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RegioneEmilia-Romagna

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA

Criteria for appropriate use of FDG-PET in breast cancer

ORIentamenti 3

Osservatorio regionale per l'innovazione

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List of abbreviations

ASSR	Agenzia sanitaria e sociale regionale
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	fluoro-deoxyglucose
FN	false negatives
FP	false positives
LR	likelihood ratio
MA	meta-analysis
MRI	magnetic resonance imaging
NICE	National Institute of Clinical Excellence
PET	positron emission tomography
RCT	randomized controlled trial
RER	Regione Emilia-Romagna
RT	radiotherapy
SIGN	Scottish Intercollegiate Guidelines Network
SMM	scintimammography
SLNB	sentinel lymph node biopsy
SR	systematic review
TN	true negatives
TP	true positives
US	ultrasonography

Sintesi dei risultati

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

Il *panel* ha esaminato e stabilito il ruolo della FDG-PET per le seguenti indicazioni cliniche:

- diagnosi di tumore primitivo della mammella - Inappropriato per assenza di ruolo diagnostico della FDG-PET
- stadiazione N del tumore primitivo della mammella - Inappropriato (livello di evidenza: molto basso)
- stadiazione M del tumore localmente avanzato della mammella - Incerto (livello di evidenza: basso)
- valutazione della risposta precoce al trattamento neoadiuvante - Incerto (livello di evidenza: basso)
- valutazione della risposta alla terapia neoadiuvante al termine del trattamento - Inappropriato per assenza di ruolo diagnostico della FDG-PET
- follow up in pazienti con nessun sospetto di recidiva - Inappropriato (livello di evidenza: molto basso)
- diagnosi e stadiazione di sospetta recidiva a distanza - Incerto (livello di evidenza: moderato)

DIAGNOSI DI TUMORE PRIMITIVO DELLA MAMMELLA - INAPPROPRIATO

Sebbene la letteratura scientifica abbia prodotto una revisione sistematica e tre ulteriori studi primari sul ruolo della FDG-PET nella diagnosi del tumore primitivo della mammella, il *panel* ha concordato nel ritenere inappropriato l'uso della FDG-PET nella diagnosi del tumore primitivo della mammella per assenza di ruolo diagnostico della FDG-PET.

STADIAZIONE N DEL TUMORE PRIMITIVO DELLA MAMMELLA - INAPPROPRIATO

Il *panel* ha raggiunto il consenso nel giudicare inappropriato l'uso della FDG-PET come esame di primo livello, per identificare i pazienti candidati all'asportazione dei linfonodi del cavo ascellare evitando la biopsia del linfonodo sentinella. Il livello di evidenza dell'accuratezza diagnostica della FDG-PET è risultato molto basso, e il danno di uno svuotamento ascellare non necessario è stato considerato più importante rispetto al beneficio ottenuto evitando una biopsia del linfonodo sentinella. L'esito per i pazienti

risultati falsi positivi - con inutile svuotamento ascellare, senza alcun impatto sulla sopravvivenza e con l'inutile esposizione ad eventi avversi - è stato infatti giudicato "critico" (mediana del punteggio pari a 8, *range* 2-9). Al contrario l'esito per i veri positivi - svuotamento ascellare necessario evitando la biopsia del linfonodo sentinella - è stato giudicato "non importante" (mediana del punteggio pari a 2, *range* 2-7) così come gli esiti per i veri e falsi negativi (mediana del punteggio pari a 2).

STADIAZIONE M DEL TUMORE DELLA MAMMELLA LOCALMENTE AVANZATO - INCERTO

Il *panel* non ha raggiunto il consenso nel giudicare il ruolo della FDG-PET come esame di primo livello nello *staging* delle pazienti con tumore della mammella localmente avanzato (T3-T4 e/o N2/N3), che avrebbe lo scopo di indirizzare i pazienti positivi alla FDG-PET a ulteriori esami diagnostici più specifici. I singoli voti sono risultati distribuiti in tutte le categorie di appropriato, incerto e inappropriato. Il livello di evidenza dell'accuratezza diagnostica della FDG-PET è risultato basso, anche a causa della eterogeneità delle stime di specificità. Il giudizio finale è perciò incerto per disaccordo.

L'esito per i pazienti falsi negativi - sottoposti a inutile trattamento chirurgico - è stato l'unico giudicato come "critico" dal *panel* (mediana del puntaggio pari a 7, *range* 2-9). Tutti gli altri esiti - per i veri e falsi positivi e i veri negativi - sono stati votati come "importanti".

VALUTAZIONE DELLA RISPOSTA PRECOCE AL TRATTAMENTO NEOADIUVANTE - INCERTO

Dopo due votazioni il *panel* ha raggiunto l'accordo nel giudicare e incerta l'appropriatezza della FDG-PET nella valutazione della risposta precoce al trattamento neoadiuvante nelle pazienti con tumore localmente avanzato o candidate alla mastectomia.

Il livello di evidenza dell'accuratezza diagnostica della FDG-PET è risultato basso, anche a causa dell'eterogeneità delle stime di specificità. Tutti gli esiti sono stati giudicati "importanti", dimostrando la necessità di un esame che possa correttamente identificare le pazienti che rispondono alla chemioterapia neoadiuvante, allo scopo di evitare inutile tossicità alle pazienti che non rispondono. Tuttavia i risultati sull'accuratezza non sono stati considerati sufficienti per proporre nella pratica clinica l'uso della FDG-PET a tale scopo.

VALUTAZIONE DELLA RISPOSTA ALLA TERAPIA NEOADIUVANTE AL TERMINE DEL TRATTAMENTO - INAPPROPRIATO

Dopo l'iniziale disaccordo registrato alla prima votazione, con i singoli punteggi compresi nelle categorie di inappropriato e incerto, il *panel* ha raggiunto il consenso nel giudicare come inappropriato l'uso della FDG-PET per la valutazione della risposta alla terapia neoadiuvante al termine del trattamento.

La discussione durante il secondo incontro ha condotto il *panel* a concordare sul fatto che non vi è razionale clinico per proporre l'uso della FDG-PET. Sebbene la risposta alla terapia pre-operatoria sia importante per decidere il successivo programma terapeutico,

per le pazienti sottoposte a trattamento chirurgico al termine della terapia neoadiuvante il risultato istopatologico ottenuto su reperto chirurgico è il *gold standard* e non necessita sostituzione.

FOLLOW UP IN PAZIENTI CON NESSUN SOSPETTO DI RECIDIVA - INAPPROPRIATO

Il *panel* ha giudicato consensualmente alla prima votazione come inappropriato l'uso della FDG-PET nel *follow up delle* pazienti con nessun sospetto di recidiva. Il livello di evidenza dell'accuratezza diagnostica della FDG-PET è risultato molto basso, a causa della presenza di un solo studio con pochi pazienti che valuta la FDG-PET nel *follow up*. Inoltre tutti gli esiti sono stati giudicati "non importanti" da parte del *panel* (mediana del punteggio pari a 3 per veri e falsi positivi e negativi).

DIAGNOSI E STADIAZIONE DI SOSPETTA RECIDIVA A DISTANZA - INCERTO

Dopo due votazioni i componenti del *panel* non hanno raggiunto un accordo - con i singoli punteggi compresi nelle categorie di incerto e appropriato - sul ruolo della FDG-PET come esame di primo livello nelle pazienti con sospetta recidiva a distanza. Il giudizio finale è quindi risultato incerto per disaccordo.

Il livello di evidenza dell'accuratezza diagnostica della FDG-PET è risultato moderato, dimostrando una migliore prestazione della FDG-PET rispetto ad altri esami di diagnostica per immagini, sebbene i risultati siano contrastanti a causa della variabilità di comparatori usati nei diversi studi.

Gli esiti per i pazienti veri positivi, i quali procedono a ulteriori e più specifici esami e ricevono trattamento appropriato, sono stati votati come "critici" (mediana del punteggio pari a 7, *range* 4-9), mentre l'inutile carico di ansia e di stress provocati ai falsi positivi da una diagnosi errata è stato votato come "importante" con una mediana del punteggio pari a 6 (*range* 3-7). Anche gli esiti per i veri e falsi negativi sono stati giudicati "importanti", con una mediana di punteggio pari a 4.

Summary of results

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

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

- Diagnosis of primary breast cancer - Inappropriate for lack of diagnostic role of FDG-PET
- N staging of primary breast cancer - Inappropriate (level of evidence: very low)
- M staging of locally advanced breast cancer - Uncertain (level of evidence: low)
- Evaluation of early response to neo-adjuvant therapy - Uncertain (level of evidence: low)
- Evaluation of response to neo-adjuvant therapy at the end of treatment - Inappropriate (no diagnostic role of FDG-PET)
- Follow up in patients with no suspicion of recurrence - Inappropriate (level of evidence: very low)
- Diagnosis and staging of suspect distant recurrence - Uncertain (level of evidence: moderate)

DIAGNOSIS OF PRIMARY BREAST CANCER - INAPPROPRIATE

Although the systematic review of scientific literature produced one systematic review and three primary studies on the role of FDG-PET in the diagnosis of primary breast cancer, the panel agreed to consider as inappropriate the use of FDG-PET in the diagnosis of primary breast cancer, due to lack of diagnostic role for FDG-PET.

N STAGING OF PRIMARY BREAST CANCER - INAPPROPRIATE

The panel agreed in judging as inappropriate the use of FDG-PET as a triage test, in order to identify patients eligible for axillary lymph node dissection, bypassing sentinel lymph node biopsy (SNLB). Level of evidence for diagnostic accuracy of FDG-PET resulted very low and the harm of an unnecessary axillary dissection was considered more severe than the benefit of bypassing SNLB. The outcome for patients resulting false positive - unnecessary axillary lymph nodes dissection, which would not impact on survival, and unnecessarily exposure to adverse effects - was in fact voted "critical" (median score 8;

range 2-9), while outcomes for true positive - necessary axillary dissection and avoidance of SNLB - was voted "not important" (median score 2; range 2-7). Outcomes for true and false negative were also voted "not important" (median score 2).

M STAGING OF LOCALLY ADVANCED BREAST CANCER - UNCERTAIN

The panel did not reach an agreement in judging the role of FDG-PET in staging patients with locally advanced breast cancer (T3-T4 and/or N/N3) as a triage test, i.e. to direct FDG-PET positive patients to further more specific diagnostic tests.

Level of evidence for diagnostic accuracy of FDG-PET was low, due partly to the heterogeneity of estimates for specificity, and ratings of panelists fell within all three regions (inappropriate, uncertain and appropriate). The final rating is therefore uncertain due to disagreement.

The outcome for patients resulting false negatives - undergoing unnecessary surgical treatment - was the only outcome voted "critical" by the panel (median score 7; range 2-9). All other outcomes - true and false positives and true negatives - were voted "important".

EVALUATION OF EARLY RESPONSE TO NEO-ADJUVANT THERAPY - UNCERTAIN

After two rounds of voting the panel agreed to judge as uncertain the introduction of FDG-PET for the evaluation of early response to neo-adjuvant therapy, in patients with locally advanced breast cancer or eligible for mastectomy.

Level of evidence for diagnostic accuracy of FDG-PET was low, due also to the heterogeneity of estimates for specificity. All outcomes were voted as "important", showing clinicians' wish for a test that could correctly identify patients who respond to neo-adjuvant chemotherapy, in order to spare unnecessary toxic treatment to non responders. However data of accuracy were not considered sufficient to suggest a use of FDG-PET results in clinical practice for this purpose.

EVALUATION OF RESPONSE TO NEO-ADJUVANT THERAPY AT THE END OF TREATMENT - INAPPROPRIATE

After an initial disagreement registered in the first round, with ratings falling in the inappropriate and uncertain regions, the panel agreed to judge as inappropriate the use of FDG-PET in evaluating response to neo-adjuvant therapy at the end of treatment.

The discussion during the second meeting brought the panel to agree that there was no clinical rationale in support of this use of FDG-PET. Although response to pre-operative therapy is important to decide on subsequent therapeutic regimens, patients undergo surgical treatment at the end of therapy and the histopathologic response evaluated on the surgical specimen represents the gold standard in no need for replacement.

FOLLOW UP IN PATIENTS WITH NO SUSPICION OF RECURRENCE - INAPPROPRIATE

The panel agreed during the first round in rating as inappropriate the use of FDG-PET during follow up of patients treated for breast cancer. Level of evidence for diagnostic accuracy of FDG-PET was very low, as only one study with very few patients evaluated FDG-PET in follow up of breast cancer. Moreover all outcomes were voted as not important by the panelists (median scores of 3 for true and false positives and negatives).

DIAGNOSIS AND STAGING OF SUSPECT DISTANT RECURRENCE - UNCERTAIN

A disagreement among panelists, with ratings falling in the uncertainty and appropriateness regions, was registered in both rounds of votes on the role of FDG-PET as a triage test in patients with suspect distant recurrence. The final rating is therefore uncertain due to disagreement.

Level of evidence for diagnostic accuracy of FDG-PET was moderate, showing FDG-PET performing better than other imaging tests, although results are mixed due to the variety of comparators used in the different studies.

The outcomes for true positive patients, proceeding to further and more specific tests and receiving appropriate treatment, were voted "critical" (median score 7; range 4-9), while the unnecessary anxiety and stress caused by a false positive results was voted "important" with a median score of 6 (range 3-7). The outcomes for true and false negatives were also voted "important" with a lower medians score of 4.

Foreword

The Regional Observatory for Innovation (ORI) is a research unit within the Regional Health and Social Agency of Emilia-Romagna (Italy), which support the Local Authority and its individual health care organisations in governing the adoption of health technologies.

The Dossiers are developed with 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 breast cancer has been carried out between September 2010 and January 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.

The evidence base was synthesized in accordance with the GRADE methodology and the consensus process was based on the RAND/UCLA Appropriateness Method.

This Dossier is published in 2011 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.

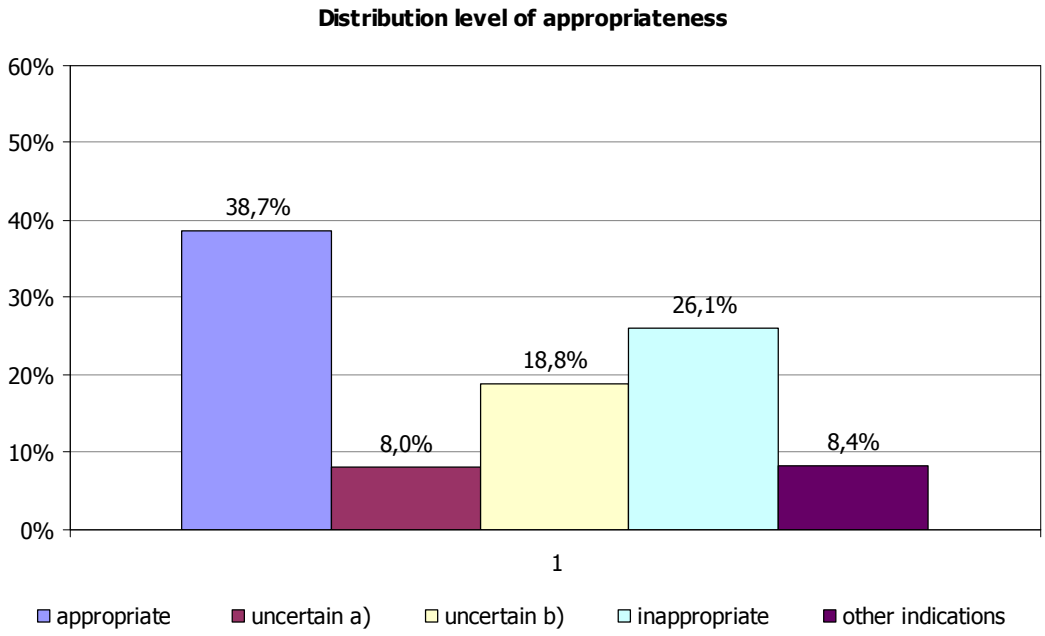
Since its introduction in the Emilia-Romagna Regional Health Service the Agenzia sanitaria e sociale regionale (ASSR) has been committed to promote and support regional research programmes aimed at assessing clinical indications for PET and supporting programming policies.

The first research programme, 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 tumour, 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 PET scans, consecutively registered and analysed between January and July 2002, about one third (38.7%) resulted to be appropriate, while 26.1% were inappropriate (*Graph 1*).

