient-important clinical outcomes and median scores of importance

Patient-important outcomes	Median score (range)
Patients with resectable loco-regional recurrence	
• True positives - patients correctly diagnosed for recurrent solitary lesions proceed to surgical radical treatment, which might improve their survival	7 (2-9)
• False negatives - patients' lesions incorrectly diagnosed as non malignant, do not receive appropriate radical treatment, which could have improved their survival	7 (2-9)
Patients with no loco-regional recurrence	
• True negatives - patients' lesions correctly diagnosed as non malignant remain in follow up	7 (2-9)
• False positives - patients incorrectly diagnosed for recurrent solitary lesions undergo unnecessary surgical treatment, with no impact on survival but possible risks and negative impact on quality of life	8 (2-8)

14.3. Voting results

The panel did not reach an agreement in neither of the two voting rounds and ratings fell both times in the regions of uncertainty and appropriateness. The use of FDG-PET in the diagnosis and staging of local recurrence resulted therefore uncertain due to disagreement.

FINAL RATING FOR THE USE OF FDG-PET FOR THE DIAGNOSIS AND STAGING OF SUSPECTED LOCO-REGIONAL RECURRENCE IN PATIENTS TREATED FOR NSCLC:

UNCERTAIN

14.4. Conclusions

Diagnostic accuracy of FDG-PET in the characterization of loco-regional recurrence has been evaluated by few studies and in relatively few patients. The level of evidence was therefore judged very low. Patient-important outcomes were voted critical by the panel, with consequences for patients wrongly diagnosed for recurrence scoring 8 (range 2-8) and consequences for true positives and true and false negatives scoring 7 (median range 2-9 for all three outcomes). There was a slight disagreement among panelists voting uncertain and appropriate in both rounds (median score 7) and the use of FDG-PET in the diagnosis and staging of suspected loco-regional recurrence in patients treated for NSCLC resulted uncertain due to disagreement.

Conclusions

The present work is part of a larger research program dedicated to the update of the 2007 Report on the appropriate use of FDG-PET in oncology.

At the end of the research program, results of the present Dossier will be used for an overall analysis and estimate of FDG-PET scans need in our Region and for setting up priorities for future research programs on the clinical use of FDG-PET in oncology.

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Peer review reports

Reviewer 1

I primarily looked at the use of the GRADE approach as you asked. I have some general comments that you might find helpful:

1. On page 29 the authors summarized the outcomes of interest.
   - Were those outcomes the same across all the questions you asked? If not, maybe it would be more beneficial to be explicit what outcomes were considered for each question separately?
   - I wonder why e.g. quality of life and adverse effects of tests were not considered? They seem like obvious outcomes one would be interested in this context.
2. On page 30 the document discusses "Level of evidence". The standard GRADE terminology is "quality of evidence". Also there are only 4 criteria listed and publication bias has been omitted. According to the GRADE approach it should be added and evaluated.
3. For some of the clinical problems investigated in the document the authors did not provide what was the exact clinical question they asked. For instance, for problem 6 - Staging of patients with Bronchioloalveolar cancer - BAC (p. 53) and some following problems there seems not be any explicit question provided. It is therefore impossible to decide what question and recommendation the systematic review and the subsequent statement are supposed to answer.

3A. For those problems for which questions were stated they were not precise enough. For instance, for problem 4 - Characterization of solitary pulmonary nodules >1 cm the question is steed as: "Has FDG-PET sufficient accuracy for characterizing malignant SPN?". The clinical question seems here to be: "Should FDG-PET be used as an add on test (i.e. compared to no additional testing) in patients with solitary pulmonary nodules >1 cm identified using contrast-enhanced CT?".
It would also be beneficial to explicitly state what was the population of interest, index test, comparator and outcomes of interest in a PICO format.

4. On page 44 the authors conclude that the "level of evidence" was moderate (this comment concerns all subsequent questions in the document). However, there is no rationale for this judgement provided. The GRADE approach requires making all the judgement about the risk of bias, indirectness, imprecision, inconsistency, and publication bias explicit and provide them in a document together with an explanation (preferably as an evidence table [evidence profile]). I could not find those evidence profiles in any of the two document you provided. <u>They are essential to the GRADE approach</u>.

5. Table 4.4. (p. 45) an similar tables later in the document, show the number of patients with particular test outcome (TP, TN, FP, FN). It is not clear if those estimates for FDG-PET are after CT compared to CT alone? It looks like a comparison of FDG-PET to CT. It would be beneficial to make clear what was the comparison.
6. The authors mention methodological quality of systematic reviews was moderate or very low (e.g. on p. 48). How did they make that judgement? If using an AMSTAR tool then how did they map AMSTAR score to the categories of moderate or very low?
7. Some of the problems seem to be answered by one physiological outcome only rather than a set of patient-important outcomes. For instance, table 8.3. lists only one outcome "target volume" that does not seem to be the patient-important outcome. It would be beneficial to clearly state what outcomes were considered when answering each of the questions and to include ALL outcomes important to patients.
8. Most considerations do not mention the 3 other outcomes suggested by the GRADE approach: uninterpretable results, complications of performing tests being compared and the resource use.
9. A minor comment about the statement in the methods section (p. 28): "As randomized clinical trials providing robust data on clinical effectiveness of diagnostic tests are very difficult to perform, and seldom found...". It is true that they are rarely performed but maybe they should. Randomized trials of therapeutic interventions are also difficult to perform. I think the main reason we have to rely on diagnostic accuracy is that people do not perform these studies for historical reasons, believing that accuracy is enough, not because they are more difficult.

It seems that in order to stet that the authors followed the GRADE approach they need to: 1) ask explicit and clear clinical questions for each of the problems, 2) include all outcomes important for patients when considering each question, 3) provide explicit judgements and rationale about the final grading of the quality of evidence, and 4) summarize the quality of evidence and magnitude of effects in evidence tables. It would also be beneficial if the authors could clarify the presentation of the results.

With kind regards,

Jan Brozek

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Reviewer 2

The working group has developed criteria for the appropriate use of positron emission tomography using F-18 fluorodeoxyglucose (FDG-PET) in patients with lung cancer. The development of this report was based on a sophisticated methodology. After defining research questions for several indications of FDG-PET in lung cancer, the available evidence was evaluated and after a critical appraisal, the appropriateness of the use of FDG-PET was judged by a panel voting process.

Everyone who ever has performed a meta-analysis following current standards knows the effort needed to complete such a project. Thus I have great respect for the authors' work. Due to the dimension of the project it is not unexpected that some minor flaws occurred which might be easy to resolve.

I have some suggestions and comments.

- The clinical indication "Staging of patients with bronchioloalveolar cancer" (BAC) is not well defined, because it is overlapping with the indication "Staging of patients with NSCLC" and a rare case in an "ex-ante" view during the workup of patients with suggested lung cancer.

  The key finding of a ground glass opacity in a chest CT is more frequent than the final pathological diagnosis of a BAC. Since the WHO criteria for the pathological typing of lung cancer were updated, the diagnosis of BAC requires the missing of any invasive component, otherwise the tumor has to be typed as an adenocarcinoma.

  Thus, BAC is a histopathologic diagnosis. As long as no histopathologic diagnosis of BAC is established a patient with suspected BAC (e.g. due to a cytopathological finding suggesting a BAC) she or he cannot be excluded from FDG-PET based on the evidence obtained from studies in patients with the final diagnosis of BACs. The FDG-PET indication is covered by the recommendation for patients with NSCLC (for which the evidence was obtained from patient populations including BACs).

  If the report serves to define capacity requirements of FDG-PET in Italy, the number of patients with the final diagnosis of a BAC cannot be taken to calculate the needs due to the above mentioned problem with the "ex-ante" view during the diagnostic workup of patients with suspected BAC.

- Page 17: Staging of patients with BAC
  The literature analysis on FDG-PET in BACs dealt with studies about the differentiation of BAC from other types of NSCLC. Differentiation is not the same as staging.

- Page 29: Data synthesis
  The methods reported for the data synthesis are appropriate for the analysis of diagnostic tests, in which patients are categorized for the presence or absence of disease versus the dichotomic results of a diagnostic test. But this kind of methodology is not applicable to the literature on FDG-PET in radiation treatment planning and tumor delineation. As stated later in the report (pages 61-62), the

change in gross tumor volume (GTV) was considered as the appropriate parameter. It remains unclear what is meant with pooled sensitivity and specificity for modification of treatment plans if no reference standard exists.

- Pages 39, 86; Appendix, pages 160, 184
  In Chapter 4 (Characterization of SPNs of at least 1 cm) I noticed a false citation, because the respective article comes from my group. The cited paper by Grgic et al. 2010 is reported in the reference list with the wrong citation.
  Please use the following reference:
  > Grgic A, Yüksel Y, Gröschel A, Schäfers HJ, Sybrecht GW, Kirsch CM, Hellwig D. Risk stratification of solitary pulmonary nodules by means of PET using F-18-fluorodeoxyglucose and SUV quantification. *Eur J Nucl Med Mol Imaging*. 2010 Jun; 37 (6): 1087-1094.

  Furthermore, the data collection form for our publication was incorrectly filled in, I suppose as a victim of Copy&Paste from the respective form for the publication of Hashimoto 2006. Please correct the country from "Japan" to "Germany". The field "Verification by reference standard for all subjects" can be set to "Yes". Due to my time limits I cannot check all the other publications and forms in Appendix 2. I suggest to review the tables in Appendix 2 carefully, especially for publications from authors with more than a single publication in one year. To improve the identification of publications in your forms in the future, I suggest to add one row in the form which contains the full reference of the article.

- Page 41, Table 4.1
  I would suggest to replace "SPECT" with "Tc-99m-depreotide SPECT" to avoid any confusion regarding the use of other radiopharmaceuticals.

- Page 43, Table 4.2
  The radiopharmaceutical used for "SPECT" should be specified.

- Page 61: Diagnostic role of FDG-PET in target volume definition in radiotherapy: By the panelists, the role of FDG-PET has been recognized "to decrease risk of severe lung acute and late toxicity". Had I been on the panel, I would have raised an additional point, namely that FDG-PET helps to avoid geographical miss and therefore might increase local control in patients irradiated for lung cancer.

- Page 62, Table 8.1, Result of systematic review ...
  Page 63, Table 8.2, Result of primary studies on diagnostic accuracy ...
  As mentioned above, it remains unclear which parameters were considered in the meta-analyses. On one hand, mediastinal lymph node staging was evaluated in the context of a planning study, on the other hand changes in GTV were considered to assess the role of FDG-PET. The underlying methodology and the research questions have to be stated clearly.

- Page 65, During-treatment evaluation of response to neo-adjuvant treatment for NSCLC
  The research question should be given more specifically. The term "response" can refer to the primary tumor, to its lymph node metastases or to distant metastases. Thus, it remains unclear to which of that the reported pre-test probability of 26% refers.
- Pages 69 and 79: Pre-test probability
  Both chapters on during - as well as post - treatment evaluation in patients with SCLC stress the same number of 90% from the publication of Fischer et al. in "Lung Cancer" 2006. In that article, a pre-test probability of 60-70% is stated as initial response rate to chemotherapy (page 42, 3rd sentence of introduction).
- I would suggest to replace "PET" with "FDG-PET" in the title of Appendix 2 to avoid any confusion regarding the use of other radiopharmaceuticals, especially F-18-fluorine which might be necessary in the future as a substitute to Tc-99m labelled bone seeking agents.
- I would suggest to replace "sensibility" by "sensitivity" throughout the report.
- In some indications, e.g. staging of small cell lung cancer or early response assessment during treatment, a bias from partial verification cannot be avoided. For this reason we cannot expect studies in the future with a higher level of evidence than that reported here. Thus, the categorization for levels of evidence may include a category "best evidence achievable", but this is a common problem with the methodology of health technology assessments and not specific to the present report.

The manuscript needs some editing:

- Index:
  The numbering of the chapters is mixed up (..., 6, 7, 8, *7*, *8*, 9, ...; see page 6).
- Page 16 "false positive" instead of "fasle positive"
- Page 26, Figure 2.2, top box:
  "(CT + histology)" instead of "(CT + histology"
- Page 27: Figure numbering: "Figure 2.3" instead of "Figure 2.2"
- Pages 29, 32:
  The references for citations dealing with the systematic review of literature are missing in the reference list (e.g. Shea 2007, Whiting 2007, Gigerenzer 2007).
- Page 29: "New Castle-Ottawa checklist": Please add a reference.
- Page 62: "One systematic review" instead of "One systematic reviews"
- Page 62: "field" instead of "filed"

- Page 70: Chapter 10.2 Clinical outcomes
  This sentence seems to be a victim of Copy&Paste from the report on FDG-PET in breast cancer. I suppose that the words "diagnosis of primary breast" have to be deleted to make sense.
- Page 73: "response to therapy" instead of "response to t therapy"
- I suggest to replace "small lung cancer" by "small *CELL* lung cancer" in some section headings. The word "cell" seems to be lost in the later part of the manuscript.

Conclusions

I have carefully reviewed the document (except its Italian summary, pages 11-14) and it mainly finds my broad support. The criteria, which were used to define the role of FDG-PET in lung cancer, are appropriate and the conclusions are widely justified.

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July 31st 2011

Reviewer 3

This report seems to be in line with current attempts to provide guide for the use of novel technology in daily clinical practice in a way of formed recommendations. This pertains to the level of evidence (suggestion) which is provided.

I found the text appropriate and easy to understand as well as to follow. Process of synthesis is well done and resulting outcome clear.

Presentation is clear and useful. I have, however found some of the most recent and important references regarding radiotherapy treatment planning missing such as those of Pommier et al (2010) and Kolodziejcyk et al (2010).

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Appendices

Appendix 1.
Voting forms

ORI
Osservatorio Regionale per l'Innovazione

CRITERIA FOR APPROPRIATE USE OF POSITRON EMISSION TOMOGRAPHY IN ONCOLOGY

2010-2011

LUNG CANCER

VOTING FORMS

NAME _____

Agenzia sanitaria e sociale regionale

RegioneEmilia-Romagna

CLINICAL QUESTION

Characterization of solitary pulmonary nodules ≥1 cm

Rationale

Solitary pulmonary nodules (SPNs) are defined as lesions up to 3 cm in size. Because of the widespread use of CT in the investigation of respiratory symptoms, the SPN is a frequent incidental finding. The prevalence of SPNs in lung cancer screening studies ranges between 8% to 51% and the prevalence of malignancy in patients with SPNs between 1.1 to 12% (Wahidi 2007).

Diagnostic role of FDG-PET

PET is a candidate test to characterize SPNs identified by CT.

Treatment effectiveness

Surgery is the cornerstone of early stage non-small cell lung cancer treatment. Five-year survival of stage I patients is over 50% (73% in stage IA, 58% in stage IB), with much room for improvement with systemic adjuvant approaches in stages II and III (ESMO 2010a).

Pre-test probability and change in management

The median pre-test probability of malignancy of solitary pulmonary nodule is 64.7% (range 27.2-86.0% from FDG-PET studies included in Cronin 2008a and from following primary studies).

Research question: FDG-PET as add on
Has FDG-PET sufficient accuracy for characterizing malignant SPN?

Diagnostic accuracy estimates **Level of evidence: moderate**

FDG-PET sensitivity: pooled 95% (95% CI 93-98%)
specificity: pooled 82% (95% CI 77-88%)

Comparators:

Dynamic contrast-enhanced CT
sensitivity: pooled 93% (95% CI 88-97%)
specificity: pooled 76% (95% CI 68-97%)

Dynamic contrast-enhanced MRI
sensitivity: pooled 94% (95% CI 91-97%)
specificity: pooled 79% (95% CI 73-86%)

Consequences of TEST for		Level of importance* (1-9)
Patients with malignant SPN	True positives: patients correctly diagnosed for malignancy, proceed to curative surgery, in order to improve survival	
	False negatives: patients incorrectly diagnosed as not having cancer, delay diagnosis and curative surgery, with possible impact on survival	
Patients with non malignant SPN	True negatives: patients correctly diagnosed as not having cancer end clinical investigation pathway	
	False positives: patients incorrectly diagnosed for malignancy proceed to unnecessary surgical intervention, with possible serious harm	

* not important (score 1-3)
important (4-6)
critical (7-9)
to a decision

Matrix of natural frequencies

		N of patients out of 100 submitted to the exam (pre-test probability range: 27.2-86%)	
		According to FDG-PET	According to CT
Patients with malignant SPN	True positives	26 - 82	25 - 80
	False negatives	1 - 4	2 - 6
Patients with non malignant SPN	True negatives	60 - 11	55 - 11
	False positives	13 - 3	18 - 3
		100	100

CLINICAL QUESTION

Role of FDG-PET in the characterization of solitary pulmonary nodules ≥1 cm

APPROPRIATENESS of FDG-PET 1-2-3 inappropriate 4-5-6 uncertain 7-8-9 appropriate									
	1	2	3	4	5	6	7	8	9
INDETERMINATE (due to lack of studies)									

CLINICAL QUESTION

Staging of patients with primary non-small cell lung cancer - NSCLC

Rationale

Staging is the assessment of the extent of disease and is performed for prognostic and therapeutic purposes. The selection of patients for radical treatment (surgery, radical chemotherapy/radiotherapy) requires an investigation pathway directed towards as much diagnostic and staging information as possible. (SIGN 2005; BTS 2010). CT is the initial imaging modality of choice for diagnosis and staging of lung cancer. Metastatic disease should be thoroughly investigated before excluding patients from radical treatment. Recent guidelines recommend use of FDG-PET as an add on test for patients with negative or unclear results. (BTS 2010; ESMO 2010; SIGN 2005; NICE 2005).

Diagnostic role of FDG-PET

To further investigate patients with negative or unclear results for mediastinal lymph node involvement or metastatic disease, in order to either direct patients to confirmatory biopsies of lesions or to radical treatment.

Treatment effectiveness

Surgery is the most recommended treatment for early stage NSCLC (AIOM 2009, BTS 2010, ACCP 2007) and five-year survival of stage I patients is over 50% (73% in stage IA, 58% in stage IB), with much room for improvement with systemic adjuvant approaches in stages II and III (ESMO 2010a). In patients with unresectable stage III or stage IV disease chemotherapy and/or following or concurrent radiotherapy is the standard of care.

Pre-test probability and change in management

The median pre-test probability of mediastinal lymph node metastases is 33.5% (range 15-78%; data from Ung 2007), while the median pre-test probability of distant metastasis, extracted from only one study, resulted to be 6% (Ung 2007).

Research question: FDG-PET as add on

Has FDG-PET sufficient sensitivity and specificity to identify mediastinal lymph nodes involvement or distant metastasis in patients with negative or unclear conventional imaging results?

Diagnostic accuracy estimates **Level of evidence: moderate**

Mediastinal lymph node staging

FDG-PET

sensitivity: (pooled) 83%
specificity: (pooled) 87%

CT

sensitivity: (pooled) 68%
specificity: (pooled) 76%

Distant metastases staging

FDG-PET

sensitivity: (pooled) 93%
specificity: (pooled) 96%

Consequences of TEST for		**Level of importance* (1-9)**
NSCLC patients with mediastinal lymph nodes involvement or distant metastasis	True positives: patients correctly diagnosed for mediastinal involvement or distant metastasis, proceed to confirmatory biopsy, in order to establish best therapeutic plan	
	False negatives: patients incorrectly diagnosed as not having mediastinal involvement or distant metastasis proceed to, possibly futile, radical surgery	
NSCLC patients with no mediastinal lymph nodes involvement or distant metastasis	True negatives: patients correctly diagnosed as not having mediastinal involvement or distant metastasis proceed to curative radical surgery	
	False positives: patients incorrectly diagnosed as having mediastinal involvement or distant metastasis proceed to confirmatory biopsy	

* not important (score 1-3)
important (4-6)
critical (7-9)
to a decision

Matrix of natural frequencies

		N of patients out of 100 submitted to the exam	
		According to FDG-PET	**According to CT**
NSCLC patients with mediastinal lymph nodes involvement	True positives	28	23
	False negatives	6	11
NSCLC patients with no mediastinal lymph nodes involvement	True negatives	57	50
	False positives	9	16
		100	100

CLINICAL QUESTION

Role of FDG-PET in staging of patients with primary lung cancer - NSCLC

APPROPRIATENESS of FDG-PET 1-2-3 inappropriate 4-5-6 uncertain 7-8-9 appropriate	1	2	3	4	5	6	7	8	9
INDETERMINATE (due to lack of studies)									

CLINICAL QUESTION

Staging of patients with bronchioloalveolar cancer (BAC)

Rationale

Bronchioloalveolar carcinoma (BAC) has been recently reclassified as essentially adenocarcinoma-in-situ. True BAC is diagnosed with a complete resection, allowing full lesion examination to rule out extended disease. Pre-operative diagnosis is based on appropriate radiology (pure localized "ground glass" lesions) and in some cases on consistent pathology (BTS 2010).

Diagnostic role of FDG-PET

There does not appear to be a role for FDG-PET in pre-operative staging.

Treatment effectiveness

Surgery represents the "gold standard" of treatment in early stage disease. Patients with resected BAC have prolonged survival and a lower recurrence rate after surgical resection than those with other subtypes of NSCLC (ACCP 2007).

Diagnostic accuracy estimates **Level of evidence: very low**

Unavailable due to sparse data.

APPROPRIATENESS of FDG-PET 1-2-3 inappropriate 4-5-6 uncertain 7-8-9 appropriate	1	2	3	4	5	6	7	8	9
INDETERMINATE (due to lack of studies)									

CLINICAL QUESTION

Staging of patients with small cell lung cancer (SCLC)

Rationale

The role of surgery for the treatment of limited SCLC is considered inappropriate due to poor overall survival. In general patients should be treated with a combination chemotherapy and radiotherapy (BTS 2010). Pre treatment staging is necessary to differentiate between limited disease - eligible for combination chemotherapy and concurrent radiotherapy - and extended disease, generally treated with chemotherapy alone (BTS 2010, ESMO 2010).

Diagnostic role of FDG-PET

To further investigate patients with negative or unclear results for mediastinal lymph node involvement or metastatic disease, in order to decide on therapeutic approach (combined chemo/radiotherapy or chemotherapy).

Treatment effectiveness

Clinical trials have reported better 5 year-survival rate (between 20 and 25%) in patients randomized to concurrent chemo-radiotherapy compared with sequential chemo-radiotherapy (BTS 2010; ESMO 2010).

The prognosis of extensive disease is poor with a median survival of 10 months and a 2-year survival rate of 10%. Long term survivors are extremely rare (ESMO 2010).

Pre-test probability and change in management

Pre-test probability of limited disease is 33% (Fischer 2007).

Research question: FDG-PET as add on

Has FDG-PET sufficient sensitivity and specificity to identify distant metastasis in patients with negative or unclear conventional imaging results?

Diagnostic accuracy estimates **Level of evidence: very low**

Not available due to sparse data.

Consequences of TEST for		Level of importance* (1-9)
SCLC patients with extended disease	True positives: patients correctly diagnosed for extended disease proceed palliative systemic treatment False negatives: patients incorrectly diagnosed for limited disease undergo combined chemotherapy and concurrent radiotherapy, with no gain on survival	
SCLC patients with limited disease	True negatives: patients correctly diagnosed for limited disease proceed to combined chemotherapy and concurrent radiotherapy, to improve their survival False positives: patients incorrectly diagnosed for extended disease do not receive combined chemo-radiotherapy with possible loss in survival	

* not important (score 1-3)
important (4-6)
critical (7-9)
to a decision

CLINICAL QUESTION

Staging of patients with primary small cell lung cancer (SCLC)

APPROPRIATENESS of FDG-PET 1-2-3 inappropriate 4-5-6 uncertain 7-8-9 appropriate	1	2	3	4	5	6	7	8	9
INDETERMINATE (due to lack of studies)									

CLINICAL QUESTION

Target volume definition of curative radiation treatment in patients with lung cancer

Rationale

Radical radiation treatment is recommended for patients with NSCLC unresectable disease. Concurrent chemo/radiation therapy is recommended for patients with limited SCLC. Post-operative radiotherapy has no indication in patients with a negative resection margin (R0) whilst its role in patients with positive resection margin (R1) is still unknown (BTS 2010).

The main limitation of radiotherapy is related to radiotherapy-induced lung toxicity. Knowledge of risk of radiotherapy is essential and a combination of parameters is generally used to guide the plan of radiation treatment (BTS 2010

Diagnostic role of FDG-PET

FDG-PET imaging could be an additional parameter to be used when planning treatment delivery, in order to decrease risk of severe lung acute and late toxicity.

Treatment effectiveness

Three dimensional treatment planning is recommended for patients undergoing radical thoracic radiotherapy. There are evidence suggesting that radical radiotherapy in patients with NSCLC, when compared to radical surgery, performs well for overall survival, though not so well for loco-regional control and disease-free survival (ESMO 2010, SIGN 2005).

Patients with limited SCLC disease are potentially curable and clinical trials have reported better 5 year-survival rate (between 20 and 25%) in patients treated with concurrent chemo-radiotherapy compared to patients treated with sequential chemo-radiotherapy (BTS 2010; ESMO 2010).

Research question: FDG-PET in addition to CT

Does adding FDG-PET imaging improve the precision of target volume definition?

Pre-test probability and change in management

Few studies report a tendency in reduction of the Gross Target Volume, GVT.

Diagnostic accuracy estimates **Level of evidence: very low**

Not available.

Consequences of TEST for		Level of importance* (1-9)
Patients	True positives (correct increase in target volume)	
	False negatives (incorrect decrease in target volume)	
Patients	True negatives (correct decrease in target volume)	
	False positives (incorrect increase in target volume)	

* not important (score 1-3)
important (4-6)
critical (7-9)
to a decision

CLINICAL QUESTION

Role of FDG-PET in target volume definition of curative radiation treatment in patients with lung cancer

APPROPRIATENESS of FDG-PET 1-2-3 inappropriate 4-5-6 uncertain 7-8-9 appropriate	1	2	3	4	5	6	7	8	9
INDETERMINATE (due to lack of studies)									

CLINICAL QUESTION

During-treatment evaluation of response to neo-adjuvant therapy in patients treated for lung cancer - NSCLC

Rationale

According to the most recent guidelines (AIOM 2009, BTS 2010, ACCP 2007), surgical resection remains the standard of care for fit for surgery patients with early (0, I, II) NSCLC; in these patients pre-surgical (neo-adjuvant) chemo and/or radiotherapy is not recommended.

Selected patients with locally advanced (stage IIIA) cancer can be eligible for surgery, but the role of neo-adjuvant therapy for them is still on debate.

Diagnostic role of FDG-PET

As neo-adjuvant treatment is short, the panel unanimously agreed that there is not a diagnostic role of PET in assessing a during-treatment response to therapy.

APPROPRIATENESS of FDG-PET 1-2-3 inappropriate 4-5-6 uncertain 7-8-9 appropriate	1	2	3	4	5	6	7	8	9
INDETERMINATE (due to lack of studies)									

CLINICAL QUESTION

During-treatment evaluation of response to neo-adjuvant therapy in patients treated for lung cancer - SCLC

Rationale

Patients with limited disease are treated with a combination chemotherapy and radiotherapy, while patients with extended disease are treated with only chemotherapy (BTS 2010; ESMO 2010). Response evaluation is recommended during and at the completion of therapy. Initial positive imaging should be repeated (ESMO 2010). While response to treatment is mainly used for prognosis, in selected patients it could influence subsequent therapeutic options.

Diagnostic role of FDG-PET

As treatment is short, the panel unanimously agreed that there is not a diagnostic role of PET in assessing a during-treatment response to therapy.

APPROPRIATENESS of FDG-PET 1-2-3 inappropriate 4-5-6 uncertain 7-8-9 appropriate	1	2	3	4	5	6	7	8	9
INDETERMINATE (due to lack of studies)									

CLINICAL QUESTION

End of treatment evaluation of response to neo-adjuvant therapy in patients treated for lung cancer - NSCLC

Rationale

In patients with unresectable stage III disease who can tolerate the treatment, chemotherapy and/or following or concurrent radiotherapy is the standard of care. Selected patients with locally advanced (stage IIIA) cancer can be considered for surgery, especially those with a good response to systemic therapy. The role of neo-adjuvant therapy is nevertheless still debated. While response to treatment is mainly used for prognosis, in selected patients it could influence subsequent therapeutic options.

Diagnostic role of FDG-PET

To identify patients with a good response to treatment, in order to decide on subsequent therapeutic approach.

Treatment effectiveness

The evidence on the effectiveness of pre-operative chemotherapy in NSCLC is still controversial and routine neo-adjuvant treatment for locally advanced NCSLC is not recommended.

Systemic and radiation therapy are the only therapeutic options for unresectable early stage (I and II), locally advanced (stage III) and metastatic (stage IV) NSCLC.

Pre-test probability and change in management

The range of pre-test probability of persistent viable malignant cells after neo-adjuvant treatment is between 30% and 50% (Stigt 2009, Eschmann 2007).

Research question: FDG-PET as add on

What is the diagnostic accuracy of FDG-PET in evaluating response to treatment of patients treated for NSCLC and with unclear results from conventional imaging?

Diagnostic accuracy estimates **Level of evidence: low**

Histopathologic response of the primary tumor re-staging

FDG-PET

- sensitivity (heterogeneous): range 80-100%
- specificity (heterogeneous): range 0-100%

Data on comparator tests not available

Consequences of TEST for		Level of importance* (1-9)
Patients not responding to neo-adjuvant therapy	True non responders: patients correctly identified as non responders change from curative treatment to palliative treatment False responders: patients incorrectly identified as responders undergo curative - possibly surgical - treatment, which will not impact on their survival	
Patients with a good response to neo-adjuvant therapy	True responders: patients correctly identified as having a good response to therapy can undergo curative surgical treatment, which might improve survival False non responders: patients incorrectly identified as non responders proceed to palliative treatment, with no gain in survival	

* not important (score 1-3)
important (4-6)
critical (7-9)
to a decision

CLINICAL QUESTION

Role of FDG-PET in end of treatment evaluation of response to therapy in patients treated for lung cancer - NSCLC

APPROPRIATENESS of FDG-PET 1-2-3 inappropriate 4-5-6 uncertain 7-8-9 appropriate	1	2	3	4	5	6	7	8	9
INDETERMINATE (due to lack of studies)									

CLINICAL QUESTION

End of treatment evaluation of response to systemic therapy in patients treated for lung cancer - SCLC

Rationale

Patients with limited disease are treated with concurrent chemo-radiotherapy whilst those with extended disease undergo chemotherapy alone (BTS 2010; ESMO 2010).). While response to treatment is mainly used for prognosis, in selected patients it could influence subsequent therapeutic options.

Diagnostic role of FDG-PET

Panel unanimously agrees that there is not a diagnostic role for PET in assessing end-of-treatment response in patients with SCLC.

APPROPRIATENESS of FDG-PET 1-2-3 inappropriate 4-5-6 uncertain 7-8-9 appropriate	1	2	3	4	5	6	7	8	9
INDETERMINATE (due to lack of studies)									

CLINICAL QUESTION

Follow up of patients treated for lung cancer (NSCLC) with no suspicion of recurrence

Rationale

No guideline recommends an active follow up with imaging tests, other than CT, in asymptomatic patients (ESMO 2010, NCCN 2011, BTS 2010).

The post-treatment management of patients with early stage and locally advanced (non-metastatic) NSCLC is controversial as evidence on a better prognosis correlated to earlier diagnosis and treatment of recurrence is still lacking (ESMO 2010).

Diagnostic role of FDG-PET

Panel unanimously agrees that there is not a diagnostic role for PET in follow up of asymptomatic patients.

APPROPRIATENESS of FDG-PET 1-2-3 inappropriate 4-5-6 uncertain 7-8-9 appropriate	1	2	3	4	5	6	7	8	9
INDETERMINATE (due to lack of studies)									

CLINICAL QUESTION

Diagnosis and staging of suspected loco-regional recurrence in patients treated for lung cancer (NSCLC)

Rationale

Although advancements in early diagnosis and treatment have been made in the hope of improving survival recurrence remains a major obstacle to achieving a complete cure for NSCLC patients. Reported recurrence rates after complete resection ranges from 30 to 75% depending on the final pathologic stage (Takenaka 2010).

While progressive disease is treated with palliative types of treatments, solitary lesions occurring in the contralateral lung should be considered as secondary primary and treated with curative intention if tumors are resectable (ESMO 2010).

Diagnostic role of FDG-PET

To characterize unclear lesions appearing after radical treatment, in order to identify a local recurrence eligible for radical treatment

Treatment effectiveness

Evidence on impact of earlier treatment of recurrence on clinical outcomes is lacking, but treatment of solitary lesions is recommended (ESMO 2010, BTS 2010).

Pre-test probability and change in management

The pre-test probability of loco-regional recurrence in patients with suspected recurrence of NSCLC is 75 is between 68.2% and 75.3% (Hellwig 2006, Isobe 2009). Evidence from 2 studies evaluating change in management following FDG-PET exams (Hicks 2001, Nakamoto 2008) shows a change ranging between 17% and 63% - with the start of a new therapeutic program.

Research question: FDG-PET as add on

Is FDG-PET sufficiently specific to characterize malignant solitary lesions in patients with unclear results from conventional imaging (CT)?

Diagnostic accuracy estimates **Level of evidence: very low**

Not available due to sparse data.

Consequences of TEST for		**Level of importance* (1-9)**
Patients with resectable loco-regional recurrence	True positives: patients correctly diagnosed for recurrent solitary lesions proceed to surgical radical treatment, which might improve their survival False negatives: patients' lesions incorrectly diagnosed as non malignant, do not receive appropriate radical treatment, which could have improved their survival	
Patients with no loco-regional recurrence	True negatives: patients' lesions correctly diagnosed as non malignant remain in follow up False positives: patients incorrectly diagnosed for recurrent solitary lesions undergo unnecessary surgical treatment, with no impact on survival but possible risks and negative impact on quality of life	

* not important (score 1-3)
important (4-6)
critical (7-9)
to a decision

CLINICAL QUESTION:

Role of FDG-PET in the diagnosis and staging of suspected loco-regional recurrence in patients treated for lung cancer (NSCLC)

APPROPRIATENESS of FDG-PET 1-2-3 inappropriate 4-5-6 uncertain 7-8-9 appropriate	1	2	3	4	5	6	7	8	9
INDETERMINATE (due to lack of studies)									

Appendix 2. Systematic review of literature: search strategy and tables of evidence

ORI
Osservatorio Regionale per l'Innovazione

CRITERIA FOR APPROPRIATE USE OF POSITRON EMISSION TOMOGRAPHY WITH FDG (FDG-PET) IN LUNG CANCER

SEARCH STRATEGY AND TABLES OF EVIDENCE

Agenzia sanitaria e sociale regionale

RegioneEmilia-Romagna

SEARCH STRATEGY

The following databases were searched for the period between January 2006 - date of the literature search for the precedent update - and September 2010:

- a Cochrane Database of Systematic Reviews (CDSR - The Cochrane Library)
- Database of Abstracts of Reviews of Effects (DARE - The Cochrane Library)
- Health Technology Assessment Database (HTA Database - The Cochrane Library)
- Cochrane Central Register of Controlled Trials (CENTRAL - The Cochrane Library)
- National Library of Medicine's Medline database (PubMed)
- Elsevier's Embase

Language restrictions: English, Italian, French and Spanish.

Reference lists of identified articles were checked for additional references.

CDSR, DARE, HTA database, CENTRAL search strategy

1. "Positron-Emission Tomography" [MeSH descriptor explode all trees]
2. "Fluorodeoxyglucose F18" [MeSH descriptor explode all trees]
3. "positron emission tomography": ti,ab,kw
4. pet*: ti,ab,kw
5. pet scan*: ti,ab,kw
6. "Fluorodeoxyglucose F18": ti,ab,kw
7. fdg NEAR/2 18: ti,ab,kw
8. **1/7 OR**
9. Lung NEAR Cancer*: ti,ab,kw
10. Pulmonary nodule*: ti,ab,kw
11. "Lung neoplasms"[Mesh explodes all trees]
12. **9/11 OR**
13. **8 AND 12**

MEDLINE search strategy

1. "Fluorodeoxyglucose F18"[Mesh]
2. "2-Fluoro-2-deoxyglucose" [All Fields]
3. "18F Fluorodeoxyglucose" [All Fields]
4. "F 18 Fluorodeoxyglucose" [All Fields]
5. Fludeoxyglucose* [All Fields]
6. "2 fluoro 2 deoxy d glucose"[All Fields]
7. 18fluorodesoxyglucose*[All Fields]
8. fluorodeoxyglucose*[All Fields]
9. "fluorine 18 fluorodeoxyglucose" [All Fields]
10. 18f dg*[All Fields])
11. 18fluorodeoxyglucose*[All Fields]
12. 18fdg [All Fields]
13. 18 fdg* [All Fields]
14. fdg 18* [All Fields]
15. fdg/* [All Fields]
16. "fdg pet"[All Fields]
17. "Positron-Emission Tomography"[Mesh]
18. "positron emission tomography" [title/abstract]
19. pet [title/abstract]

20. "pet scan" [All Fields]
21. "pet scans" [All Fields]
22. "pet scanner" [All Fields]
23. petscan [All Fields]
24. **1/23 OR**
25. "Lung Neoplasms"[Mesh:noexp]
26. "Bronchial Neoplasms"[Mesh])
27. "Multiple Pulmonary Nodules"[Mesh]
28. "Solitary Pulmonary Nodule"[Mesh]
29. "non-small cell lung cancer"[Title/Abstract]
30. "non-small cell lung carcinoma"[Title/Abstract]
31. "non-small cell lung carcinomas"[Title/Abstract]
32. "non-small lung cancers"[Title/Abstract]
33. "lung cancer"[Title/Abstract]
34. "pulmonary cancer"[Title/Abstract]
35. "pulmonary cancers"[Title/Abstract]
36. "lung cancers"[Title/Abstract]
37. "bronchogenic carcinoma"[Title/Abstract]
38. "bronchogenic carcinomas"[Title/Abstract]
39. "bronchial carcinoma"[Title/Abstract]
40. "bronchial carcinomas"[Title/Abstract]
41. "small cell lung cancer"[Title/Abstract]
42. "small cell lung cancers"[Title/Abstract]
43. "multiple pulmonary nodules"[Title/Abstract]
44. "solitary pulmonary nodule"[Title/Abstract]
45. "solitary pulmonary nodules"[Title/Abstract]
46. "solitary pulmonary tumor"[Title/Abstract]
47. "solitary pulmonary tumors"[Title/Abstract]
48. "pulmonary coin lesion"[Title/Abstract]
49. "pulmonary coin lesions"[Title/Abstract]
50. **25/49 OR**
51. **24 AND 50**

Limits: Humans

Publication date: 2006-2010

Languages: English, French, Italian, Spanish

EMBASE search strategy

1. "positron emission tomography"/syn
2. "fluorodeoxyglucose f 18"/exp
3. "fluorodeoxyglucose f 18"/syn
4. "computer assisted emission tomography"/exp
5. "computer assisted emission tomography" OR
6. pet
7. "pet scans"
8. "pet scanner"
9. "pet scan"
10. "pet/ct scan"
11. "pet/ct scans"
12. "pet/ct"
13. "positron emission tomography/computed tomography"
14. pet NEAR/4 scan*
15. pet NEAR/4 ct
16. **1/15 OR**
17. "lung cancer"/ de,syn, keyword
18. "lung metastasis"/ de,syn, keyword
19. "lung sarcoma"/ de,syn, keyword
20. "lung nodule"/ de,syn, keyword
21. "lung metastasis"/ de,syn, keyword
22. "lung sarcoma"/ de,syn, keyword
23. "lung nodule"/ de,syn, keyword
24. "lung carcinoma"/ de,syn, keyword
25. "lung carcinoma"/ de,syn, keyword
26. lung adenocarcinoma/ de,syn, keyword
27. lung alveolus cell carcinoma/ de,syn, keyword
28. lung non-small cell cancer/ de,syn, keyword
29. lung small cell cancer/ de,syn, keyword
30. lung squamous cell carcinoma/ de,syn, keyword
31. "lung nodule": ab,ti
32. "pulmonary nodule": ab,ti
33. "lung cancer": ab,ti
34. "pulmonary cancer": ab,ti
35. "lung metastastis": ab,ti

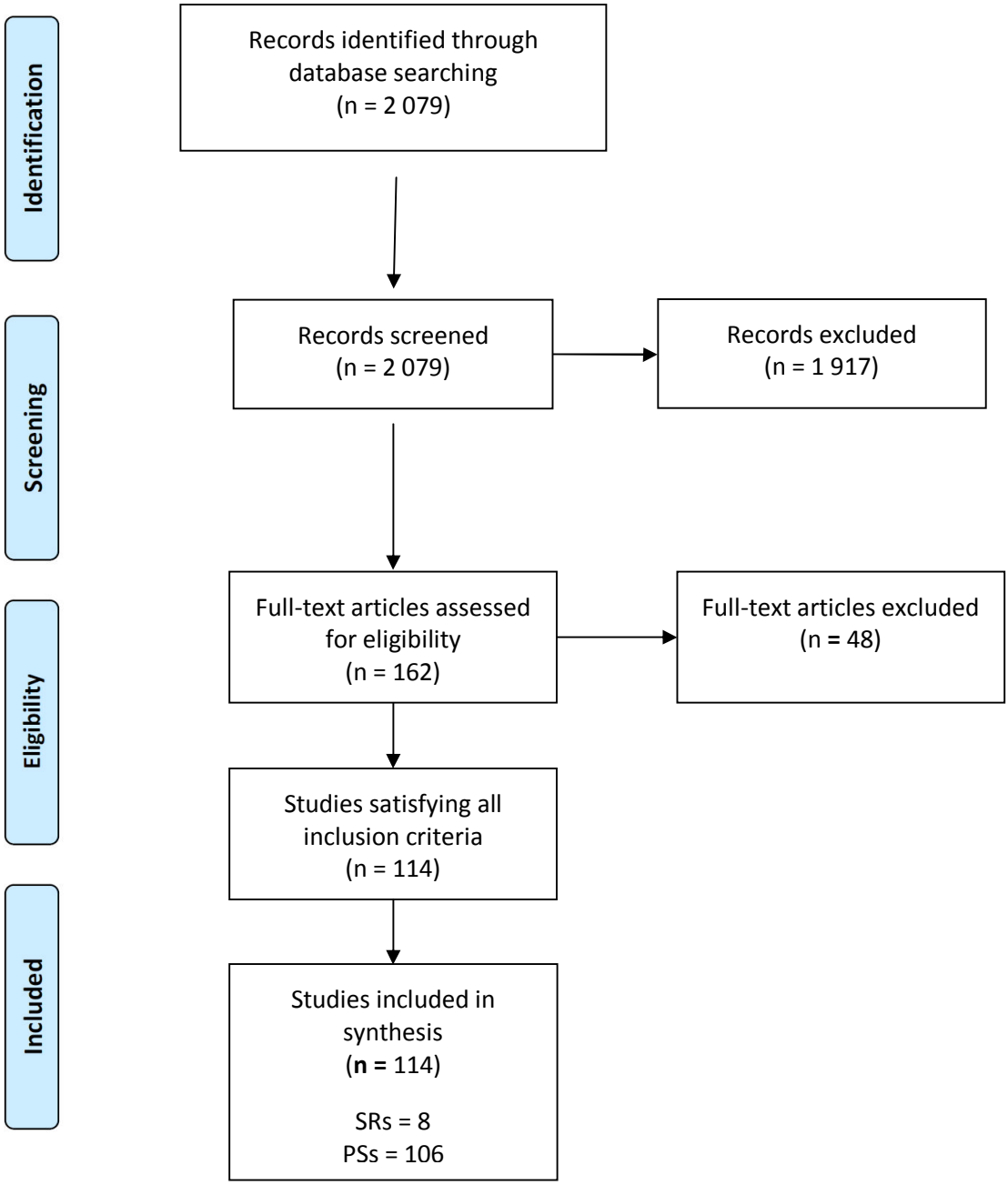
36. "bronchopulmonary metastasis": ab,ti
37. "bronchus metastasis": ab,ti
38. "lung near/3 sarcoma": ab,ti
39. "lung alveolus sarcoma": ab,ti
40. "malignant lung sarcoma": ab,ti
41. "pulmonary sarcoma": ab,ti
42. "bronchial carcinoma": ab,ti
43. "lung sarcoma": ab,ti
44. "bronchopulmonary carcinoma": ab,ti
45. "bronchus carcinoma": ab,ti
46. "lung carcinoma": ab,ti
47. "pulmonary adenocarcinoma": ab,ti
48. "alveobronchial carcinoma": ab,ti
49. "lobular carcinoma": ab,ti
50. "lung cavitary carcinoma": ab,ti
51. "peribronchial carcinoma": ab,ti
52. "lung alveolus cell carcinoma": ab,ti
53. "alveolar carcinoma": ab,ti
54. "bronchioalveolar lung carcinoma": ab,ti
55. "bronchoalveolar carcinoma": ab,ti
56. "bronchoalveolar cancer": ab,ti
57. "alveolar cell cancer": ab,ti
58. "alveolar cell carcinoma": ab,ti
59. "lung alveolus cell cancer": ab,ti
60. "pulmonary alveolar cell cancer": ab,ti
61. "lung non-small cell cancer": ab,ti
62. "non-small-cell lung cancer": ab,ti
63. "lung small cell cancer": ab,ti
64. "small cell lung carcinoma": ab,ti
65. "small cell lung cancer": ab,ti
66. "lung squamous cell carcinoma": ab,ti
67. "lung epidermoid cancer": ab,ti
68. "lung squamous cell cancer": ab,ti
69. **17/68 OR**
70. **16 AND 69**
71. 70 AND ("article" OR "review"/it OR "short survey")

Limits: Humans

Publication date: 2006-2010

Languages: English, French, Italian, Spanish

Figure A.1. Lung cancer: study selection process according to PRISMA Flow Diagram (Moher 2009)



CHAPTER 4.
Characterization of solitary pulmonary nodule

Diagnostic accuracy

Systematic reviews

Author, year	**Cronin 2008a, Cronin 2008b**
Technology	PET
Disease	lung cancer
Objective	to assess: ▪ **X** primary diagnosis (to assess malignancy of solitary pulmonary nodules) ▪ staging (before treatment) ▪ response to treatment (during treatment) ▪ re-staging (after treatment) (residual disease) ▪ follow up in asymptomatic patients ▪ diagnosis of suspected recurrence ▪ staging recurrence ▪ impact on management ▪ impact of clinical outcomes
Inclusion criteria	P patients with solitary pulmonary lymph nodules I FDG-PET C CT, MRI, Tc-99m-depreotide SPECT R histopathology (percutaneous or surgical biopsy, surgical resection) for more than 50% of patients O diagnostic accuracy S diagnostic accuracy studies with prospective or retrospective recruitment with at least 10 patients
Years covered by the search	up to December 2005
Study selection data abstraction, quality assessment performed by two authors independently	no for study selection yes for data abstraction and quality assessment
Comprehensive bibliographic search: at least two databases searched	yes Medline, Cancerlit, Cochrane Library
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	no
Searched also unpublished studies	no
Language restriction	no: data from non English studies extracted from abstracts
Overall number of references retrieved and n of included studies reported	yes

N. and references of excluded studies reported, reason given	yes (only reasons, not references)
Characteristics of included studies clearly reported in tables	yes
Methodological quality of primary studies assessed; criteria reported	yes: QUADAS checklist
Results of quality assessment used to formulate results and conclusions	yes: meta-regression performed to explore for causes of heterogeneity, out of that also quality score
Meta-analysis performed with appropriate statistic methods	yes
Publication bias assessed	yes
N. of included studies study design	44 CT: 10 MRI: 6 Tc-99m-depreotide SPECT: 7 PET: 22
N. of included patients	2 867 CT: 1 093 MRI: 284 TC-99M-depreotide SPECT: 421 PET: 1 069
Reference standard	histopathology for more than 50% of patients
Comparator	CT, MRI, SPECT
Performance results	PET sensitivity: 95% (95% CI 93-98); statistical heterogeneity specificity: 82% (95% CI 77-88); statistical heterogeneity LR+: 5.4 (95% CI 3.6-7.3) LR-: 0.06 (95% CI 0.02-0.09) CT: sensitivity: 93% (95% CI 88-97); statistical heterogeneity specificity: 76% (95% CI 68-97); statistical heterogeneity LR+: 3.9 (95% CI 2.4-5.4) LR-: 0.10 (95% CI 0.03-0.16) MRI sensitivity: 94% (95% CI 91-97); statistical heterogeneity specificity: 79% (95% CI 73-86); statistical heterogeneity LR+: 4.6 (95% CI 3-6.1) LR-: 0.08 (95% CI 0,03-0.12) TC-99M- depreotide SPECT sensitivity: 95% (95% CI 93-97); statistical heterogeneity specificity: 82% (95% CI 78-85); statistical heterogeneity LR+: 5.2 (95% CI 4-6.3) LR-: 0.06 (95% CI 0.04-0.08) For all measures studies quality accounted for 95 to 97% of heterogeneity

Impact on management	not assessed
Impact on clinical outcome	not assessed
Recommendations and conclusions	Although small differences in the point estimates of performance were noted, the 95% confidence intervals excluded significant differences. From a clinician perspective, differences on performances for all tests were negligible; therefore, the clinician may confidentially use any of the four tests in further evaluation a solitary pulmonary nodule. It is reasonable to choose the least expensive, or the most easily available, or the modality that the radiologists have more expertise with or the modality the patients have the least disutility of.
Comments of ASSR reviewers	Indirect comparison among different modalities

Author, year	**Ung 2007**
Technology	PET
Disease	NSCLC
Objective	to assess: ▪ **X** diagnosis (to assess malignancy of solitary pulmonary nodules) ▪ staging (before treatment): ▪ response to treatment (during treatment) ▪ re-staging (after treatment) (residual disease) ▪ follow up in asymptomatic patients ▪ diagnosis of suspected recurrence ▪ staging recurrence ▪ impact on management ▪ impact of clinical outcomes
Inclusion criteria	P patients with NSCLC or SCLC or SPN I PET, PET-CT C any kind R histological exam followed by CT or additional imaging, follow up O diagnostic accuracy for diagnosis, N staging, M staging S HTA reports, practice guidelines, systematic reviews, meta-analyses published after 1999. Primary studies published after September 2004 randomized or single-arm prospective studies/studies were excluded if they have fewer than 35 subject
Years covered by the search	1996-2006
Study selection data abstraction, quality assessment performed by two authors independently	no
Comprehensive bibliographic search: at least two databases searched	yes Cochrane Database of Systematic Reviews, Embase and Medline
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	yes (conference proceedings)
Searched also unpublished studies	yes (physician data query clinical trials)
Language restriction	English
Overall number of references retrieved and n of included studies reported	yes
N. and references of excluded studies reported, reason given	no

Characteristics of included studies clearly reported in tables	yes
Methodological quality of primary studies assessed; criteria reported	yes
Results of quality assessment used to formulate results and conclusions	yes
Meta-analysis performed with appropriate statistic methods	meta-analysis was not performed
Publication bias assessed	no
N. of included studies study design	SPN 2 systematic review 7 prospective studies NSCLC impact on outcomes: 3 RCT accuracy staging: 22 prospective observational studies accuracy (staging in mediastinal lymph node): 1 systematic review, 2 meta-analyses, 5 prospective observational studies (already included in 22 of staging) accuracy (extra thoracic staging): 1 prospective observational studies (already included in 22 of staging) SCLC 3 prospective studies
Patients of included studies Pre-test probability when given	data on patients characteristics were reported
n. of included patients	SPN 1 909 patients from one review and in the other review the number of patients was not reported 497 patients from 6 prospective studies in 1 study the number of patients not reported NSCLC - accuracy (staging) 2 186 patients from primary studies 833 from 1 meta-analysis (already included in SPN) the number of patients in 1 meta-analyses and 1 review was not reported NSCLC - impact on outcomes 836 patients from primary studies SCLC 162 patients from primary studies
Reference standard	histology followed by CT or additional imaging, follow up biopsy
Comparator	biopsy, follow up, CT, Gamma Camera

Performance results	*SPN: diagnosis* primary studies PET sensitivity: range 79-100% specificity: range 40-90% systematic reviews PET sensitivity: mean 96% (SE = 1%) - median 97% specificity: mean 78% (SE = 3%) - median 78% Gamma Camera PET sensitivity: mean 92% (SE = 4%) specificity: mean 86% (SE = 4%) *NSCLC* Accuracy (M staging): PET sensitivity: range 82-90% specificity: range 90-98% Accuracy (N staging mediastinum) PET sensitivity: mean 83% (SE = 2%) - median 81% specificity: mean 96% (SE = 1%) - median 90% Gamma Camera PET sensitivity: mean 81% (SE = 4%) specificity: mean 95% (SE = 2%) Impact on management: addition of PET to conventional workup led to a 51% (95% CI = 32 to 80, P = .003) relative reduction in futile thoracotomies (from 41% in the conventional workup arm to 21% in the conventional plus PET arm) and prevented unnecessary surgery in 20% of patients with suspected NSCLCC *SCLC* PET N staging sensitivity: range 89-100% specificity: range 78-98%
Impact on management	assessed
Impact on clinical outcome	not assessed

Authors' recommendations and conclusions	PET appears superior to computed tomography imaging for mediastinal staging in non - small cell lung cancer (NSCLCC). Randomized trials evaluating the utility of PET in potentially resectable NSCLCC report conflicting results in terms of the relative reduction in the number of non curative thoracotomies. PET has not been studied as extensively in patients with small cell lung cancer, but the available data show that it has good accuracy in staging extensive-versus limited-stage disease. Although the current evidence is conflicting, PET may improve results of early-stage lung cancer by identifying patients who have evidence of metastatic disease that is beyond the scope of surgical resection and that is not evident by standard pre-operative staging procedures. Further trials are necessary to establish the clinical utility of PET as part of the standard pre-operative assessment of early-stage lung cancer.