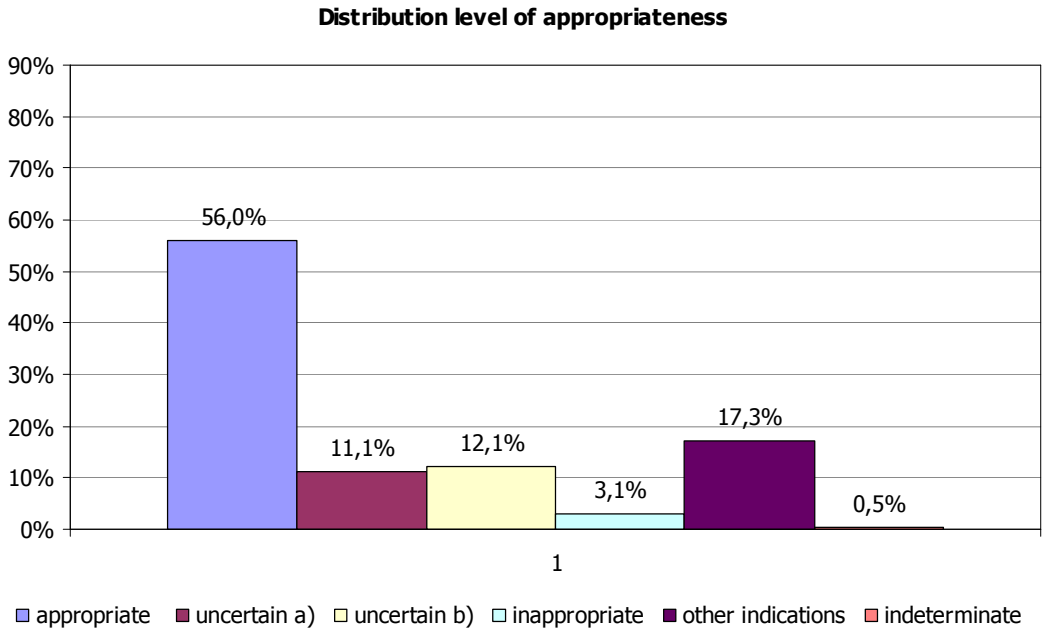
Following the increase in number of PET scanners (from 1 to 6) an update of the 2003 report was commissioned to a second regional panel and published in 2007. The second report addressed the role of PET in 18 types of cancer for a total of 65 clinical indications, and a second clinical audit was carried out in the 6 regional PET centres. From the 600 consecutive PET exams analysed, 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 programme 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 programme. 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 breast cancer: objectives

This work is part of a wider research programme covering the use of 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 breast cancer.

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

- supporting clinicians on the use of FDG-PET in breast 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 breast cancer.

1.2. Context

Incidence of breast cancer in RER

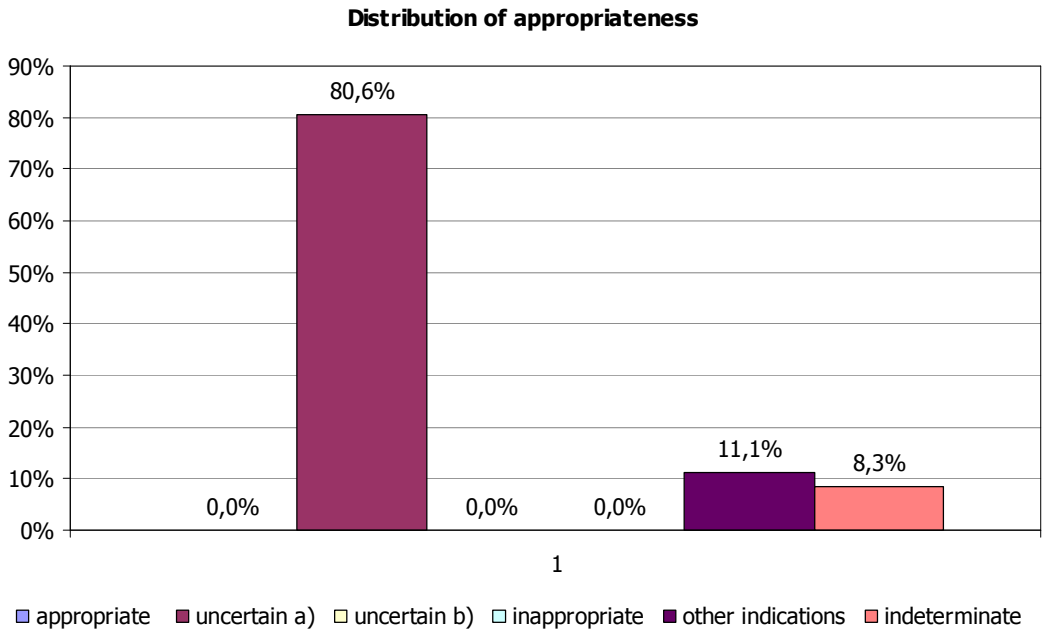
Crude incidence rate of breast cancer in Emilia-Romagna Region in 2004 (RER 2009): 171.1 per 100 000 female inhabitants per year.

Prevalence of breast cancer in RER

Cumulative 10 years prevalence estimate of breast cancer in Emilia-Romagna Region at 1/1/2005 (RER 2009): 1 300.6 per 100 000 female inhabitants, corresponding to 26 243 cases in Emilia-Romagna region.

In the regional audit carried out in 2002 audit, FDG-PET scans requested for patients with breast cancer represented 10% of the total sample included, and 56% of these requests were considered inappropriate, while the remaining 44% fell in the uncertain category. In the 2007 audit, following the criteria update in 2006, FDG-PET scans for breast cancer went down to 6.1% of the total sample and 83% of these fell in the uncertain category, with no inappropriate requests (*Graph 3*). The remaining 11% fell into the "other indications" category.

Graph 3. Clinical audit 2006 - appropriate use of FDG-PET in breast cancer (36 FDG-PET scans)



2. Methods

A panel of 23 experts, comprising nuclear physicians, radiologists, radiotherapists, surgeons, oncologists, pneumologists, haematologists and health directors working in Health Trusts and Teaching Hospitals of Emilia-Romagna was convened to discuss and agree on the methodology for a research programme aimed at defining the criteria for appropriate use of PET in oncology.

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

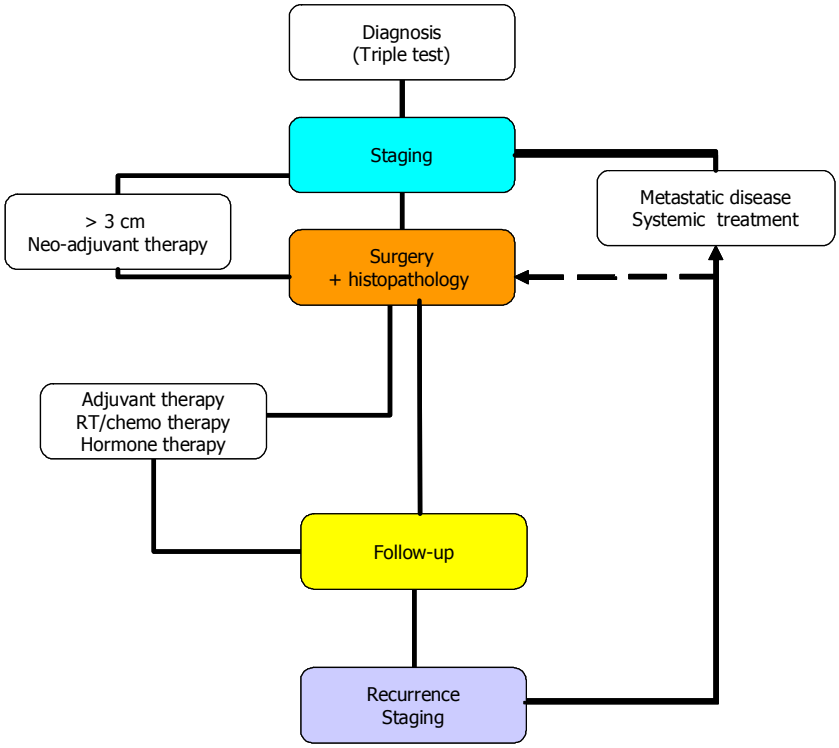
On the basis of the clinical pathway of patients with breast cancer (*Figure 2.1*), shared by most international clinical practice guidelines, the panel examined and assessed the role of FDG-PET for 7 clinical indications (*Table 2.1*).

The panel agreed not to take into consideration the role of FDG-PET in the prediction of response to endocrine therapy in metastatic cancer, although two case series had been retrieved.

Table 2.1. Clinical indications selected by the panel

• Diagnosis of primary breast cancer
• *N* staging of primary breast cancer
• *M* staging of locally advanced breast cancer
• Evaluation of early response to neo-adjuvant therapy
• Evaluation of response to neo-adjuvant therapy at the end of treatment
• Follow up in patients with no suspicion of recurrence
• Diagnosis and staging of suspect distant recurrence

Figure 2.1. Clinical pathway for breast cancer

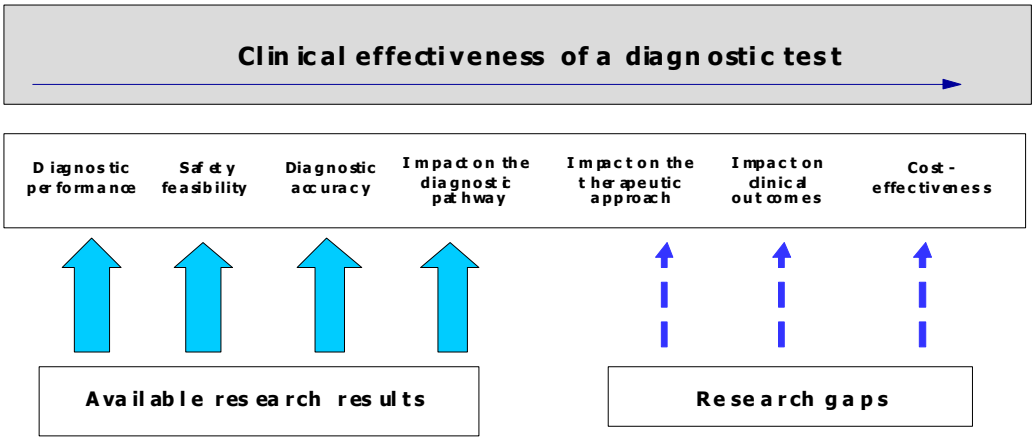


The starting point for the development of answerable "research questions", based on the PICO structure (patient intervention comparator outcome), has been the broad definition of appropriateness of a diagnostic test, which implies:

- 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 2.2.

Figure 2.2. 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 CT/PET 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 July 2010:

- 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 [LV].

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 breast cancer
Intervention	FDG-PET or CT/PET
Reference standard	histology or clinical follow up (for diagnostic accuracy studies)
Comparator	any other imaging technique
Outcomes	sensitivity, specificity, LR, metabolic/tumor response, time to recurrence, local, local-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

Case series: no standardized checklist have 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, analysed 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.

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 SRs/MA 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 SRs/MA, results from primary studies were analysed only for consistency.

With SRs/MA and primary studies available, if patients included in primary studies published after SRs/MA added up to a number greater than the patients included in the SRs/MA, 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).

Level of evidence for estimates of diagnostic accuracy were assigned according to GRADE categorization of the quality of evidence (Guyatt 2008), and defined as follows:

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 breast 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 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 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

One round of votes was required for the importance of the clinical outcomes and median scores were presented to the panel.

Two rounds of votes were requested for the judgment of appropriateness and results were analysed using the RAND/UCLA Appropriateness Method,[1] 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

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 diagnostic accuracy of FDG-PET and the presumed benefit - resulting from test results - is greater than the presumed harm.

[1] http://www.rand.org/pubs/monograph_reports/MR1269.html

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.

INAPPROPRIATE

- Clinical indications for which there is NO rationale for change in management related to a patient-important clinical outcome
- 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 diagnostic accuracy of FDG-PET and the presumed harm - resulting from 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 full in Appendix 2. The initial search identified 654 records; 577 were excluded as they did not meet the inclusion criteria or were duplicates. Full text was acquired for the remaining potentially eligible 78 records, from which 40 studies were excluded on the basis of inclusion criteria while for another 3 we were unable to retrieve the full text. Thirty-five studies were finally included. Table 3.1 reports number and type of studies for each clinical question and endpoint as well as conclusions from the previous 2007 report (Liberati 2007 - *Dossier 157*).

Only studies evaluating diagnostic accuracy were found and retrieved.

Table 3.1. Number of included studies for questions and endpoints

Clinical question / Endpoint	Diagnosis	Staging	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	Systematic reviews: 2 *N staging: 2* *M staging: 1*	Systematic reviews: 1	Systematic reviews: 1	Systematic reviews: 0	Systematic reviews: 4
	Primary studies: 3	Primary studies: *N staging: 15* *M staging: 2*	Primary studies: 7	Primary studies: 3	Primary studies: 1	Primary studies: 2
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	Not considered	N staging: not considered M staging: Uncertain A	Indeterminate	Not considered	Not considered	Uncertain A

4. Diagnosis of primary breast cancer

Rationale

Diagnosis of breast cancer in women with suspicion of cancer is placed through triple assessment (clinical assessment, mammography and/or ultrasound imaging followed by core biopsy and/or fine needle aspiration cytology) (NICE 2009; NCCN 2010; SIGN 2005).

However mammography has diagnostic limitations in women under 35 years and ultrasound - indicated for women under 35 years - could be operator-dependent.

Diagnostic role of FDG-PET

The panel unanimously agreed that there is no diagnostic role for FDG-PET in the diagnosis of primary breast cancer.

4.1. Systematic review of literature: results

Dossier 157

Not considered.

Results from update of systematic review of literature from Jan 2006

Systematic reviews

One systematic review has been retrieved (Escalona 2010) assessing the accuracy of FDG-PET for the primary diagnosis of breast cancer in patients with suspect or confirmed breast cancer.

The methodological quality was judged intermediate. Sixteen studies were included, but according to inclusion criteria, only 8 studies out of the 16 are eligible (possibility of computation of both sensitivity and specificity). The overall judgment of the review authors on quality of the studies was low due to small sample sizes and uncertainty about blinding of reference standard results when interpreting FDG-PET images.

The studies included patients with suspected or confirmed primary breast cancer submitted to FDG-PET and other diagnostic tests (5 studies: 2 MRI, 1 scintimammography, 1 physical examination + mammography + ultrasound, 1 physical examination + mammography). In all cases the reference standard was the histological examination. The pooling of data was not performed due to the document design and purpose. The authors conclude qualitatively that FDG-PET "does not appear to be sufficiently accurate to be used in isolation from other tests for ruling out the presence of a primary tumor" (see *Table 4.1* for a synthesis of data).

Primary studies

Three studies, published after the above systematic review and evaluating diagnostic accuracy of FDG-PET in the primary diagnosis of suspected breast cancer were included (Alberini 2009; Buchmann 2007; Imbriaco 2008). All studies recruited women with known or suspect breast cancer based on clinical, radiological and post biopsy pathological investigation; one of these recruited only women with suspected inflammatory breast cancer. Three studies used FDG-PET, two used FDG-PET/CT. All studies suffer from uncertainty of blind comparison between index test and reference standard.

One more study (Berg 2006) applied a different technique (FDG-PEM i.e. the positron emission mammography).

As a meta-analysis of studies was not performed in the above cited systematic review (Escalona 2010), estimates from all 11 studies were pooled and heterogeneity of diagnostic estimates of FDG-PET tested (*Table 4.1*).

Comments of ASSR reviewer

The clinical spectrum of patients included in studies is seriously biased, as mainly patients over 35 years of age are recruited. Results are therefore limited by serious indirectness.

The results from 11 studies show heterogeneity both in sensitivity and specificity of FDG-PET and FDG-PET does not seem to be sufficiently accurate for the diagnosis of primary breast cancer.

Diagnostic accuracy estimates

It is not possible to provide estimates.

LEVEL OF EVIDENCE: VERY LOW

Table 4.1. Overall results on diagnostic accuracy of FDG-PET for diagnosis of primary breast cancer

Diagnostic accuracy	
Number of studies	11
Number of patients	578 (median number per study 40, range 22-117)
Pre-test probability	median 75% (range 47.5-96%)
FDG-PET/PET-CT	sensitivity: median 80% (range 48-100%) *heterogeneity chi-squared = 101.22 (d.f. = 10) p = 0.000* *inconsistency (I-square) = 90.1%* specificity: median 91% (range 33-100%) *heterogeneity chi-squared = 18.38 (d.f. = 10) p = 0.049* *inconsistency (I-square) = 45.6%*
Comparator	MRI (3 studies, 120 patients) sensitivity: median 95% (range 89-98%) specificity: median 74% (range 73-80%) 123 I-SPECT (1 study, 10 patients) sensitivity: 67% specificity: 100% scintimammography (1 study, 22 patients) sensitivity: 80% specificity: 86% physical examination (1 study, 26 patients) sensitivity: 80% specificity: 67% mammography (1 study, 26 patients) sensitivity: 79% specificity: 25%
Reference standard	histopathological confirmation by core or excisional biopsy, lumpectomy or mastectomy
References	Alberini 2009; Buchmann 2007; Escalona 2010; Imbriaco 2008

4.2. Clinical outcomes

As the panel agreed on lack of diagnostic role of FDG-PET in diagnosis of primary breast cancer no patient-important outcomes have been proposed and voted.

4.3. Appropriateness

The panel decided not to carry out the full voting procedure and unanimously agreed to judge the use of FDG-PET in the diagnosis of primary breast cancer as inappropriate.

FINAL RATING FOR THE USE OF FDG-PET FOR DIAGNOSIS OF PRIMARY BREAST CANCER:

INAPPROPRIATE

4.4. Conclusions

The panel clearly expressed no clinical need for an additional or alternative test for the diagnosis of primary breast cancer and unanimously decided to judge this use of FDG-PET as inappropriate.

5. N staging of patients with primary breast cancer

Rationale

Surgery is the core treatment for ductal carcinoma in situ (DCIS) and invasive breast cancer and is the proposed first treatment option (NICE 2009).

Regional lymph node status remains the strongest predictor of long-term prognosis in primary breast cancer. Sentinel lymph node biopsy (SLNB) is the standard care to decide for axillary lymph node dissection (ESMO 2010a; NICE 2009; SIGN 2005).

Diagnostic role of FDG-PET

It is suggested that a highly specific and non-invasive diagnostic tool aimed at detecting axillary cancer involvement could be used as a triage test in order to refer patients testing positive directly to axillary lymph node dissection, thus avoiding SNLB (Veronesi 2007).

Treatment effectiveness

Axillary lymph node dissection is recommended for patients with confirmed or suspect axillary node involvement (ESMO 2010a; NICE 2009; SIGN 2005).

Pre-test probability and change in management

The median pre-test probability of cancer involvement of regional nodes is 42.4% (range 21.7-70.6%) (Cermik 2008; Chae 2009; Chung 2006; Fuster 2008; Gil-Rendo 2006; Heusner 2009; Kim 2009; Kumar 2006; Monzawa 2009; Mustafa 2007; Sloka 2007; Stadnik 2006; Taira 2009; Ueda 2008; Uematsu 2009; Veronesi 2007), which could be considered to be the hypothetical maximum extent of change in management, achievable through accurate N staging.

Research question: FDG-PET as triage

Has FDG-PET sufficient specificity to identify patients who should proceed directly to axillary lymph node dissection?

5.1. Systematic review of literature: results

Dossier 157

Not considered.

Results from update of systematic review of literature from Jan 2006

Systematic reviews

Two systematic reviews have been retrieved (Escalona 2010; Sloka 2007); one (Sloka 2007) assessed the diagnostic accuracy of FDG-PET for N staging in patients with breast cancer, the other (Escalona 2010) assessed the accuracy of FDG-PET both for N staging and for any kind of distant metastasis. The methodological quality was judged as intermediate for both reviews (*Table 5.1*).

Table 5.1. Results from systematic reviews on N staging with FDG-PET

Reference	Sloka 2007	Escalona 2010
Update to	2005	February 2007
Number of studies	18 (6 in common with Escalona 2010)	19 (6 in common with Sloka 2007)
Number of patients	1 271 median 39.5 (range 11-308)	1 583 median 51 (range 10-360)
FDG-PET/ PET-CT	sensitivity high quality studies: mean 78% intermediate quality studies: mean 67% low quality studies: mean 96% very low quality studies: mean 78% specificity high quality studies: mean 85% intermediate quality studies: mean 89% low quality studies: mean 84% very low quality studies: mean 99%	not calculated: only descriptive results. *"FDG-PET does not appear to be accurate enough to detect occult axillary metastases or micrometastases (sensitivity 20% and 50%, respectively); sentinel node biopsy is required for confirmation"*
Comparator	data not reported	palpation (2 studies) sensitivity 44%, 58% specificity 85%, 90% US (1 study) sensitivity 65% specificity 100% CT (1 study) sensitivity 54% specificity 85% USPIO-MRI (1 study) sensitivity 100% specificity 80%
Reference standard	histology by axillary lymph node dissection or biopsy	histology by axillary lymph node dissection or biopsy

Primary studies

Fifteen studies evaluating diagnostic accuracy of FDG-PET in the N staging of patients with breast cancer published after the SR by Sloka 2007 were included (Cermik 2008; Chae 2009; Chung 2006; Fuster 2008; Gil-Rendo 2006; Heusner 2009; Kim 2009; Kumar 2006; Monzawa 2009; Mustafa 2007; Stadnik 2006; Taira 2009; Ueda 2008; Uematsu 2009; Veronesi 2007) (*Table 5.2*). Eight of them applied FDG-PET/CT. Five studies included patients with breast cancer without specifying the stage of the disease, five studies included women with proven breast cancer and clinically negative lymph node, two studies included patients with large or locally advanced breast cancer, and the remaining three studies included women with early, suspected and stage I-III breast cancer (one each).

As patients included in primary studies published after Sloka's (Sloka 2007) and Escalona's (Escalona 2010) updates added up to a number greater than the patients included in the SRs/MA, estimates of all studies have been pooled and re-calculated and heterogeneity of diagnostic estimates of FDG-PET tested (*Table 5.3*).

Comments of ASSR reviewer

For N staging, a great variability in the estimates of diagnostic accuracy is reported. Without careful analysis of source of variability it proves difficult to draw conclusions regarding the applicability of FDG-PET for N staging.

Diagnostic accuracy estimates

FDG-PET sensitivity: (heterogeneous) range 20-100%.

FDG-PET specificity: (heterogeneous) range 66-100%.

LEVEL OF EVIDENCE: VERY LOW

Table 5.2. Results from primary studies on N staging with FDG-PET

Reference	Cermik 2008; Chae 2009; Chung 2006; Fuster 2008; Gil-Rendo 2006; Heusner 2009; Kim 2009; Kumar 2006; Monzawa 2009; Mustafa 2007; Stadnik 2006; Taira 2009; Ueda 2008; Uematsu 2009; Veronesi 2007
Number of studies	15
Number of patients	1 609 (median 80, range 10-275)
FDG-PET/PET-CT	sensitivity: median 58% (range 20-84.5%) specificity: median 96% (range 84-100%)

Table 5.3. Overall results on diagnostic accuracy of FDG-PET for N staging

Diagnostic accuracy	
Number of studies	42
Number of patients	3 342 (median 52, range 10-308)
Pre-test probability	median 42.4% (range 21.7-70.6%)
FDG-PET/PET-CT	sensitivity: median: 70% (range 20-100%) *heterogeneity chi-squared = 314.96 (d.f. = 39) p = 0.000* *inconsistency (I-square) = 87.6%* specificity: median 97% (range 66-100%) *heterogeneity chi-squared = 164.56 (d.f. = 39) p = 0.000* *inconsistency (I-square) = 76.3%*
Reference	Cermik 2008; Chae 2009; Chung 2006; Fuster 2008; Gil-Rendo 2006; Heusner 2009; Kim 2009; Kumar 2006; Monzawa 2009; Mustafa 2007; studies from Sloka 2007; Stadnik 2006; Taira 2009; Ueda 2008; Uematsu 2009; Veronesi 2007

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

The main benefit brought by the introduction of FDG-PET (avoidance of SNLB for true positives) was voted "not important", while the main risk associated with the exam (unnecessary axillary lymph nodes dissection for false positives) was voted "critical".

No studies investigating the impact of FDG-PET on the above clinical outcomes were found.

Given the heterogeneity of both estimates, no matrix of "natural frequencies" was provided.

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

Patient-important outcomes	Median score (range)
Consequences of test for patients with involvement of regional nodes	
• True positives - patients avoid SNLB and a prolonged surgical session, proceed directly to axillary lymph nodes dissection, aimed at improving survival	2 (2-7)
• False negatives - patients undergo SNLB, prolonging the surgical session, before proceeding to axillary lymph nodes dissection, aimed at improving survival	2 (1-3)
Consequences of test for patients without involvement of regional nodes	
• True negatives - patients undergo SNLB, prolonging surgical session, and do not proceed to axillary lymph nodes dissection, which would not improve their survival	2 (1-5)
• False positives - patients incorrectly proceed directly to axillary lymph nodes dissection, which would not impact on their survival, and are unnecessarily exposed to adverse effects	8 (2-9)

5.3. Appropriateness

The first voting round registered a slight disagreement with ratings falling in the inappropriate and uncertain regions (median score 3.5; range 1-5).

The second voting round registered an agreement on inappropriate with a median score of 2 and range from 1 to 2.

FINAL RATING FOR THE USE OF FDG-PET FOR N STAGING OF BREAST CANCER:

INAPPROPRIATE

5.4. Conclusions

The panel agreed in judging as inappropriate the use of FDG-PET in order to identify patients eligible for axillary lymph node dissection, bypassing sentinel lymph node biopsy. Level of evidence for diagnostic accuracy of FDG-PET resulted very low and the harm of an unnecessary axillary dissection was considered more severe than the benefit of bypassing SNLB. The outcome for patients resulting false positive - unnecessary axillary lymph nodes dissection, which would not impact on survival, and unnecessarily exposure to adverse effects - was in fact voted "critical" (median score 8; range 2-9), while outcomes for true positive - necessary axillary dissection and avoidance of SNLB - was voted "not important" (median score 2; range 2-7). Outcomes for true and false negative were also voted "not important" (median score 2).

6. M staging of patients with locally advanced breast cancer

Rationale

In patients with locally advanced disease (large tumors T3/T4 and/or N2/N3) or with clinical/laboratory signs indicating the presence of metastatic spread (bone, brain, liver, and lung), additional investigations should be considered to exclude metastatic disease (ESMO 2010a; NCCN 2010).

Diagnostic role of FDG-PET

It is suggested that FDG-PET could be introduced as a triage test in order to safely rule out the presence of distant metastases for patients testing negative, and refer patients testing positive to further and more specific diagnostic tests.

Treatment effectiveness

Presence of metastatic spread determines the choice of treatment (type of surgery, endocrine treatment, systemic therapy, radiation therapy).

Pre-test probability and change in management

The median pre-test probability of occurrence of distant metastases is 26.2% (range 12.5-58% - data from five studies on FDG-PET: Dose 2002; Landheer 2005; Port 2006; Fuster 2008; Mahner 2008), which could be considered to be the hypothetical maximum extent of change in management, achievable through accurate M staging.

Evidence from 5 studies (majority of patients with locally advanced breast cancer - Jager 2010; Groheux 2008; Heusner 2008; Klaeser 2007; Port 2006) on change in management following FDG-PET exams shows a median estimate of 13%, without a prevalent action of change (from a curative to a palliative approach or vice versa or change of treatment intent).

Research question: FDG-PET as triage

Has FGD-PET sufficient sensitivity to be used as triage test in the staging for distant metastasis of patients with locally advanced breast cancer (T3/T4)?

6.1. Systematic review of literature: results

Results of Dossier 157

Potentially useful - Uncertain A.

Evidence from 1 HTA report (reporting 4 primary studies) and 1 additional primary study.

Results from update of systematic review of literature from Jan 2006

Systematic reviews

One systematic review has been retrieved (Escalona 2010) assessing the accuracy of FDG-PET for any kind of distant metastasis (*Table 6.1*). The methodological quality was judged as intermediate. Authors found 3 studies including patients at staging (all or the majority of them). Pooled diagnostic accuracy estimates were not calculated and only descriptive results are reported. These studies are therefore evaluated together with primary studies in the next paragraph.

Primary studies

Two studies (Fuster 2008; Mahner 2008) on M staging (one applied FDG-PET/CT) published after the SR by Escalona (Escalona 2010) were included. Together with the above cited three studies from Escalona 2010 (Dose 2002; Landheer 2005; Port 2006), a total of 5 studies on M staging are included (*Table 6.2*). The overall number of patients studied is 301 (median number per study 60, range 42-80). All studies included patients with advanced breast cancer at staging (two studies included also some patients with suspected recurrence). In the majority of studies blind reading of tests is not clear.

Comments of ASSR reviewer

For M staging FDG-PET seems to have a better sensitivity than conventional imaging. On the other hand, due to heterogeneity or results, FDG-PET specificity could be lower than conventional imaging. Moreover studies use an heterogeneous mix of conventional imaging as comparator

Diagnostic accuracy estimates

FDG-PET sensitivity: (median) 93%

FDG-PET specificity: (heterogeneous) range 62-98%

Comparator sensitivity:[2] (median) 58.5%

Comparator specificity:[2] (heterogeneous) range 81.5-98%

LEVEL OF EVIDENCE: LOW

[2] Data from studies evaluating FDG-PET.

Table 6.1. Results from systematic reviews on M staging with FDG-PET

Reference	Escalona 2010
Update to	February 2007
Number of studies	3 (Dose 2002; Landheer 2005; Port 2006)
Number of patients	172 (median 50; range 42-80)
FDG-PET/PET-CT	not calculated pooled estimates of sensitivity and specificity
Reference standard	histopathology and clinical follow up

Table 6.2. Overall results on diagnostic accuracy of FDG-PET for M staging

Diagnostic accuracy	
Number of studies	5
Number of patients	301 (median 60, range 42-80)
Pre-test probability	median 26.2% (range 12.5-58%)
FDG-PET/PET-CT	sensitivity: median 93% (range 80-100%) *heterogeneity chi-squared = 3.55 (d.f. = 4) p = 0.470* *inconsistency (I-square) = 0.0%* specificity: median 90% (range 62-98%) *heterogeneity chi-squared = 25.21 (d.f. = 4) p = 0.000* *inconsistency (I-square) = 84.1%*
Comparator	conventional imaging (data from 4 studies, 259 patients) sensitivity: median: 58.5% (range 39-80%) *heterogeneity chi-squared = 5.59 (d.f. = 3) p = 0.134* *inconsistency (I-square) = 46.3%* specificity: median 82.5% (range 81-98%) *heterogeneity chi-squared = 10.88 (d.f. = 3) p = 0.012* *inconsistency (I-square) = 72.4%*
Reference standard	histopathology and clinical follow up
Notes	conventional imaging are heterogeneous between studies. In some studies the comparison with FDG-PET could be unfair
Reference	Dose 2002; Fuster 2008; Landheer 2005; Mahner 2008; Port 2006

6.2. Clinical outcomes

To evaluate the balance between benefits and risks, the panel agreed to consider the presumed patient-important outcomes reported below (*Table 6.3*), and voted on the level of importance for each outcome. Median scores and ranges are reported for each outcome.

Table 6.3. Patient-important clinical outcomes and median scores of importance

Patient-important outcomes	**Median score (range)**
Consequences of test for patients with distant metastasis	
• True positives - patients undergo further tests to confirm positive results and receive systemic treatment for metastatic breast cancer (with or without surgical intervention), aimed at improving survival and quality of life	6 (3-9)
• False negatives - patients receive unnecessary surgical treatment, which would improve their survival	7 (2-9)
Consequences of test for patients without distant metastasis	
• True negatives - patients proceed without further tests to surgical treatment for primary breast cancer (with or without neo-adjuvant treatment), aimed at improving survival	5 (2-7)
• False positives - patients proceed to systemic treatment and do not receive necessary surgical treatment, which could have improved their survival	5 (5-8)

The main benefit brought by the introduction of FDG-PET (ruling out of true negatives) was voted "important", while the main risk associated with the exam (testing false negative and delaying treatment) was voted "critical".

No studies investigating the impact of FDG-PET on the above clinical outcomes were found.

The following matrix of "natural frequencies" was provided (*Table 6.4*).

Table 6.4. "Natural frequencies" of patients assessed for distant metastasis

		N of patients out of 100 submitted to the exam	
		According to FDG-PET	**According to comparator**
Patients with distant metastasis	True positives	24	15
	False negatives	2	11
Patients without distant metastasis	True negatives	46 - 72	60 - 72
	False positives	28 - 2	14 - 2
		100	100

6.3. Appropriateness

The first voting round registered a slight disagreement with ratings falling in the uncertain and appropriate regions (median score 6.5; range 5-8).

The second voting round registered a stronger disagreement with ratings falling within all three regions - inappropriate, uncertain and appropriate (median score 6; range 3-7). The final rating resulted uncertain due to disagreement.

FINAL RATING FOR THE USE OF FDG-PET
FOR M STAGING OF LOCALLY ADVANCED BREAST CANCER:
UNCERTAIN

6.4. Conclusions

The panel did not reach an agreement in judging the role of FDG-PET in staging patients with locally advanced breast cancer (T3-T4 / N2-N3) as a triage test, i.e. to direct FDG-PET positive patients to further more specific diagnostic tests.

Level of evidence for diagnostic accuracy of FDG-PET was low, partly due to the heterogeneity of estimates for specificity and ratings of panelists fell within all three regions (inappropriate, uncertain and appropriate). The final rating is therefore uncertain due to disagreement.

The outcome for patients resulting false negatives - receiving treatment for primary breast cancer and delaying treatment for distant metastasis - was the only outcome voted "critical" by the panel (median score 7; range 2-9). All other outcomes - true and false positives and true negatives - were voted as "important".

7. Evaluation of early response to neo-adjuvant therapy in patients treated for locally advanced breast cancer or eligible for mastectomy

Rationale

According to the most recent guidelines (ESMO 2010a; NICE 2009; NCCN 2010; SIGN 2005), primary systemic therapy (neo-adjuvant therapy), involving chemotherapy, is indicated for locally advanced breast cancer including inflammatory breast cancer and for large operable tumors in order to reduce tumor size and enable breast conserving surgical treatment.