Synoptic table of primary studies: diagnosis of solitary pulmonary nodule

Author, year	Patient number	Patient characteristics	Technology	Reference standard	Sensitivity	Specificity
Alkhawaldeh 2010	265	suspected malignant solitary pulmonary nodules detected by conventional CT	FDG-PET/CT visual assessment	histological findings or follow up for at least 24 months	97%	58%
			FDG-PET/CT first time SUV ≥2.5		65%	92%
			FDG-PET/CT partial volume corrected first time SUV ≥2.5		84%	91%
			FDG-PET/CT second time SUV ≥2.5		90%	80%
			FDG-PET/CT increase SUV over time		84%	95%
			FDG-PET/CT increase or no change in SUV		92%	92%
			FDG-PET/CT first time SUV ≥2.5 and/or increase or no change in SUV		95%	90%
Bryant 2006	585	indeterminate solitary pulmonary nodules	FDG-PET/CT	histological findings (transthoracic or transbronchial biopsy followed by complete resection of the nodule)	93%	75%
Chang 2010	170	indeterminate solitary pulmonary nodules by CT	FDG-PET	histological findings or follow up for at least 24 months	90.7%	82.4%
			FDG-PET/CT		88.4%	89.2%

Author, year	Patient number	Patient characteristics	Technology	Reference standard	Sensitivity	Specificity
Christensen 2006	41	indeterminate solitary pulmonary nodule	FDG-PET cut off SUV: 2.5	histological findings or follow up for at least 18 months	84%	82%
			FDG-PET visual		96%	76%
			FDG-PET nodule enhancement CT		100%	29%
Chun 2009	45	indeterminate solitary pulmonary nodule composed of ≥50% ground glass opacity and with a diameter of ≥100 mm by CT	FDG-PET/CT cut off SUV: 1.2	histological findings or follow up for at least 9 months	62.1%	80%
Degirmenci 2008	46	indeterminate solitary pulmonary nodule by CT	FDG-PET/CT cut off SUV: 2.4	histological findings or follow up for at least 24 months	62%	80%
Ferran 2006	29	indeterminate solitary pulmonary nodule	FDG-PET threshold SUV: 3.5	histological findings (surgery, FNA or bronchoalveolar lavage)	95%	89%
			FDG-PET threshold SUV: 1.3		85%	88%
			FDG-PET visual		100%	88%
			TC-99M- depreotide SPECT		85%	88%
Fletcher 2008	344	indeterminate solitary pulmonary nodule	FDG-PET	histological findings and/or clinical and imaging follow up	91.7%	82.3%
			CT		95.6%	40.6%

Author, year	Patient number	Patient characteristics	Technology	Reference standard	Sensitivity	Specificity
Grgic 2010	140	indeterminate solitary pulmonary nodule	FDG-PET visual	histological findings or follow up for at least 24 months	94%	70%
			FDG-PET SUV max cut off 2		96%	55%
			FDG-PET SUV max cut off 2.5		94%	63%
			FDG-PET SUV max cut off 4		85%	85%
Hashimoto 2006	43	indeterminate solitary pulmonary nodule seen at CT, lesion with F-FDG-PET SUV <2.5	FDG-PET visual	histological findings or follow up for at least 6 months	100%	63%
			FDG-PET SUV max cut off 1.59		81%	85%
			FDG-PET contrast ratio cut off 0.29		75%	82%
Hau 2008	93	indeterminate solitary pulmonary nodule	FDG-PET/CT	histological findings and/or clinical and imaging follow up	97.8%	79.2%
Hsieh 2008	15	malignant or benign solitary pulmonary nodule	FDG-PET	histological findings and/or clinical and imaging follow up	50%	20%
			C methionine PET		100%	90%
Huang 2010	56	indeterminate solitary pulmonary nodule	FDG-PET/CT Visual, non attenuated corrected	histopathology or clinical and radiological follow up	100%	64%
			FDG-PET/CT Visual attenuated corrected		91%	59%
			FDG-PET/CT SUV cut off 2		79%	77%
Jeong 2008	100	biopsy proven malignant or benign solitary pulmonary nodule	FDG-PET	histopathology	88%	71%
			FDG-PET/CT		88%	77%
			CT		82%	66%

Author, year	Patient number	Patient characteristics	Technology	Reference standard	Sensitivity	Specificity
Kagna 2009	93	indeterminate solitary pulmonary nodule and clinically high risk of lung cancer	FDG-PET/CT visual	histological findings or follow up for at least 24 months	94%	70%
			FDG-PET/CT SUV max cut off 2.2		77%	83%
Kaira 2009	43	indeterminate solitary pulmonary nodule	FDG-PET/CT visual	histopathology	89%	not reported
			F-FMT PET visual		84%	100%
Khalaf 2008	173	indeterminate solitary pulmonary nodule seen at CT, and a positive PET scan for nodule(s) to measure the SUV	FDG-PET cut off 2.5	histological findings (biopsy)	data reported by nodule dimension	data reported by nodule dimension
Kim 2007	42	indeterminate solitary pulmonary nodule smaller than 30 mm	FDG-PET/CT	histological findings (biopsy or surgical resection)	97%	85%
Kim 2008	158	indeterminate solitary pulmonary nodule smaller than 30 mm	FDG-PET/CT cut off 2.5 SUV max	histological findings (biopsy or surgical resection)	89.3%	50.9%

Author, year	Patient number	Patient characteristics	Technology	Reference standard	Sensitivity	Specificity
Kim 2009	30	indeterminate solitary pulmonary nodule detected by CT and PET SUV max <2.5	FDG-PET/CT visual	histological findings or clinical and/or radiological follow up for at least 12 months	46.1%	82.3%
			FDG-PET/CT Images 60 min after administration of F-18 FDG; cut off SUV max 2		61.5%	94.1%
			FDG-PET/CT Images 120 min after administration of F-18 FDG; cut off SUV max 1.8		69.2%	94.1%
			FDG-PET/CT Images 60 min after administration of F-18 FDG; cut off contrast ratio 0.68		76.9%	70.5%
			FDG-PET/CT Images 120 min after administration of F-18 FDG; cut off contrast ratio 0.58		100%	70.5%
Lu 2007	85	indeterminate solitary pulmonary nodule	FDG-PET	histopathology	89.8%	61.5%
			FDG-PET/CT		96.6%	80.8%
			CT		88.1%	64.5%
Mori 2008	104	indeterminate solitary pulmonary nodule	FDG-PET	histopathology or clinical and radiological follow up for at least 2 years	72%	79%
			DWMRI		70%	97%

Author, year	Patient number	Patient characteristics	Technology	Reference standard	Sensitivity	Specificity
Nunez 2007	173	indeterminate solitary pulmonary nodule at CT	dual time point FDG-PET early reading visual	histological findings	74%	58%
			dual time point FDG-PET late reading visual		85%	41%
			dual time point FDG-PET early reading quantitative		92%	25%
			dual time point FDG-PET late reading visual quantitative		95%	33%
Ohba 2009a	107	indeterminate solitary pulmonary nodule <3 cm at CT	FDG-PET visual	histological findings or clinical follow up for at least 12 months	78%	76%
			FDG-PET cut off SUV 1.10		74%	79%
			FDG-PET CR lung T-N/T+N l		89%	76%
			FDG-PET CR lung T/N		99%	31%
Ohba 2009b	110	indeterminate solitary pulmonary nodule <3 cm seen at CT	FDG-PET	histological findings or clinical follow up for at least 24 months	72%	82%
			DWMRI		73%	96%
Ohno 2008a	175	indeterminate solitary pulmonary nodule <3 cm seen at CT or chest RX	FDG-PET/CT SUV cut off 1.8	microbiological examination, cytological or histological examinations of specimens obtained by needle biopsy, transbronchial lung biopsy, VATS, or surgical resection and follow up MDCT examinations	93.4%	54.0%

Author, year	Patient number	Patient characteristics	Technology	Reference standard	Sensitivity	Specificity
Pauls 2008	276	indeterminate solitary pulmonary nodule seen at MDCT or chest RX	FDG-PET/CT	histopathology and clinical follow up for 3 years	assuming the equivocal findings as benign 96% assuming the equivocal findings as malignant 98%	assuming the equivocal findings as benign 87% assuming the equivocal findings as malignant 68%
			FDG-PET		assuming the equivocal findings as benign 97% assuming the equivocal findings as malignant 98%	assuming the equivocal findings as benign 83% assuming the equivocal findings as malignant 77%
			MDCT		assuming the equivocal findings as benign 94% assuming the equivocal findings as malignant 99%	assuming the equivocal findings as benign 75% assuming the equivocal findings as malignant 37%

Author, year	Patient number	Patient characteristics	Technology	Reference standard	Sensitivity	Specificity
Suga 2009	137	patients with NSCLC solitary pulmonary nodule and patients with benign lesions	FDG-PET/CT delayed SUV max cut off 5.5	histopathology or clinical and radiological follow up	77.6%	80.7%
			FDG-PET/CT early SUV max cut off 2.5		80.2%	43.8%
Tian 2008	55	indeterminate solitary pulmonary nodule less than 2 cm	FDG-PET/CT	histopathology or clinical and radiological follow up	87.5%	69.2%
			FLT-PET/CT		75.0%	82.2%
			dual tracer FLT-and FDG-PET/CT		100%	89.7%
Tsunezuka 2007	150	indeterminate solitary pulmonary nodule less than 2 cm	FDG-PET	histopathology	75.9%	64.1%
Tsushima 2008	53	indeterminate solitary pulmonary nodule with non-solid components seen by CT	FDG-PET/CT Visual	histopathology. (wedge resection or lobectomy)	80%	93%
			FDG-PET/CT SUV max cut off 1.5		100%	96%
Yamamoto 2008a	54	solitary pulmonary nodules seen at CT	FDG-PET/CT visual analysis	histopathology or clinical and radiological follow up for at least 12 months	97%	50%
			FLG-PET visual analysis		83%	83%
			FLG-PET SUV cut off 1.9		86%	72%
			FDG-PET SUV cut off: 4.7		89%	67%

Author, year	Patient number	Patient characteristics	Technology	Reference standard	Sensitivity	Specificity
Yi 2006	119	solitary pulmonary nodules seen at CT	FDG-PET/CT	histopathology or clinical and radiological follow up for at least 12 months	96%	88%
			HDCT		81%	93%

Primary studies

Author, year	Alkhawaldeh 2010
Technology	FDG-PET
Disease	solitary pulmonary nodule
Objective	to assess diagnostic accuracy in the evaluation of solitary pulmonary nodule for malignancy
Patients characteristics	265 patients with suspected malignant solitary pulmonary nodules detected by conventional CT mean age 67 years (range 41-92)
Index test	FDG-PET/CT
Comparator	
Reference standard	histological findings (n. 107 nodules) or clinical and radiological follow up for at least 24 months (n. 158 nodules)
Country	USA
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with retrospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	no
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported for histological confirmation, not applicable for follow up
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	no, histological confirmation for positive, follow up for negatives
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	not clear
Withdrawals from the study explained	no withdrawals

Results	FDG-PET visual assessment sensitivity: 97% specificity: 58% FDG-PET first time SUV ≥2.5 sensitivity: 65% specificity: 92% FDG-PET partial volume corrected first time SUV ≥2.5 sensitivity: 84% specificity: 91% FDG-PET second time SUV ≥2.5 sensitivity: 90% specificity: 80% FDG-PET increase SUV over time sensitivity: 84% specificity: 95% FDG-PET increase or no change in SUV sensitivity: 92% specificity: 92% FDG-PET first time SUV ≥2.5 and/or increase or no change in SUV sensitivity: 95% specificity: 90%
Authors' recommendations and conclusions	Dual time point FDG-PET has potential impact on improving the diagnostic accuracy for malignant lung nodules. It should be included in the clinical work up of patients with pulmonary nodule

Author, year	**Baram 2008**
Technology	FDG-PET
Disease	solitary pulmonary nodules
Objective	to assess diagnostic accuracy in the evaluation of thoracic lesion for malignancy (from data it is clear that authors deal with solitary pulmonary nodules)
Patients characteristics	313 patients with suspected malignant solitary pulmonary nodules mean age 62 years
Index test	FDG-PET
Comparator	clinical suspicion
Reference standard	issue sampling or follow up (2 years)
Country	USA
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with retrospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	no
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported for histological confirmation, not applicable for follow up
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	no, histological confirmation for positive, follow up for negatives
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	not clear
Withdrawals from the study explained	no withdrawals

Results	FDG-PET SUV ≥2.5 sensitivity: 82.4% specificity: 78.1% FDG-PET SUV >0 sensitivity: 94.5% specificity: 57.3% Clinical suspicion (high versus intermediate/low) sensitivity: 91.7% specificity: 83.3% Clinical suspicion (high/intermediate versus low) sensitivity: 99.5% specificity: 28.1%
Authors' recommendations and conclusions	Clinical suspicion and PET are both accurate in diagnosing thoracic malignancy. When suspicion and PET are concordant, diagnostic accuracy is very high; when discordant, clinical suspicion was more accurate. When clinical suspicion or PET were intermediate, there is a significant likelihood for cancer.

Author, year	**Bryant 2006**
Technology	FDG-PET/CT
Disease	solitary pulmonary nodule
Objective	to assess diagnostic accuracy in the evaluation of solitary pulmonary nodule for malignancy
Patients characteristics	585 patients with indeterminate solitary pulmonary nodules mean age 60.5 years
Index test	FDG-PET/CT
Comparator	
Reference standard	histological findings (transthoracic or transbronchial biopsy followed by complete resection of the nodule)
Country	USA
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with prospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	yes, for index test; not reported for reference standard
Withdrawals from the study explained	no withdrawals
Results	FDG-PET /CT sensitivity: 93% specificity: 75%

Authors' recommendations and conclusions	Although FDG-PET/CT is a valuable non invasive study for indeterminate pulmonary nodule, tissue is still required. There significant overlaps in the SUV max values between benign and malignant lesions and one must be aware of the various pathologic condition that can cause false positive and false negative results.

Author, year	**Chang 2010**
Technology	FDG-PET/CT
Disease	solitary pulmonary nodule
Objective	to assess diagnostic accuracy in the evaluation of solitary pulmonary nodule for malignancy
Patients characteristics	170 patients with indeterminate solitary pulmonary nodules based on clinical evaluation, chest X ray, conventional CT and no previous history of malignancy mean age 61.7 years (range 31-86)
Index test	FDG-PET/CT
Comparator	
Reference standard	histological findings (n. 52) or clinical and radiological follow up for at least 24 months (n. 65)
Country	Taiwan
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with retrospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	no
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported for histological confirmation, not applicable for follow up
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	no, histological confirmation for positive, follow up for negatives
Execution of the reference standard described	no
Independent and blind interpretation of index test and reference standard results	yes for index test, not clear for reference standard
Withdrawals from the study explained	no withdrawals

Results	FDG-PET alone sensitivity: 90.7% specificity: 82.4% PPV: 75% NPV: 93.8% FDG-PET/CT sensitivity: 88.4% specificity: 89.2% PPV: 82.6% NPV: 93%
Authors' recommendations and conclusions	Although the additional contribution of the CT component of the integrated PET/CT is limited, it appears to significantly increase the diagnostic value of PET in indeterminate cases of solitary pulmonary nodes

Author, year	**Christensen 2006**
Technology	FDG-PET
Disease	solitary pulmonary nodule
Objective	to assess diagnostic accuracy in the assessment of solitary pulmonary nodule of indeterminate malignancy
Patients characteristics	41 patients with indeterminate solitary pulmonary nodule mean age 66 years (range 36-84)
Index test	FDG-PET
Comparator	nodule enhancement CT
Reference standard	histological findings or clinical and/or radiological follow up for at least 18 months
Country	USA
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with retrospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported for histological confirmation, not applicable for follow up
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	not reported
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	yes
Withdrawals from the study explained	no withdrawals

Results	FDG-PET cut off SUV: 2.5 sensitivity: 84% specificity: 82% PPV: 88% NPV: 78% FDG-PET visual interpretation: sensitivity: 96% specificity: 76% PPV: 86% NPV: 93% FDG-PET nodule enhancement CT: sensitivity: 100% specificity: 29% PPV: 68% NPV: 100%
Authors' recommendations and conclusions	Due to its higher specificity and only slightly reduced sensitivity FDG-PET is preferable to nodule enhancement CT in evaluating indeterminate pulmonary nodules. However CT remains useful due to its high NPV, convenience and lower cost. Qualitative FDG-PET provides the best balance of sensitivity and specificity.

Author, year	Chun 2009
Technology	FDG-PET/CT
Disease	solitary pulmonary nodule composed of ≥50% ground glass opacity
Objective	to assess diagnostic accuracy in the differentiation of malignancy from inflammation of solitary pulmonary nodule composed of ≥50% ground glass opacity for malignancy
Patients characteristics	45 patients with indeterminate solitary pulmonary nodule composed of ≥50% ground glass opacity and with a diameter of ≥100 mm detected by CT mean age 61 years
Index test	FDG-PET/CT
Comparator	
Reference standard	histological findings or clinical and/or radiological follow up for at least 9 months
Country	Korea
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with retrospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported for histological confirmation, not applicable for follow up
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	not reported
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	not reported
Withdrawals from the study explained	no withdrawals

Results	FDG-PET/CT cut off SUV: 1.2 sensitivity: 62.1% specificity: 80% PPV: 78.3% NPV: 64.5%
Authors' recommendations and conclusions	The maximum SUV of part solid nodules was higher in inflammation than in malignant tumors. This is a quite paradoxical results considering the basic knowledge that the malignant pulmonary nodules have higher glucose metabolism. Therefore, when we find a part solid nodules showing high glucose metabolism, especially a maximum SUV greater than 2.6, we should recommend follow up in imaging instead of performing immediate invasive procedure for tissue diagnosis.

Author, year	**Degirmenci 2008**
Technology	FDG-PET/CT
Disease	solitary pulmonary nodule
Objective	to assess diagnostic accuracy in the evaluation of solitary pulmonary nodule for malignancy
Patients characteristics	46 patients with indeterminate solitary pulmonary nodule seen by CT; mean age 69 years (range 34-83)
Index test	FDG-PET/CT
Comparator	
Reference standard	histopathology (n. 33) or clinical and radiological follow up for at least 24 months (n. 16)
Country	Turkey
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with retrospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	no
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	no: histopathology for positives, follow up for negatives
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	not reported
Withdrawals from the study explained	no withdrawals
Results	FDG-PET/CT SUV max cut off 2.4 sensitivity: 62% specificity: 80%
Authors' recommendations and conclusions	Obtaining SUV max may be sufficient in the clinical setting.

Author, year	**Ferran 2006**
Technology	FDG-PET
Disease	solitary pulmonary nodule
Objective	to assess diagnostic accuracy in the evaluation of solitary pulmonary nodule for malignancy
Patients characteristics	29 patients with indeterminate solitary pulmonary nodule mean age 52 years, range 38-80
Index test	FDG-PET
Comparator	TC-99M- depreotide SPECT
Reference standard	histological findings (surgery, FNA or bronchoalveolar lavage
Country	Spain
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with prospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	yes for index test and comparator; no for reference standard
Withdrawals from the study explained	no withdrawals

Results	FDG-PET SUV threshold 3.5 sensitivity: 95% specificity: 89% FDG-PET SUV threshold 1.3 sensitivity: 85% specificity: 88% FDG-PET visual assessment sensitivity: 100% specificity: 88% TC-99M- depreotide SPECT sensitivity: 85% specificity: 88%
Authors' recommendations and conclusions	Has a greater sensitivity and diagnostic accuracy for assessing malignancy of indeterminate lung lesions.

Author, year	**Fletcher 2008**
Technology	FDG-PET
Disease	solitary pulmonary nodule
Objective	to assess diagnostic accuracy in the evaluation of solitary pulmonary nodule for malignancy
Patients characteristics	344 patients with indeterminate solitary pulmonary nodule mean age not reported
Index test	FDG-PET
Comparator	CT
Reference standard	histological findings and/or clinical and imaging follow up
Country	USA
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with prospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported for histology, not applicable for follow up
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	no: follow up for negatives, histology for positives
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	yes for index test and comparator; no for reference standard
Withdrawals from the study explained	no withdrawals

Results	FDG-PET sensitivity: 91.7% specificity: 82.3% AUC: 0.93 CT sensitivity: 95.6% specificity: 40.6% AUC: 0.82
Authors' recommendations and conclusions	PET was more accurate and reliable than CT and resulted in a fewer indeterminate results. Probably or definitely benign results on PET and CT are strongly associated with a benign diagnosis; definitely malignant diagnosis on PET are strong associated with a final malignant diagnosis.

Author, year	**Grgic 2010**
Technology	FDG-PET
Disease	solitary pulmonary nodule
Objective	to assess diagnostic accuracy in the evaluation of solitary pulmonary nodule for malignancy
Patients characteristics	140 patients with indeterminate solitary pulmonary nodule mean age 62 years (age range 24-84)
Index test	FDG-PET
Comparator	
Reference standard	histological findings and/or clinical and imaging follow up for at least 24 months
Country	Germay
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with retrospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	no: histology for positives; histology or clinical and imaging follow up for negatives
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	not reported
Withdrawals from the study explained	no withdrawals

Results	FDG-PET Visual sensitivity: 94% specificity: 70% PPV: 81% NPV: 89% SUV max; cut off 2 sensitivity: 96% specificity: 55% PPV: 74% NPV: 92% SUV max; cut off 2.5 sensitivity: 94% specificity: 63% PPV: 77% NPV: 88% SUV max; cut off 4 sensitivity: 85% specificity: 85% PPV: 88% NPV: 81%
Authors' recommendations and conclusions	FDG-PET allows assessment of the individual risk for malignancy in SPNs by considering tumoral SUV and pre-test probability. Higher FDG uptake in lung cancer as measured by SUV analysis is a prognostic factor. In patients with low FDG uptake in an SPN and increased risk during surgery omission of diagnostic thoracotomy may be warranted.

Author, year	**Hashimoto 2006**
Technology	FDG-PET
Disease	solitary pulmonary nodule
Objective	to assess diagnostic accuracy in the evaluation of solitary pulmonary nodule for malignancy
Patients characteristics	43 patients with indeterminate solitary pulmonary nodule seen at CT, lesion with F-FDG-PET SUV <2.5 and definite diagnosis made by histology or clinical follow up for at least 6 months, out of 360 consecutive patients who had been evaluated for SPN mean age not reported
Index test	FDG-PET
Comparator	
Reference standard	histological findings and/or clinical and imaging follow up for at least 6months
Country	Japan
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with retrospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes for patients included; it should be noted, however, that this is a sub-cohort drawn from 360 patients who received FDG-PET, who had histological confirmation; no information about PET results is provided for the 317 patients who had not histological confirmation and where excluded form the study
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	no: histology for positives; histology or clinical and imaging follow up for negatives
Execution of the reference standard described	yes

Independent and blind interpretation of index test and reference standard results	yes for PET/CT; no for reference standard
Withdrawals from the study explained	no withdrawals
Results	FDG-PET Visual sensitivity: 100% specificity: 63% PPV: 62% NPV: 100% SUV max; cut off 1.59 sensitivity: 81% specificity: 85% PPV: 77% NPV: 89% CR (contrast ratio); cut off 0.29 sensitivity: 75% specificity: 82% PPV: 71% NPV: 85%
Authors' recommendations and conclusions	Our results suggest that the abilities of visual and semiquantitative methods to identifies malignancies are equal. The probability of malignancy for pulmonary lesions with absent uptake is very low. In contrast, the probability of any visually obvious lesion being malignant is about 60%.

Author, year	**Hau 2008**
Technology	FDG-PET/CT
Disease	solitary pulmonary nodule
Objective	to assess diagnostic accuracy in the evaluation of solitary pulmonary nodule for malignancy
Patients characteristics	93 patients with indeterminate solitary pulmonary nodule mean age 60.7 years (range 28-88)
Index test	FDG-PET/CT
Comparator	
Reference standard	histological findings and/or clinical and imaging follow up
Country	France
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with retrospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	no: follow up for negatives, histology for positives
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	not reported
Withdrawals from the study explained	no withdrawals
Results	FDG-PET/CT sensitivity: 97.8% specificity: 79.2% PPV: 81.5% NPV: 97.4%
Authors' recommendations and conclusions	These results support the validity of FDG-PET for the diagnosis of malignancy of pulmonary nodules.

Author, year	**Hsieh 2008**
Technology	FDG-PET
Disease	solitary pulmonary nodule
Objective	to assess diagnostic accuracy in the evaluation of solitary pulmonary nodule for malignancy
Patients characteristics	15 patients with biopsy proven malignant or benign solitary pulmonary nodule mean age 65 years (range 25-87)
Index test	FDG-PET
Comparator	C methionine PET
Reference standard	histopathology or clinical and radiological follow up
Country	Taiwan
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with retrospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	no, histopathology for positives, clinical and radiological follow up for negatives
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	not reported
Withdrawals from the study explained	no withdrawals

Results	FDG-PET sensitivity: 50% specificity: 20% PPV: 20% NPV: 50% C-MET-PET sensitivity: 100% specificity: 90% PPV: 80% NPV: 100%
Authors' recommendations and conclusions	PET seems more specific and sensitive when compared with 18F-FDG-PET for the purpose of differentiating benign and malignant thoracic nodules/masses. Patient selection may also contribute to the unexpected excellent performance of 11C-MET-PET because the lung lesions that are readily diagnosed by FDG-PET and CT would not be referred for 11C-MET PET. If 11C-MET-PET were performed for all these lesions, we could expect a large patient group and when these data are analyzed, a more similar diagnostic power may be achieved between 18F-FDG-PET and 11C-METPET studies as described in the previous literature.

Author, year	**Huang 2010**
Technology	non attenuation corrected FDG-PET/CT
Disease	solitary pulmonary nodule
Objective	to assess diagnostic accuracy in the evaluation of solitary pulmonary nodule for malignancy
Patients characteristics	56 patients with indeterminate solitary pulmonary nodule mean age 59 years (range 31-90)
Index test	FDG-PET/CT
Comparator	
Reference standard	histopathology or clinical and radiological follow up.
Country	USA
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with retrospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	no, histopathology for positives, clinical and radiological follow up for negatives
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	yes for index test, not reported for reference standard
Withdrawals from the study explained	no withdrawals

Results	FDG-PET/CT visual, non attenuated corrected sensitivity: 100% specificity: 64% PPV: 81% NPV: 100% visual, attenuated corrected sensitivity: 91% specificity: 59% PPV: 78% NPV: 81% SUV cut off: 2 sensitivity: 79% specificity: 77% PPV: 84% NPV: 71%
Authors' recommendations and conclusions	Visual assessment of NAC 18F-FDG-PET images alone may provide a more accurate characterization of solitary pulmonary lesions.

Author, year	**Jeong 2008**
Technology	FDG-PET/CT
Disease	solitary pulmonary nodule
Objective	to assess diagnostic accuracy in the evaluation of solitary pulmonary nodule for malignancy
Patients characteristics	100 patients with biopsy proven malignant (n. 40) or benign (n. 60) solitary pulmonary nodule mean age 58 years
Index test	FDG-PET/CT
Comparator	PET alone, CT alone
Reference standard	histopathology (for 53 biopsy-proven benign nodules, histological diagnoses were made by percutaneous core biopsy (n = 16) and video-assisted thoracoscopic surgery biopsy or wedge resection (n = 37). For 40 malignant nodules, histological diagnoses were made by percutaneous needle aspiration or core biopsy (n = 5) and video-assisted thoracoscopic surgery biopsy (n = 3) or lobectomy (n = 32). For 7 benign nodules reference standard was follow up
Country	Korea
Outcomes considered	sensitivity, specificity
Study design	case control diagnostic retrospective study; patients selected on the basis of biopsy proven benign or malignant nodule
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes

Independent and blind interpretation of index test and reference standard results	yes for index test and comparators, not reported for reference standard
Withdrawals from the study explained	no withdrawals
Results	FDG-PET sensitivity: 88% specificity: 71% PPV: 67% NPV: 90% CT sensitivity: 82% specificity: 66% PPV: 61% NPV: 84% FDG-PET/CT sensitivity: 88% specificity: 77% PPV: 72% NPV: 90%
Authors' recommendations and conclusions	For the characterization of SPNs, integrated PET/CT provides significantly better specificity than CT alone or PET alone and both integrated PET/CT and PET alone allow more confidence than CT alone.

Author, year	**Kagna 2009**
Technology	FDG-PET/CT
Disease	solitary pulmonary nodule
Objective	to assess diagnostic accuracy in the evaluation of solitary pulmonary nodule for malignancy
Patients characteristics	93 patients with indeterminate solitary pulmonary nodule and clinically considered at high risk of lung cancer (current or former smokers aged 40 or more, with a smoking history of a minimum 10 pack/years) out of 307 consecutive patients who had been evaluated for SPN mean age 67 years (range 46-90)
Index test	FDG-PET/CT
Comparator	
Reference standard	histological findings and/or clinical and imaging follow up for at least 24 months
Country	Israel
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with retrospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	no: histology for positives; histology or clinical and imaging follow up for negatives
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	yes for PET/CT; no for reference standard
Withdrawals from the study explained	no withdrawals

Results	FDG-PET/CT visual sensitivity: 94% specificity: 70% PPV: 66% NPV: 95% SUV max cut off 2.2 sensitivity: 77% specificity: 83% PPV: 73% NPV: 86%
Authors' recommendations and conclusions	The results of the present study demonstrate that integrated FDG-PET/low dose CT improves noninvasive characterization of SPN in patients at high risk of lung cancer. Mainly by higher specificity A single screening procedure with FDG-PET/CT may improve screening for lung cancer in high risk patients.

Author, year	**Kaira 2009**
Technology	FDG-PET/CT
Disease	solitary pulmonary nodule
Objective	to assess diagnostic accuracy in the evaluation of solitary pulmonary nodule for malignancy
Patients characteristics	43 patients with indeterminate solitary pulmonary nodule mean age 67 years (range 41-79)
Index test	FDG-PET/CT
Comparator	F-FMT-PET
Reference standard	histopathology
Country	Japan
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with retrospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	14 days between FDG-PET and FMT-PET; not reported for reference standard
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	not reported
Withdrawals from the study explained	no withdrawals
Results	FDG-PET/CT sensitivity: 89% specificity: not reported F-FMT-PET sensitivity: 84% specificity: 100%

Authors' recommendations and conclusions	The specificity was higher by F-FMT-PET than by FDG-PET.
Comment of ASSR reviewers	Authors reported that specificity of F FMT-PET was higher than specificity of FDG-PET but results for FDG-PET were nor reported.

Author, year	**Khalaf 2008**
Technology	FDG-PET
Disease	solitary pulmonary nodule
Objective	to assess diagnostic accuracy in the evaluation of solitary pulmonary nodule for malignancy and the correlation between the size of pulmonary nodules and the SUV for benign as well as for malignant nodules
Patients characteristics	173 patients with indeterminate solitary pulmonary nodule seen at CT, and a positive PET scan for nodule(s) to measure the SUV mean age: 67 years(range 25-89)
Index test	FDG-PET
Comparator	
Reference standard	histological findings (biopsy)
Country	USA
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with retrospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	not reported
Withdrawals from the study explained	no withdrawals

Results	FDG-PET SUV cut off 2.5 nodules ≤1cm sensitivity: 85% specificity: 36% nodules 1.1-2 cm sensitivity: 91% specificity: 47% nodules 2.1-3 cm sensitivity: 94% specificity: 23% nodules 2.1-3 cm sensitivity: 100% specificity: 17% nodules >3 cm sensitivity: 100% specificity: 17%
Authors' recommendations and conclusions	Although, the SUV max cut off of 2.5 is a useful tool in the evaluation of large pulmonary nodules (>1.0 cm), it has no or minimal value in the evaluation of small pulmonary nodules (≤1.0 cm).