Diagnostic role of FDG-PET

A selection of responders to primary systemic therapy after the first cycles could spare non-responders the risks associated with primary systemic therapy.

Treatment effectiveness

Randomised trials of primary systemic therapy have failed to show significant difference in overall survival or disease-free survival between pre-operative and postoperative only chemotherapy; however a statistically significant difference in rate of mastectomy in favour of pre-operative chemotherapy was observed (NICE 2010).

Pre-test probability and change in management

The median pre-test probability of histopathological response after pre-operative chemotherapy is 28.4% (range 18.7-80%) (data from primary studies Berriolo-Riedinger 2007; Dose-Schwarz 2010; Duch 2009; Kumar 2009; Martoni 2010; Rousseau 2006; Schelling 2000; Smith 2000) which could be considered to be the hypothetical maximum extent of change in management, achievable with an accurate evaluation of early response to pre-operative therapy.

Research question: FDG-PET as replacement

What is the diagnostic accuracy of FDG-PET in evaluating the early response to neo-adjuvant chemotherapy of patients treated for locally advanced breast cancer or eligible for mastectomy?

7.1. Systematic review of literature: results

Results of Dossier 157

Indeterminate.

Evidence: absence of studies.

Results from update of systematic review of literature from Jan 2006

Systematic reviews

One systematic review has been retrieved (Escalona 2010) assessing the diagnostic accuracy of FDG-PET in early response to systemic treatment. Only two studies (Schelling 2000; Smith 2000) considered the response after 1 or 2 cycles of chemotherapy as neo-adjuvant treatment (before surgical resection) in patients with large or locally advanced breast cancer. The methodological quality of the SR was judged as intermediate. Since this SR did not perform a quantitative analysis with pooled estimates, the results of single studies were included in the section below (*Table 7.1*).

Primary studies

We retrieved seven studies (Berriolo-Riedinger 2007; Dose-Schwarz 2010; Duch 2009; Kumar 2009; Martoni 2010; McDermott 2007; Rousseau 2006) assessing diagnostic accuracy of FDG-PET (4 studies) or FDG-PET/CT (3 studies); FDG-PET was performed at the end of the first cycle in 3 studies, at the end of the second cycle in 5 studies, and at the end of the third cycle in 2 studies; the reference standard was histopathology at surgery. The overall quality of studies is judged to be *moderate* because of the unknown blinding of readers of tests.

Comments of ASSR reviewer

All the retrieved studies are consistent in showing that FDG-PET could predict response to treatment at the end of first or second cycle of neo-adjuvant therapy, but estimates for specificity are heterogeneous. Sensitivity seems higher than specificity.

Diagnostic accuracy estimates

FDG-PET sensitivity (median): 89%

FDG-PET specificity (heterogeneous): range 30-96%

Comparator current practice: all patients complete pre-operative treatment

LEVEL OF EVIDENCE: LOW

Table 7.1. Overall results on diagnostic accuracy of FDG-PET in evaluating early response to 1 or 2 cycles of neo-adjuvant therapy

Diagnostic accuracy	
Number of studies	9
Number of patients	379 (median 45, range 22-64)
Pre-test probability (responders)	median 28.4% (range 18.7-80%)
FDG-PET	sensitivity: median 89% (range 69-100%) *heterogeneity chi-squared = 7.93 (d.f. = 7) p = 0.339* *inconsistency (I-square) = 11.7%* specificity: median 78% (range 30-96%) *heterogeneity chi-squared = 43.97 (d.f. = 7) p = 0.000* *inconsistency (I-square) = 84.1%*
Comparator	clinical examination (1 study) sensitivity: 27% specificity: 63% CT (1 study) sensitivity: 46% specificity: 75%
Reference standard	histopathology
References	Berriolo-Riedinger 2007; Dose-Schwarz 2010; Duch 2009; Kumar 2009; Martoni 2010; Mc Dermott 2007; Rousseau 2006; Schelling 2000; Smith 2000

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 7.2*), and voted on the level of importance for each outcome. Median scores and ranges are reported for each outcome.

All outcomes were voted "important".

No studies investigating the impact of FDG-PET on the above clinical outcomes were found.

The following matrix of "natural frequencies" was provided (*Table 7.3*).

Table 7.2. Patient-important clinical outcomes and median scores of importance

Patient-important outcomes	Median score (range)
Consequences of test for patients responding to neo-adjuvant chemotherapy	
• True responders - responders complete clinically effective treatment which could reduce tumor size and allow breast conserving surgery	6 (1-8)
• False non responders - responders interrupt clinically effective treatment, which could have reduced tumor size, and undergo a large resection/mastectomy	6 (2-8)
Consequences of test for patients not responding to neo-adjuvant chemotherapy	
• True non responders - non responders interrupt clinically ineffective treatment, which would not have reduced tumor size, and proceed to required large resection/mastectomy	6 (4-8)
• False responders - non responders complete clinically ineffective treatment, which does not reduce tumor size, and then proceed to required large resection/mastectomy	5 (2-6)

Table 7.3. "Natural frequencies" of patients assessed for early response to therapy

		N of patients out of 100 submitted to the exam	
		According to FDG-PET	**According to comparator**
Patients responders	True responders	25	28
	False non responders	3	0
Patients non responders	True non responders	22 - 69	0
	False responders	50 - 3	72
		100	100

7.3. Appropriateness

The first voting round registered a slight disagreement with ratings falling in the uncertain and appropriate regions (median score 5.5; range 4-7).

The second voting round registered an agreement on uncertain (median score 5; range 4-6).

FINAL RATING FOR THE USE OF FDG-PET FOR EVALUATION OF EARLY RESPONSE TO NEO-ADJUVANT THERAPY IN PATIENTS TREATED FOR LOCALLY ADVANCED BREAST CANCER OR ELIGIBLE FOR MASTECTOMY:

UNCERTAIN

7.4. Conclusions

After two rounds of voting the panel agreed to judge as uncertain the introduction of FDG-PET for the evaluation of early response to neo-adjuvant therapy, in patients with locally advanced breast cancer or eligible for mastectomy.

Level of evidence for diagnostic accuracy of FDG-PET was low, due to the heterogeneity of estimates for specificity. All outcomes were voted as "important", showing a need for a test that could correctly identify patients who respond to neo-adjuvant chemotherapy, in order to spare unnecessary toxic treatment to non responders. However data of accuracy were not considered sufficient to suggest use of FDG-PET results in clinical practice for this purpose.

8. Evaluation of response to neo-adjuvant therapy at the end of treatment in patients treated for locally advanced breast cancer or eligible for mastectomy

Rationale

Evaluation of the efficacy of the primary systemic therapy can help to identify effective post-operative systemic treatment regimen (NICE 2010).

Evaluation of response to pre-operative chemotherapy, aimed at supporting the choice of adjuvant treatment, is best carried out on the surgical specimen through histopathologic assessment. No alternative tests are therefore necessary.

Diagnostic role of FDG-PET

The panel agreed unanimously that there is no diagnostic role of FDG-PET in the evaluation of response to neo-adjuvant therapy at the end of treatment.

8.1. Systematic review of literature: results

Dossier 157

Not considered.

Results from update of systematic review of literature from Jan 2006

Only studies evaluating metabolic response to therapy were found and results are reported below

Systematic reviews

One systematic review has been retrieved (Escalona 2010) assessing the diagnostic accuracy of FDG-PET in evaluating response to therapy at the end of treatment. In this context two studies were eligible: one (Burcombe 2002) considered the results of FDG-PET before surgical resection (i.e. after 4 to 6 cycles of chemotherapy as neo-adjuvant treatment) in patients with locally advanced breast cancer; the other (Kim 2004) considered the reduction of FDG-PET before and after neo-adjuvant treatment in patients

with large or locally advanced breast cancer. The methodological quality of the SR was judged as intermediate. Since this SR did not performed a quantitative analysis with pooled estimates, the results of single studies were included in the section below.

Primary studies

Three more studies were retrieved. Two diagnostic cross sectional studies (Dose-Schwarz 2010; McDermott 2007) assessing the diagnostic accuracy of FDG-PET in predicting histopathologic response in 156 patients with newly diagnosed breast cancer treated with neo-adjuvant therapy before surgery. One more study (Prati 2009) considered the same population of patients nevertheless FDG-PET was not used for evaluating breast cancer response but lymph nodes response; this latter study was, thus, not considered to estimate diagnostic accuracy. All studies are burdened by a possible bias due to unknown or no blinding of readers of tests.

Comments of ASSR reviewer

Heterogeneity in choosing FDG-PET cut offs and in diagnostic accuracy estimates was observed between the studies retrieved. Moreover, the overall number of patients studied are low thus firm conclusions cannot be drawn.

Diagnostic accuracy estimates

It is not possible to provide estimates.

LEVEL OF EVIDENCE: VERY LOW

Table 8.1. Results from studies on diagnostic accuracy of FDG-PET in evaluating response to therapy at the end of treatment

Diagnostic accuracy	
Number of studies	3
Number of patients	206 (range 50-89)
Pre-test probability (responders)	median 36% (range 18-54%)
FDG-PET/PET-CT	sensitivity (data from 1 study for each cut off) SUV threshold 2.0: 32.9% SUV threshold 1.5: 57.5% -88% reduction rate of peak: 100% -79% reduction rate of peak: 85.2% specificity (data from 1 study for each cut off) SUV threshold 2.0: 87.5% SUV threshold 1.5: 62.5% -88% reduction rate of peak: 56.5% -79% reduction rate of peak: 82.6%
Comparator	mammography(1 study) sensitivity: 92.5% specificity: 57.1% ultrasound (1 study) sensitivity: 92% specificity: 37.5% MRI (1 study) sensitivity: 97.6% specificity: 40% physical examination (1 study) sensitivity: 91.5% specificity: 52.9%
Reference standard	histopathology
References	Dose-Schwarz 2010; Kim 2004; Mc Dermott 2007

8.2. Clinical outcomes

Due to the lack of a clinical rationale in support of use of FDG-PET for the evaluation of response to neo-adjuvant therapy at the end of treatment, the panel agreed not to express judgements of clinical outcomes and to proceed directly to the vote on appropriateness.

8.3. Appropriateness

The first voting round registered a slight disagreement with ratings falling in the inappropriate and uncertain regions (median score 3.5; range 1-5). The second voting round registered an agreement on inappropriate.

FINAL RATING FOR THE USE OF FDG-PET FOR EVALUATION OF RESPONSE TO NEO-ADJUVANT THERAPY AT THE END OF TREATMENT IN PATIENTS TREATED FOR LOCALLY ADVANCED BREAST CANCER OR ELIGIBLE FOR MASTECTOMY:

INAPPROPRIATE

8.4. Conclusions

After an initial disagreement registered in the first round, with ratings falling in the inappropriate and uncertain regions, the panel agreed to judge as inappropriate the use of FDG-PET in evaluating response to neo-adjuvant therapy at the end of treatment.

The discussion during the second meeting brought the panel to agree that there was no clinical rationale in support of this use of FDG-PET. Although response to pre-operative therapy is important to decide on subsequent therapeutic regimens, patients undergo surgical treatment at the end of therapy and the histopathologic response evaluated on the surgical specimen represents the gold standard in no need for replacement.

9. Follow up in patients with no suspicion of recurrence

Rationale

Recurrence strongly depends on the stage of the primary tumor; up to 30% of node-negative and up to 70% of node-positive breast cancers could relapse at some time within the course of their disease (ESMO 2010b). Patients with local recurrence have a significantly better prognosis than patients who develop nodal or distant recurrence. In particular the 5-year disease-specific survival for patients with a local recurrence is about 41%, while it is 20% in case of regional nodes involvement and 13% in case of distant metastasis (Elder 2006).

No guideline recommends an active follow up with imaging tests, other than mammography, in asymptomatic patients (ASCO 2006; ESMO 2010a; NICE 2009; NCCN 2010; SIGN 2005).

Diagnostic role of FDG-PET

To anticipate identification of patients with potential relapse in order to start appropriate therapy earlier.

Treatment effectiveness

Isolated local-regional recurrence should be treated like a new primary tumor with a curative intent. The vast majority of metastatic breast cancer is incurable and hence the main treatment goal is palliation.

Pre-test probability and change in management

About 15-20% of patients with breast cancer will suffer from any kind of relapse in the five-year period after treatment for the initial disease (Elder 2006; Lamerato 2006). This rate could be considered the hypothetical five-year cumulative maximum extent of change in management in this clinical scenario.

Research question: FDG-PET as replacement

Is FDG-PET useful during follow up of patients with no suspicion of recurrence?

9.1. Systematic review of literature: results

Dossier 157

Not considered.

Results from update of systematic review of literature from Jan 2006

Systematic reviews

None retrieved.

Primary studies

One study (Iagaru 2007) was retrieved on the diagnostic accuracy of FDG- CT/PET for follow up in asymptomatic patients after surgery (*Table 9.1*). The study is retrospective, the follow up is opportunistic and of very short length (median 51 days). It is unclear if blinding of readers of imaging was applied.

Table 9.1. Results from studies on diagnostic accuracy of FDG-PET in the follow up of asymptomatic patients after surgery

References	Iagaru 2007
Number of studies	1
Number of patients	15
Recurrence	20% for breast disease 6.7% for axilla recurrence 33.3% for metastatic disease
FDG-PET/PET-CT	sensitivity 33.3% for breast disease 100% for axilla recurrence 100% for metastatic disease specificity 91.7% for breast disease 100% for axilla recurrence 90% for metastatic disease
Reference standard	histology and clinical-radiological follow up for at least 12 months

Comments of ASSR reviewer

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

LEVEL OF EVIDENCE: VERY LOW

9.2. Clinical outcomes

To evaluate the balance between benefits and risks, the panel agreed to consider the presumed patient-important outcomes reported below (*Table 8.2*), and voted on the level of importance for each outcome. Median scores and ranges are reported for each outcome.

All outcomes were voted "not important".

No studies investigating the impact of FDG-PET on the above clinical outcomes were found.

No matrix of "natural frequencies" was provided because of heterogeneity of both estimates.

Table 9.2. Patient-important clinical outcomes and median scores of importance

Patient-important outcomes	**Median score (range)**
Consequences of test for patients relapsing	
• True positives - patients undergo further test to confirm positive results and proceed to appropriate treatment (surgery of local recurrence or palliative treatment)	3 (1-8)
• False negatives - patients remain in follow up and delay treatment for recurrence	3 (1-7)
Consequences of test for patients not relapsing	
• True negatives - patients remain in follow up and are reassured, after a certain amount of stress	3 (1-8)
• False positives - patients undergo unnecessary further tests to prove negative and are exposed to unnecessary anxiety	3 (1-8)

9.3. Appropriateness

The first voting round registered an agreement on inappropriate (median score 2.5; range 1-3).

FINAL RATING FOR THE USE OF PET DURING FOLLOW UP OF PATIENTS WITH NO SUSPICION OF RECURRENCE:

INAPPROPRIATE

9.4. Conclusions

The panel agreed during the first round in rating as inappropriate the use of PET during follow up of patients treated for breast cancer. Level of evidence for diagnostic accuracy of PET was very low, as only one study with very few patients evaluated PET in follow up of breast cancer. Moreover all outcomes were voted as not important by the panelists (median scores of 3 for true and false positives and negatives).

10. Diagnosis and staging of suspect distant recurrence

Rationale

About 15-20% of patients with breast cancer will suffer from any kind of relapse in the five-year period after treatment for the initial disease (Elder 2006; Lamerato 2006).

Early detection and accurate restaging of recurrent breast cancer is important to define appropriate therapeutic strategies (Pan 2010). A timely diagnosis could prove useful for patients with long disease free interval or for specific types of breast cancer (HER2+) (Niwinska 2010).

Diagnostic role of FDG-PET

The use of an imaging test ruling out negative patients could direct patients testing positive to more specific diagnostic tests.

Treatment effectiveness

The vast majority of metastatic breast cancer is incurable and hence the main treatment goal is palliation, with the aim of maintaining/improving quality of life, and possibly improving survival (ESMO 2010b).

Pre-test probability and change in management

The median pre-test probability of recurrence and/or metastasis in patients with suspected recurrence of breast cancer is 63.0% (range 11.1-93.3%) (data from primary studies included in Pennant 2010). For bone metastasis the median pre-test probability is 34.2% (range 17.6-61.8%) (data from primary studies included in Shie 2008).

Evidence from 11 studies evaluating change in management in following FDG-PET exams in patients with suspected recurrence and/or metastasis (707 patients) (studies from Pennant 2010) shows a range estimate of change in management from 41% to 74% with the majority of patients being upstaged.

Research question: FDG-PET as triage

Has FDG-PET sufficient sensitivity to rule out relapse in patients with suspect of recurrence?

10.1. Systematic review of literature: results

Results of Dossier 157

Potentially useful (Uncertain A).

Evidence: 1 HTA report summarizing 10 primary studies.

Results from update of systematic review of literature from Jan 2006

Systematic reviews

Four systematic reviews (Escalona 2010; Pan 2010; Pennant 2010; Shie 2008) which compared the diagnostic accuracy of FDG-PET with other imaging modalities in detecting suspected recurrence and/or metastases were included (*Tables 10.1 and 10.2*). Shie 2008 assessed FDG-PET diagnostic accuracy for bone metastases only; Escalona 2010, Pan 2010 and Pennant 2010 considered any kind of suspected recurrence. In very few studies (only 3 of those included in the systematic reviews) the diagnostic intent was restaging. The methodological quality was judged as intermediate for Escalona 2010 and good for Shie 2008, Pan 2010 and Pennant 2010.

The systematic review by Pan 2010 point out that at least 12 out of 17 studies included could be burdened by verification bias while in the systematic review by Pennant 2010 at least 19 out of 28 studies included had uncertain blinding.

As the results between the reported systematic reviews (Escalona 2010; Pan 2010; Pennant 2010) are consistent, we chose the diagnostic estimates from the more exhaustive and of good quality systematic review (Pennant 2010 - *Table 10.3*), adding the calculation for the pre-test probability.

Table 10.1. Systematic reviews on diagnostic accuracy of FDG-PET in patients with suspected recurrence / metastasis of breast cancer after surgery

Reference	Pan 2010	Escalona 2010	Pennant 2010
Update to	August 2008	February 2007	May 2009
Number of studies	43 studies (US: 10, CT: 8, MRI: 11, SPECT: 7, FDG-PET: 17) (7 in common with Escalona 2010 and 12 with Pennant 2010)	19 (7 in common with Pan 2010 and 13 with Pennant 2010)	28 studies (13 in common with Escalona 2010 and 12 with Pan 2010)
Number of patients	1 356 (median 57, range 10-263)	960 (median 44, range 15-133)	1 679 (median 44, range 7-291)
FDG-PET/ PET-CT	sensitivity: pooled 95.3% (95% CI 93.7-96.7) specificity: pooled 86.3% (95% CI 82.4-89.5)	reported only data by single study	FDG-PET (25 studies) sensitivity: pooled 91% (95% CI 87-93) specificity: pooled 86% (95% CI 79-91) FDG-PET/CT (5 studies) sensitivity: pooled 95% (95% CI 89-97) specificity: pooled 89% (95% CI 76-96)
Comparator	sensitivity US sensitivity: pooled 85.7% (95% CI 80.4-89.9) specificity: pooled 96.2% (95% CI 95.4-97) CT sensitivity: pooled 84.8% (95% CI 81.1-88.1) specificity: pooled 75.3% (95% CI 69.2-80.7) MRI sensitivity: pooled 95% (95% CI 92.3-97) specificity: pooled 92.9% (95% CI 90.2-95)	reported only data by single study	conventional imaging tests (11 studies) sensitivity: pooled 81% (95% CI 73-87) specificity: pooled 73% (95% CI 59-83)

(continue)

Reference	Pan 2010	Escalona 2010	Pennant 2010
Update to	August 2008	February 2007	May 2009
Comparator *(continue)*	SMM sensitivity: pooled 90% (95% CI 85.3-93.7) specificity: pooled 79.8% (95% CI 71.5-86.6)		
Reference standard	histopathologic analysis and/or clinical follow up longer than 6 months	histopathologic analysis and/or clinical follow up longer than 6 months	histopathologic analysis and/or long clinical follow

Table 10.2. Systematic reviews on diagnostic accuracy of FDG-PET in patients with suspected bone metastasis of breast cancer after surgery

Reference	Shie 2008	Escalona 2010
Update to	November 2006	February 2007
Number of studies	6 (5 in common with Escalona 2010)	8 (5 in common with Shie 2008)
Number of patients	277 (median 42, range 15-89)	385 (median 47, range 15-89)
FDG-PET/PET-CT	patient based sensitivity: pooled 81% (95% CI 70-89) specificity: pooled 93% (95% CI 84-81) lesion based sensitivity: pooled 69% (95% CI 28-93) specificity: pooled 98% (95% CI 87-100)	reported only data by single study
Comparator	bone scintigraphy sensitivity: pooled 78% (95% CI 67-86) specificity: pooled 79% (95% CI 40-95)	reported only data by single study
Reference standard	CT, MRI or bone biopsy with clinical follow up longer than 6 months	CT, MRI or bone biopsy with clinical follow up longer than 6 months

Table 10.3. Results on diagnostic accuracy of FDG-PET in patients with suspected recurrence / metastasis of breast cancer after surgery

Diagnostic accuracy	
Number of studies	28
Number of patients	1 679 (median 44, range 7-291)
Pre-test probability	median 63.0% (range 11.1-93.3%)
FDG-PET/PET-CT	FDG-PET (25 studies) sensitivity: pooled 91% (95% CI 87-93) specificity: pooled 86% (95% CI 79-91) FDG-PET/CT (5 studies) sensitivity: pooled 95% (95% CI 89-97) specificity: pooled 89% (95% CI 76-96)
Comparator	conventional imaging tests (11 studies) sensitivity: pooled 81% (95% CI 73-87) specificity: pooled 73% (95% CI 59-83)
Reference standard	histopathologic analysis and/or long clinical follow
Reference	Pennant 2010

Primary studies

Two studies (Aukema 2010; Palomar Munoz 2007) not included in the above reported systematic reviews have been retrieved. One assessed the accuracy of FDG-PET/CT in detecting suspected recurrence on 70 patients, the other in detecting distant metastases in 56 patients with confirmed local recurrence (*Table 10.4*).

Table 10.4. Primary studies on diagnostic accuracy of FDG-PET in patients with suspected bone metastasis of breast cancer after surgery

References	Aukema 2010; Palomar Munoz 2007
Number of studies	2
Number of patients	126
FDG-PET/PET-CT	suspected recurrence (1 study) sensitivity: 87.8% specificity: 86.4% distant metastases (1 study) sensitivity: 97% specificity: 92%
Reference standard	histopathological confirmation and clinical follow up

Comments of ASSR reviewer

The systematic reviews are of good methodological quality, with a comprehensive and updated (up to May 2009) bibliographic search and a large number of studies included. FDG-PET seems to be more accurate in detecting recurrence and/or distant metastasis than conventional imaging test, although MRI alone seems to have a slight better performance. FDG-PET/CT seems to have a slightly better sensitivity and equal specificity than FDG-PET. For bone metastasis FDG-PET has a sensitivity similar to bone scintigraphy but a better specificity. The study published after the last systematic review's update confirms the diagnostic accuracy of FDG-PET in detecting suspected recurrence.

Diagnostic accuracy estimates

FDG-PET sensitivity: (pooled) 91%

FDG-PET specificity: (pooled) 86%

Conventional diagnostic tests sensitivity:[3,4] (pooled) 81%

Conventional diagnostic tests specificity:[3,4] (pooled) 73%

LEVEL OF EVIDENCE: MODERATE

10.2. Clinical outcomes

To evaluate the balance between benefits and risks, the panel agreed to consider the presumed patient-important outcomes reported below (*Table 10.5*), and voted on the level of importance for each outcome. Median scores and ranges are reported for each outcome.

The one outcome voted "critical" related to true positive patients correctly diagnosed, staged and treated for distant recurrence, while outcomes for false positive patients incorrectly diagnosed with distant recurrence were voted "important". Outcomes for patients testing negative (true and false negatives) were also voted "important", though with a lesser median score.

No studies investigating the impact of FDG-PET on the above clinical outcomes were found.

The following matrix of "natural frequencies" was provided (*Table 10.6*).

[3] Excluding MRI.

[4] Data from studies evaluating FDG-PET.

Table 10.5. Patient-important clinical outcomes and median scores of importance

Patient-important outcomes	Median score (range)
Consequence of test for patients with recurrence	
• True positives - patients proceed to specific test to confirm FDG-PET results and proceed to appropriate treatment for metastatic recurrence, which could improve quality of life and might impact on survival	7 (4-9)
• False negatives - patients delay start of treatment until symptoms occur, with a possible negative impact on quality of life and survival	4 (2-8)
Consequence of test for patients without recurrence	
• True negatives - patients remain in follow up and are reassured, after a certain amount of stress	4 (2-7)
• False positives - patients undergo unnecessary further tests to prove negative and are exposed to unnecessary anxiety	6 (3-7)

Table 10.6. "Natural frequencies" of patients assessed for suspect recurrence

		N of patients out of 100 submitted to the exam	
		According to FDG-PET	According to conventional imaging
Patients with recurrence	True positives	57	51
	False negatives	6	12
Patients without recurrence	True negatives	32	27
	False positives	5	10
		100	100

10.3. Appropriateness

Both the first and second voting rounds registered a slight disagreement, with ratings falling in the uncertain and appropriate regions (first round median score 6.5; range 5-8; second round median score 7; range 6-7).

The final rating resulted to be uncertain due to disagreement.

FINAL RATING FOR THE USE OF FDG-PET IN DIAGNOSIS AND STAGING OF SUSPECT RECURRENCE:

UNCERTAIN

10.4. Conclusions

A disagreement among panelists, with ratings falling in the uncertain and appropriate regions, was registered in both rounds of voting the role of FDG-PET as a triage test in patients with suspect distant recurrence. The final rating is therefore uncertain due to disagreement.

Level of evidence for diagnostic accuracy of FDG-PET was moderate, showing FDG-PET performing better than other imaging tests, although results are mixed due to the variety of comparators used in the different studies.

The outcomes for true positive patients, proceeding to further and more specific tests and receiving appropriate treatment, were voted "critical" (median score 7; range 4-9), while the unnecessary anxiety and stress caused by a false positive results was voted "important" with a median score of 6 (range 3-7). The outcomes for true and false negatives were also voted "important" with a lower medians score of 4.

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 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

The authors have developed criteria for the appropriate use of positron emission tomography in breast cancer. The development was based on an elaborate and meticulous procedure, which included an evaluation of the existing evidence with critical appraisal and a panel-based voting process.

Methods

There is no standard methodology for developing recommendations for practice about medical tests and markers. This also includes the use of imaging. The investigators therefore had to develop a methodology that, in itself, is built on a number of existing elements.

- Well-phrased clinical questions;
- Systematic review of the medical literature;
- Critical appraisal of the identified studies;
- Majority based voting in a panel.

A strong point in defining the clinical questions was the explicit comparative nature: PET was compared against the currently used or existing test for the diagnostic role under consideration.

A somewhat more moot point was the rationale for making the recommendations, which was defined in different ways. Page 24 lists four steps, which point to the capacity of the test to modify the initial diagnosis and to change the therapeutic approach. These steps are then expected to result in a clinical benefit. Similar reasoning is found in the criteria for defining appropriate use (page 30). Here the authors present a mixture of arguments. They point to clinical indications with a rationale for change in management related to an important clinical outcome, a high or moderate level of evidence for diagnostic accuracy of PET and the presumed benefit from testing being greater than the presumed harm.

The problem with this multiple definition is that diagnostic accuracy does not completely align with evaluations of tests for purposes other than diagnosis, such as staging (to some extent), evaluation of early response, and surveillance. Similar problems apply to the notion of pre-test probability.

It probably would have been more consistent to start from clinical benefit explicitly, although a major challenge - as the authors recognize on page 25 - is that there is little direct evidence linking imaging to outcomes. The other outcomes accepted by the authors - changes in probability and changes in management - are at best proxy measures for clinical utility.

Was any attempt made to quantify the uncertainty in the clinical outcomes?

The GRADE approach for developing recommendations about medical tests has not yet been completely finalized. The authors were able to use the GRADE logic for developing recommendations in an innovative and consistent way, by evaluating the risk of bias in the evidence and rating the importance of outcomes. The weak link - weak in the GRADE approach itself, not in the application presented here - is the indirect nature of the evidence, and the integration of the multiple sources of evidence and multiple valuations. The GRADE style levels of evidence - with downgrading for study limitations, inconsistency, and indirectness and imprecision - were well applied.

Style and readability

The resulting recommendations are well expressed and easy to read.

Conclusions

Given the stage of development of the methods for developing evidence-based recommendations about imaging and testing in general, the authors have completed a formidable task, by using a very consistent and elaborate procedure to rate and grade the existing evidence.

Patrick Bossuyt PhD
Professor of Clinical Epidemiology
Dept. Clinical Epidemiology & Biostatistics
Academic Medical Center - University of Amsterdam
April 1st 2011

Reviewer 2

I have carefully reviewed the document and it finds my full support. The criteria which were used to define the role of FDG-PET in breast cancer are appropriate and the conclusions are justified.

I have only a minor comment: I would suggest to replace PET with FDG-PET throughout the document to be consistent and to avoid any confusion regarding the use of other radiopharmaceuticals.

Norbert Avril MD
Professor of Nuclear Medicine
Barts Cancer Institute, Centre for Molecular Oncology and Imaging
Queen Mary University of London
April 12th 2011

Reviewers 3 & 4

The methodology followed is that of a systematic review of the literature (evidence-based) followed by discussion and voting to reach the ultimate objective: the definition of criteria for the appropriate use of PET in patients with breast cancer.

This is an outstanding work that should not be limited to use in the Emilia-Romagna Region but its conclusions are valid for the whole of Italy and beyond. We think the work has to be published in the peer-reviewed literature and probably the authors are aware of this.

The conclusions will be particularly useful for both, the routine medical practice but also for the definition of criteria for funding by national or insurance bodies.

The document on the appropriate use of PET in breast cancer surprisingly reveals that the indications for PET in this disease are either inappropriate or uncertain. This is however in line with an already existing IAEA document on "Appropriate use of FDG-PET for the management of cancer patients".

Thank you for sharing this valuable work.

Eduardo Rosenblatt MD
Section Head - Radiation Oncology

Maurizio Dondi MD
Section Head - Nuclear Medicine

Division of Human Health
International Atomic Energy Agency (IAEA)
Vienna

April 27th 2011

Reviewer 5

My overall impression is that these are carefully done systematic reviews, and they certainly address deficiencies in the published literature for use of FDG-PET in breast cancer.

Although I know these reviews are stated not to be recommendations for whether or not to reimburse for PET in specific circumstances, there is always a concern that these will adopted outright and rigidly applied, thus not allowing for use of clinical judgment.

With regard to the breast cancer review:

- I would like to have seen more information on the recent papers on PEM for local staging of disease within the breast.
- Had I been on the panel, I would have voted more favorably for use of PET for M staging of locally advanced disease, and for detection and staging of suspected recurrent disease.
- Interim PET does reliably predict outcome of neo-adjuvant therapy, but to date this has not been translated into response-adapted clinical strategies. One hopes this recommendation won't keep that from happening.
- I also would like to have seen consideration of the papers on use of FDG-PET to predict response to hormonal therapy (metabolic flare response). I am obviously biased on this, since the three key studies are from my group.

Barry A. Siegel, M.D.
Professor of Radiology and Medicine
Director, Division of Nuclear Medicine
Mallinckrodt Institute of Radiology
Washington University School of Medicine

May 2nd 2011

Appendices

Appendix 1. Voting forms

ORI
Osservatorio Regionale per l'Innovazione

CRITERIA FOR APPROPRIATE USE OF POSITRON EMISSION TOMOGRAPHY IN ONCOLOGY

2010-2011

FDG-PET IN BREAST CANCER

VOTING FORMS

NAME

_____

Agenzia sanitaria e sociale regionale

RegioneEmilia-Romagna

CLINICAL QUESTION

Staging of patients with primary breast cancer

a - N staging of patients with primary breast cancer

Rationale

Regional lymph node status remains the strongest predictor of long-term prognosis in primary breast cancer. Sentinel lymph node biopsy (SLNB) is the standard care to decide for axillary lymph node dissection (SIGN 2005; NICE 2009; ESMO 2010a). It is suggested that a highly specific and non-invasive diagnostic tool aimed at detecting axillary cancer involvement, could be used to refer positive patients directly to axillary lymph node dissection, thus avoiding SNLB (Veronesi 2007).

Treatment effectiveness

Axillary lymph node dissection is recommended for patients with confirmed or suspect axillary node involvement.

Research question: FDG-PET as triage

Has FDG-PET sufficient specificity to identify patients who should proceed directly to axillary lymph node dissection?

Pre-test probability

The median pre-test probability of cancer involvement of regional nodes is 42.4% (range 29-71%) (data from Sloka 2007; Cermik 2008; Chae 2009; Chung 2006; Fuster 2008; Gil-Rendo 2006; Heusner 2009; Kim 2009; Kumar 2006; Monzawa 2009; Mustafa 2007; Stadnik 2006; Taira 2009; Ueda 2008; Uematsu 2009; Veronesi 2007).