Author, year	**Kim 2007**
Technology	FDG-PET/CT
Disease	solitary pulmonary nodule
Objective	to assess diagnostic accuracy in the evaluation of solitary pulmonary nodule for malignancy
Patients characteristics	42 patients with indeterminate solitary pulmonary nodule smaller than 30 mm in axial diameter mean age 67 years (range 35-84)
Index test	FDG-PET/CT
Comparator	
Reference standard	histological findings (biopsy or surgical resection)
Country	USA
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with retrospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	yes
Withdrawals from the study explained	no withdrawals

Results	FDG-PET /CT sensitivity: 97% specificity: 85% PPV: 93% NPV: 92%
Authors' recommendations and conclusions	FDG-PET/CT demonstrates an excellent performance in classifying SPNs as benign or malignant. The combination of anatomic and metabolic imaging is synergistic by maintaining the sensitivity of CT and the specificity of PET, resulting in an overall significantly improved accuracy.

Author, year	**Kim 2008**
Technology	FDG-PET
Disease	solitary pulmonary nodule
Objective	to assess diagnostic accuracy in the evaluation of solitary pulmonary nodule for malignancy
Patients characteristics	158 patients with indeterminate solitary pulmonary nodule smaller than 30 mm in axial diameter mean age 67 years (range 35-84)
Index test	FDG-PET/CT
Comparator	
Reference standard	histological findings (biopsy or surgical resection)
Country	USA
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with retrospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes for patients included; it should be noted, however, that this is a sub-cohort drawn from 288 patients who received FDG-PET, who had histological confirmation; no information about PET results is provided for the 130 patients who had not histological confirmation and where excluded form the study
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	not reported
Withdrawals from the study explained	no withdrawals

Results	FDG-PET small (<2 cm) nodules; cut off 2.5 SUV max sensitivity: 75% specificity: 72.2% large (≥2 cm) nodules; cut off 2.5 SUV max sensitivity: 91.9% specificity: 40.7% overall sensitivity: 89.3% specificity: 50.9%
Authors' recommendations and conclusions	FDG-PET/CT is reasonably accurate and useful tool for characterizing the nature of indeterminate pulmonary lesions.

Author, year	**Kim 2009**
Technology	FDG-PET/CT
Disease	solitary pulmonary nodule
Objective	to assess diagnostic accuracy in the evaluation of solitary pulmonary nodule for malignancy
Patients characteristics	30 patients with indeterminate solitary pulmonary nodule detected by CT and PET SUV max <2.5 mean age not reported
Index test	FDG-PET/CT
Comparator	
Reference standard	histological findings or clinical and/or radiological follow up for at least 12 months
Country	USA
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with retrospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported for histological confirmation, not applicable for follow up
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	no
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	not reported
Withdrawals from the study explained	no withdrawals

Results	FDG-PET/CT Visual: sensitivity: 46.1% specificity: 82.3% PPV: 66.7% NPV: 66.7% AUC: 0.658 Images 60 min after administration of F-18 FDG; cut off SUV max 2: sensitivity: 61.5% specificity: 94.1% PPV: 88.9% NPV: 76.2% AUC: 0.785 Images 120 min after administration of F-18 FDG; cut off SUV 1.8: sensitivity: 69.2% specificity 94.1% PPV: 90% NPV: 80% AUC: 0.848 Images 60 min after administration of F-18 FDG; cut off CR (contrast ratio) 0.68: sensitivity: 76.9% specificity: 70.5% PPV: 66.7% NPV: 80% AUC: 0.801 Images 120 min after administration of F-18 FDG; cut off CR (contrast ratio) 0.58: sensitivity: 100% specificity: 70.5% PPV: 72.2% NPV: 100% AUC: 0.842
Authors' recommendations and conclusions	Both visual and quantitative analysis could differentiate benign from malignant nodules. Quantitative indices are more accurate than visual analysis.

Author, year	**Lu 2007**
Technology	FDG-PET/CT
Disease	solitary pulmonary nodule
Objective	to assess diagnostic accuracy in the evaluation of solitary pulmonary nodule for malignancy
Patients characteristics	85 patients with indeterminate solitary pulmonary nodule mean age 58 years (range 36-87)
Index test	FDG-PET/CT
Comparator	PET alone, CT alone
Reference standard	histopathology
Country	China
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with retrospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	no
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	not reported
Withdrawals from the study explained	no withdrawals

Results	FDG-PET/CT sensitivity: 96.6% specificity: 80.8% PPV: 91.9% NPV: 91.3% FDG-PET sensitivity: 89.8% specificity: 61.5% PPV: 84.1% NPV: 72.7% CT sensitivity: 88.1% specificity: 64.5% PPV: 85.2% NPV: 60.8%
Authors' recommendations and conclusions	PET/CT is of greater value in characterization of lung masses than PET and CT performed separately.

Author, year	**Mori 2008**
Technology	FDG-PET
Disease	solitary pulmonary nodule
Objective	to assess diagnostic accuracy in the evaluation of solitary pulmonary nodule for malignancy
Patients characteristics	104 patients with indeterminate solitary pulmonary nodule mean age 68 years (range 20-80)
Index test	FDG-PET
Comparator	diffusion weighted magnetic resonance (DWI)
Reference standard	histopathology or clinical and radiological follow up for at least 2 years
Country	Japan
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with prospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	two weeks between PET and DWI; time interval between index test and histological examination not reported
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	no, histopathology for positives, clinical and radiological follow up for negatives
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	yes for index test and comparator, no for reference standard
Withdrawals from the study explained	no withdrawals

Results	FDG-PET sensitivity: 72% specificity: 79% DWI sensitivity: 70% specificity: 97%
Authors' recommendations and conclusions	DWI may be able to be used in place of FDG-PET to distinguish malignant from benign pulmonary nodules/masses with fewer false-positive results compared with FDG-PET.

Author, year	**Nunez 2007**
Technology	dual time point FDG-PET
Disease	solitary pulmonary nodule
Objective	to assess diagnostic accuracy in the evaluation of solitary pulmonary nodule for malignancy and the correlation between the size of pulmonary nodules and the SUV for benign as well as for malignant nodules
Patients characteristics	173 patients with indeterminate solitary pulmonary nodule seen at CT mean age: 69 years (range 38-88)
Index test	late reading (3 h and 17 min after injection FDG-PET)
Comparator	early reading (1 h after injection)
Reference standard	histological findings
Country	USA
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with prospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	yes for PET; not reported for reference standard
Withdrawals from the study explained	no withdrawals

Results	FDG-PET early reading visual analysis sensitivity: 74% specificity: 58% PPV: 91% NPV: 28% FDG-PET late reading visual analysis sensitivity: 85% specificity: 41% PPV: 89% NPV: 32% FDG-PET early reading quantitative analysis (T:B count ratios above optimum thresholds of 10%) sensitivity: 92% specificity: 25% PPV: 88% NPV: 37% FDG-PET late reading quantitative analysis (T:B count ratios above optimum thresholds of 10%) sensitivity: 95% specificity: 33% PPV: 89% NPV: 57%
Authors' recommendations and conclusions	In malignant pulmonary lesions, there is a progressive, although variable, increase in FDG uptake over time. Increasing FDG uptake is a nonspecific finding, as some benign lesions also demonstrate increasing uptake. The use of delayed PET imaging with semi quantitative analysis improves the sensitivity and accuracy of the characterization of pulmonary lesions, with no statistically significant change in the specificity. Therefore, appears to be possible to avoid the early image without affecting the results of the study.

Author, year	**Ohba 2009a**
Technology	FDG-PET
Disease	solitary pulmonary nodule
Objective	to assess diagnostic accuracy in the evaluation of solitary pulmonary nodule for malignancy
Patients characteristics	107 patients with indeterminate solitary pulmonary nodule less than 3 cm seen at CT mean age not reported
Index test	FDG-PET
Comparator	
Reference standard	histological findings or clinical follow up for at least 12 months
Country	Japan
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with prospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	no, histology for positives, follow up for negatives
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	yes for PET; not reported for reference standard
Withdrawals from the study explained	no withdrawals

Results	FDG-PET visual analysis sensitivity: 78% specificity: 76% FDG-PET quantitative analysis cut off SUV: 1.10 sensitivity: 74% specificity: 79% FDG-PET CR lung T-N/T+N sensitivity: 89% specificity: 76% FDG-PET CR lung T/N sensitivity: 99% specificity: 31%
Authors' recommendations and conclusions	The FDG uptake evaluated by the CR lung is superior to that evaluated using the visual assessment, SUV max, for the diagnosis of pulmonary malignancies, especially for well-differentiated lung adenocarcinoma. The simplified formula of CR lung with T/N can be used in place of that with T-N/T+N.

Author, year	**Ohba 2009b**
Technology	FDG-PET
Disease	solitary pulmonary nodule
Objective	to assess diagnostic accuracy in the evaluation of solitary pulmonary nodule for malignancy
Patients characteristics	110 patients with indeterminate solitary pulmonary nodule less than 3 cm seen at CT mean age 68 years (range 36-82)
Index test	FDG-PET
Comparator	diffusion weighted MRI
Reference standard	histological findings or clinical follow up for at least 24 months
Country	Japan
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with retrospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	two weeks between PET and MRI; not reported for histological assessment
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	no, histology for positives, follow up for negatives
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	yes for PET and MRI; not reported for reference standard
Withdrawals from the study explained	no withdrawals

Results	FDG-PET sensitivity: 72% specificity: 82% MRI sensitivity: 73% specificity: 96%
Authors' recommendations and conclusions	Diffusion-weighted magnetic resonance imaging is equivalent to positron emission tomography in distinguishing non-small cell lung cancer from benign pulmonary nodules.

Author, year	**Ohno 2008a**
Technology	FDG-PET/CT
Disease	solitary pulmonary nodule
Objective	to assess diagnostic accuracy in the evaluation of solitary pulmonary nodule for malignancy
Patients characteristics	175 patients with indeterminate solitary pulmonary nodule less than 3 cm seen at CT or chest RX mean age 72 years (range 36-85)
Index test	FDG-PET/CT
Comparator	dynamic MRI, dynamic MDCT
Reference standard	microbiological examination (n. 202), cytological or histological examinations of specimens obtained by CT guided transthoracic needle biopsy (n. 9), transbronchial lung biopsy (n. 30), VATS (n. 28), or surgical resection (n. 135) and follow up MDCT examinations (n. 39)
Country	Japan
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with prospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	Yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	three weeks between index test and comparators; not reported for histological assessment
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	no
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	not reported
Withdrawals from the study explained	no withdrawals

Results	FDG-PET SUV cut off: 1.8 sensitivity: 93.4% specificity: 54% PPV: 86% NPV: 73%
Authors' recommendations and conclusions	

Author, year	**Pauls 2008**
Technology	FDG-PET/CT
Disease	solitary pulmonary nodule
Objective	to assess diagnostic accuracy in the evaluation of solitary pulmonary nodule for malignancy
Patients characteristics	276 consecutive patients with indeterminate solitary pulmonary nodule seen at MDCT or chest RX mean age 64 years (range 38-86)
Index test	FDG-PET/CT
Comparator	PET alone, CT alone
Reference standard	histopathology and clinical follow up for three years
Country	Germany
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with prospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	no, histology for positives, follow up for negatives
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	yes for index test and comparators, not reported for reference standard
Withdrawals from the study explained	no withdrawals

Results	Assuming the equivocal findings as benign FDG-PET sensitivity: 97% specificity: 83% PPV: 95% NPV: 88% MDCT sensitivity: 94% specificity: 75% PPV: 93% NPV: 78% FDG-PET/CT sensitivity: 96% specificity: 87% PPV: 96% NPV: 87% Assuming the equivocal findings as malignant FDG-PET sensitivity: 98% specificity: 77% PPV: 94% NPV: 94% MDCT sensitivity: 99% specificity: 37% PPV: 85% NPV: 96% FDG-PET/CT sensitivity: 98% specificity: 68% PPV: 92% NPV: 91%
Authors' recommendations and conclusions	For differentiation of benign from malignant lung lesions, integrated FDG-PET/CT imaging was significantly more accurate than CT but not FDG-PET. The addition of metabolic imaging (FDG-PET) to morphological imaging (CT) leads to an increase in specificity and significantly reduced equivocal findings and is therefore recommended to further specify newly diagnosed lung lesions.

Author, year	**Suga 2009**
Technology	FDG-PET/CT
Disease	solitary pulmonary nodule
Objective	to assess diagnostic accuracy in the evaluation of solitary pulmonary nodule for malignancy
Patients characteristics	76 patients with NSCLC solitary pulmonary nodule and 61 patients benign lesions mean age 67 years
Index test	dual tracer FDG-and FLT PET/CT
Comparator	F FLT PET/CT; FDG-PET/CT
Reference standard	histopathology or clinical and radiological follow up
Country	Japan
Outcomes considered	sensitivity, specificity
Study design	case control diagnostic with retrospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	no
Patients selection criteria clearly described	yew
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	no: histology for positives, clinical follow up for negatives
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	not reported
Withdrawals from the study explained	no withdrawals

Results	FDG-PET/CT Delayed SUV max cut off 5.5 sensitivity: 77.6% specificity: 80.7% PPV: 84.2% NPV: 71.9 % Early SUV max cut off 2.5 sensitivity: 80.2% specificity: 43.8% PPV: 65.5% NPV: 62.5 %
Authors' recommendations and conclusions	Although delayed PET/CT scan enhances the difference of FDG uptake between FDG-avid NSCLC and benign lesions, and the use of delayed SUV max appears to improve the differentiation of these hypermetabolic lesions compared with an early scan, careful interpretation and management for correct differentiation are still required.

Author, year	**Tian 2008**
Technology	dual tracer PET/CT
Disease	solitary pulmonary nodule
Objective	to assess diagnostic accuracy in the evaluation of solitary pulmonary nodule for malignancy
Patients characteristics	55 patients with indeterminate solitary pulmonary nodule less than 2 cm mean age 64.5 years (range 34-78)
Index test	dual tracer FDG-and FLT PET/CT
Comparator	F FLT PET/CT; FDG-PET/CT
Reference standard	histopathology or clinical and radiological follow up
Country	China
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with prospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yew
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	no: histology for positives, clinical follow up for negatives
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	yes
Withdrawals from the study explained	no withdrawals

Results	FDG-PET/CT sensitivity: 87.5% specificity: 69.2% PPV: 53.8% NPV: 93.1 % FLT-PET/CT sensitivity: 75% specificity: 87.2% PPV: 70.6% NPV: 89.5 % Dual tracer FLT-and FDG-PET/CT sensitivity: 100% specificity: 89.7% PPV: 80% NPV: 100 %
Authors' recommendations and conclusions	PET/CT using F FLT and FDG improved the diagnostic accuracy of differentiating pulmonary nodules. FLT and FDG reflect different aspects of biologic features but neither tracer alone could guarantee satisfactory diagnostic performance.

Author, year	**Tsunezuka 2007**
Technology	FDG-PET
Disease	solitary pulmonary nodule
Objective	to assess diagnostic accuracy in the evaluation of solitary pulmonary nodule for malignancy
Patients characteristics	150 patients with indeterminate solitary pulmonary nodule less than 2 cm mean age 64.5 years (range 34-78)
Index test	FDG-PET
Comparator	
Reference standard	histopathology
Country	Japan
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with prospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	no
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	not reported
Withdrawals from the study explained	no withdrawals

Results	FDG-PET sensitivity: 75.9% specificity: 64.1% PPV: 72.4% NPV: 68.3 %
Authors' recommendations and conclusions	The accuracy of FDG-PET is generally low in distinguishing malignancy from benign lesions in small lesions (<2 cm). The significance of PET as a diagnostic tool is small, especially when the tumor has a ground glass component of high grade.

Author, year	**Tsushima 2008**
Technology	FDG-PET/CT
Disease	solitary pulmonary nodule
Objective	to assess diagnostic accuracy in the evaluation of solitary pulmonary nodule with non-solid components for malignancy
Patients characteristics	53 consecutives patients with indeterminate solitary pulmonary nodule with non-solid components seen by CT mean age 63 years (range 49-85)
Index test	FDG-PET/CT
Comparator	
Reference standard	histopathology: wedge resection (n = 43) or lobectomy (n = 10)
Country	Japan
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with retrospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	yes for index test, not reported for reference standard
Withdrawals from the study explained	no withdrawals

Results	FDG-PET/CT visual sensitivity: 80% specificity: 93% PPV: 87% NPV: 83% SUV max cut off 1.5 sensitivity: 100% specificity: 96% PPV: 96% NPV: 100%
Authors' recommendations and conclusions	[F-18] FDG-PET/CT is a potentially useful tool for the differential diagnosis of SPNs with non-solid components. When [F-18] FDG-PET/CT reveals a significant uptake in SPNs with non-solid components, the lesion may have potentially benign characteristics and should be followed up with serial CT scans. On the basis of our results, when FDG uptake is not observed in SPNs with non-solid components, the findings are more suggestive of malignant lesions, which should be surgically resected.

Author, year	**Yamamoto 2008a**
Technology	FDG-PET
Disease	solitary pulmonary nodule
Objective	to assess diagnostic accuracy in the evaluation of solitary pulmonary nodule for malignancy
Patients characteristics	54 patients solitary pulmonary nodules seen at CT mean age 70 years (range 52-88)
Index test	FDG-PET
Comparator	F FLT PET
Reference standard	histopathology or clinical and radiological follow up for at least 12 months
Country	Japan
Outcomes considered	sensitivity, specificity
Study design	cross sectional diagnostic accuracy study with retrospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	no
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	5 days between FLT and FDG-PET; not reported for histology
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	no: histology for positives, clinical follow up for negatives
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	yes for index test and comparator, not reported for reference standard
Withdrawals from the study explained	no withdrawals

Results	FDG-PET/CT visual analysis sensitivity: 97% specificity: 50% PPV: 80% NPV: 90 % FLG-PET visual analysis sensitivity: 83% specificity: 83% PPV: 91% NPV: 71 % FLG-PET SUV cut off: 1.9 sensitivity: 86% specificity: 72% PPV: 86% NPV: 72 % FDG-PET SUV cut off: 4.7 sensitivity: 89% specificity: 67% PPV: 84% NPV: 75 %
Authors' recommendations and conclusions	These preliminary results indicate that FLT PET may be specific for malignant tumors although uptake of FLT in lung cancer was significantly lower than that of FDG.

Author, year	**Yi 2006**
Technology	FDG-PET/CT
Disease	solitary pulmonary nodule
Objective	to assess diagnostic accuracy in the evaluation of solitary pulmonary nodule for malignancy
Patients characteristics	119 patients solitary pulmonary nodules seen at CT mean age 55 years (range 52-88)
Index test	FDG-PET
Comparator	HDCT
Reference standard	histopathology or clinical and radiological follow up for at least 12 months
Country	Korea
Outcomes considered	sensitivity, specificity
Study design	cross sectional diagnostic accuracy study with retrospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	no: histology for positives, clinical follow up for negatives
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	yes
Withdrawals from the study explained	no withdrawals

Results	FDG-PET/CT sensitivity: 96% specificity: 88% PPV: 94% NPV: 92 % HDCT sensitivity: 81% specificity: 93% PPV: 96% NPV: 71 %
Authors' recommendations and conclusions	Integrated PET/CT is more sensitive and accurate than HDCT for the malignant nodule characterization; therefore, PET/CT may be performed as the first-line evaluation tool for SPN characterization. Because HDCT has high specificity and acceptable sensitivity and accuracy, it may be a reasonable alternative for nodule characterization when PET/CT is unavailable.

CHAPTER 5.
Staging of patients with primary lung cancer

5.a. Non-small cell lung cancer (NSCLC)

Diagnostic accuracy

Systematic reviews

Author, year	**Schimmer 2006**
Technology	PET
Disease	NSCLC
Objective	to assess: ▪ **X** diagnosis and staging (N; M) ▪ curative intent RT field definition (only solid tumors) ▪ early response to therapy (PET during treatment) only when not adjuvant therapy ▪ response to therapy at the end of treatment ▪ diagnosis of suspected recurrence and staging of recurrence ▪ follow up in asymptomatic patients
Inclusion criteria	P patients with NSCLC or SCLC or SPN I FDG-PET C mediastinoscopy R not reported O diagnostic accuracy for N staging S not reported
Years covered by the search	2000-2005
Study selection data abstraction, quality assessment performed by two authors independently	not reported
Comprehensive bibliographic search: at least two databases searched	no only Medline
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	no
Searched also unpublished studies	no
Language restriction	English
Overall number of references retrieved and n of included studies reported	yes
N. and references of excluded studies reported, reason given	no

Characteristics of included studies clearly reported in tables	yes
Methodological quality of primary studies assessed; criteria reported	no
Results of quality assessment used to formulate results and conclusions	yes
Meta-analysis performed with appropriate statistic methods	meta-analysis was not performed
Publication bias assessed	no
N. of included studies study design	28 studies (2 meta-analyses, 17 prospective studies and 8 retrospective studies)
Patients of included studies pre-test probability when given	data on patients characteristics were not reported in all studies
N. of included patients	6 859; only 23/28 studies reported the number of patients
Reference standard	not reported
Comparator	mediastinoscopy
Performance results	FDG-PET sensitivity: range 58-94% specificity: range 76-96% Mediastinoscopy sensitivity: range 80-96% specificity: 100%
Impact on management	not assessed
Impact on clinical outcome	not assessed
Authors' recommendations and conclusions	The results of these studies indicate that in patients with NSCLCC incorporating FDG-PET in clinical staging can prevent unnecessary invasive procedures in a significant number of cases. If FDG-PET imaging and CT scan is negative for mediastinal lymph node involvement routinely mediastinoscopy can be omitted and thoracotomy can immediately be performed. In patients with negative FDG-PET scan, but positive CT scan, histological verification by invasive methods can individually be considered. In patients with positive FDG-PET scan mediastinoscopy still remains the definitive method for exact lymph node staging.

Author, year	**Ung 2007**
Technology	PET
Disease	NSCLC
Objective	to assess: ▪ **X** diagnosis and staging (N;M) ▪ curative intent RT field definition (only solid tumors) ▪ early response to therapy (PET during treatment) only when not adjuvant therapy ▪ response to therapy at the end of treatment ▪ diagnosis of suspected recurrence and staging of recurrence ▪ follow up in asymptomatic patients
Inclusion criteria	P patients with NSCLC or SCLC or SPN I PET, PET-CT C any kind R histological exam followed by CT or additional imaging, follow up O diagnostic accuracy for diagnosis, N staging, M staging S HTA reports, practice guidelines, systematic reviews, meta-analyses published after 1999. Primary studies published after September 2004 randomized or single-arm prospective studies/studies were excluded if they have fewer than 35 subject
Years covered by the search	1996-2006
Study selection data abstraction, quality assessment performed by two authors independently	no
Comprehensive bibliographic search: at least two databases searched	yes, Cochrane Database of Systematic Reviews, Embase and Medline
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	yes (conference proceedings)
Searched also unpublished studies	yes (physician data query clinical trials)
Language restriction	English
Overall number of references retrieved and n of included studies reported	yes
N. and references of excluded studies reported, reason given	no
Characteristics of included studies clearly reported in tables	yes

Methodological quality of primary studies assessed; criteria reported	yes
Results of quality assessment used to formulate results and conclusions	yes
Meta-analysis performed with appropriate statistic methods	meta-analysis was not performed
Publication bias assessed	no
N. of included studies study design	SPN 2 systematic review 7 prospective studies NSCLC impact on outcomes: 3 RCT accuracy staging: 22 prospective observational studies accuracy (staging in mediastinal lymph node): 1 systematic review, 2 meta-analyses, 5 prospective observational studies (already included in 22 of staging) accuracy (extrathoracic staging): 2 systematic reviews (one of them 19 studies) SCLC 3 prospective studies
Patients of included studies Pre-test probability when given	data on patients characteristics were reported
n. of included patients	SPN 1 909 patients from one review and in the other review the number of patients was not reported 497 patients from 6 prospective studies in 1 study the number of patients not reported NSCLC - accuracy (staging) 2 186 patients from primary studies 833 from 1 meta-analysis (already included in SPN) the number of patients in 1 meta-analyses and 1 review was not reported NSCLC - impact on outcomes 836 patients from primary studies SCLC 162 patients from primary studies
Reference standard	histology followed by CT or additional imaging, follow up biopsy
Comparator	biopsy, follow up, CT, Gamma Camera

Performance results	*SPN: diagnosis* primary studies PET sensitivity: range 79-100% specificity: range 40-90% systematic reviews PET sensitivity: mean 96% (SE = 1%) - median 97% specificity: mean 78% (SE = 3%) - median 78% Gamma Camera PET sensitivity: mean 92% (SE = 4%) specificity: mean 86% (SE = 4%) *NSCLC* Accuracy (M staging - pooled data from a 2005 systematic review): PET sensitivity: range 93% specificity: range 96% Accuracy (N staging mediastinum - pooled from a 2001 systematic review) PET sensitivity: mean 83% (SE = 2%) - median 81% specificity: mean 96% (SE = 1%) - median 90% Gamma Camera PET sensitivity: mean 81% (SE = 4%) specificity: mean 95% (SE = 2%) Impact on management: addition of PET to conventional workup led to a 51% (95% CI = 32 to 80, P = .003) relative reduction in futile thoracotomies (from 41% in the conventional workup arm to 21% in the conventional plus PET arm) and prevented unnecessary surgery in 20% of patients with suspected NSCLCC. *SCLC* PET N staging sensitivity: range 89-100% specificity: range 78-98%
Impact on management	assessed
Impact on clinical outcome	not assessed

Authors' recommendations and conclusions	PET appears superior to computed tomography imaging for mediastinal staging in non - small cell lung cancer (NSCLCC). Randomized trials evaluating the utility of PET in potentially resectable NSCLCC report conflicting results in terms of the relative reduction in the number of non curative thoracotomies. PET has not been studied as extensively in patients with small cell lung cancer, but the available data show that it has good accuracy in staging extensive-versus limited-stage disease. Although the current evidence is conflicting, PET may improve results of early-stage lung cancer by identifying patients who have evidence of metastatic disease that is beyond the scope of surgical resection and that is not evident by standard pre-operative staging procedures. Further trials are necessary to establish the clinical utility of PET as part of the standard pre-operative assessment of early-stage lung cancer.