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

Heterogeneity in both estimates for diagnostic accuracy of FDG-PET

FDG-PET sensitivity: range 20-100%

FDG-PET specificity: range 66-100%

Consequences of TEST for		**Level of importance* (1-9)**
Patients with involvement of regional nodes	True positives: patients avoid SNLB and a prolonged surgical session, proceed directly to axillary lymph nodes dissection, aimed at improving survival False negatives: patients undergo SNLB, prolonging the surgical session, before proceeding to axillary lymph nodes dissection, aimed at improving survival	
Patients without involvement of regional nodes	True negatives: patients undergo SNLB, prolonging surgical session, and do not proceed to axillary lymph nodes dissection, which would not improve their survival False positives: patients incorrectly proceed directly to axillary lymph nodes dissection, which would not impact on their survival, and are unnecessarily exposed to adverse effects	

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

CLINICAL QUESTION

Role of FDG-PET in N staging of patients with primary breast 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									

b - M staging for locally advanced breast cancer

Rationale

In patients with locally advanced disease (large tumors T3/T4) or with clinical/laboratory signs indicating the presence of metastatic spread (bone, brain, liver, and lung), additional investigations should be considered to exclude metastatic disease (ESMO 2010a; NCCN 2010).

Treatment effectiveness

Presence of metastatic spread determines the choice of treatment (type of surgery, endocrine treatment, systemic therapy, radiation therapy).

Research question: FDG-PET as triage

Has FGD-PET sufficient sensitivity to be used as triage test in the staging for distant metastasis of patients with locally advanced breast cancer (T3/T4 or N2/N3)?

Pre-test probability

The median pre-test probability of occurrence of distant metastases is 26.2% (range 12.5-58%) (data from five studies on FDG-PET: Dose 2002; Landheer 2005; Port 2006; Fuster 2008; Mahner 2008).

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

FDG-PET
- sensitivity (median): 92%
- specificity (heterogeneous): range 62-98%

Comparator (mixed)
- sensitivity (median): 58.5%
- specificity (heterogeneous): range 81.5-98%

Consequences of TEST for		Level of importance* (1-9)
Patients with distant metastasis	True positives: patients undergo further tests to confirm positive results and receive systemic treatment for metastatic breast cancer (with or without surgical intervention), aimed at improving survival and quality of life	
	False negatives: patients receive surgical treatment for primary breast cancer while treatment for metastasis, aimed at improving survival and quality of life, is delayed until metastasis is detected	
Patients without distant metastasis	True negatives: patients proceed without further tests to surgical treatment for primary breast cancer (with or without neo-adjuvant treatment), aimed at improving survival	
	False positives: patients undergo unnecessary further tests, are exposed to additional anxiety and then proceed to surgical treatment for primary breast cancer, aimed at improving survival	

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

		N of patients out of 100 submitted to the exam	
		According to FDG-PET	According to comparator (mixed)
Patients with distant metastasis	True positives	24	15
	False negatives	2	11
Patients without distant metastasis	True negatives	46 - 72	60 - 72
	False positives	28 - 2	14 - 2
		100	100

CLINICAL QUESTION

Role of FDG-PET in M staging of patients with locally advanced breast 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									

CLINICAL QUESTION

Evaluation of early response to neo-adjuvant therapy in patients treated for locally advanced breast cancer or eligible for mastectomy

Rationale

Primary systemic therapy (neo-adjuvant chemotherapy) is indicated for locally advanced breast cancer including inflammatory breast cancer and for large operable tumors in order to reduce tumor size and enable breast conserving surgical treatment.

Treatment effectiveness

Data report no significant difference in overall survival or disease-free survival between pre-operative and postoperative only chemotherapy; however a statistically significant difference in rate of mastectomy in favour of pre-operative chemotherapy was observed (NICE 2010).

Research question*: *FDG-PET as new test (replacement)

What is the diagnostic accuracy of FDG-PET in evaluating the early response to neo-adjuvant chemotherapy of patients treated for locally advanced breast cancer or eligible for mastectomy?

Pre-test probability

Median pre-test probability of histopathological response after pre-operative chemotherapy is 28.4% (range 18.7-80%, data from primary studies Berriolo-Riedinger 2007; Dose-Schwarz 2010; Duch 2009; Kumar 2009; Martoni 2010; Rousseau 2006; Schelling 2000; Smith 2000).

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

FDG-PET

sensitivity (median): 89%

specificity (heterogeneous): range 30-96%

Comparator current practice: all patients complete pre-operative treatment

Consequences of TEST for		Level of importance* (1-9)
Responders	True responders: responders complete clinically effective treatment which could reduce tumor size and allow breast conserving surgery	
	False non responders: responders interrupt clinically effective treatment, which could have reduced tumor size, and undergo a large resection/mastectomy	
Non responders	True non responders: non responders interrupt clinically ineffective treatment, which would not have reduced tumor size, and proceed to required large resection/mastectomy	
	False responders: non responders complete clinically ineffective treatment, which does not reduce tumor size, and then proceed to required large resection/mastectomy	

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

		N of patients out of 100 submitted to the exam	
		According to FDG-PET	According to comparator
Patients responders	True responders	25	28
	False non responders	3	0
Patients non responders	True non responders	22 - 69	0
	False responders	50 - 3	72
		100	100

CLINICAL QUESTION

Role of FDG-PET in evaluating early response to neo-adjuvant therapy in patients treated for locally advanced breast cancer or eligible for mastectomy

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									

CLINICAL QUESTION

Evaluation of response to neo-adjuvant therapy at the end of treatment in patients treated for breast cancer

Rationale

Evaluation of response to pre-operative chemotherapy, aimed at supporting the choice of adjuvant treatment, is best carried out on the surgical specimen through histopathologic assessment. No alternative tests are therefore necessary and there is no clinical rationale in support of use of FDG-PET.

Diagnostic accuracy estimates **Level of evidence: none**

No studies were found assessing diagnostic accuracy of FDG-PET for the definition of residual tumor mass.

CLINICAL QUESTION

Role of FDG-PET in evaluating response to neo-adjuvant therapy at the end of treatment in patients treated for breast 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									

CLINICAL QUESTION

Follow up of patients treated for breast cancer with no suspicion of recurrence

Rationale

No guideline recommends an active follow up with diagnostic tests, other than mammography, in patients with no suspicion of recurrence (SIGN 2005; NICE 2009; ESMO 2010a; NCCN 2010).

Treatment effectiveness

No significant difference on survival and on quality of life has been demonstrated between follow up with regular clinical visits and more intensive surveillance regimen involving testing or measurement of serum tumor markers (ESMO 2010a; ASCO 2006; NICE 2009; NCCN 2010; SIGN 2005).

Research question: FDG-PET introduced as new test (replacement)
Is FDG-PET useful during follow up of patients with no suspicion of recurrence?

Pre-test probability

15-20% (five-year cumulative probability).

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

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

Consequences of TEST for		Level of importance* (1-9)
Patients relapsing	True positives: patients undergo further test to confirm positive results and proceed to appropriate treatment (surgery of local recurrence or palliative treatment)	
	False negative: patients remain in follow up and delay treatment for recurrence	
Patients not relapsing	True negatives: patients remain in follow up and are reassured, after a certain amount of stress	
	False positives: patients undergo unnecessary further tests to prove negative and are exposed to unnecessary anxiety	

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

CLINICAL QUESTION

Role of FDG-PET during follow up of patients treated for breast cancer with no suspicion of recurrence

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									

CLINICAL QUESTION

Diagnosis and staging of suspect distant recurrence in patients treated for breast cancer

Rationale

Diagnosis and staging of recurrent breast cancer is important to define appropriate therapeutic strategies (Pan 2010). A timely diagnosis could prove useful for patients with long disease free interval o for specific types of breast cancer (HER2+).

Treatment effectiveness

Isolated local-regional recurrence should be treated with curative intent like a new primary tumor. The vast majority of metastatic breast cancer is incurable and hence the main treatment goal is palliation, with the aim of maintaining/improving quality of life, and possibly improving survival (ESMO 2010b).

Research question: FDG-PET in triage
Has FDG-PET sufficient sensitivity to rule out relapse in patients with suspect of recurrence?

Pre-test probability

The median pre-test probability of recurrence and/or metastasis in patients with suspected recurrence of breast cancer is 63% (range 11.1-93.3%; Pennant 2010).

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

FDG-PET
- sensitivity (pooled): 91%
- specificity (pooled): 86%

Conventional diagnostic tests
- sensitivity (pooled): 81%
- specificity (pooled): 73% (excluding MRI)

Consequences of TEST for		Level of importance* (1-9)
Patients with recurrence	True positives: patients proceed to specific test to confirm FDG-PET results and proceed to appropriate treatment for metastatic recurrence, which could improve quality of life and might impact on survival	
	False negatives: patients delay start of treatment until symptoms occur, with a possible negative impact on quality of life and survival	
Patients not relapsing	True negatives: patients remain in follow up, after a certain amount of stress	
	False positives: patients undergo unnecessary further tests and suffer unnecessary distress	

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

		N of patients out of 100 submitted to the exam	
		According to FDG-PET	According to conventional imaging
Patients with recurrence	True positives	57	51
	False negatives	6	12
Patients without recurrence	True negatives	32	27
	False positives	5	10
		100	100

CLINICAL QUESTION

Role of FDG-PET in the diagnosis and staging of suspect distant recurrence in patients treated for breast 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									

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 BREAST CANCER

January 2011

Agenzia sanitaria e sociale regionale

RegioneEmilia-Romagna

SEARCH STRATEGY

The following databases were searched for the period between January 2006 and July 2010:

- 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,k*w
5. pet scan*: *ti,ab,kw*
6. "Fluorodeoxyglucose F18": *ti,ab,kw or*
7. fdg NEAR/2 18: *ti,ab,kw*
8. **1/7 OR**
9. "Breast neoplasm" *MeSH descriptor*
10. "Carcinoma, Ductal, Breast" *MeSH descriptor*
11. "Phyllodes Tumor**"** *MeSH descriptor*
12. breast NEAR (tumor* OR cancer* OR neoplasm*): *ti,ab,kw*
13. Mammary NEAR (neoplasm * or carcinoma*): *ti,ab,kw*
14. Philloides: *ti,ab,kw*
15. **10/14 OR**
16. **8 AND 15**

Publication date: 2006-2010

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. **1/24 OR**
25. "Breast Tumor" [title/abstract]
26. "Breast Cancer" [title/abstract]
27. "Mammary Carcinoma" [title/abstract]
28. "breast neoplasm" [title/abstract]
29. "breast neoplasms" [title/abstract]
30. "Mammary Neoplasm" [title/abstract]
31. "Breast Neoplasms" [Mesh: NoExp]
32. "Carcinoma, Ductal, Breast" [Mesh]
33. "Mammary Ductal Carcinoma" [ti/ab]
34. "Phyllodes Tumor" [Mesh: NoExp]
35. "Phyllodes" [titile/abstract]

36. **25/36 OR**
37. **24 AND 36**
38. "editorial" [Publication Type]
39. "comment" [Publication Type]
40. "letter" [Publication Type]
41. "review" [Publication Type]
42. "case reports" [Publication Type]
43. **38/42 OR**
44. **37 NOT 43**

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. "breast cancer"/syn
18. "breast cancer"
19. "breast neoplasm"
20. mammary NEAR/2 carcinoma
21. "breast sarcoma"
22. "breast adenocarcinoma"
23. phyllodes
24. "inflammatory breast cancer"
25. "intraductal carcinoma"
26. "ductal carcinoma"
27. "paget breast disease"
28. "breast cancer"/de
29. "breast adenocarcinoma"/exp
30. "breast carcinoma"/exp
31. "breast metastasis"/exp
32. "breast sarcoma"/exp
33. cystosarcoma phylloides"/exp
34. inflammatory breast cancer"/exp
35. "intraductal carcinoma"/exp

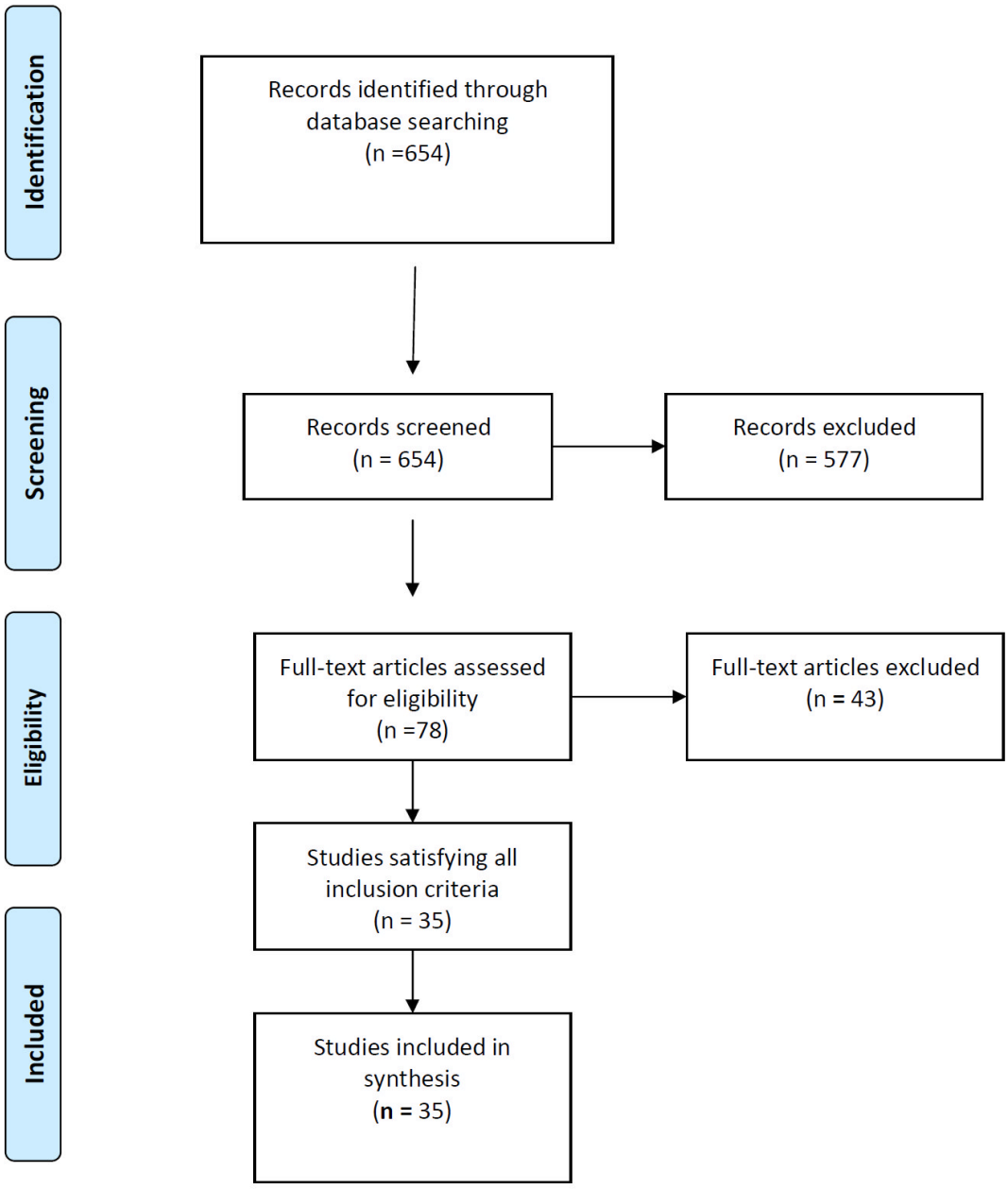
36. "paget nipple disease"/exp
37. 17/36
38. 37 AND 16

Limits: Humans

Publication date: 2006-2010

Languages: English, French, Italian, Spanish

Figure A.1. Study selection process according to PRISMA Flow Diagram



TABLES OF EVIDENCE

CHAPTER 4.
Diagnosis of primary breast cancer

Diagnostic accuracy

Systematic reviews

Author, year	Escalona 2010
Technology	FDG-PET
Disease	breast cancer
Objective	to assess: ▪ primary diagnosis ▪ staging (before treatment): N axillary staging and M staging ▪ response to therapy (after treatment) ▪ diagnosis of suspected recurrence
Inclusion criteria	P patients with breast cancer I FDG-PET C all available R not specified O diagnostic accuracy for primary diagnosis, staging, re-staging after treatment, recurrence S retrospective and prospective studies
Years covered by the search	up to February 2007
Study selection data abstraction, quality assessment performed by two authors independently	not specified
Comprehensive bibliographic search: at least two databases searched	yes Medline, Embase, Cinahl, CancerLit, Pascal Biomed, DARE, Cochrane Library, HTA database
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	yes (only reference lists)
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	yes
Characteristics of included studies clearly reported in tables	yes
Methodological quality of primary studies assessed; criteria reported	yes (JAMA 2004)
Results of quality assessment used to formulate results and conclusions	yes: qualitative report in the result section
Meta-analysis performed with appropriate statistic methods	not performed
Publication bias assessed	no
N. of included studies Study design	16 studies: primary diagnosis; 8 with complete data cross sectional diagnostic accuracy studies, with prospective or retrospective recruitment
N. of included patients	443
Reference standard	histological examination in all primary diagnosis studies
Comparator	SPECT, MRI, physical examination, ultrasonography, mammography, scintimammography, conventional imaging
Pre-test probability	median 68% (range 47.5-88.5%)
Performance results	<u>primary diagnosis</u> FDG-PET sensitivity: (our calculation) median 72% (48-96%) specificity: (our calculation) median 93.5% (73-100%) MRI (2 studies) sensitivity: 89%, 95% specificity: 73%, 74% scintimammography (1 study) sensitivity: 80% specificity: 86% palpation + US + mammography (1 study) sensitivity: 32% specificity: 93% palpation + mammography (1 study) sensitivity: 79% specificity: 25%
Recommendations and conclusions	FDG-PET is insufficiently sensitive to rule out small primary tumors
Note	meta-analysis not performed

Synoptic table of primary studies

Author, year	Technology	Patient number	Patient characteristics	Pre-test probability	Sensitivity	Specificity	PPV	NPV	AUROC
Berg 2006 Possible innovation	FDG-PEM	77	patients with known or suspected breast cancer based on clinical, radiological and post biopsy pathological investigation	54%	90%	86%	88%	88%	0.918
Buchmann 2007	FDG-PET	29	patients suspected to have breast cancer on mammography and/or ultrasound	96%	89%	100%			
	123 I-SPECT	10		90%	67%	100%			
	99m Tc-Pertechnetate SPECT	19		100%	63%	nc			
Imbriaco 2008	FDG-PET/CT	44	patients suspected to have breast cancer on physical examination, mammography and/or ultrasound	82%	single point: 62% dual point: 80%	single point: 100% dual point: 100%			
	MRI				98%	80%			
Alberini 2009	FDG-PET/CT	62	patients with suspected inflammatory breast cancer	95%	100%	33.3%	96.7%	100%	

Primary studies

Author, year	Berg 2006
Technology	FDG-PEM
Disease	breast cancer
Objective	to assess diagnostic accuracy in detecting suspected primary tumor
Patients characteristics	77 patients with known or suspected breast cancer based on clinical, radiological and post biopsy pathological investigation; mean age 53 years (range 25-88)
Index test	FDG-PEM
Comparator	none
Reference standard	histopathological confirmation with biopsy, surgical excision
Country	USA
Outcomes considered	sensitivity, specificity, PPV, NPV, AUROC
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
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 clear
Withdrawals from the study explained	no withdrawals
Pre-test probability	54% (42 out of 77)

Results	FDG-PEM sensitivity: 90% (95% CI 77-96) DCIS: 91%, invasive cancer: 89% specificity: 86% (95% CI 73-94) PPV: 88% (95% CI 75-94) NPV: 88% (95% CI 76-95) AUROC: 0.918
Authors recommendations and conclusions	The most striking finding in this study was the ability of high-resolution FDG PEM to depict DCIS, whether as a single focus or extensive intraductal component. When integrated with mammographic and clinical findings, high sensitivity and specificity were achieved with PEM. In summary, FDG PEM appears to be highly accurate in the depiction of primary breast cancer.

Author, year	**Buchmann 2007**
Technology	FDG-PET
Disease	breast cancer
Objective	to assess diagnostic accuracy in detecting suspected primary tumor
Patients characteristics	29 patients suspected to have breast cancer on mammography and/or ultrasound; mean age 50.5 years (range 29-75)
Index test	FDG-PET
Comparator	123 I-SPECT 99m Tc-Pertechnetate SPECT
Reference standard	histopathological confirmation by tissue sample
Country	Germany
Outcomes considered	sensitivity
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
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
Pre-test probability	96% (28 out of 29 patients)
Results	FDG-PET

	sensitivity: 89%; specificity 100% (our calculation) 123 I-SPECT (10 patients: 9 with cancer; 1 with fibro adenoma) sensitivity: 67% (specificity 100% our calculation) 99m Tc-Pertechnetate SPECT (19 patients; all with cancer) sensitivity: 63% (specificity not calculable)
Authors recommendations and conclusions	FDG-PET is superior to 99mTcO4 SPECT and 123 I SPECT in the imaging of breast cancer, and FDG-PET imaging in the prone position, initiated 135 minutes after the injection, should be considered. 99mTcO4 and 123I SPECT are not efficient in the detection of the primary breast tumor in clinical practice.

Author, year	**Imbriaco 2008**
Technology	FDG-PET/CT
Disease	breast cancer
Objective	to assess diagnostic accuracy in detecting suspected primary tumor
Patients characteristics	44 patients suspected to have breast cancer on physical examination, mammography and/or ultrasound; mean age 54 years
Index test	FDG-PET/CT single time point dual time point
Comparator	MRI
Reference standard	histopathological confirmation by excisional or core biopsy
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
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 clear
Withdrawals from the study explained	no withdrawals
Pre-test probability	82% (45 out of 55 lesions; not reported patient-based data)

Results	FDG-PET single time point sensitivity: 62% (95% CI 47-76) specificity: 100% (95% CI 66-100) FDG-PET dual time point sensitivity: 80% (95% CI 63-89) specificity: 100% (95% CI 63-100) MRI sensitivity: 98% (95% CI 87-100) specificity: 80% (95% CI 44-96)
Authors recommendations and conclusions	Dual-time-point imaging with acquisition in the prone position improve PET/CT accuracy in patients with suspected breast malignancy over single time-point PET/CT. Dual-time-point PET/CT performer in the prone position should be preferred to single-time-point PET/CT and is recommended for imaging patients with suspected breast malignancy. However, the limited sensitivity of FDG PET/CT, especially for lesions ≤10 mm, as observed in our study, suggests that PET/CT cannot be used as a routine imaging procedure for patients with suspected breast carcinoma and cannot significantly reduce the necessity of invasive procedures in patients suspected of having primary breast cancer. MRI shows higher sensitivity and lower specificity than PET/CT for disclosing breast malignancy and should be preferred for the detection and characterization of lesions ≤10 mm.

Author, year	**Alberini 2009**
Technology	FDG-PET/CT
Disease	breast cancer
Objective	to assess diagnostic accuracy in detecting suspected primary tumor and N staging
Patients characteristics	62 patients with suspected inflammatory breast cancer; mean age 50.4 years (range 29-79)
Index test	FDG-PET/CT
Comparator	none
Reference standard	histopathological confirmation by excisional biopsy
Country	France
Outcomes considered	sensitivity, specificity, PPV, NPV
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
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 clear
Withdrawals from the study explained	no withdrawals
Pre-test probability	95% (59 out of 62 patients)

Results	primary tumor sensitivity: 100% specificity: 33.3% PPV: 96.7% NPV: 100% N staging (38 patients) sensitivity: 91.6% PPV: 94.3%
Authors recommendations and conclusions	PET/CT provided additional invaluable information regarding lymph node and distant metastases. To recommend the most adequate treatment, PET/CT should be considered in the initial staging of IBC patients.
Comment of ASSR reviewers	Data reported on distant metastases did not allow the computation of sensitivity and specificity.

CHAPTER 5.
N staging of patients with primary breast cancer

Diagnostic accuracy

Systematic reviews

Author, year	Sloka 2007
Technology	FDG-PET
Disease	breast cancer
Objective	to assess N staging (axillary staging)
Inclusion criteria	P not specified I FDG-PET C not used R biopsy or axillary lymph node dissection O diagnostic accuracy for staging S retrospective and prospective studies
Years covered by the search	Up to 2005
Study selection data abstraction, quality assessment performed by two authors independently	not specified
Comprehensive bibliographic search: at least two databases searched	yes Medline, Current Contents, Embase
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	yes (only reference lists)
Searched also unpublished studies	no
Language restriction	yes: English, French, Spanish
Overall number of references retrieved and n of included studies reported	yes
N. and references of excluded studies reported, reason given	yes
Characteristics of included studies clearly reported in tables	yes
Methodological quality of primary studies assessed; criteria reported	yes; studies graded as of high, intermediate, low or very low methodological quality according to the method of Flynn and Adams (Flynn K, Abams E. Technology Assessment program No 1. Assessing diagnostic technologies. Health Service Research and Development Service. Management Decision and Research Service. 1996)

Results of quality assessment used to formulate results and conclusions	yes sub group meta-analysis of studies of high, intermediate, low and very low quality
Meta-analysis performed with appropriate statistic methods	method used not reported
Publication bias assessed	no
N. of included studies Study design	18 studies cross sectional diagnostic accuracy studies, 15 with prospective recruitment, 4 with retrospective recruitment
Characteristic of included patients	patients with primary diagnosis of breast cancer; further details not given
N. of included patients	1 271; median 39.5 (range 11-308)
Reference standard	histology by axillary lymph node dissection or biopsy
Comparator	
Performance results	high quality studies (3 studies, 675 patients) sensitivity: 78% specificity: 85% PPV: 80% NPV: 84% intermediate quality studies (4 studies, 222 patients) sensitivity: 67% specificity: 89% PPV: 82% NPV: 78% low quality studies (5 studies, 207 patients) sensitivity: 96% specificity: 84% PPV: 78% NPV: 97% very low quality studies (6 studies, 167 patients) sensitivity: 78% specificity: 99% PPV: 99% NPV: 76% LR+ and LR-: not reported
Impact on management	not assessed
Impact on clinical outcome	not assessed

Authors recommendations and conclusions	The great variability among study results, study designs and their methodological quality made it difficult to compare and aggregate their results. Also the variability among studies of higher quality needs to be explained in order to maximize the benefits of PET. Without addressing scan times, reconstruction algorithms, patients positioning, fasting, attenuation correction, tumor size, diabetes and other factors as source of variability in the accuracy results, it may be difficult to draw conclusions regarding the applicability of PET for axillary staging. Further studies controlling for contributory variables should be performed.

Author, year	**Escalona 2010**
Technology	FDG-PET
Disease	breast cancer
Objective	to assess: ▪ primary diagnosis ▪ staging (before treatment): N axillary staging and M staging ▪ response to therapy (after treatment) ▪ diagnosis of suspected recurrence
Inclusion criteria	P patients with breast cancer I FDG-PET C all available R not specified O diagnostic accuracy for primary diagnosis, staging, re-staging after treatment, recurrence S retrospective and prospective studies
Years covered by the search	up to February 2007
Study selection data abstraction, quality assessment performed by two authors independently	not specified
Comprehensive bibliographic search: at least two databases searched	yes Medline, Embase, Cinahl, CancerLit, Pascal Biomed, DARE, Cochrane Library, HTA database
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	yes (only reference lists)
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	yes
Characteristics of included studies clearly reported in tables	yes
Methodological quality of primary studies assessed; criteria reported	yes (JAMA 2004)
Results of quality assessment used to formulate results and conclusions	yes: qualitative report in the result section

Meta-analysis performed with appropriate statistic methods	not performed
Publication bias assessed	no
N. of included studies Study design	22 studies: N staging; 19 with complete data cross sectional diagnostic accuracy studies, with prospective or retrospective recruitment
N. of included patients	1 583 = N staging studies
Reference standard	axillary lymph node dissection or sentinel lymph node in N staging studies
Comparator	SPECT, MRI, physical examination, ultrasonography, mammography, scintimammography, conventional imaging
Pre-test probability	N axillary staging: not reported and not computable M staging: not reported
Performance results	N axillary staging FDG-PET sensitivity: (our calculation) median 70% (20-90%) specificity: (our calculation) median 97% (74-100%) palpation (2 studies) sensitivity: 44%, 58% specificity: 85%, 90% US (1 study) sensitivity: 65% specificity: 100% CT (1 study) sensitivity: 54% specificity: 85% USPIO-MRI (1 study) sensitivity: 100% specificity: 80%
Recommendations and conclusions	Due to the high number of false positive returned, it cannot replace axillary dissection in lymph gland staging.
Comments of ASSR reviewers	meta-analyses not performed

Synoptic table of primary studies on N staging of patients with primary breast cancer

Author, year	Technology	Patient number	Patient characteristics	SUV threshold	Sensitivity	Specificity	PPV	NPV
Chung 2006	FDG-PET	51	women with proven invasive breast cancer	0.5-1.0	79%	67% to 72%	85% to 87%	57% to 59%
				1.3-2.0	76% to 64%	78% to 89%	89% to 94%	60% to 52%
				2.3 *	60%	100%	100%	51%
				2.5-4.0	52% to 31%	100%	100%	47% to 38%
Stadnik 2006	FDG-PET	10	women with proven invasive breast cancer scheduled for surgery and axillary resection		80%	100%	100%	80%
Kumar 2006	FDG-PET	80	women with proven invasive breast cancer and clinically negative axillary nodes		44%	95%	89%	68%
Gil-Rendo 2006	FDG-PET	275	women with proven invasive breast cancer and clinically and US negative axillary nodes (excluded stage III or IV)		84.5%	98.5%	98.4%	85.6%
Mustafa 2007	FDG-PET	27	women with large (T2-T4) or advanced (N1,N2 or M1) breast cancer		83%	100%	100%	88%

Author, year	Technology	Patient number	Patient characteristics	SUV threshold	Sensitivity	Specificity	PPV	NPV
Veronesi 2007	FDG-PET/CT	236	women with proven invasive breast cancer (T1-T3) and clinically negative axillary nodes		37%	96%	88%	66%
Ueda 2008	FDG-PET/CT	183	women with proven invasive operable breast cancer	visual assessment	58%	95%	85%	83%
				0.8-1.5	50.8%-35.6%	95.2%-99.2%	83.3%-95.5%	80.3%-76.4%
				1.8 *	35.6%	100%	100%	76.5%
				2.0-3.0	33.9%-27.1%	100%	100%	76.1%-74.3%
Chae 2008	FDG-PET/CT	108	women with proven breast cancer and non palpable axillary lymph node		48.5%	84%	57%	79%
Cermik 2008	FDG-PET	219	women with proven breast cancer		50.6%	89%		
Fuster 2008	FDG-PET/CT	60	60 patients with newly diagnosed large (>3 cm) breast cancer		70%	100%		

Author, year	Technology	Patient number	Patient characteristics	SUV threshold	Sensitivity	Specificity	PPV	NPV
Kim 2009	FDG-PET/CT	137	women with proven early breast cancer and scheduled to have sentinel lymph node biopsy		77.1%	100%	100%	92.7%
Heusner 2009	FDG-PET/CT	61	women with proven breast cancer		58%	92%	82%	77%
Uematsu 2009	FDG-PET	22	women with proven breast cancer		60%	94%	75%	89%
Taira 2009	FDG-PET/CT	90	women with proven invasive breast cancer and clinically negative axillary nodes		48.1%	92.3%	72.2%	81.1%
Monzawa 2010	FDG-PET/CT	50	women with proven breast cancer stage I-III		20%	97%	75%	74%

* considered the best cut off

CHAPTER 6.
M staging of patients with locally advanced breast cancer

Diagnostic accuracy

Systematic reviews

Author, year	Escalona 2010
Technology	FDG-PET
Disease	breast cancer
Objective	to assess: ▪ primary diagnosis ▪ staging (before treatment): N axillary staging and M staging ▪ response to therapy (after treatment) ▪ diagnosis of suspected recurrence
Inclusion criteria	P patients with breast cancer I FDG-PET C all available R not specified O diagnostic accuracy for primary diagnosis, staging, re-staging after treatment, recurrence S retrospective and prospective studies
Years covered by the search	up to February 2007
Study selection data abstraction, quality assessment performed by two authors independently	not specified
Comprehensive bibliographic search: at least two databases searched	yes Medline, Embase, Cinahl, CancerLit, Pascal Biomed, DARE, Cochrane Library, HTA database
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	yes (only reference lists)
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	yes

Characteristics of included studies clearly reported in tables	yes
Methodological quality of primary studies assessed; criteria reported	yes (JAMA 2004)
Results of quality assessment used to formulate results and conclusions	yes: qualitative report in the result section
Meta-analysis performed with appropriate statistic methods	not performed
Publication bias assessed	no
N. of included studies Study design	23: M staging and recurrent disease (only 3 with patients at first staging) cross sectional diagnostic accuracy studies, with prospective or retrospective recruitment
N. of included patients	172 = M staging studies
Reference standard	histopathology and follow up in M staging
Comparator	SPECT, MRI, physical examination, ultrasonography, mammography, scintimammography, conventional imaging
Pre-test probability	M staging: not reported
Performance results	M staging: not computable pooled estimates
Recommendations and conclusions	none
Comments of ASSR reviewers	meta-analyses not performed

Sinoptic table of primary studies on M staging of patients with locally advanced breast cancer

Author, year	Technology	Patient number	Patient characteristics	Sensitivity	Specificity
Mahner 2008	FDG-PET	119	patients with newly diagnosed locally advanced breast cancer (59) or previous history of breast cancer (50) with clinical suspicious of metastatic disease	87%	83%
Fuster 2008	FDG-PET/CT	60	patients with newly diagnosed large (>3 cm) breast cancer	100%	98%

Primary studies

Author, year	Mahner 2008
Technology	FDG-PET
Disease	breast cancer
Objective	to assess diagnostic accuracy in detecting metastatic disease
Patients characteristics	111 patients with newly diagnosed locally advanced breast cancer (59) or previous history of breast cancer (50) with clinical suspicious of metastatic disease; mean age 54.5 years (range 28-89)
Index test	FDG-PET
Comparator	CT, conventional imaging (chest RX, abdominal US and bone scintigraphy)
Reference standard	histopathology and clinical follow up for a mean of 11 months (range 1-62)
Country	Germany
Outcomes considered	sensitivity, specificity, PPV, NPV
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 histopathology, not applicable for follow up; time period between FDG-PET and conventional imaging: 20 ± 30 days; between FDG-PET and CT 13 ± 7 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 (histopathology for 71 patients, follow up for others)
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 (119 patients) sensitivity: 87% specificity: 83% PPV: 89% NPV: 82% CT (61 patients) sensitivity: 83% specificity: 85% PPV: 95% NPV: 58% conventional imaging (116 patients) sensitivity: 43% specificity: 98% PPV: 96% NPV: 69%
Authors recommendations and conclusions	FDG-PET was considerably superior to conventional imaging for detection of distant breast cancer metastases while the overall diagnostic performance of FDG-PET was comparable with that of contrast-enhanced CT. FDG-PET had clinically relevant advantages in the detection of lymph node metastases particularly if the nodes were not enlarged. FDG-PET also identified bone metastases with higher accuracy compared with bone scintigraphy. On the other hand, CT had distinct advantages in the identification of both small lung and liver metastases. Thus, combined FDG-PET/CT could potentially replace the array of conventional imaging procedures and detect distant metastases in breast cancer patients with sufficient accuracy. Therefore, prospective studies on new FDG-PET/CT-based imaging algorithms in breast cancer patients are highly desirable.