Author, year	**Alongi 2006**
Technology	PET
Disease	lung cancer (NSCLC)
Objective	to assess: ▪ primary diagnosis (to assess malignancy of solitary pulmonary nodules) ▪ **X** staging (before treatment): N staging (mediastinal lymph node) ▪ response to treatment (during treatment) ▪ re-staging (after treatment) (residual disease) ▪ follow up in asymptomatic patients ▪ diagnosis of suspected recurrence ▪ staging recurrence ▪ impact on management ▪ impact of clinical outcomes
Inclusion criteria	P patients with NSCLC I FDG-PET C CT R histopathology (thoracotomy, mediastinoscopy) or imaging follow up with CT O diagnostic accuracy S diagnostic accuracy studies with prospective or retrospective recruitment with at least 18 patients
Years covered by the search	up to December 2005
Study selection data abstraction, quality assessment performed by two authors independently	not reported for study selection yes for data abstraction and quality assessment
Comprehensive bibliographic search: at least two databases searched	databases searched
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	not reported
Searched also unpublished studies	no
Language restriction	no
Overall number of references retrieved and n of included studies reported	no, only number of included studies reported
N. and references of excluded studies reported, reason given	no
Characteristics of included studies clearly reported in tables	yes

Methodological quality of primary studies assessed; criteria reported	yes: STARD checklist
Results of quality assessment used to formulate results and conclusions	no
Meta-analysis performed with appropriate statistic methods	yes
Publication bias assessed	no
N. of included studies study design	13
N. of included patients	674
Reference standard	histopathology (thoracotomy, mediastinoscopy) or imaging follow up with CT
Comparator	CT
Performance results	PET sensitivity: 83% (95% CI 75-91) specificity: 87% (95% CI 80-95) CT sensitivity: 68% (95% CI 58-79) specificity: 76% (95% CI 67-86)
Impact on management	not assessed
Impact on clinical outcome	not assessed
Authors' recommendations and conclusions	PET is more accurate than CT in detecting mediastinal lymph node metastases in patients with NSCLC. PET is an essential functional diagnostic test for detecting lymph nodes metastases in lung cancer. The main drawback is its limitation in anatomic localization precision and spatial resolution. At present PET is not able to replace CT as imaging method for staging. In the future, advances in PET technology, including the integrated PET/CT may overcome this limitation.
Notes	direct comparison between the two modalities

Synoptic table of primary studies on staging of NSCLC

Author, year	Patient number	Outcome	Technology	Reference standard	Sensitivity	Specificity
Al Sarraf 2008a	206	mediastinal staging	FDG-PET/CT visual assessment nodes ≤1 cm	histological findings (mediastinoscopy and biopsy, thoracotomy)	40%	98%
			FDG-PET/CT visual assessment nodes >1 cm		74%	81%
Al Sarraf 2008b	206	N staging	FDG-PET/CT ages ≤65 cm	histological findings (mediastinoscopy and biopsy, thoracotomy)	52%	98%
			CT ages 65 cm		21%	97%
			FDG-PET/CT ages >65 cm		42%	98%
			CT ages >65 cm		15%	92%
An 2008	124	N staging	FDG-PET/CT N1-N3 lymph nodes with max SUV cut off = 4.4	histological exam	76.5%	72.4%
Bernasconi 2006	113	N staging	FDG-PET	histological exam	68%	89%
			transbronchial needle aspiration		54%	100%
Billé 2009	159	mediastinal staging	FDG-PET/CT	mediastinoscopy and biopsy, thoracotomy	54.2%	91.9%
Carnochan 2009	200	mediastinal staging	FDG-PET/CT	mediastinoscopy and biopsy	51%	83%

Author, year	Patient number	Outcome	Technology	Reference standard	Sensitivity	Specificity
Cerfolio 2007a	239 NSCLC with at least 1 positive lymph node	N staging	FDG-PET/CT	biopsy, EUS and fine needle aspiration	94%	72%
Chen 2010	56	N staging	FDG-PET/CT	histological findings or clinical and radiological follow up for at least 6 months	98%	97%
			WB-DWI		91%	90%
		metastatic staging	FDG-PET/CT		98%	100%
			WB-DWI		90%	95%
Craanen 2007	20	N staging	FDG-PET	histological exam	100%	89%
			endoscopic ultrasound guided fine-needle aspiration (EUS-FNA)		86%	100%
De Wever 2007a	217	metastatic staging	FDG-PET/CT	pathological exam, follow up	92%	98%
			CT		18%	98%
De Wever 2007b	50	N staging	FDG-PET/CT	pathological exam, follow up	83%	84%
			CT		83%	68%
			FDG-PET		83%	81%
		metastatic staging	FDG-PET/CT		100%	98%
Hellwig 2007	95	mediastinal staging	FDG-PET visual	histological findings (mediastinoscopy and biopsy)	91%	85%
			FDG-PET cut off SUV max 2.5		89%	84%

Author, year	Patient number	Outcome	Technology	Reference standard	Sensitivity	Specificity
Jeon 2010	42 NSCLC with histopathologic counterpart of usual interstitial pneumonia	N staging	FDG-PET/CT	histopathologic exam	60%	91%
			CT		60%	47
	168 NSCLC without histopathologic counterpart of usual interstitial pneumonia	N staging	FDG-PET/CT		62%	96%
			CT		40%	84%
Joo Lee 2009	43	N staging	FDG-PET/CT N1 stage	surgical pathologic results	50%	96.4%
			CT N1 stage		20%	80.6%
			FDG-PET/CT N2 stage		41.7%	96.4%
			CT N2 stage		33.3%	80.6%
Kaira 2007	50	N staging	FDG-PET	histological exam	65.7%	57.8%
			FMT-PET		57.8%	100%

Author, year	Patient number	Outcome	Technology	Reference standard	Sensitivity	Specificity
Kasai 2010	129	mediastinal staging	FDG-PET/CT SUV cut off: 2.5	histological findings	78%	81%
Kelly 2006	107	N staging	FDG-PET/CT	pathological exam	90%	82%
		metastatic staging			100%	100%
Kim 2006	150	mediastinal staging	FDG-PET/CT	histological findings (mediastinoscopy or thoracotomy)	47%	100%
Lee 2007	126	mediastinal staging	FDG-PET/CT	histological findings (surgical mediastinal lymph node biopsy by mediastinoscopy or thoracotomy)	85.7%	80.6%
	210		FDG-PET		61.1%	94.3%
Lee 2008	110	mediastinal staging	FDG-PET/CT SUV cut off: 2.5	histological findings (surgical mediastinal lymph node biopsy by mediastinoscopy or thoracotomy)	93%	86%
			FDG-PET/CT SUV cut off: 5.3		81%	98%
Liu 2008	39	mediastinal staging	FDG-PET/CT SUV cut off: 2.5	histological findings (surgical mediastinal lymph node biopsy by mediastinoscopy or thoracotomy)	65%	96.8%
Liu 2010	362	metastatic staging (bone metastases)	FDG-PET/CT	clinical and imaging follow up for at least 6 months; biopsy	93.9%	98.9%
			FDG-PET		84.1%	93.2%
			FDG-PET/CT		74.4%	90.7%
Melek 2008	170	N staging	FDG-PET	mediastinoscopy	74%	73%

Author, year	Patient number	Outcome	Technology	Reference standard	Sensitivity	Specificity
Min 2009	182	metastatic staging (bone metastases)	FDG-PET/CT	progressing bone lesion on the follow up; confirmed bone metastasis by simple radiography, CT or (MRI); positive initial findings on both BS and PET/CT in the same bone lesion with symptoms; histological confirmation	93.3%	94.1%
			bone scintigraphy		93.3%	44.1%
			serum alkaline phosphatase		26.7%	94.1%
Nambu 2010	34	N staging	FDG-PET	pathological exam	25%	98%
			CT		25%	94%
			thin section CT		25%	97%
Nishiyama 2008	83	N staging	FDG-PET early SUV	pathological exam	54%	89%
			FDG-PET combined delayed SUV and retention		62%	96%
			FDG-PET delayed SUV		62%	89%
Nomori 2008	88	N staging	FDG-PET/CT	pathological exam	72%	97%
			DW-MRI		67%	99%

Author, year	Patient number	Outcome	Technology	Reference standard	Sensitivity	Specificity
Nosotti 2008	413	N staging	FDG-PET	histological and cytological exam, biopsy	97%	96%
			CT		59%	76%
		metastatic staging (bone metastases)	FDG-PET		96%	99%
			scintigraphy		67%	94%
		metastatic staging (adrenal metastases)	FDG-PET		100%	100%
			CT		72%	98%
		metastatic staging (liver metastases)	FDG-PET		100%	100%
			CT		62%	99%
		metastatic staging lung metastases	FDG-PET		95%	98%
			CT		78%	98%
Ohno 2007	90	metastatic staging (included brain metastases)	FDG-PET	pathological exam, other imaging, biopsies, follow up	70%	74.3%
Ohno 2008b	203	metastatic staging	FDG-PET/CT	clinical and imaging follow up for at least 12 months; biopsy	62.5%	94.5%
			whole-body DW imaging		57.5%	87.7%
			whole-body MR imaging without DW		60%	92%
			whole-body MR imaging with DW		70%	92%
			MRI		80%	80%
Perigaud 2009	51	N staging	FDG-PET/CT	histopathologic exam	40%	85%

Author, year	Patient number	Outcome	Technology	Reference standard	Sensitivity	Specificity
Plathow 2008	52	N staging	FDG-PET/CT	surgery, follow up, mediastinoscopy	98.1%	100%
			wbMRI		88.5%	96.1%
Quaia 2008	76	N staging	FDG-PET/CT	histopathologic exam	90%	18%
			FDG-PET/CT		79%	27%
			CT		83%	53%
Rodriguez Fernandez 2007	108	N staging	FDG-PET/CT	histopathologic exam for patients underwent surgery, other imaging (US, MR) or biopsy patient did not receive surgery	87%	92%
			CT		52%	64%
Şanli 2009	78	N staging	FDG-PET/CT	histopathologic exam	81.8%	89.5%
			CT		45.4%	80.5%
Shinya 2009	34	N staging	FDG-PET/CT early-phase SUV max with the cut off value = 3.61	pathological exam	86.7%	88%
			FDG-PET/CT delayed-phase SUV max with the cut off value = 4.00		91.6%	92.9%
			FDG-PET/CT for RI-SUV max with the cut off value = 20.91		73.6%	75.9%
Song 2008	1000	metastatic staging (bone metastases)	FDG-PET/CT	biopsy, other imaging as CT or MRI, follow up	94.3%	98.8%
			TC-DPD bone scintigraphy		78.1%	97.4%

Author, year	Patient number	Outcome	Technology	Reference standard	Sensitivity	Specificity
Takenaka 2009	115	metastatic staging (bone metastases)	FDG-PET/CT	histopathologic exam, follow up for more than 12 month	96%	85.6%
			whole-body MR imaging without DWI		64%	90%
			whole-body MR imaging with DWI		96%	90%
			bone scintigraphy		96%	83.3%
			DWI		96%	78.9%
Tourmoy 2007	52	N staging	FDG-PET/CT visual interpretation	pathological exam	84%	85%
			FDG-PET/CT with a ratio SUV max/SUV liver = 1.5		82%	93%
Ventura 2010	31	N staging	FDG-PET/CT	histopathologic exam (mediastinoscopy, thoracotomy)	94%	73%
			CT		81%	50%
			FDG-PET		90%	31%
Yamamoto 2008b	34	N staging	FDG-PET	N stage: histopathologic exam	57%	78%
			FLD-PET		57%	93%
Yang 2008	122	N staging	FDG-PET/CT	pathological exam	86%	85%
			CT		69%	71%
Yang 2010	31	N staging	FDG-PET/CT	pathological exam	85%	84%
			FLT-PET/CT		65%	98%

Author, year	Patient number	Outcome	Technology	Reference standard	Sensitivity	Specificity
Yi 2007	143	N staging	FDG-PET	pathological exam	56%	100%
			CT		65%	89%
Yi 2008	165	metastatic staging	FDG-PET/CT	pathological exam, follow up	48%	96%
			MRI		52%	94%
Yun Lee 2009	442	metastatic staging (brain metastases included)	FDG-PET/CT	pathological exam, other imaging, follow up	68%	98%
		metastatic staging (only brain metastases)	FDG-PET/CT		24%	100%
			MRI		88%	98%

Primary studies

Author, year	Al Sarraf 2008a
Technology	FDG-PET/CT
Disease	NSCLC
Objective	to assess diagnostic accuracy in the mediastinal staging of NSCLC
Patients characteristics	206 consecutive patients with NSCLC who underwent mediastinoscopy/mediastinal lymphoadenectomy after FDG-PET mean age 64.5
Index test	FDG-PET/CT
Comparator	
Reference standard	histological findings (mediastinoscopy and biopsy, thoracotomy)
Country	Ireland
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with retrospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	not reported
Withdrawals from the study explained	no withdrawals

Results	FDG-PET/CT nodes ≤1 cm sensitivity: 40% specificity: 98% PPV: 74% NPV: 91% nodes >1 cm sensitivity: 74% specificity: 81% PPV: 71% NPV: 83%
Authors' recommendations and conclusions	Integrated PET-CT remains superior to CT in nodal staging of non-small cell lung cancer. However, in the presence of enlarged lymph nodes, PET-CT becomes less specific, less accurate but more sensitive in detecting metastatic spread to the lymph nodes. Interpretation of PET-CT findings in NSCLC patients with enlarged lymph nodes (>1 cm) should be with caution as the specificity of PET-CT is lower and its ability to detect truly negative nodes become reduced. NSCLC patients with enlarged nodes by CT criteria who are PET-CT negative may require cervical mediastinoscopy to rule out metastatic spread to these nodes. Prospective studies are warranted.

Author, year	**Al Sarraf 2008b**
Technology	FDG-PET/CT
Disease	NSCLC
Objective	to compare diagnostic accuracy of FDG-PET/CT and CT in staging (N staging) of N NSCLC and to identify the impact of age on sensitivity and specificity
Patients characteristics	206 patients with NSCLC (84 women and 122 men) mean age 64.5, range 25-83 years
Index test	FDG-PET/CT
Comparator	CT
Reference standard	pathological exam
Country	Ireland
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with retrospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	not reported
Withdrawals from the study explained	no withdrawals

Results	age<65 years FDG-PET/CT sensitivity: 52% specificity: 98% CT sensitivity: 21% specificity: 97% Age ≥65 years FDG-PET/CT sensitivity: 42% specificity: 98% CT sensitivity: 15% specificity: 92%
Authors' recommendations and conclusions	PET-CT staging of the mediastinum is less sensitive in elderly patients with NSCLC who have a lower PPV. Positive mediastinal uptake on PET-CT should be verified by mediastinoscopy, irrespective of age. Elderly patients with positive mediastinal uptake should not be refuted a curative intent surgical resection on the basis of positive mediastinal uptake alone.

Author, year	**An 2008**
Technology	FDG-PET/CT
Disease	NSCLC
Objective	to assess diagnostic accuracy of FDG-PET/CT in staging (N staging) of NSCLC
Patients characteristics	124 patients with NSCLC (22 women and 102 men) mean age 63
Index test	FDG-PET/CT
Comparator	
Reference standard	histological exam
Country	Korea
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with retrospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported
Execution of the index and comparator tests adequately described	no
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	not reported
Withdrawals from the study explained	no withdrawals

Results	N1-N3 lymph nodes with max SUV cut off = 4.4 FDG-PET/CT sensitivity: 76.5% specificity: 72.4% N1-N2 lymph nodes with max SUV cut off = 4.8 FDG-PET/CT sensitivity: 70.5% specificity: 75.5%
Authors' recommendations and conclusions	Maximum SUV was the most valuable PET/CT parameter for lymph node staging in patients with operable non-small cell lung cancer and the only predictor for lymph node metastasis in those with coexisting inflammatory lung disease. Therefore, maximum SUV is to be recommended for clinical PET/CT interpretation in such patients.

Author, year	**Bernasconi 2006**
Technology	FDG-PET
Disease	NSCLC
Objective	to compare diagnostic accuracy of FDG-PET and TBNA in staging (N staging) of NSCLC
Patients characteristics	113 patients with NSCLC (38 women and 75 men) mean age 65
Index test	FDG-PET
Comparator	TBNA (transbronchial needle aspiration)
Reference standard	histopathologic exam
Country	Switzerland
Outcomes considered	sensitivity, specificity, impact on management
Study design	diagnostic cross sectional study with retrospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	not reported
Withdrawals from the study explained	no withdrawals

Results	FDG-PET sensitivity: 68% specificity: 89% TBNA sensitivity: 54% specificity: 100% Combined FDG-PET and TBNA sensitivity: 100% specificity: 94% Impact on management: applying the approach of combining a negative TBNA and a negative PET result in patients with enlarged lymph nodes, it can be estimated that mediastinoscopy could be avoided in 29/51 (57%) patients
Authors' recommendations and conclusions	Combination of transbronchial needle aspiration and positron emission tomography has the potential to allow adequate mediastinal staging of non-small cell lung cancer with enlarged lymph nodes in most patients without the need for mediastinoscopy.

Author, year	**Billé 2009**
Technology	FDG-PET/CT
Disease	NSCLC
Objective	to assess diagnostic accuracy in the mediastinal staging of NSCLC
Patients characteristics	159 patients with NSCLC who underwent mediastinoscopy/ mediastinal lymphoadenectomy after FDG-PET mean age 63.7 (range 40-81)
Index test	FDG-PET/CT
Comparator	
Reference standard	histological findings (mediastinoscopy and biopsy, thoracotomy)
Country	Italy
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with retrospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	3 weeks
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	not reported
Withdrawals from the study explained	no withdrawals

Results	FDG-PET/CT sensitivity: 54.2% specificity: 91.9% PPV: 74.3% NPV: 82.3%
Authors' recommendations and conclusions	Our data show that integrated PET/CT provides high specificity but low sensitivity and accuracy in intrathoracic nodal staging of NSCLC patients and underscore the continued need for surgical staging.

Author, year	**Carnochan 2009**
Technology	FDG-PET/CT
Disease	NSCLC
Objective	to assess diagnostic accuracy in the mediastinal staging of NSCLC
Patients characteristics	200 patients with NSCLC who underwent mediastinoscopy/ mediastinal lymphoadenectomy after FDG-PET mean age 63.7 (range 40-81)
Index test	FDG-PET/CT
Comparator	
Reference standard	histological findings (mediastinoscopy and biopsy)
Country	Germany
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with retrospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	4 weeks
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	no
Withdrawals from the study explained	no withdrawals

Results	FDG-PET/CT sensitivity: 51% specificity: 83% PPV: 41% NPV: 12%
Authors' recommendations and conclusions	Our experience would suggest that PET CT alone is not sufficiently accurate to replace mediastinoscopy and other conventional biopsy techniques in the evaluation of NSCLC cases. It may better be viewed as a valuable additional tool with which to inform decision making and to screen for disseminated disease

Author, year	**Cerfolio 2007a**
Technology	FDG-PET
Disease	NSCLC
Objective	to determine whether the SUV max ratio was a universal predictor of lymph node malignancy (N staging) in NSCLC
Patients characteristics	239 patients with NSCLC with at least one lymph node positive to PET (105 women and 134 men); mean age 68
Index test	FDG-PET and FDG-PET/CT
Comparator	
Reference standard	biopsy, EUS-FNA
Country	USA
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with retrospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	no
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	not reported
Withdrawals from the study explained	no withdrawals
Results	Stage N sensitivity: 94% specificity: 72%
Authors' recommendations and conclusions	The ratio of the SUV max of the mediastinal (N2) lymph node to the SUV max of the primary tumor in patients with non-small cell lung cancer predicts mediastinal nodal pathology across different PET centers.

Author, year	**Chen 2010**
Technology	FDG-PET/CT
Disease	NSCLC
Objective	to assess diagnostic accuracy for the metastases detection (N, M) in patients with NSCLC
Patients characteristics	56 patients with NSCLC mean age not reported
Index test	FDG-PET/CT
Comparator	WB-DWI
Reference standard	histological findings or clinical and radiological follow up for at least six months
Country	China
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with prospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported for pathology, not applicable for follow up
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	no: pathology for positives, follow up for negatives
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	not reported
Withdrawals from the study explained	no withdrawals

Results	Lymph node metastases FDG-PET/CT sensitivity: 98% specificity: 97% PPV: 99% NPV: 93% WB-DWI sensitivity: 91% specificity: 90% PPV: 96% NPV: 93% Other metastases FDG-PET/CT sensitivity: 98% specificity: 100% PPV: 100% NPV: 95% WB-DWI sensitivity: 90% specificity: 95% PPV: 97% NPV: 83%
Authors' recommendations and conclusions	WB-DWI is a feasible clinical technique for the assessment of NSCLC.

Author, year	**Craanen 2007**
Technology	FDG-PET
Disease	NSCLC
Objective	to compare diagnostic accuracy of FDG-PET and Endoscopic ultrasound guided fine-needle aspiration (EUS-FNA) in staging (N) of NSCLC
Patients characteristics	20 patients with NSCLC (4 women and 16 men) median age 70, range age 48-73
Index test	FDG-PET
Comparator	EUS-FNA
Reference standard	histological exam
Country	Netherlands
Outcomes considered	sensitivity, specificity, impact on management
Study design	diagnostic cross sectional study with prospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported, the author said that reference standard was done after surgery
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	not reported
Withdrawals from the study explained	no withdrawals

Results	FDG-PET sensitivity: 100% specificity: 89% EUS-FNA sensitivity: 86% specificity: 100%. Impact on management Unnecessary surgery was prevented in six out of 16 patients otherwise considered as surgical candidates (37%)
Authors' recommendations and conclusions	We conclude that both EUS-FNA and 18FDG-PET have excellent operating characteristics. However, initial 18FDG-PET findings should guide the complementary use of EUS-FNA to define treatment options and to prevent unnecessary surgery in selected patients.

Author, year	De Wever 2007a
Technology	FDG-PET/CT
Disease	NSCLC
Objective	to compare diagnostic accuracy of FDG-PET/CT and CT in staging (M staging) of NSCLC
Patients characteristics	217 patients with NSCLC
Index test	FDG-PET/CT
Comparator	CT
Reference standard	pathological exam, follow up
Country	Belgium
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with retrospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	no
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	yes for index test; not reported for reference standard
Withdrawals from the study explained	no withdrawals

Results	Imaging based malignant lesion FDG-PET/CT sensitivity: 92% specificity: 98% CT sensitivity: 18% specificity: 98% Imaging based (malignant lesion + benign lesion) FDG-PET/CT sensitivity: 100% specificity: 81% CT sensitivity: 91% specificity: 80%
Authors' recommendations and conclusions	PET/CT was demonstrated to depict more distant malignant extrapulmonary lesions than computed tomography and positron emission tomography alone. The introduction of PET/CT results in a computed tomography of the total abdomen and provides additional anatomical information. Combining metabolic and anatomical information, PET/CT has been advocated as a useful novel imaging tool leading to a decrease in the number of false-positive and false-negative positron emission tomography and computed tomography findings in cancer patients. However, the precise localization of increased F-fluoro-2-deoxyglucose foci using PET/CT cannot always solve the diagnostic dilemma of abnormal tracer uptake at present. A solitary F-fluoro-2-deoxyglucose accumulation that determines the possibility for radical treatment presently still requires a histopathologic diagnosis.

Author, year	De Wever 2007b
Technology	FDG-PET/CT
Disease	NSCLC
Objective	to compare diagnostic accuracy of FDG-PET/CT and CT in staging (N and M staging) of NSCLC
Patients characteristics	50 patients with NSCLC
Index test	FDG-PET/CT
Comparator	FDG-PET, CT
Reference standard	pathological exam, follow up
Country	Belgium
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with retrospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	not clear
Patients selection criteria clearly described	no
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	yes for index test; not reported for reference standard
Withdrawals from the study explained	no withdrawals

Results	N staging FDG-PET/CT sensitivity: 83% specificity: 84% CT sensitivity: 83% specificity: 68% FDG-PET sensitivity: 83% specificity: 81% M staging FDG-PET/CT sensitivity: 100% specificity: 98%
Authors' recommendations and conclusions	Integrated PET-CT improves the staging of lung cancer through a better anatomic localization and characterization of lesions and is superior to CT alone and PET alone. If this technique is not available visual correlation of PET and CT can be a valuable alternative.

Author, year	**Hellwig 2007**
Technology	FDG-PET
Disease	NSCLC
Objective	to assess diagnostic accuracy in the mediastinal staging of NSCLC
Patients characteristics	95 patients with NSCLC who underwent mediastinoscopy/ mediastinal lymphoadenectomy after FDG-PET mean age not reported
Index test	FDG-PET
Comparator	
Reference standard	histological findings (mediastinoscopy and biopsy)
Country	Germany
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with retrospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	6 weeks
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	not reported
Withdrawals from the study explained	no withdrawals

Results	FDG-PET visual sensitivity: 91% specificity: 85% PPV: 64% NPV: 97% AUC: 0.922 cut off SUV max 2.5 sensitivity: 89% specificity: 84% PPV: 61% NPV: 96% AUC: 0.899
Authors' recommendations and conclusions	For mediastinal staging, the choice of a SUV of 2.5 as the threshold is justified because FNR 1 FPR is minimized. The resulting high negative predictive value of 96% allows the omission of mediastinoscopy in patients with negative mediastinal findings on 18F-FDG-PET images. For the experienced observer, visual analysis should be relied on primarily, with calculation of the SUV used, at most, as a secondary aid. For the less experienced observer, the SUV may be of greater value.

Author, year	**Jeon 2010**
Technology	FDG-PET/CT
Disease	NSCLC
Objective	to compare diagnostic accuracy of FDG-PET/CT and CT in staging (N staging) of NSCLC
Patients characteristics	case group: 42 patients with NSCLC and IPF (histopathologic counterpart of usual interstitial pneumonia) (2 women and 40 men) mean age 66 control group: 168 patients with NSCLC and without IPF (histopathologic counterpart of usual interstitial pneumonia) (38 women and 130 men) mean age 65
Index test	FDG-PET/CT
Comparator	CT
Reference standard	histopathologic exam
Country	Korea
Outcomes considered	sensitivity, specificity
Study design	diagnostic case-control study with retrospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	yes

Withdrawals from the study explained	no withdrawals
Results	Per patients accuracy and with IPF FDG-PET/CT sensitivity: 60% specificity: 91% CT sensitivity: 60% specificity: 47% Per patients accuracy and without IPF FDG-PET/CT sensitivity: 62% specificity: 96% CT sensitivity: 40% specificity: 84%%
Authors' recommendations and conclusions	PET/CT offers significantly increased accuracy versus CT in mediastinal nodal staging in patients with NSCLC and IPF compared with patients with NSCLC but without IPF, mainly because of improved specificity.

Author, year	**Joo Lee 2009**
Technology	FDG-PET/CT
Disease	NSCLC
Objective	to compare diagnostic accuracy of FDG-PET/CT and CT in staging (N staging) of NSCLC
Patients characteristics	43 patients with NSCLC (9 women and 34 men) median age 64, range 32.9-83.1
Index test	FDG-PET/CT
Comparator	CT
Reference standard	surgical pathologic results
Country	Singapore
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with prospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	not reported
Withdrawals from the study explained	no withdrawals

Results	N1 stage FDG-PET/CT sensitivity: 50% specificity: 96.4% CT sensitivity: 20% specificity: 80.6% N2 stage FDG-PET/CT sensitivity: 41.7% specificity: 96.8% CT sensitivity: 33.3% specificity: 80.6%
Authors' recommendations and conclusions	Our results demonstrate that although PET/CT seems to offer an improved method to evaluate mediastinal lymph nodes, mediastinoscopic biopsy currently remains the standard method. A high false-positive rate for N2 lymph nodes on PET/CT limits its use for selecting patients for neo-adjuvant treatments, and as a result, PET/CT would not be an appropriate choice to replace mediastinoscopy.

Author, year	**Kaira 2007**
Technology	FDG-PET
Disease	NSCLC
Objective	to compare diagnostic accuracy of FDG-PET and FMT-PET in staging (N) of NSCLC
Patients characteristics	50 patients with NSCLC (15 women and 35 men) mean age 69, range 42-82
Index test	FDG-PET
Comparator	FMT-PET
Reference standard	histological exam
Country	Japan
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with prospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	not reported
Withdrawals from the study explained	no withdrawals

Results	FDG-PET sensitivity: 65.7% specificity: 91% FMT-PET sensitivity: 57.8% specificity: 100%
Authors' recommendations and conclusions	The specificity for diagnosing lymph node involvement was higher by FMT-PET than FDG-PET. The uptake of FMT was closely correlated with LAT1 expression. Further studies are warranted to verify the clinical implication of LAT1 expression as determined by FMT PET in terms of clinical outcome in various histologies of NSCLC.

Author, year	**Kasai 2010**
Technology	FDG-PET/CT
Disease	NSCLC
Objective	to assess diagnostic accuracy in the mediastinal staging of NSCLC
Patients characteristics	129 patients with NSCLC without metastases or history of chemo-radiotherapy before PET; median age 67 (range 24-83)
Index test	FDG-PET/CT
Comparator	
Reference standard	histological findings (surgery for 126 and EBUS for 3)
Country	Japan
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with retrospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	yes for index test; not reported for reference standard
Withdrawals from the study explained	no withdrawals
Results	FDG-PET/CT SUV cut off: 2.5 sensitivity: 78% specificity: 81%
Authors' recommendations and conclusions	Single scanning of PET/CT is sufficiently useful for evaluating mediastinal and hilar nodes for metastases.

Author, year	**Kelly 2006**
Technology	FDG-PET
Disease	NSCLC
Objective	to assess diagnostic accuracy of FDG-PET in diagnoses, staging (N and M staging) and diagnoses of recurrence in NSCLC
Patients characteristics	107 patients with NSCLC (18 women and 89 men) mean age 65
Index test	FDG-PET/CT
Comparator	
Reference standard	pathological exam
Country	France
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with retrospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	no
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	no
Independent and blind interpretation of index test and reference standard results	not reported
Withdrawals from the study explained	no withdrawals

Results	Diagnoses sensitivity: 92% specificity: 88% Stage N sensitivity: 90% specificity: 82% Stage M sensitivity: 100% specificity: 100% Loco-regional recurrence sensitivity: 100% specificity: 83%
Authors' recommendations and conclusions	The study confirm the importance of PET-CT in the diagnosis, staging, detection of recurrence and management of NSLC.

Author, year	**Kim 2006**
Technology	FDG-PET/CT
Disease	NSCLC
Objective	to assess diagnostic accuracy in the mediastinal staging of NSCLC
Patients characteristics	150 patients with stage T1 NSCLC without distant metastases or history of chemo-radiotherapy before PET mean age 59 (range 33-81)
Index test	FDG-PET/CT
Comparator	
Reference standard	histological findings (mediastinoscopy or thoracotomy)
Country	Korea
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with prospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described:	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	mean 10 days, range 1-96
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	yes for index test; not reported for reference standard
Withdrawals from the study explained	no withdrawals

Results	FDG-PET/CT sensitivity: 47% specificity: 100% PPV: 100% NPV: 88%
Authors' recommendations and conclusions	Integrated FDG-PET/CT provides high specificity and PPV of mediastinal nodal staging in stage T1 NSCLC, although sensitivity is low.

Author, year	**Lee 2007**
Technology	FDG-PET; FDG-PET/CT
Disease	NSCLC
Objective	to compare diagnostic accuracy in the mediastinal staging of NSCLC of PET versus PET/CT
Patients characteristics	336 patients with NSCLC who underwent PET before mediastinal staging by mediastinoscopy or thoracotomy mean age 66 (range 32-86)
Index test	FDG-PET/CT (126 patients)
Comparator	FDG-PET(210 patients)
Reference standard	histological findings (surgical mediastinal lymph node biopsy by mediastinoscopy or thoracotomy)
Country	USA
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with retrospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described:	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	14 days
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	not reported
Withdrawals from the study explained	no withdrawals

Results	FDG-PET/CT sensitivity: 85.7% specificity: 80.6% PPV: 55.8% NPV: 95.2% FDG-PET sensitivity: 61.1% specificity: 94.3% PPV: 68.8% NPV: 92.1%
Authors' recommendations and conclusions	Improvement in PET technology have increased integrated PET/CT sensitivity at the cost of significantly decreased specificity. Although it may appear that integrated PET/CT incurs fewer false negative results, the dramatic increase in false positive results reinforces the notion that integrated PET/CT should be used only as an adjunct to clinical staging and that surgical staging remains the gold standard in SNCLC.

Author, year	**Lee 2008**
Technology	FDG-PET/CT
Disease	NSCLC
Objective	to assess the diagnostic accuracy in the mediastinal staging of NSCLC at different SUV cut off
Patients characteristics	110 patients with NSCLC who underwent PET/CT before mediastinal staging by mediastinoscopy or thoracotomy mean age 65 (range 32-86)
Index test	FDG-PET/CT
Comparator	
Reference standard	histological findings (surgical mediastinal lymph node biopsy by mediastinoscopy or thoracotomy)
Country	USA
Outcomes considered	sensitivity, specificity in detecting N2 lymph nodes
Study design	diagnostic cross sectional study with retrospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described:	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	14 days
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	not reported
Withdrawals from the study explained	no withdrawals

Results	FDG-PET/CT SUV cut off: 2.5 sensitivity: 93% specificity: 86% PPV: 22% NPV: 99% SUV cut off 5.3 sensitivity: 81% specificity: 98% PPV: 64% NPV: 99%
Authors' recommendations and conclusions	The maximum standardized uptake value is a predictor of individual lymph node metastases in NSCLC. Accuracy of integrated PET/CT is significantly improved using a maximum cut off of 5.3, dramatically decreasing the number of false positive results. More importantly, some patients with SNCLC with SUV max less than 5.3 may be able to forego mediastinoscopy and proceed directly to thoracotomy. This represent a significant change in the current management of standardized uptake value positive mediastinal lymph nodes in NSCLC.

Author, year	**Liu 2008**
Technology	FDG-PET/CT
Disease	NSCLC
Objective	to assess the diagnostic accuracy in the mediastinal staging of NSCLC
Patients characteristics	39 patients with NSCLC who underwent PET/CT before mediastinal staging by mediastinoscopy or thoracotomy median age 57.5 (range 39-76)
Index test	FDG-PET/CT
Comparator	
Reference standard	histological findings (surgical mediastinal lymph node biopsy by mediastinoscopy or thoracotomy)
Country	China
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with retrospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described:	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	not reported
Withdrawals from the study explained	no withdrawals

Results	FDG-PET/CT SUV cut off: 2.5 sensitivity: 65% specificity: 96.8% PPV: 78.5% NPV: 90%
Authors' recommendations and conclusions	PET/CT showed good accuracy in the pre-operative diagnosis of mediastinal and hilar lymph node metastases in the patients with NSCLC. We recommend that PET/CT scanning be used as a first line evaluation tool for tumor diagnosis, therapy evaluation and follow up.
Comment of ASSR reviewers	

Author, year	**Liu 2010**
Technology	FDG-PET/CT
Disease	NSCLC
Objective	to assess the diagnostic accuracy in the diagnosis of bone metastases of NSCLC
Patients characteristics	362 consecutive patients with proven NSCLC who underwent PET/CT median age 56.9 (range 17-85)
Index test	FDG-PET/CT
Comparator	CT alone; PET alone
Reference standard	clinical and imaging follow up for at least 6 months; biopsy
Country	China
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with retrospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described:	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not applicable
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	not clear
Execution of the reference standard described	no
Independent and blind interpretation of index test and reference standard results	not reported
Withdrawals from the study explained	no withdrawals

Results	FDG-PET/CT sensitivity: 93.9% specificity: 98.9% PPV: 96.3% NPV: 98.2% FDG-PET alone sensitivity: 84.1% specificity: 93.2% PPV: 78.4% NPV: 95.3% CT alone sensitivity: 74.4% specificity: 90.7% PPV: 70.1% NPV: 92.4%
Authors' recommendations and conclusions	FDG-PET/CT is superior to PET or CT alone in detecting bone metastases of NSCLC because of the complementation of PET and CT.

Author, year	**Maziak 2009**
Technology	FDG-PET/CT
Disease	NSCLC
Objective	to compare diagnostic accuracy of FDG-PET/CT and conventional staging (CS) in staging (N staging) of NSCLC
Patients characteristics	337 patients with NSCLC (167 CT and 170 PET/CT), mean age 67 (PET/CT), mean age 66 (conventional staging) 320 patients with available data
Index test	FDG-PET/CT
Comparator	abdominal CT or bone scan plus cranial imaging
Reference standard	biopsy, other imaging, histopathologic exam
Country	Canada
Outcomes considered	change in staging
Study design	RCT
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	no
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	not reported
Withdrawals from the study explained	8 patients: 5 patients who had PET-CT and 3 patients who had conventional staging did not undergo planned surgery and therefore did not have an outcome

Results	FDG-PET/CT correctly upstaged disease: 14%% incorrectly upstaged disease: 4.8% incorrectly understaged disease: 14.9% Conventional staging correctly upstaged disease: 7% incorrectly upstaged disease: 0.6% incorrectly understaged disease: 29.6%
Authors' recommendations and conclusions	Pre-operative staging with PET-CT and cranial imaging identifies more patients with mediastinal and extrathoracic disease than conventional staging, thereby sparing more patients from stage-inappropriate surgery, but the strategy also incorrectly upstaged disease in more patients.

Author, year	**Melek 2008**
Technology	FDG-PET
Disease	NSCLC
Objective	to assess diagnostic accuracy of FDG-PET in staging (N) of NSCLC
Patients characteristics	170 patients with NSCLC (15 women and 155 men) mean age 59.3, range 35-84
Index test	FDG-PET
Comparator	
Reference standard	mediastinoscopy
Country	Japan
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with prospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	yes, within 30 days
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	not reported
Withdrawals from the study explained	no withdrawals
Results	FDG-PET sensitivity: 74% specificity: 73%
Authors' recommendations and conclusions	PET results do not provide acceptable accuracy rates. Mediastinoscopy still remains the gold standard for mediastinal staging of NSCLC, although it cannot reach to all the mediastinal stations.

Author, year	Min 2009
Technology	FDG-PET/CT
Disease	NSCLC and SCLC
Objective	to compare diagnostic accuracy of FDG-PET/CT and bone scintigraphy, serum alkaline phosphatase in staging (M staging, bone metastases) of NSCLC and SCLC
Patients characteristics	182 patients, 168 with NSCLC and 14 with SCLC (46 women and 136 men) mean age 61.8
Index test	FDG-PET/CT
Comparator	bone scintigraphy, Serum Alkaline Phosphatase
Reference standard	progressing bone lesion on the follow up; confirmed bone metastasis by simple radiography, CT or (MRI); positive initial findings on both BS and PET/CT in the same bone lesion with symptoms; histological confirmation
Country	Korea
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with retrospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	no
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	not reported

Withdrawals from the study explained	no withdrawals
Results	FDG-PET/CT sensitivity: 93.3% specificity: 94.1% bone scintigraphy sensitivity: 93.3% specificity: 44.1% Serum Alkaline Phosphatase sensitivity: 26.7% specificity: 94.1%
Authors' recommendations and conclusions	Although the data did not show a superior sensitivity of PET/CT over BS in the screening of metastatic bone lesions, PET/CT had higher specificity and accuracy. These data suggest that BS can be eliminated in staging workup for pre-operative patients who need PET/CT for nodal staging. However, in patients with disseminated disease who do not need evaluation of nodal staging, BS and the measurement of serum ALP concentration are sufficient for detecting asymptomatic metastatic bone lesions.

Author, year	**Nambu 2010**
Technology	FDG-PET
Disease	NSCLC
Objective	to compare diagnostic accuracy of FDG-PET with conventional CT and thin section CT in N staging of NSCLC
Patients characteristics	34 patients with NSCLC mean age 69, range 47-83
Index test	FDG-PET
Comparator	conventional CT and thin-section CT
Reference standard	pathological exam
Country	Japan
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with retrospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	not clear
Patients selection criteria clearly described	no
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	no
Independent and blind interpretation of index test and reference standard results	yes
Withdrawals from the study explained	no withdrawals

Results	FDG-PET sensitivity: 25% specificity: 98% Conventional CT sensitivity: 25% specificity: 94% Thin-section CT sensitivity: 25% specificity: 97%
Authors' recommendations and conclusions	Thin-section CT of the mediastinum using multiple criteria was comparable to PET in pre-operative N-staging of lung cancer.

Author, year	**Nishiyama 2008**
Technology	FDG-PET
Disease	NSCLC
Objective	to evaluate whether delayed additional FDG-PET can improve the certainty of this modality in evaluating the stage (N staging) of NSCLC
Patients characteristics	83 patients with NSCLC (20 women and 63 men) mean age 70, range 44-85
Index test	FDG-PET combined delayed SUV and retention index
Comparator	FDG-PET early SUV, FDG-PET delayed SUV
Reference standard	pathological exam
Country	Japan
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with retrospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	no
Independent and blind interpretation of index test and reference standard results	yes
Withdrawals from the study explained	no withdrawals

Results	FDG-PET combined delayed SUV and retention index sensitivity: 62% specificity: 96% FDG-PET early SUV sensitivity: 54% specificity: 89% FDG-PET delayed SUV sensitivity: 62% specificity: 89%
Authors' recommendations and conclusions	Our evaluation of lymph node staging in NSCLC using dual-time-point FDG-PET (combined delayed PET and RI value) showed better (although not statistically signify cant) specificity, PPV, and accuracy than early or delayed FDG-PET alone.

Author, year	**Nomori 2008**
Technology	FDG-PET/CT
Disease	NSCLC
Objective	to compare diagnostic accuracy of FDG-PET/CT and diffusion weighted MRI in staging (N staging) of NSCLC
Patients characteristics	88 patients with NSCLC
Index test	FDG-PET/CT
Comparator	diffusion weighted MRI
Reference standard	pathological exam
Country	Japan
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with prospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	no
Independent and blind interpretation of index test and reference standard results	not reported
Withdrawals from the study explained	no withdrawals
Results	FDG-PET/CT sensitivity: 72% specificity: 97% diffusion-weighted MRI sensitivity: 67% specificity: 99%

Authors' recommendations and conclusions	Diffusion-weighted magnetic resonance imaging can be used in place of positron emission tomography-computed tomography for N staging of non-small cell lung cancer with fewer false-positive results compared with positron emission tomography-computed tomography.

Author, year	**Nosotti 2008**
Technology	FDG-PET
Disease	NSCLC
Objective	to compare diagnostic accuracy of FDG-PET and other imaging (CT, scintigraphy) in staging (N,M staging) of NSCLC
Patients characteristics	413 patients with NSCLC (116 women and 297 men) mean age 67.2
Index test	FDG-PET
Comparator	CT, scintigraphy
Reference standard	histological and cytological exam, biopsy
Country	Italy
Outcomes considered	sensitivity, specificity, impact on management
Study design	diagnostic cross sectional study with prospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	not reported
Withdrawals from the study explained	no withdrawals

Results	N stage FDG-PET sensitivity: 97% specificity: 96% CT sensitivity: 59% specificity: 76% M stage Bone metastases FDG-PET sensitivity: 96% specificity: 99% Scintigraphy sensitivity: 67% specificity: 94% Adrenal metastases FDG-PET sensitivity: 100% specificity: 100% CT sensitivity: 72% specificity: 98% Liver metastases FDG-PET sensitivity: 100% specificity: 100% CT sensitivity: 62% specificity: 99% Lung metastases FDG-PET sensitivity: 95% specificity: 98% CT sensitivity: 78% specificity: 98% Impact on management unnecessary surgeries: 24 for the conventional diagnostic imaging and 8 for the PET strategy
Authors' recommendations and conclusions	PET has established role in the staging of NSCLC, and this study confirm that the PET strategy is more accurate than the conventional imaging strategy for the diagnosis of mediastinal and extracerebral metastases. Detection of unsuspected metastatic disease by PET permits reduction in the number of thoracotomies performed for non-resectable disease.

Author, year	**Ohno 2007**
Technology	FDG-PET
Disease	NSCLC
Objective:	to compare diagnostic accuracy of FDG-PET and MRI in staging (M staging) of NSCLC
Patients characteristics	90 patients with NSCLC (42 women and 48 men) mean age 68, range 35-83 years
Index test	FDG-PET
Comparator	MRI
Reference standard	pathological exam, other imaging, biopsies, follow up
Country	Japan
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with prospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported, only the follow up period (more than 20 months)
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	not reported
Withdrawals from the study explained	no withdrawals

Results	Per patient basis included brain metastases FDG-PET sensitivity: 70% specificity: 74.3% MRI sensitivity: 80% specificity: 80% Per patient basis excluded brain metastases FDG-PET sensitivity: 80% specificity: 74.3% MRI sensitivity: 80% specificity: 80%
Authors' recommendations and conclusions	In conclusion, our study showed that whole-body MR imaging is an accurate diagnostic technique and may be considered at least as effective as FDG-PET for assessment of the M-stage of lung cancer patients.

Author, year	Ohno 2008b
Technology	FDG-PET/CT
Disease	NSCLC
Objective	to assess the diagnostic accuracy in the M staging of NSCLC
Patients characteristics	203 consecutive patients with proven NSCLC who underwent PET/CT median age 56.9 (range 17-85)
Index test	FDG-PET/CT
Comparator	whole-body DW imaging; whole-body MR imaging with DW imaging; whole-body MR imaging without DW imaging
Reference standard	clinical and imaging follow up for at least 12 months; biopsy
Country	Japan
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with prospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described:	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not applicable
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	no: biopsy or clinical and radiological follow up for positives, clinical and radiological follow up for negatives
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	yes for index test; no for reference standard
Withdrawals from the study explained	no withdrawals

Results	FDG-PET/CT sensitivity: 62.5% specificity: 94.5% PPV: 73.5% NPV: 91.1% AUC: 0.89 whole-body DW imaging sensitivity: 57.5% specificity: 87.7% PPV: 53.3% NPV: 89.4% AUC: 0.79 whole-body MR imaging without DW sensitivity: 60% specificity: 92% PPV: 64.9% NPV: 90.4% AUC: 0.83 whole-body MR imaging with DW sensitivity: 70% specificity: 92% PPV: 68.3% NPV: 92.6% AUC: 0.87
Authors' recommendations and conclusions	Whole-body MR with DW imaging can be used for M stage assessment in NSCLC patients with accuracy as good as that of PET/CT.

Author, year	**Perigaud 2009**
Technology	FDG-PET/CT
Disease	NSCLC
Objective	to assess diagnostic accuracy of FDG-PET staging (N) of NSCLC
Patients characteristics	51 patients with NSCLC (7 women and 44 men) mean age 60.6
Index test	FDG-PET/CT
Comparator	
Reference standard	histopathologic exam
Country	France
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with prospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	yes, mean time to surgery 31 days (range 2-27 days)
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	yes for index test; no for reference standard
Withdrawals from the study explained	no withdrawals
Results	FDG-PET/CT sensitivity: 40% specificity: 85%

Authors' recommendations and conclusions	The sensitivity and positive predictive value of integrated FDG-PET/CT for mediastinal lymph node staging in patients with operable non-small-cell lung cancer are low. In the presence of positive mediastinal lymph nodes, invasive mediastinal lymph node staging must be performed to exclude a possible false positive of integrated FDG-PET/CT. The specificity and negative predictive value are high. In the presence of negative mediastinal lymph nodes, patients can be operated without invasive mediastinal lymph node staging.

Author, year	**Plathow 2008**
Technology	FDG-PET/CT
Disease	NSCLC
Objective	to compare diagnostic accuracy of FDG-PET and CT in staging (T,N,M staging) of NSCLC
Patients characteristics	52 patients with NSCLC (16 women and 36 men) mean age 62, range age 49-71
Index test	FDG-PET/CT
Comparator	wbMRI
Reference standard	surgery, follow up, mediastinoscopy
Country	Germany
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with prospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	no
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	yes for index test; no for reference standard
Withdrawals from the study explained	no withdrawals

Results	T staging FDG-PET/CT sensitivity: 96.1% specificity: 100% wbMRI sensitivity: 100% specificity: 100% N staging FDG-PET/CT sensitivity: 98.1% specificity: 100% wbMRI sensitivity: 88.5% specificity: 96.1%
Authors' recommendations and conclusions	In advanced NSCLCC wbMRI has advantages in T-staging, especially in tumors with potential infiltration of the thoracic or mediastinal wall. PET/CT has advantages concerning correct N-staging that influences operability. Using both techniques in consensus reading the positive effects of both techniques are additive and a correct TN- and M-staging in all patients was possible.

Author, year	**Quaia 2008**
Technology	FDG-PET/CT
Disease	NSCLC
Objective	to compare diagnostic accuracy of FDG-PET/CT and CT in staging (N staging) of NSCLC
Patients characteristics	76 patients with NSCLC (56 male, 20 female; mean age +/- SD, 63.4 +/- 20 years)
Index test	FDG-PET
Comparator	CT
Reference standard	histopathologic exam
Country	Italy
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with prospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	yes, from 1 to 15 days
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	no
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	yes
Withdrawals from the study explained	no withdrawals

Results	FDG-PET/CT sensitivity: 90% specificity: 18% FDG-PET sensitivity: 79% specificity: 27% CT sensitivity: 83% specificity: 53%
Authors' recommendations and conclusions	In patients with lung neoplasms considered eligible for surgical resection, 18F-FDG-PET/CT versus contrast-enhanced CT revealed higher sensitivity in nodal staging, but lower specificity both in lesion characterization and nodal staging.

Author, year	Rodriguez Fernandez 2007
Technology	FDG-PET
Disease	NSCLC
Objective	to compare diagnostic accuracy of FDG-PET and CT in staging (N staging) of NSCLC
Patients characteristics	108 patients with NSCLC (7 women and 101 men) mean age 63, range age 55-65
Index test	FDG-PET
Comparator	CT
Reference standard	histopathologic exam for patients underwent surgery, other imaging (US, MR) or biopsy patient did not receive surgery
Country	Spain
Outcomes considered	sensitivity, specificity, impact on management
Study design	diagnostic cross sectional study with prospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	no
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	yes
Withdrawals from the study explained	no withdrawals

Results	FDG-PET sensitivity: 87% specificity: 92% CT sensitivity: 52% specificity: 64%
Authors' recommendations and conclusions	Although complementary, the functional method (FDG-PET) is significantly superior to the structural method (CT) for detection of mediastinal tumor disease.

Author, year	**Şanli 2009**
Technology	FDG-PET/CT
Disease	NSCLC
Objective	to assess diagnostic accuracy of FDG-PET in staging (N staging) of NSCLC and to determine whether this could decrease the need for mediastinoscopy
Patients characteristics	78 patients with NSCLC (5 women and 73 men) mean age 61.3, range age 44-79
Index test	FDG-PET/CT
Comparator	CT
Reference standard	histopathologic exam
Country	Turkey
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with prospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	yes
Withdrawals from the study explained	no withdrawals

Results	FDG-PET/CT sensitivity: 81.8% specificity: 89.5% CT sensitivity: 45.4% specificity: 80.5%
Authors' recommendations and conclusions	PET-CT scanning yields better results than CT scanning. Negative appearances of MLNs in PET-CT scanning results in high success in predicting the mediastinal content; in positive appearances the success of prediction is limited. Therefore there is the need for mediastinoscopy in PET-CT scanning-positive MLNs, but it might not be necessary for PET-CT scanning-negative lymph nodes.

Author, year	**Shinya 2009**
Technology	FDG-PET/CT
Disease	NSCLC
Objective	to assess diagnostic accuracy of FDG-PET in staging (N staging) of NSCLC
Patients characteristics	34 patients with NSCLC (10 women and 24 men) mean age 68.65, range age 46-85
Index test	FDG-PET/CT
Comparator	
Reference standard	pathological exam
Country	Japan
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with retrospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported
Execution of the index and comparator tests adequately described	Yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	no
Independent and blind interpretation of index test and reference standard results	not reported
Withdrawals from the study explained	no withdrawals

Results	FDG-PET/CT for early-phase SUV max with a the cut off value = 3.61 sensitivity: 86.67% specificity: 88.00% for delayed-phase SUV max with a the cut off value = 4.00 sensitivity: 91.6% specificity: 92.9% for RI-SUV max with a the cut off value = 20.91 sensitivity: 73.6% specificity:75.9%
Authors' recommendations and conclusions	DTP PET/CT with a semiquantitative technique may improve diagnostic capacity for nodal staging of NSCLCC.

Author, year	**Song 2008**
Technology	FDG-PET/CT
Disease	NSCLC
Objective	to compare diagnostic accuracy of FDG-PET/CT and TC-DPD bone scintigraphy in staging (M staging) of NSCLC
Patients characteristics	1 000 patients with NSCLC (265 women and 735 men) median age 65, range 18-89
Index test	FDG-PET/CT
Comparator	TC-DPD bone scintigraphy
Reference standard	biopsy, other imaging as CT or MRI, follow up
Country	Korea
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with retrospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	no
Withdrawals from the study explained	no withdrawals
Results	FDG-PET/CT sensitivity: 94.3% specificity: 98.8% TC-DPD bone scintigraphy sensitivity: 78.1% specificity: 97.4%

Authors' recommendations and conclusions	PET/CT was superior to bone scan in the detection of bone metastases of NSCLC with the lower incidence of false positive as well as false negative results.

Author, year	**Takenaka 2009**
Technology	FDG-PET/CT
Disease	NSCLC
Objective	to compare the diagnostic accuracy of FDG-PET/CT, in detecting bone metastases (M staging) of NSCLC, with whole-body diffusion-weighted imaging (DWI), magnetic resonance imaging (MRI) without and with DWI, [18F] fluoro-2-D-glucose positron emission tomography with computed tomography (FDG-PET/CT) and bone scintigraphy.
Patients characteristics	115 patients with NSCLC (49 women and 66 men) mean age 72, range age 45-83
Index test	FDG-PET/CT
Comparator	DWI, MRI with and without DWI, bone scintigraphy
Reference standard	histopathologic exam, follow up for more than 12 months
Country	Japan
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with prospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	yes for index test; no for reference standard
Withdrawals from the study explained	no withdrawals

Results	Per patient diagnostic capability PET/CT sensitivity: 96% specificity: 85.6% Whole-body MR imaging without DWI sensitivity: 64% specificity: 90% Whole-body MR imaging with DWI sensitivity: 96% specificity: 90% Bone scintigraphy sensitivity: 96% specificity: 83.3% DWI sensitivity: 96% specificity: 78.9% Per site diagnostic capability PET/CT sensitivity: 97% specificity: 95.4% Whole-body MR imaging without DWI sensitivity: 73.1% specificity: 96.4% Whole-body MR imaging with DWI sensitivity: 95.5% specificity: 96.1% Bone scintigraphy sensitivity: 95.5% specificity: 95% DWI sensitivity: 95.5% specificity: 93.7%
Authors' recommendations and conclusions	Whole-body MRI with DWI used for bone metastasis assessment of NSCLCC patients was found to be more specific and accurate than bone scintigraphy and/or integrated FDG-PET/CT. In addition, when whole-body DWI is used as an adjunct for whole-body MRI without whole-body DWI, the sensitivity and accuracy of whole-body MR examination can be improved.

Author, year	**Tourmoy 2007**
Technology	FDG-PET/CT
Disease	NSCLC
Objective	to assess diagnostic accuracy of FDG-PET/CT in staging (N staging) of NSCLC
Patients characteristics	52 patients with NSCLC (13 women and 39 men) median age 68, range age 48-80
Index test	FDG-PET/CT
Comparator	
Reference standard	pathological exam
Country	USA
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with prospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	yes. 14 days between PET/CT and histological confirm
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	yes for index test; no for reference standard
Withdrawals from the study explained	no withdrawals

Results	FDG-PET/CT visual interpretation sensitivity: 84% specificity: 85% FDG-PET/CT with a ratio SUV max/SUV liver = 1.5 sensitivity: 82% specificity: 93%
Authors' recommendations and conclusions	Integrated FDG-PET/CT scanning has an overall accuracy which is too low to replace invasive intrathoracic lymph node staging in patients with NSCLCC. The visual interpretation of the fusion images of the integrated FDG-PET/CT scan can be replaced by the quantitative variable SUV max/SUV liver without loss of accuracy for staging of intrathoracic lymph nodes.

Author, year	**Ventura 2010**
Technology	FDG-PET/CT
Disease	NSCLC
Objective	to compare diagnostic accuracy of FDG-PET/Ct and CT in staging (N staging) of NSCLC
Patients characteristics	31 patients with NSCLC (16 women and 15 men) mean age 66.32, range age 46-83 with histologically proven lung cancer
Index test	FDG-PET/CT
Comparator	CT
Reference standard	histopathologic exam (mediastinoscopy, thoracotomy)
Country	USA
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with retrospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	no
Independent and blind interpretation of index test and reference standard results	yes
Withdrawals from the study explained	no withdrawals

Results	FDG-PET/CT sensitivity: 94% specificity: 73% CT sensitivity: 81% specificity: 50% FDG-PET sensitivity: 90% specificity: 31%
Authors' recommendations and conclusions	The integration of CT anatomic data definitely increases the diagnostic accuracy of PET alone in the assessment of nodal metastatic disease. Nonetheless, even considering the high sensitivity, specificity, and negative predictive value obtained in this study, combined PET-CT still presents a limited positive predictive value; this finding implies that PET-CT, despite being routinely used for nodal staging in lung cancer patients, is associated with a significant amount of false positives. Hence a positive lymph node at combined PET-CT is not a definite evidence for malignancy and should be biopsied to rule out metastatic or systemic inflammatory disease; in these cases, PET-CT may help to correctly target the suspicious lymph node at biopsy.

Author, year	**Yamamoto 2008b**
Technology	FDG-PET
Disease	NSCLC
Objective	to compare diagnostic accuracy of FDG-PET and FLD-PET in diagnoses and staging (N, M staging) of NSCLC
Patients characteristics	34 patients with NSCLC (11 women and 23 men) mean age 69, range age 55-81
Index test	FDG-PET
Comparator	FLD-PET
Reference standard	N stage: histopathologic exam M stage: biopsy and radiological follow up
Country	Japan
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with prospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	yes
Withdrawals from the study explained	no withdrawals

Results	Detection of primary lung tumor FDG-PET sensitivity: 94% FLT-PET sensitivity: 67% N-staging FDG-PET sensitivity: 57% specificity: 78% FLT-PET sensitivity: 57% specificity: 93%
Authors' recommendations and conclusions	In NSCLCC, FLT PET showed better specificity, positive predictive value and accuracy for N staging on a per-patient basis than FDG-PET. However, FDG-PET was found to have higher sensitivity for depiction of primary tumor than FLT PET.

Author, year	**Yang 2008**
Technology	FDG-PET/CT
Disease	NSCLC
Objective	to compare diagnostic accuracy of FDG-PET/CT and CT in staging (N) of NSCLC
Patients characteristics	122 patients with NSCLC (44 women and 78 men) median age 69, range age 32-84
Index test	FDG-PET/CT
Comparator	CT
Reference standard	pathological exam
Country	China
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with prospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	no
Independent and blind interpretation of index test and reference standard results	not reported
Withdrawals from the study explained	no withdrawals

Results	FDG-PET/CT sensitivity: 86% specificity: 85% CT sensitivity: 69% specificity: 71%
Authors' recommendations and conclusions	Integrated PET/CT improves the sensitivity, specificity, accuracy, positive predictive value, and negative predictive value than enhanced CT in the assessment of locoregional lymph nodes, and provides more efficient and accurate data of nodal staging, with a better effect on diagnosis and therapy in non-small cell lung cancer.

Author, year	**Yang 2010**
Technology	FDG-PET/CT
Disease	NSCLC
Objective	to compare diagnostic accuracy of FLT-PET/CT and FDG-PET/CT in staging (N staging) of NSCLC
Patients characteristics	31 patients with NSCLC (9 women and 22 men) mean age 59, range age 38-84
Index test	FDG-PET/CT
Comparator	FLT-PET/CT
Reference standard	pathological exam
Country	China
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with prospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	yes, 2 weeks
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	no
Independent and blind interpretation of index test and reference standard results	not reported
Withdrawals from the study explained	no withdrawals

Results	FDG-PET/CT sensitivity: 85% specificity: 84% FLT-PET/CT sensitivity: 65% specificity: 98%
Authors' recommendations and conclusions	FLT PET/CT resulted in understaging of more patients but overstaging of fewer patients than FDG-PET/CT in NSCLCC. Tumor FLT uptake was correlated with tumor cell proliferation as indicated by the cyclin D1 labeling index, suggesting that further studies are needed to evaluate the use of FLT PET/CT for the assessment of therapy response to anticancer drugs.

Author, year	**Yi 2007**
Technology	FDG-PET/CT
Disease	NSCLC
Objective	to compare diagnostic accuracy of FDG-PET and CT in staging (N staging) of NSCLC
Patients characteristics	143 patients with NSCLC (61 women and 82 men) mean age 60, range age 31-72
Index test	FDG-PET/CT
Comparator	CT
Reference standard	pathological exam
Country	Korea
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with prospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	yes
Withdrawals from the study explained	no withdrawals

Results	Per patient diagnostic capability FDG-PET sensitivity: 56% specificity: 100% CT sensitivity: 65% specificity: 89% Per node diagnostic capability FDG-PET sensitivity: 44% specificity: 99% CT sensitivity: 42% specificity: 99%
Authors' recommendations and conclusions	Helical dynamic CT in stage T1 NSCLCC shows better (although not statistically significant) sensitivity for the prediction of mediastinal nodal metastasis on a per-patient basis than PET/CT, whereas PET/CT was found to have perfect specificity and positive predictive values. Therefore, mediastinoscopy may be omitted and direct neo-adjuvant therapy given to patients with positive nodal metastasis results on PET/CT. Mediastinoscopy may be recommended in patients with malignant lung nodules showing high enhancement on helical dynamic CT even though PET/CT does not suggest the presence of mediastinal nodal metastasis.

Author, year	**Yi 2008**
Technology	FDG-PET/CT
Disease	NSCLC
Objective	to compare diagnostic accuracy of FDG-PET/CT and MRI in staging (T,N,M staging) of NSCLC
Patients characteristics	165 patients with NSCLC (40 women and 125 men) mean age 61
Index test	FDG-PET/CT
Comparator	MRI
Reference standard	pathological exam, follow up
Country	Korea
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with prospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	yes
Withdrawals from the study explained	no withdrawals

Results	N-stage FDG-PET correct staging 70% MRI correct staging 68% M-stage FDG-PET sensitivity: 48% specificity: 96% MRI sensitivity: 52% specificity: 94%
Authors' recommendations and conclusions	Both PET/CT and MR imaging appear to provide acceptable accuracy and comparable efficacy for NSCLC staging, but for M-stage determination, each modality has its own advantages.

Author, year	**Yun Lee 2009**
Technology	FDG-PET/CT
Disease	NSCLC
Objective	to compare diagnostic accuracy of FDG-PET/CT and MRI in staging (M staging) of NSCLC (adenocarcinoma)
Patients characteristics	442 patients with NSCLC (204 women and 238 men) mean age 54, range 23-88
Index test	FDG-PET/CT
Comparator	MRI
Reference standard	pathological exam, other imaging, follow up
Country	Korea
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with prospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	yes
Withdrawals from the study explained	no withdrawals

Results	All extrathoracic metastases FDG-PET/CT sensitivity: 68% specificity: 98% combined FDG-PET/CT and brain MRI sensitivity: 84% specificity: 95% Brain metastases FDG-PET/CT sensitivity: 24% specificity: 100% brain MRI sensitivity: 88% specificity: 98%
Authors' recommendations and conclusions	In conclusion, with the addition of dedicated brain MRI to PET/CT and thus with enhanced brain metastasis detection, a significant increase in diagnostic sensitivity can be achieved for detecting extrathoracic metastases in patients with lung adenocarcinoma.

5.b. Bronchioloalveolar cancer (BAC)

Synoptic table of primary studies on staging of patients with bronchioloalveolar cancer

Author, year	Patient number	Outcome	Technology	Reference standard	Sensitivity	Specificity
Balogova 2010	15	accuracy in differentiating BAC from other histological NSCLC subtypes	FCH-PET/CT	histology, follow up	78%	75%
		accuracy in detecting malignancy			82%	
		accuracy in differentiating BAC from other histological NSCLC subtypes	FDG-PET/CT		78%	75%
		accuracy in detecting malignancy			82%	
Sun 2009	125	accuracy in detecting BAC	FDG-PET/CT	histology	81.3%	85.3%
			FDG-PET		68.8%	86.2%
			CT		50%	98.2%

Primary studies

Author, year	Balogova 2010
Technology	FDG-PET/CT
Disease	NSCLC-BAC
Objective:	to compare diagnostic accuracy of FDG-PET/CT and FCH-PET/CT in detection of bronchioloalveolar cancer (BAC)
Patients characteristics	15 patients with lung nodule or lesion for suspected BAC (10 women and 5 men) mean age 67.5 (range 57-92)
Index test	FDG-PET/CT
Comparator	FCH-PET/CT
Reference standard	histological examination, follow up
Country	France
Outcomes considered	sensitivity and specificity
Study design	diagnostic cross sectional study with prospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	only for the follow uptime (6 months)
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	yes
Withdrawals from the study explained	no withdrawals

Results	Sensitivity for cancer with a BAC component FDG-PET/CT: 78% FCH-PET/CT: 78% Specificity for cancer with a BAC component FDG-PET/CT: 75% FCH-PET/CT: 75% Sensitivity for malignancy FDG-PET/CT: 82% FCH-PET/CT: 82%
Authors' recommendations and conclusions	This study revealed that FCH had similar performance to FDG in terms of diagnostic accuracy in the detection of lesion with a BAC component.

Author, year	**Sun 2009**
Technology	FDG-PET/CT
Disease	NSCLC- adenocarcinoma
Objective:	to compare the diagnostic accuracy of FDG-PET/CT and CT for differentiation of adenocarcinoma with bronchioloalveolar carcinoma (BAC) from other subtypes of non-small cell lung cancer (NSCLC)
Patients characteristics	125 patients with NSCLC (21 women and 104 men) mean age 64
Index test	FDG-PET/CT
Comparator	CT
Reference standard	histological examination
Country	Korea
Outcomes considered	sensitivity and specificity
Study design	diagnostic cross sectional study with retrospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	no
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	yes
Withdrawals from the study explained	no withdrawals

Results	Sensitivity for differentiating adenocarcinoma with BAC from other subtypes: FDG-PET/CT: 81.3% FDG-PET: 68.8% CT: 50% Specificity for differentiating adenocarcinoma with BAC from other subtypes: FDG-PET/CT: 85.3% FDG-PET: 86.2% CT: 98.2%
Authors' recommendations and conclusions	Careful combined assessment of the FDG-PET maximal SUV and CT findings have the potential to differentiate an adenocarcinoma with BAC from other NSCLC subtypes, such as a pure BAC. These findings might be useful for imaging interpretations and will help initial planning of NSCLC management.

5.c. Small cell lung cancer (SCLC)

Primary studies

Author, year	Fischer 2007
Technology	FDG-PET/CT
Disease	SCLC - staging
Objective	to examine the role of combined PET/CT and PET compared with CT, bone scintigraphy and immunocytochemical assessment of bone marrow biopsy in the staging of patients with SCLC
Patients characteristics	29 patients with SCLC (21 patients with extensive disease and 8 with limited disease)
Index test	FDG-PET/CT
Comparator	CT, bone scintigraphy and immunocytochemical assessment of bone marrow biopsy
Reference standard	histology "gold standard": ▪ histology if available ▪ concordance between structural and metabolic imaging modalities ▪ results of supplemental examinations (magnetic resonance imaging or ultra sound) ▪ follow up of the patient with emphasis on relevant foci
Country	Denmark
Outcomes considered	diagnostic accuracy was calculated as sensitivity, specificity, positive and negative predictive values as well as likelihood ratio (LR) for standard staging, PET and PET/CT
Study design	cross-sectional prospective study
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	no
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	n.a.
Execution of the index and comparator tests adequately described	yes

Did patients receive the same reference standard regardless of the index test result	n.a
Execution of the reference standard described	n.a.
Independent and blind interpretation of index test and reference standard results	yes
Withdrawals from the study explained	yes
Pre-test probability	for limited disease: 28%
Results	Sensitivity standard*: 0.79 [0.52-0.92] PET: 0.93 [0.69-0.99] PET/CT: 0.93 [0.69-0.99] Specificity standard*: 1.00 [0.61-1.00] PET: 0.83 [0.44-0.97] PET/CT: 1.00 [0.61-1.00] * Includes CT of thorax and upper abdomen, bone scintigraphy and/or analysis of bone marrow
Authors' recommendations and conclusions	Is there a role for PET/CT in the staging of SCLC? Taking all the reservations necessary when concluding on a small material, the answer is: most likely. By including whole-body PET/CT in staging patients with SCLC, it is possible that conventional CT of thorax and upper abdomen, bone scintigraphy and bone marrow biopsy can be omitted saving precious time and making rapid initiation of therapy possible. Whether PET/CT can significantly improve the accuracy of SCLC staging and positively influence patient management remains to be settled. Thus, a larger clinical trial, preferably with histological confirmation in case of discordance, is warranted before final conclusions can be draw.

CHAPTER 6.
Field definition of curative radiation treatment in patients with lung cancer

Diagnostic accuracy

Systematic reviews

Author, year	Van Baardwijk 2006
Technology	PET
Disease	all neoplasms
Objective	to assess: ▪ primary diagnosis (to assess malignancy of solitary pulmonary nodules ▪ staging (before treatment): N staging (mediastinal lymph node) ▪ **X** curative intent RT field definition ▪ response to treatment (during treatment) ▪ re-staging (after treatment) (residual disease) ▪ follow up in asymptomatic patients ▪ diagnosis of suspected recurrence ▪ staging recurrence ▪ impact on management ▪ impact of clinical outcomes
Inclusion criteria	P patients with any kind of neoplasm I FDG-PET before radiotherapy C CT, MRI R pathologic examination O change in gross tumor volume (GTV), in planning target volume (PTV), in volume receiving the established dose S cross sectional
Years covered by the search	up to August 2005
Study selection data abstraction, quality assessment performed by two authors independently	not reported
Comprehensive bibliographic search: at least two databases searched	no: Medline
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	no
Searched also unpublished studies	no
Language restriction	English

Overall number of references retrieved and n of included studies reported	no
n. and references of excluded studies reported, reason given	no
Characteristics of included studies clearly reported in tables	yes
Methodological quality of primary studies assessed; criteria reported	no
Results of quality assessment used to formulate results and conclusions	no
Meta-analysis performed with appropriate statistic methods	not applicable
Publication bias assessed	no
N. of included studies study design	8 studies
N. of included patients	304 (data reported for 6 studies); range 11-73
Reference standard	1 study: lymph nodes histology
Comparator	CT
Performance results	PET change in GTV, PTV "In conclusion, most studies have shown a significant alteration in the target volume in 25-50% of patients with NSCLC. Mostly a decrease in target volume was noticed, with a change of about 20-25%, when adding PET information for radiotherapy planning. The main causes for an increase in target volume are a larger primary tumor and most of all inclusion of nodal disease. The major cause for a decrease in target volume was the ability of PET to exclude atelectasis." In NSCLC, PET-CT has a high diagnostic accuracy for detecting mediastinal lymph nodes and adding PET information for radiation treatment planning will lead to modified plans. In a clinical study, it was shown that it was safe to only irradiate PET positive mediastinal lymph nodes. 1 study: a significant lower average maximum dose for the spinal cord was found for the PET-CT plans compared to the CT plans.
Impact on management	not assessed
Impact on clinical outcome	not assessed

Recommendations and conclusions	Looking at issues concerning the role of PET in treatment planning, combined PET-CT information seems to influence target volume delineation, especially in lung cancer. However, data on the confirmation of the relation between delineation based on (CT-) PET and pathologic examination are lacking in most tumor regions. More research is needed to address the question whether PET does allow accurate tumor delineation in regard to pathological tumor extension.
Notes	Few studies with few patients about few kind of tumors; studies considering surrogate endpoints.

Synoptic table of primary studies on field definition of radical radiation treatment

Author, year	Patient number	Patient characteristics	Outcome	Technology	Reference standard	Change in GTV FDG-PET/CT vs CT
Boursot 2009	17	NSCLC	change in GTV	FDG-PET/CT vs CT	none	nestle technique: -8% ±36% black technique: -22% ±24% Tylsky technique: -31% ±24%
Ceresoli, 2007	18	NSCLC	change in GTV	FDG-PET/CT vs CT	none	39% (7/18 patients) of significant (≥25%) change / larger 28% and smaller in 11%
Devic 2010	31	NSCLC	GTV Ratio	FDG-PET/CT vs CT	none	GTV-PET-QVM (qualitative visual method): 0.725 ±0.294 GTV-PET-15%-max (15% of maximal uptake value method): 1.420 ±0.875 GTV-PET-40%-ave (15% of average maximum uptake): 0.521 ±0.271 GTV-PET-40%-max (40% of single maximal uptake value): 0.297 ±0.188
Faria 2008	32	NSCLC	change in GTV	FDG-PET/CT vs CT	pathologic examination or histological examination (2 patients)	56% (12 had a decrease and 6 an increase of the initial planned GTV,16 had differences in the GTV of >30% and 2 had changes only in the nodal status) change in TNM stage (compared with pathologic examination): 50%

Author, year	Patient number	Patient characteristics	Outcome	Technology	Reference standard	Change in GTV FDG-PET/CT vs CT
Grills 2007	21	NSCLC	change in GTV	FDG-PET vs CT	none	for primary tumor and nodal volumes (CT vs PET): larger in 52%, smaller in 29%, equal in 19%
Hanna 2010	28	NSCLC	change in GTV	FDG-PET vs CT	none	median of mean percentage of volume change (GTV) radiotherapy alone group (CT vs PET/CT): 18.88%
Hong 2007	19	NSCLC	change in GTV	FDG-PET vs CT	none	change in GTV volume (PET vs CT) average volume difference (SUV ≥2.5 and CT): -259% average volume difference (SUV 40% max and CT): -162%
Lewandowska 2006	20	NSCLC	change in GTV	FDG-PET/CT vs CT	none	difference in GTV volume (CT vs PET): in 16/20 = 80% the GTV/PET volume decrease GTV mean difference: 53 cm^3 (0.3-148 cm^3) GTV % mean difference: 45% (3-28%) in 4/20 = 20% the GTV/PET volume increase GTV mean difference: -18 cm^3 (-9-(-35) cm^3) GTV % mean difference: -32% (-10-(-80%))

Author, year	Patient number	Patient characteristics	Outcome	Technology	Reference standard	Change in GTV FDG-PET/CT vs CT
MacManus 2007	10	NSCLC	change in GTV	FDG-PET/CT vs CT	none	change in PTV volume (PET/CT vs CT) in 3 (30%) cases the PTV volume was more than 10% greater in 6 (60%) cases the PTV volume was smaller by 10% or more in 1 case the volumes were identical
Nestle 2007	51	NSCLC	change in GTV	FDG-PET/CT vs CT	none	GTV volume (range) GTVvis: 8.9 (2.1-33.5) ml GTV2.5: 7.9 (0.3-30.6) ml GTV40: 9.0 (2.6-22.5) ml GTVbg: 3.8 (0.1-16.2) ml GTVCT: 4.3 (0.2-21.2) ml
Spratt 2010	11	NSCLC	change in GTV	FDG-PET/CT vs CT	none	percentage of volume change (GTV) PET vs CT (cut off of 15% of difference was considered significant) primary tumor GTV decreased in 36% (n = 4) of patients GTV increased in 27% (n = 3) of patients Lymph nodal GTV GTV increased in 27% (n = 3) of patients distant metastases detected mean GTV decrease of 5% (-39 to 13%)

Author, year	Patient number	Patient characteristics	Outcome	Technology	Reference standard	Change in GTV FDG-PET/CT vs CT
Videtic 2008	87	NSCLC	change in the nodal target (NT)	FDG-PET/CT vs CT	mediastinoscopy	results of comparison with PET and mediastinoscopy for the 54 patients who had MLN abnormalities of 36 stage IIIA cancer patients, 18 (50%) had NT-PET equivalent to NT-M 10 (28%) had smaller NT-Ps 8 (22%) had larger NT-PET compared with NT-M of 18 stage IIIB cancer patients, NTs were equivalent in 6 (34%) in 1 patient (5%) NT-PET was larger than the corresponding NT-M in 11 (61%) smaller than the corresponding NT-M
Yap, 2010	10	NSCLC	accuracy of registration of the CT components of the planning PET/CT scan (pCT) and diagnostic PET/CT scan (dCT) scan with the NSCLC	FDG-PET/CT vs CT	none	mean absolute error(MAE) $\pm$ root mean square error (RMSE) MAE of dCT-rCT: 4.15 $\pm$ 2.43 MAE of pCT-rCT: 4.15 $\pm$ 2.43 RMSE of dCT-rCT: 4.48 $\pm$ 1.76 RMSE of pCT-rCT: 4.39 $\pm$ 1.78

Primary studies

Author, year	Boursot 2009
Technology	FDG-PET/CT
Disease	NSCLC
Objective	to compare three method of automatic segmentation by FDG-PET/CT vs CT in definition of the gross target volume (GTV) in patients with NSCLC
Patients characteristics	17 patients with NSCLC (5 female and 12 male) mean age 68.4 (range 49-80)
Index test	FDG-PET/CT
Comparator	CT
Reference standard	histological examination
Country	France
Outcomes considered	change in the contouring of GTV for RT
Study design	diagnostic cross sectional study with retrospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	no
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	no
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	no
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	not reported
Withdrawals from the study explained	no withdrawals

Results	% difference in GTV (FDG-PET/CT vs CT) nestle technique: -8 ± 36% black technique: -22 ± 24% Tylsky technique: -31 ± 24% % difference in GTV for the 6 patients underwent surgery (FDG-PET/CT vs histological) nestle technique: 68 ± 64% black technique: 48 ± 49% Tylsky technique: 15 ± 48%
Authors' recommendations and conclusions	The method of Black et al. was the most discrepant one. For tumor less than 45 cm3 Nestle algorithm tends to overestimate the CT volume. The method of Tylsky presents an interesting approach but still requires developments because it under evaluates too much the target volume.

Author, year	**Ceresoli 2007**
Technology	FDG-PET
Disease	NSCLC
Objective	to compare the gross target volume (GTV) definitions for computed tomography (CT) vs positron emission tomography (PET) in non-small cell lung cancer (NSCLC)
Patients characteristics	18 patients with NSCLC
Index test	FDG-PET fused images with CT
Comparator	CT
Reference standard	
Country	Italy
Outcomes considered	change in the contouring of GTV for RT
Study design	diagnostic cross sectional study with retrospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	
Execution of the reference standard described	
Independent and blind interpretation of index test and reference standard results	
Withdrawals from the study explained	no withdrawals
Results	% change of GTV volume CT vs PET/CT: 39% (7/18 patients) of significant (≥25%) change / larger 28% and smaller in 11%

Authors' recommendations and conclusions	The study confirms the impact of PET/CT in patients with NSCLC due to the alteration of GTV definition in a relevant percentage of cases. For all the parameters considered for healthy lung, esophagus, spinal cord and heart, mediastinal elective node irradiation (ENI) plans had dose values significantly greater that no-ENI and PET plans. Even though large prospective trials are needed this study suggest that PET can be integrated in no-ENI techniques, thereby improving target volume delineation without major concerns about toxicity.

Author, year	**Devic 2010**
Technology	FDG-PET/CT
Disease	NSCLC
Objective	to compare the gross target volume (GTV) definitions for computed tomography (CT) vs positron emission tomography (PET) in non-small cell lung cancer (NSCLC)
Patients characteristics	31 patients with NSCLC
Index test	FDG-PET/CT
Comparator	CT
Reference standard	
Country	Canada
Outcomes considered	change in the contouring of GTV for RT
Study design	diagnostic cross sectional study with retrospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	
Execution of the reference standard described	
Independent and blind interpretation of index test and reference standard results	
Withdrawals from the study explained	no withdrawals

Results	GTV-PET/GTV-CT GTV-PET-QVM (qualitative visual method): 0.725 ± 0.294 GTV-PET-15%-max(15% of maximal uptake value method): 1.420 ± 0.875 GTV-PET-40%-ave (15% of average maximum uptake): 0.521 ± 0.271 GTV-PET-40%-max (40% of single maximal uptake value): 0.297 ± 0.188
Authors' recommendations and conclusions	The fluctuations in tumor volume using different quantitative PET threshold approaches did not depend on the threshold method used. They originated from the nature of functional imaging in general and PET imaging in particular. Functional imaging will eventually be used for biologically tailored target radiotherapy volume definition not as a replacement of CT- or magnetic resonance imaging-based anatomic gross tumor volumes but with the methods complementing each other in a complex mosaic of distinct biologic target volumes.

Author, year	**Faria 2008**
Technology	FDG-PET/CT
Disease	NSCLC
Objective	to compare FDG-PET/CT vs CT in definition of the gross target volume (GTV) and change in TNM stage in patients with NSCLC
Patients characteristics	32 patients with NSCLC
Index test	FDG-PET/CT
Comparator	CT
Reference standard	pathologic examination (30 patients) and histological examination (2 patients)
Country	Canada
Outcomes considered	change in the contouring of GTV for RT and change in TNM stage
Study design	diagnostic cross sectional study with retrospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	no
Execution of the index and comparator tests adequately described	no
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	no
Independent and blind interpretation of index test and reference standard results	not reported
Withdrawals from the study explained	no withdrawals

Results	FDG-PET/CT change in GTV contouring for RT compared with CT: 56% (12 had a decrease and 6 an increase of the initial planned GTV, 16 had differences in the GTV of >30% and 2 had changes only in the nodal status) change in TNM stage (compared with pathologic examination): 50% CT change in TNM stage (compared with pathologic examination): 69%
Authors' recommendations and conclusions	The contour of the tumor volume of non-small cell lung cancer patients with co-registered FDG-PET/CT resulted in >50% alterations compared with CT targeting, findings similar to those of other publications. However, the significance of this change is unknown. Furthermore, pathologic examination showed that PET is not always accurate and histological examination should be obtained to confirm the findings of PET whenever possible.

Author, year	**Grills 2007**
Technology	FDG-PET
Disease	NSCLC
Objective	to compare the gross target volume (GTV) definitions for computed tomography (CT) vs. positron emission tomography (PET) in non-small cell lung cancer (NSCLC)
Patients characteristics	21 patients with NSCLC
Index test	FDG-PET
Comparator	CT
Reference standard	
Country	USA
Outcomes considered	change in the contouring of GTV for RT
Study design	diagnostic cross sectional study with retrospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	
Execution of the reference standard described	
Independent and blind interpretation of index test and reference standard results	
Withdrawals from the study explained	no withdrawals

Results	% change in GTV volume for primary tumor (CT vs PET): larger in 50%, smaller in 33%, equal in 14% for primary tumor and nodal volumes (CT vs PET): larger in 52%, smaller in 29%, equal in 19% PET combined with CT vs PET or CT: larger in 60%, smaller in 25%, and equal in 15%
Authors' recommendations and conclusions	Computed tomography and PET are complementary and should be obtained in the treatment position and fused to define the GTV for NSCLC. Although the quantitative absolute target volume is sometimes similar, the qualitative target locations can be substantially different, leading to underdosage of the target when planning is done using CT alone without PET fusion.

Author, year	**Hanna 2010**
Technology	FDG-PET/CT
Disease	NSCLC
Objective	to compare the gross target volume (GTV) definitions for computed tomography (CT) vs. positron emission tomography (PET) in non-small cell lung cancer (NSCLC)
Patients characteristics	28 patients with NSCLC
Index test	FDG-PET/CT
Comparator	CT
Reference standard	
Country	Ireland
Outcomes considered	change in the contouring of GTV for RT
Study design	diagnostic cross sectional study with retrospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	
Execution of the reference standard described	
Independent and blind interpretation of index test and reference standard results	
Withdrawals from the study explained	no withdrawals
Results	median of mean percentage of volume change (GTV) induction chemotherapy group (CT vs PET/CT): -5.21% radiotherapy alone group (CT vs PET/CT): 18.88%

Authors' recommendations and conclusions	PET-CT RT planning scan, in addition to a staging PET-CT scan, reduces inter-observer variability in GTV definition for NSCLC. The GTV size with PET-CT compared with CT in the RT-alone group increased and was reduced in the induction chemotherapy group. Additional work is needed to optimize its use and avoid the pitfalls of incorrect interpretation of PET information for this patients.

Author, year	**Hong 2007**
Technology	FDG-PET
Disease	NSCLC
Objective	to compare the gross target volume (GTV) definitions for computed tomography (CT) vs. positron emission tomography (PET) in non-small cell lung cancer (NSCLC)
Patients characteristics	19 patients with NSCLC
Index test	FDG-PET
Comparator	CT
Reference standard	
Country	USA
Outcomes considered	change in the contouring of GTV for RT
Study design	diagnostic cross sectional study with retrospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	
Execution of the reference standard described	
Independent and blind interpretation of index test and reference standard results	
Withdrawals from the study explained	no withdrawals
Results	change in GTV volume (PET vs CT) average volume difference (SUV ≥2.5 and CT): -259% average volume difference (SUV 40% max and CT): -162% GTV-25 (with a 25% volume difference as cut off): 58% GTV-40 (with a 25% volume difference as cut off): 95%

Authors' recommendations and conclusions	The optimal way to incorporate the PET SUV thresholds to contour GTV depends on the maximum tumor SUV and volume. Due to tumor heterogeneity, and the wide variability in volumes obtain by using SUV 40% max, we recommend using areas of SUV ≥2.5 for radiotherapy planning in non-small cell lung cancer.

Author, year	**Lewandowska 2006**
Technology	FDG-PET/CT
Disease	NSCLC
Objective	to compare the gross target volume (GTV) definitions for computed tomography (CT) vs positron emission tomography (PET) in non-small cell lung cancer (NSCLC)
Patients characteristics	20 patients with NSCLC (18 men, 2 women) mean age: 60
Index test	FDG-PET/CT
Comparator	CT
Reference standard	
Country	Poland
Outcomes considered	change in the contouring of GTV for RT
Study design	diagnostic cross sectional study with retrospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	
Execution of the reference standard described	
Independent and blind interpretation of index test and reference standard results	
Withdrawals from the study explained	no withdrawals

Results	difference in GTV volume (CT vs PET) in 16/20 = 80% the GTV/PET volume decrease GTV mean difference: 53 cm^3 (0.3-148 cm^3) GTV % mean difference 45% (3-28%) in 4/20 = 20% the GTV/PET volume increase GTV mean difference: -18 cm^3 (-9-(-35) cm^3) GTV % mean difference: -32% (-10-(-80%))
Authors' recommendations and conclusions	Positron emission tomography cannot take the place of morphologic imaging but it provides additional data concerning the character of observed pathologies. The application of PET/CT image fusion for radiotherapy treatment planning in patients with NSCLC has a significant impact of GTVs.

Author, year	**MacManus 2007**
Technology	FDG-PET
Disease	NSCLC
Objective:	to compare the planning target volume (PTV) definitions for computed tomography (CT) vs positron emission tomography (PET) in non-small cell lung cancer (NSCLC)
Patients characteristics	10 patients with NSCLC
Index test	FDG-PET with coregistered CT images
Comparator	CT
Reference standard	
Country	Australia
Outcomes considered	change in the contouring of PTV for RT
Study design	diagnostic cross sectional study with prospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	
Execution of the reference standard described	
Independent and blind interpretation of index test and reference standard results	
Withdrawals from the study explained	no withdrawals

Results	change in PTV volume (PET/CT vs CT) in 3 (30%) cases the PTV volume was more than 10% greater in 6 (60%) cases the PTV volume was smaller by 10% or more in 1 case the volumes were identical
Authors' recommendations and conclusions	Use of coregistered PET/CT images significantly altered treatment plans in a majority of cases. This method could be used in routine practice at centers without access to a combined PET/CT scanner.

Author, year	**Nestle 2007**
Technology	FDG-PET
Disease	NSCLC
Objective	to compare the gross target volume (GTV) definitions for computed tomography (CT) vs positron emission tomography (PET) in non-small cell lung cancer (NSCLC)
Patients characteristics	51 patients with NSCLC
Index test	FDG-PET
Comparator	CT
Reference standard	
Country	Germany
Outcomes considered	change in the contouring of GTV for RT
Study design	diagnostic cross sectional study with prospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	
Execution of the reference standard described	
Independent and blind interpretation of index test and reference standard results	
Withdrawals from the study explained	no withdrawals

Results	GTV volume (range) GTVvis: 8.9 (2.1-33.5) ml GTV2.5: 7.9 (0.3-30.6) ml GTV40: 9.0 (2.6-22.5) ml GTVbg: 3.8 (0.1-16.2) ml GTVCT: 4.3 (0.2-21.2) ml
Authors' recommendations and conclusions	For nodal GTVs, different methods of contouring did not lead to clinically relevant differences in volumes. However, there were significant differences in technical delineability, especially after early acquisition. Overall, our data favor a late acquisition of FDG-PET scans for radiotherapy planning, and the use of a target/background algorithm for GTV contouring.

Author, year	**Spratt 2010**
Technology	FDG-PET/CT
Disease	NSCLC
Objective	to compare the gross target volume (GTV) definitions for computed tomography (CT) vs positron emission tomography (PET) in non-small cell lung cancer (NSCLC)
Patients characteristics	11 patients with NSCLC (7 men and 4 women) mean age 71
Index test	FDG-PET/CT
Comparator	CT
Reference standard	
Country	USA
Outcomes considered	change in the contouring of GTV for RT
Study design	diagnostic cross sectional study with retrospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	
Execution of the reference standard described	
Independent and blind interpretation of index test and reference standard results	
Withdrawals from the study explained	no withdrawals

Results	percentage of volume change (GTV) PET vs CT (cut off of 15% of difference was considered significant) primary tumor GTV decreased in 36% (n = 4) of patients GTV increased in 27% (n = 3) of patients lymph nodal GTV GTV increased in 27% (n = 3) of patients distant metastases detected mean GTV decrease of 5% (-39 to 13%) 18% (n = 2) patients changing RT planning from curative to palliative and vice versa
Authors' recommendations and conclusions	Our results are consistent with the published data of PET/CT altering GTV in a significant number of patients, detecting tumor spread to additional lymph nodes and distant metastases. While these advantages support the use of PET/CT in RT planning, it remains unknown what impact this will have on patient outcomes.

Author, year	**Van Loon 2008**
Technology	FDG-PET - radiotherapy field
Disease	SCLC (limited disease)
Objective	to investigate the possible role of FDG-PET scanning in the radiotherapy planning of patients with LD-SCLC hypotheses: ▪ there would be changes in the radiotherapy fields using FDG-PET scanning compared to CT, theoretically resulting in less geographical miss ▪ there would be differences in the radiation exposure of dose limiting normal tissues such as lungs, esophagus and spinal cord, when radiation treatment planning is performed based on FDG-PET compared to CT
Patients characteristics	21 patients diagnosed with LD-SCLC and referred for radical radiotherapy for whom either both a pre-treatment FDG-PET and a contrast-enhanced CT scan, or a combined FDG-PET-CT scan (with contrast-enhancement) was available
Index test	FDG-PET
Comparator	CT
Reference standard	histology (not performed)
Country	The Netherlands
Outcomes considered	change in treatment field
Study design	retrospective cohort study
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	no
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	n.a.
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	n.a.
Execution of the reference standard described	n.a. (reference standard was not performed)

Independent and blind interpretation of index test and reference standard results	n.a.
Withdrawals from the study explained	yes
Pre-test probability	number of patients in which FDG-PET could change the treatment field: 25%
Results	In 5 of 21 patients (24%, 95% CI: 5-40%), there was a change in RT plans with the incorporation of the PET-data For 2 patients (10%), the radiation fields based on PET were larger than based on CT, while in 3/21 (14%) patients the CT-based radiation fields were larger Taken all 21 patients together, the nodal GTV was 57.9 ± 67.0 cm^3 on CT and 56.8 ± 66.5 cm^3 on PET (p = 0.92) For the 3 patients with a nodal GTV on PET that was smaller than on CT, the nodal GTV was 81.0 ± 50.9 cm^3 on CT and 61.5 ± 29.0 cm^3 on PET Two patients had a nodal GTV on PET that was larger than on CT. Their nodal GTV was 72.5 ± 71.4 cm^3 on CT and 81.0 ± 76.4 cm^3 on PET
Authors' recommendations and conclusions	Incorporating FDG-PET information in radiotherapy planning for patients with LD-SCLC changed the treatment plan in 24% of patients compared to CT. Both increases and decreases of the GTV were observed, theoretically leading to the avoidance of geographical miss or a decrease of radiation exposure of normal tissues, respectively. Based on these findings, a phase II trial, evaluating PET-scan based selective nodal irradiation, is ongoing in our department.

Author, year	**Videtic 2008**
Technology	FDG-PET
Disease	NSCLC
Objective	to compare the nodal target (NT) for mediastinoscopy vs. positron emission tomography (PET) in non-small cell lung cancer (NSCLC)
Patients characteristics	122 patients with NSCLC (78 men, 44 women) mean age: 61, range 31-78 but after exclusion 87 patients were analyzed
Index test	FDG-PET
Comparator	
Reference standard	mediastinoscopy
Country	Poland
Outcomes considered	change in the nodal target (NT)
Study design	diagnostic cross sectional study with prospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	no
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	not reported
Withdrawals from the study explained	no withdrawals

Results	Results of comparison with PET and mediastinoscopy for the 54 patients who had MLN abnormalities of 36 stage IIIA cancer patients, 18 (50%) had NT-PET equivalent to NT-M 10 (28%) had smaller NT-Ps 8 (22%) had larger NT-PET compared with NT-M of 18 stage IIIB cancer patients, NTs were equivalent in 6 (34%) in 1 patient (5%) NT-PET was larger than the corresponding NT-M in 11 (61%) smaller than the corresponding NT-M
Authors' recommendations and conclusions	In this study PET had modest sensitivity to detect MLN involvement and underestimated the extent of involved nodes for target definition. The role of PET in mediastinal contouring needs to be evaluated prospectively and ideally correlated with a pathology standard.

Author, year	**Yap 2010**
Technology	FDG-PET/CT
Disease	NSCLC
Objective:	to compare the accuracy of registration of the CT components of the planning PET/CT scan (pCT) and diagnostic PET/CT scan (dCT) scan with the rCT in non-small cell lung cancer (NSCLC)
Patients characteristics	10 patients with NSCLC (8 mean and 2 women) mean age 71.5
Index test	FDG-PET/CT
Comparator	CT
Reference standard	
Country	Australia
Outcomes considered	mean absolute error
Study design	diagnostic cross sectional study with prospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	
Execution of the reference standard described	
Independent and blind interpretation of index test and reference standard results	
Withdrawals from the study explained	no withdrawals

Results	mean absolute error (MAE) ± root mean square error (RMSE) MAE of dCT-rCT: 4.15 ± 2.43 MAE of pCT-rCT: 4.15 ± 2.43 RMSE of dCT-rCT: 4.48 ± 1.76 RMSE of pCT-rCT: 4.39 ± 1.78 * dCT, CT component of diagnostic PET/CT; rCT, radiotherapy planning CT; pCT, CT component of planning PET/CT
Authors' recommendations and conclusions	There is an average of 4mm of misregistration when registering the CT components of PET/CT scans to the rCT for NSCLC. Using a rigid registration technique, the registration of a diagnostic PET/CT is as good as the registration of a planning PET/CT.

CHAPTER 7.
During-treatment evaluation of response to therapy in patients treated for lung cancer

7.a. Non-small cell lung cancer (NSCLC)

Diagnostic accuracy

Primary studies

Author, year	**Aukema, 2010**
Technology	FDG-PET/CT
Disease	NSCLC
Objective	to prospectively evaluate the role of integrated F-FDG-PET/CT for early identification of response to neo-adjuvant erlotinib
Patients characteristics	23 patients with operable stage I-III NSCLC included in a trial to study the response to and toxicity of erlotinib mean age 63 years
Index test	F-FDG-PET/CT
Comparator	
Reference standard	histology
Country	The Netherlands
Outcomes considered	association of F-FDG-PET/CT with pathologic results
Study design	prospective study
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described:	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	yes
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes

Independent and blind interpretation of index test and reference standard results	yes
Withdrawals from the study explained	n.a.
Pre-test probability	6/23 = 26.1%
Results	the k-agreement between the metabolic and the pathologic responders was 0.55 (p = 0.008) calculated (by ASSR reviewers) value for sensitivity and specificity are as follows: sensitivity: 4/6 = 66.7% specificity: 15/17 = 88.2%
Authors' recommendations and conclusions	Early during the course of epidermal growth factor receptor tyrosine kinase inhibitor therapy, F-FDG-PET/CT can predict response to erlotinib treatment in patients with non-small cell lung cancer.

7.b. Small cell lung cancer (SCLC)

Primary studies

Author, year	Fischer 2006
Technology	FDG-PET/CT
Disease	SCLC - response to therapy
Objective	to assess the use of PET and PET/CT in early and final response evaluation of patients with small cell lung cancer (SCLC)
Patients characteristics	20 patients with SCLC (15 patients with extensive disease and 5 with limited disease)
Index test	F-FDG-PET/CT
Comparator	early response: chest X-ray; response at the end of treatment: CT (RECIST)
Reference standard	histology
Country	Denmark
Outcomes considered	sensitivity and specificity
Study design	cross-sectional prospective study
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	no
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	n.a.
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	n.a
Execution of the reference standard described	n.a.
Independent and blind interpretation of index test and reference standard results	unclear
Withdrawals from the study explained	yes

Pre-test probability	Complete or partial responders: 90% (17 out of 19 patients)
Results	It is not possible to draw sensitivity and specificity for PET and PET/CT versus the reference standard.
Authors' recommendations and conclusions	Response evaluation of SCLC by PET/CT is feasible, but it is uncertain whether it adds further information to evaluation by RECIST, thus further studies and standardization of methods are needed.

CHAPTER 8.
End of treatment evaluation of response to therapy in patients treated for lung cancer

8.a. Non-small cell lung cancer (NSCLC)

Diagnostic accuracy

Systematic reviews

Author, year	**Geus-Oei 2007**
Technology	PET
Disease	non-small cell lung cancer (NSCLC)
Objective	to assess: ▪ primary diagnosis (to assess malignancy of solitary pulmonary nodules ▪ staging (before treatment): N staging (mediastinal lymph node) ▪ response to treatment (during treatment) ▪ **X** re-staging (after treatment) (residual disease) ▪ follow up in asymptomatic patients ▪ diagnosis of suspected Recurrence ▪ staging recurrence ▪ impact on management ▪ impact of clinical outcomes
Inclusion criteria	P patients with "locally advanced" (not otherwise defined) NSCLC, before and after therapy (radiotherapy, chemotherapy or both) I FDG-PET C CT R histopathology O pathologic response S diagnostic accuracy studies with prospective or retrospective recruitment
Years covered by the search	up to July 2006
Study selection data abstraction, quality assessment performed by two authors independently	not reported
Comprehensive bibliographic search: at least two databases searched	no: only Medline
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	only the references lists of retrieved articles
Searched also unpublished studies	no

Language restriction	yes: only English articles
Overall number of references retrieved and n of included studies reported	no: only number of included studies reported
N. and references of excluded studies reported, reason given	no
Characteristics of included studies clearly reported in tables	no
Methodological quality of primary studies assessed; criteria reported	no
Results of quality assessment used to formulate results and conclusions	no
Meta-analysis performed with appropriate statistic methods	not applicable; meta-analysis not performed
Publication bias assessed	no
N. of included studies study design	9
N. of included patients	not reported
Reference standard	histopathology
comparator	CT
Performance results	PET prediction of histopathologic response sensitivity: median (range) 88% (80-97) specificity: median (range) 80% (64-100) CT data not reported about this test; however PET is found to be a "better" predictor of histopathologic response in 5 out of 9 studies
Impact on management	not assessed
Impact on clinical outcome	not assessed
Recommendations and conclusions	Despite the finding that these 9 studies were very heterogeneous with respect to the applied methods of PET quantification, the primary targets of PET evaluation (primary tumor and/or lymph nodes), and the clinical endpoints (histology, survival), all studies showed that FDG-PET is a significant predictor of therapy outcome and provides results of great prognostic significance. It seems that FDG-PET is able to predict pathological response more accurately and at earlier timepoints than conventional imaging methods.
Notes	Only 1 study dealing with "response to treatment, during treatment". All the other studies are about "response to treatment, after treatment". The overall rate of response (pre-test probability) is not reported.

Author, year	**Rebollo-Aguire 2010**
Technology	FDG-PET or FDG-PET/CT
Disease	non-small cell lung cancer (NSCLC)
Objective	to assess: ▪ primary diagnosis (to assess malignancy of solitary pulmonary nodules ▪ staging (before treatment): N staging (mediastinal lymph node) ▪ response to treatment (during treatment) ▪ **X** re-staging (after treatment) (residual disease) ▪ follow up in asymptomatic patients ▪ diagnosis of suspected recurrence ▪ staging recurrence ▪ impact on management ▪ impact of clinical outcomes
Inclusion criteria	P patients with proven NSCLC suitable for neo-adjuvant treatment I FDG-PET or FDG-PET/CT C other imaging techniques R pathology confirmation O sensitivity, specificity, PPV, NPV S prospective studies carried out in humans with a sample size of at least 10 patients, systematic reviews, meta-analysis, health agencies reports
Years covered by the search	1999 - August 2006
Study selection data abstraction, quality assessment performed by two authors independently	yes
Comprehensive bibliographic search: at least two databases searched	yes
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	yes
Searched also unpublished studies	no
Language restriction	no
Overall number of references retrieved and n of included studies reported	yes
N. and references of excluded studies reported, reason given	only number (not references) and reasons for exclusion
Characteristics of included studies clearly reported in tables	yes

Methodological quality of primary studies assessed; criteria reported	yes (QUADAS)
Results of quality assessment used to formulate results and conclusions	yes
Meta-analysis performed with appropriate statistic methods	yes
Publication bias assessed	no
n. of included studies study design	9
n. of included patients	367
Reference standard	histopathology
comparator	
Performance results	FDG-PET Prediction of histopathologic response of the primary tumor re-staging (no meta-analysis performed due to heterogeneity among studies) sensitivity: 80-100% specificity: 0-100% PPV: 42.9-100% NPV: 0-100% Prediction of histopathologic mediastinal lymph node re-staging sensitivity: 63.8% (95% CI 53.3-73.5%) specificity: 85.3% (95% CI 80.4-89.4%)
Impact on management	not assessed
Impact on clinical outcome	not assessed

Recommendations and conclusions	FDG-PET seems to be an accurate non-invasive method to predict long-term outcome and may be an important step towards patient tailored induction therapy response in NSCLC patients at the primary tumor. Despite of better results of FDG-PET compared to cross-sectional imaging in re-staging after neo-adjuvant therapy in the reviewed publications, the results do not recommend the use of this non-invasive diagnostic approach as the only re-assessment tool for mediastinal lymph node evaluation in routine clinical use. More invasive techniques such as endoscopic ultrasound-guided aspiration biopsy or redo-mediastinoscopy should be considered for re-staging purposes. However, FDG-PET could help to guide these procedures, as in baseline staging. There are few high-quality publications on this subject and larger prospective studies are required to confirm the diagnostic accuracy of FDG-PET in the evaluation of neo-adjuvant therapy response in patients with NSCLC. Standardizing scanning protocols, SUV measurement and consensus about the best cut off values for response are also needed to make them comparable before this technique can be used as a clinical diagnostic tool to select patients for neo-adjuvant treatments.
Notes	The overall rate of response (pre-test probability) not reported.

Synoptic table of primary studies on end of treatment evaluation of response to therapy in patients treated for NSCLC

Author, year	Patient number	Outcome	Technology	Reference standard	Sensitivity	Specificity	Accuracy
Cerfolio 2007b	109	overall staging (primary tumor + N2 lymph nodes)	F-FDG-PET/CT	histology (pathology or biopsy)	85% (calculated by ASSR reviewer from ROC curve)	70% (calculated by ASSR reviewer from ROC curve)	max accuracy: 0.88 (optimal time to restage: 26 days)
		N2 lymph node staging			80% (calculated by ASSR reviewer from ROC curve)	70% (calculated by ASSR reviewer from ROC curve)	max accuracy: 0.82 (optimal time to restage: 29 days)
Eschmann 2007	70	primary tumor staging	F-FDG-PET	histology (pathology or biopsy)	94.5%	80%	
			CT		NA	NA	
		N2 lymph node staging	F-FDG-PET		77%	68%	
			CT		NA	NA	
Stigt 2009	28	primary tumor re-staging	FDG-PET/CT	histology	14%	100%	
			EUS-FNA		NA	NA	
		N2 lymph node re-staging	FDG-PET/CT		0%	91.6%	
			EUS-FNA		50%	100%	

Primary studies

Author, year	Cerfolio 2007b
Technology	F-FDG-PET/CT
Disease	NSCLC
Objective	to determine the ideal time to repeat a PET scan in patients with NSCLC who underwent induction chemo-radiotherapy
Patients characteristics	109 consecutive patients with NSCLC who underwent neo-adjuvant radio-chemotherapy median age 61 years
Index test	F-FDG-PET/CT
Comparator	
Reference standard	histology (pathology or biopsy)
Country	USA
Outcomes considered	
Study design	retrospective cohort study (using a prospective database)
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not specified
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	not specified
Withdrawals from the study explained	yes
Pre-test probability	not assessable

Results	F-FDG-PET/CT for overall staging (primary tumor + N2 lymph nodes) max accuracy: 0.88 (optimal time to restage: 26 days) sensitivity: 85% specificity: 70% (sensitivity and specificity calculated by ASSR reviewer from ROC curve) F-FDG-PET for N2 lymph node max accuracy: 0.82 (optimal time to restage: 29 days) sensitivity: 80% specificity: 70% (sensitivity and specificity calculated by ASSR reviewer from ROC curve)
Authors' recommendations and conclusions	The optimal time to perform a repeat FDG-PET/CT scan after the completion of neo-adjuvant chemotherapy and high-dose radiotherapy to maximize its accuracy for re-staging patients with NSCLC is about 1 month after the last dose of radiation.

Author, year	**Eschmann 2007**
Technology	F-FDG-PET
Disease	NSCLC
Objective	to evaluate FDG-PET for assessment of therapy response and for prediction of patient outcome after neo-adjuvant radio-chemotherapy (NARCT) of advanced non-small cell lung cancer (NSCLC)
Patients characteristics	70 patients with histologically proven stage III NSCLC treated with neo-adjuvant radio-chemotherapy mean age 56 years
Index test	F-FDG-PET
Comparator	CT
Reference standard	histology (after surgery or repeat mediastinoscopy)
Country	Germany
Outcomes considered	accuracy of re-staging after neo-adjuvant radio-chemotherapy for the primary tumor and lymph node metastases
Study design	cross-sectional prospective study
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	no
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	yes
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	yes
Withdrawals from the study explained	yes

Pre-test probability	primary tumor: 78.7% lymph node metastases: 55.4%
Results	F-FDG-PET primary tumor sensitivity: 94.5% specificity: 80% PPV: 94.5% NPV: 80% F-FDG-PET lymph node metastases sensitivity: 77% specificity: 68% PPV: 75% NPV: 70.8%
Authors' recommendations and conclusions	FDG-PET is suitable to assess response to NARCT in patients with stage III NSCLC accurately. It was highly predictive for treatment outcome and patient survival. PET may be helpful in improving re-staging after NARCT by allowing reliable assessment of residual tumor viability.

Author, year	**Stigt 2009**
Technology	FDG-PET/CT
Disease	NSCLC
Objective	to compare the performance of both PET-CT and EUS-FNA with histological analysis in re-staging patients with stage III NSCLC after induction therapy
Patients characteristics	28 patients with stage III NSCLC, initially staged with MRI o CT of the brain and integrated PET-CT, with pathologically metastatic (nodal) disease proved by EUS-FNA and treated with chemotherapy or chemo-radiotherapy median age 60 years
Index test	FDG-PET/CT
Comparator	EUS-FNA (endoscopic ultrasound-guided fine needle aspiration)
Reference standard	histology
Country	The Netherlands
Outcomes considered	accuracy and negative predictive value for EUS-FNA and FDG-PET/CT
Study design	cross-sectional prospective study
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	no
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	yes
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	no
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	no
Withdrawals from the study explained	yes

Pre-test probability	
Results	FDG-PET/CT for nodal re-staging sensitivity: 0% specificity: 91.6% FDG-PET/CT for primary tumor re-staging sensitivity: 14% specificity: 100% EUS-FNA for nodal re-staging sensitivity: 50% specificity: 100%
Authors' recommendations and conclusions	Re-staging with EUS-FNA after induction chemo(-radiotherapy) is well tolerated and predicts the absence of nodal metastasis reliably. Although changes in mediastinal FDG-PET uptake show a high concordance with EUS-FNA, pathological confirmation is still superior and therefore necessary. EUS-FNA is the procedure of first choice for mediastinal re-staging.

8.b. Small cell lung cancer (SCLC)

Primary studies

Author, year	Fischer 2006
Technology	FDG-PET/CT
Disease	SCLC - response to therapy
Objective	to assess the use of PET and PET/CT in early and final response evaluation of patients with small cell lung cancer (SCLC)
Patients characteristics	20 patients with SCLC (15 patients with extensive disease and 5 with limited disease)
Index test	F-FDG-PET/CT
Comparator	early response: chest X-ray; response at the end of treatment: CT (RECIST)
Reference standard	histology
Country	Denmark
Outcomes considered	sensitivity and specificity
Study design	cross-sectional prospective study
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	no
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	n.a.
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	n.a
Execution of the reference standard described	n.a.
Independent and blind interpretation of index test and reference standard results	unclear
Withdrawals from the study explained	yes
Pre-test probability	Complete or partial responders: 90% (17 out of 19)

Results	It is not possible to draw sensitivity and specificity for PET and PET/CT versus the reference standard.
Authors' recommendations and conclusions	Response evaluation of SCLC by PET/CT is feasible, but it is uncertain whether it adds further information to evaluation by RECIST, thus further studies and standardization of methods are needed.

CHAPTER 9.
Follow up of patients treated for lung cancer with no suspicion of recurrence (NSCLC)

Primary studies

Author, year	Onishi 2010
Technology	F-FDG-PET/CT
Disease	NSCLC
Objective	to prospectively and directly compare the capability of integrated FDG-PET/CT to assess postoperative intra- and extrathoracic recurrence in NSCLC patients with that of standard radiological examinations, and determine the utility of FDG uptake assessment at suspected lesions for integrated FDG-PET/CT in routine clinical practice
Patients characteristics	121 consecutive pathologically diagnosed NSCLC patients who had undergone whole-body integrated FDGPET/CT and standard radiological examinations before treatment and pathologically and surgically proven complete resection mean age 71 years
Index test	F-FDG-PET/CT
Comparator	MRI, CT, bone scintigraphy
Reference standard	histological examination or (when not feasible) follow up
Country	Japan
Outcomes considered	sensitivity, specificity, PPV, NPV, accuracy
Study design	prospective cross-sectional study
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	yes
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	no

Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	no
Withdrawals from the study explained	yes
Pre-test probability	21.5%
Results	F-FDG-PET/CT including brain metastases (qualitative assessment) sensitivity: 80.8% specificity: 76.8% PPV: 48.8% NPV: 93.5% accuracy: 77.7% F-FDG-PET/CT including brain metastases (qualitative + quantitative assessment) sensitivity: 73.1% specificity: 87.4% PPV: 61.3% NPV: 92.2% accuracy: 84.3% F-FDG-PET/CT excluding brain metastases (qualitative assessment) sensitivity: 84% specificity: 76.8% PPV: 48.8% NPV: 94.8% accuracy: 78.3% F-FDG-PET/CT excluding brain metastases (qualitative + quantitative assessment) sensitivity: 76% specificity: 87.4% PPV: 61.3% NPV: 93.3% accuracy: 85.0% Standard radiological examinations including brain metastases sensitivity: 73.1% specificity: 73.7% PPV: 43.2% NPV: 90.9% accuracy: 73.6% Standard radiological examinations excluding brain metastases sensitivity: 72% specificity: 73.7% PPV: 41.9% NPV: 90.9% accuracy: 73.3%

Authors' recommendations and conclusions	Accuracy of assessment of postoperative intra- and extrathoracic recurrence in NSCLC patients by qualitative and/or quantitative FDG-PET/CT is equivalent to or higher than that by standard radiological examinations.

CHAPTER 10.

Diagnosis and staging of suspected loco-regional recurrence in patients treated for lung cancer (NSCLC)

Synoptic table of primary studies on diagnosis and staging of suspected loco-regional recurrence in patients treated for lung cancer (NSCLC)

Author, year	Patient number	Patient characteristics	Technology	Reference standard	Pre-test probability	Sensitivity	Specificity
Hellwig 2006	62	NSCLC with suspected recurrence after surgery	FDG-PET	histology, cytology or clinical evolution and serial imaging	75.3% (55 out of 73 exams)	93% (95% CI 86-100%)	89% (95% CI 74-100%)
Nakamoto 2008	41	consecutive patients, with suspected recurrence after surgical therapy of lung cancer	FDG-PET/CT	histology or at least 6-month clinical follow up	not reported and not computable	87%	50%
			CT			77%	70%
Isobe 2009	22	NSCLC patients after potentially curative surgery generally and CEA elevation	FDG-PET	histology or cytology or clinical and radiological follow up of at least 6 months	68.2% (15 out of 22 patients)	93%	86%

Primary studies

Author, year	Hellwig 2006
Technology	FDG-PET/CT
Disease	NSCLC
Objective	to assess diagnostic accuracy detecting recurrence of NSCLC
Patients characteristics	62 consecutive patients, with suspected recurrence after surgical therapy of lung cancer
Index test	FDG-PET
Comparator	none
Reference standard	the final diagnosis was confirmed by histology (n = 38), cytology (n = 9) or clinical evolution and serial imaging (n = 8)
Country	Germany
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with retrospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described:	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	not reported
Withdrawals from the study explained	no withdrawals
Pre-test probability	75.3% (55 out of 73 exams)

Results	FDG-PET sensitivity 93% (95% CI: 86-100%) specificity 89% (95% CI: 74-100%)
Authors' recommendations and conclusions	FDG-PET accurately detects recurrent lung cancer. SUV in recurrent tumor is an independent prognostic factor. FDG-PET helps in the selection of patients who will benefit from surgical re-treatment.

Author, year	**Isobe 2009**
Technology	FDG-PET
Disease	NSCLC
Objective	to assess diagnostic accuracy detecting recurrence of NSCLC
Patients characteristics	22 patients, with suspected recurrence after surgical therapy of lung cancer
Index test	FDG-PET
Comparator	
Reference standard	histology or cytology or clinical and radiological follow up of at least 6 months
Country	Japan
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with retrospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	no
Patients selection criteria clearly described	no
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	not reported
Withdrawals from the study explained	no withdrawals
Pre-test probability	68.2% (15 out of 22 patients)
Results	FDG-PET sensitivity 93% specificity 86%

Authors' recommendations and conclusions	In 64% of the patients with unexplained increased CEA levels, FDG-PET provided decisive diagnostic clues guiding further diagnostic and therapeutic interventions. The selected use of FDG-PET for patients with re-elevated serum CEA levels after surgery can be a practical and effective mode of surveillance for detecting recurrent lung cancer.

Author, year	**Nakamoto 2008**
Technology	FDG-PET/CT
Disease	NSCLC
Objective	to assess diagnostic accuracy detecting recurrence of NSCLC
Patients characteristics	53 non consecutive patients (28 M, 25 F), with suspected recurrence after surgical therapy of lung cancer
Index test	FDG-PET/CT
Comparator	CT
Reference standard	histopathologic examination or at least 6-month clinical follow up was used as the standard of reference. Surgery and biopsy were performed in 3 and 2 patients, respectively, with histopathologic confirmation. For the remaining 48 patients, final diagnoses were determined by clinical follow up
Country	Japan
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with retrospective recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described:	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not reported
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	not reported
Withdrawals from the study explained	no withdrawals

Pre-test probability	not reported and not computable
Results	FDG-PET/CT sensitivity 87% specificity 50% CT sensitivity 77% specificity 70% clinical impact on 9 patients (17%)
Authors' recommendations and conclusions	These results suggest that interpreting fused images increased diagnostic certainty for detecting recurrence and provided more accurate diagnoses.

COLLANA DOSSIER

a cura dell'Agenzia sanitaria e sociale regionale

1990

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