Author, year	**Fuster 2008**
Technology	FDG-PET/CT
Disease	breast cancer
Objective	to assess diagnostic accuracy in the initial staging
Patients characteristics	60 patients with newly diagnosed large (>3 cm) breast cancer; mean age 57 years (range 40-82)
Index test	FDG-PET/CT
Comparator	
Reference standard	histopathology for all patients and clinical follow up for a mean of 12 months (range 1-62)
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 for histopathology, 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	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	axillary lymph nodes sensitivity: 70% specificity: 100% distant metastases sensitivity: 100% specificity: 98% change in staging: 42%
Authors recommendations and conclusions	FDG-PET/CT shows higher values of sensitivity and specificity in detecting distant metastases compared with conventional imaging, which makes this technique recommendable in the stage of patients with large primary breast cancer.

CHAPTER 7.
Evaluation of early response to neo-adjuvant therapy in patients treated for locally advanced breast cancer or eligible for mastectomy

Diagnostic accuracy

Systematic reviews

Author, year	Escalona 2010
Technology	FDG-PET
Disease	breast cancer
Objective	to assess: ▪ primary diagnosis ▪ staging (before treatment): N axillary staging and M staging ▪ response to therapy (after treatment) ▪ diagnosis of suspected recurrence
Inclusion criteria	P patients with breast cancer I FDG-PET C all available R not specified O diagnostic accuracy for primary diagnosis, staging, re-staging after treatment, recurrence S retrospective and prospective studies
Years covered by the search	up to February 2007
Study selection data abstraction, quality assessment performed by two authors independently	not specified
Comprehensive bibliographic search: at least two databases searched	yes Medline, Embase, Cinahl, CancerLit, Pascal Biomed, DARE, Cochrane Library, HTA database
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	yes (only reference lists)
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	yes
Characteristics of included studies clearly reported in tables	yes
Methodological quality of primary studies assessed; criteria reported	yes (JAMA 2004)
Results of quality assessment used to formulate results and conclusions	yes: qualitative report in the result section
Meta-analysis performed with appropriate statistic methods	not performed
Publication bias assessed	no
N. of included studies Study design	3: early response to therapy cross sectional diagnostic accuracy studies, with prospective or retrospective recruitment
N. of included patients	92 = early response to treatment studies
Reference standard	histopathology after surgery in response to early treatment studies
Comparator	SPECT, MRI, physical examination, ultrasonography, mammography, scintimammography, conventional imaging
Pre-test probability	not reported
Performance results	early response: not computable pooled estimates
Recommendations and conclusions	A complete biochemical response identified by FDG-PET should not be relied upon to mean an absence of disease since technique cannot detect residual microscopical elements.
Comments of ASSR reviewers	meta-analyses not performed

Synoptic table of primary studies on evaluation of early response to neo-adjuvant therapy in patients treated for locally advanced breast cancer or eligible for mastectomy

Author, year	Technology	Patient number	Sensitivity	Specificity
Dose-Schwarz 2010	FDG-PET	69/64	1st cycle level of FDG uptake: 73% change if FDG uptake: 73% 2nd cycle level of FDG uptake: 77% change if FDG uptake: 69%	1st cycle level of FDG uptake: 59% change if FDG uptake: 63% 2nd cycle level of FDG uptake: 59% change if FDG uptake: 63%
Duch 2009	FDG-PET/CT	50	2nd cycle: 77%	2nd cycle: 80%
Kumar 2009	FDG-PET/CT	23	2nd cycle: 93%	2nd cycle: 75%
Mc Dermott 2007	FDG-PET	96	1st cycle: 100% midtherapy: 100%	1st cycle: 66% midtherapy: 77%
Rousseau 2006	FDG-PET	64	1st cycle: 61% 2nd cycle: 89% 3rd cycle: 88%	1st cycle: 96% 2nd cycle: 95% 3rd cycle: 73%
Berriolo-Riedinger 2007	FDG-PET	47	1st cycle, 60% decrease in the SUVmax measures at baseline: 91% 1st cycle, -50% for ΔSUVavg- BSA-G: 82%	1st cycle, 60% decrease in the SUVmax measures at baseline: 86% 1st cycle, -50% for ΔSUVavg- BSA-G: 92%

Primary studies

Author, year	Dose-Schwarz 2010
Technology	FDG-PET
Disease	breast cancer
Objective	to assess early response to neo-adjuvant treatment (pre-operative chemotherapy)
Patients characteristics	104 patients with newly diagnosed locally advanced (stage III) or large (≥3 cm) non inflammatory breast cancer; mean age: 50 years (range 29-65)
Index test	FDG-PET performed after the first and second cycle of chemotherapy
Comparator	
Reference standard	histopathology (all women underwent surgery)
Country	Germany
Outcomes considered	sensitivity and specificity for predicting histological response
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	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	level of FDG uptake after 1st cycle (69 patients considered): sensitivity: 73% specificity: 59% NPV: 89% (threshold SUV of 3.5) after 2nd cycle (64 patients considered): sensitivity: 77% specificity: 59% NPV: 91% (threshold SUV of 2.5) relative change of FDG uptake after 1st cycle (69 patients considered): sensitivity: 73% specificity: 63% NPV: 90% (threshold of 45% decrease) after 2nd cycle (64 patients considered): sensitivity: 69% specificity: 63% NPV: 89% (threshold of 55% decrease)
Authors recommendations and conclusions	FDG-PET allows for prediction of treatment response by the level of FDG uptake in terms of SUV at baseline and after each cycle of chemotherapy. Moreover, relative changes in SUV after the first and second cycle are a strong predictor of response. Thus, FDG-PET may be helpful for individual treatment stratification in breast cancer patients.

Author, year	Duch 2009
Technology	FDG-PET/CT
Disease	breast cancer
Objective	to assess early response to neo-adjuvant treatment (pre-operative chemotherapy)
Patients characteristics	50 patients with newly diagnosed locally advanced (stage III) or large (≥3 cm) non inflammatory breast cancer; mean age: 57 years (range 32-82)
Index test	FDG-PET/CT performed after the 2nd cycle of chemotherapy
Comparator	
Reference standard	histopathology; results classified according the 1 to 5 scale established by Miller and Payne (score 4-5: good prognosis, score 1-3: bad prognosis); RECIST criteria for tumor response were also used (respondent: partial and complete response; non respondent: stable and progressive disease)
Country	Spain
Outcomes considered	sensitivity and specificity for predicting histological response
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 clear
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 clear
Withdrawals from the study explained	no withdrawals

Results	response to treatment (RECIST criteria) relative change of FDG uptake: sensitivity: 77% specificity: 80% (threshold of 40% decrease) significant differences in SUVmax decrease after the second cycle of chemotherapy were found between patients with bad prognosis (M&P grades 1-3) (39.79 ± 7.03%) vs those with good prognosis (M&P grades 4-5) (57.31 ± 13.52%) (p = 0.025)
Authors recommendations and conclusions	We can conclude that 18F-FDG PET/CT can predict neo-adjuvant chemotherapy response after two cycles of chemotherapy. A cut off value of >40% is the most appropriate to detect responder patients. A low baseline SUVmax can underestimate response to treatment. For patients with large breast cancer, the addition of PET/CT may improve management by avoiding ineffective treatment and delay before undergoing surgery for non-responder patients and support the decision to continue chemotherapy in responding patients.

Author, year	Kumar 2009
Technology	FDG-PET/CT
Disease	breast cancer
Objective	to assess early response to neo-adjuvant treatment (pre-operative chemotherapy)
Patients characteristics	23 patients with newly diagnosed locally advanced (stage III) or large (≥3 cm) non inflammatory breast cancer; mean age: 44.9 years (range 25-60)
Index test	FDG-PET performed after the second cycle of chemotherapy
Comparator	CT, clinical examination performed after the second cycle of chemotherapy
Reference standard	histopathology; RECIST criteria for tumor response were also used (respondent: partial and complete response; non respondent: stable and progressive disease)
Country	India
Outcomes considered	sensitivity and specificity for predicting histological response
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	yes
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	clinical examination sensitivity: 27 specificity: 63% CT sensitivity: 46% specificity: 75% FDG-PET/CT sensitivity: 93% specificity: 75%
Authors recommendations and conclusions	FDG-PET/CT can accurately predict treatment response after two cycles of neo-adjuvant chemotherapy in patients with locally advanced breast cancer.

Author, year	**Mc Dermott 2007**
Technology	FDG-PET
Disease	breast cancer
Objective	to assess early response to neo-adjuvant treatment (pre-operative chemotherapy)
Patients characteristics	96 patients with newly diagnosed locally advanced (stage III) or large (≥3 cm) non inflammatory breast cancer; mean age: 51 years
Index test	FDG-PET performed at end of first cycle, midpoint, end of chemotherapy
Comparator	
Reference standard	histopathology; tumor response graded according to the 1-5 scale established by Miller Payne (responders: 4-5) non responders (1-3)
Country	UK
Outcomes considered	sensitivity, specificity and AUC for predicting histological response
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	yes
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	change in mean SUV uptake FDG-PET at the end of treatment (67 patients) sensitivity: 100% specificity: 68% AUROC: 0.91 threshold: -76% fixed to have 100% sens. FDG-PET at midtherapy (58 patients) sensitivity: 100% specificity: 77% AUROC: 0.93 threshold: -72% FDG-PET after the first cycle (75 patients) sensitivity: 100% specificity: 66% AUROC: 0.88 threshold: -34%
Authors recommendations and conclusions	FDG-PET is an effective technique for predicting the pathological response of breast tumor tissue and findings here and in the research literature indicate it will outperform conventional clinical methods in most circumstances. Therefore, a large-scale multi-centre clinical trial for FDG-PET response monitoring of primary breast cancers should be considered, such that definitive guidelines for its correct application in the clinical setting can be established.

Author, year	**Rousseau 2006**
Technology	FDG-PET
Disease	breast cancer
Objective	to assess early response to neo-adjuvant treatment (pre-operative chemotherapy)
Patients characteristics	64 patients with newly diagnosed locally advanced (stage III) or large (≥3 cm) non inflammatory breast cancer; mean age: 44.9 years (range 25-60)
Index test	FDG-PET performed after the 1st, 2nd, 3rd cycle of chemotherapy
Comparator	US, mammography, clinical examination performed after the 2nd cycle of chemotherapy
Reference standard	histopathology; tumor response graded according to the A-D Scale established by Sataloff: responders: A, B; non responders: C, D
Country	France
Outcomes considered	sensitivity and specificity for predicting histological response
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	yes
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	US at the end of treatment: sensitivity: 64% specificity: 43%, PPV: 53%, NPV: 55% mammography at the end of treatment: sensitivity: 31% specificity: 56% PPV: 423% NPV: 45% physical examination at the end of treatment: sensitivity: 100% specificity: 31% PPV: 100% NPV: 67% FDG-PET 1st course sensitivity: 61% specificity: 96% PPV: 95% NPV: 68% (threshold of 40% reduction) 2nd course sensitivity: 89% specificity: 95% PPV: 89% NPV: 85% 3rd course sensitivity: 88% specificity: 73% PPV: 81% NPV: 83%
Authors recommendations and conclusions	In contrast to mammography and US, FDG PET, using a simple imaging protocol, is able to provide early information on tumor response after the second course of neo-adjuvant chemotherapy in stage II and III breast cancer. Early information about tumor response is extremely helpful in deciding the most appropriate therapeutic strategy. A prospective randomized study is needed that uses PET assessment after two cycles to determine a change to a different neo-adjuvant regimen or to discontinue chemotherapy versus continuing chemotherapy in those patients without clinical or radiologic progression.

Author, year	**Berriolo-Riedinger 2007**
Technology	FDG-PET
Disease	breast dancer
Objective	to predict early response to endocrine therapy in metastatic breast cancer
Patients characteristics	47 patients with newly diagnosed locally advanced (stage III) or large (≥3 cm) non inflammatory breast cancer; age: ≤50 years: 60%; >50 years 40%
Index test	FDG- PET performed after the first course of chemotherapy
Comparator	
Country	France
Outcomes considered	▪ pathological response assessed at surgery according to the Sataloff classification (complete response: T-A, N-A, N-b; non complete response: T-B,T-C,T-D,N-C,N-D) ▪ metabolic response: change in SUV uptake
Study design	prospective case series
Consecutive recruitment	
Follow up	until surgery
Results	60% decrease in the SUVmax measures at baseline: sensitivity 91%; specificity 86% -50% for ΔSUVavg- BSA-G: sensitivity 82%; specificity 92% In a multivariate regression analysis ΔSUVs were found to be the only independent predictive factors of pathological response ΔSUV max and ΔSUV max BSA-G cut off -60%: OR 62; 95% CI 6.5-595 ΔSUV avg cut off -40%: OR: 36; 95% CI 5.7-229 ΔSUV avg BSA-G cut off -50% OR: 50; 95% CI 7.2-343
Authors recommendations and conclusions	In patients with breast cancer undergoing neo-adjuvant therapy, the pCR can be predicted accurately by the decrease in [18F]FDG PET uptake after only one course of chemotherapy. This may improve patient management by avoiding ineffective chemotherapy or supporting the decision to continue dose-intensive pre-operative chemotherapy in responding patients. The cut off value of -60% for the relative change in SUVmax-BSA-G or -50% for SUVavg-BSA-G is highly predictive of a pCR.

CHAPTER 8.
Evaluation of response to neo-adjuvant therapy at the end of treatment in patients treated for locally advanced breast cancer or eligible for mastectomy

Diagnostic accuracy

Systematic reviews

Author, year	Escalona 2010
Technology	FDG-PET
Disease	breast cancer
Objective	to assess: ▪ primary diagnosis ▪ staging (before treatment): N axillary staging and M staging ▪ response to therapy (after treatment) ▪ diagnosis of suspected recurrence
Inclusion criteria	P patients with breast cancer I FDG-PET C all available R not specified O diagnostic accuracy for primary diagnosis, staging, re-staging after treatment, recurrence S retrospective and prospective studies
Years covered by the search	up to February 2007
Study selection data abstraction, quality assessment performed by two authors independently	not specified
Comprehensive bibliographic search: at least two databases searched	yes Medline, Embase, Cinahl, CancerLit, Pascal Biomed, DARE, Cochrane Library, HTA database
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	yes (only reference lists)
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	yes
Characteristics of included studies clearly reported in tables	yes
Methodological quality of primary studies assessed; criteria reported	yes (JAMA 2004)
Results of quality assessment used to formulate results and conclusions	yes: qualitative report in the result section
Meta-analysis performed with appropriate statistic methods	not performed
Publication bias assessed	no
N. of included studies Study design	2: end of neo-adjuvant treatment cross sectional diagnostic accuracy studies, with prospective or retrospective recruitment
N. of included patients	60 (range 10-50)
Reference standard	histopathology after surgery in response to neo-adjuvant treatment
Comparator	
Pre-test probability	not reported
Performance results	descriptive
Recommendations and conclusions	none

Synoptic table of primary studies on evaluation of response to neo-adjuvant therapy at the end of treatment in patients treated for locally advanced breast cancer or eligible for mastectomy

Author, year	Technology	Therapy	Patient number	Patient characteristics	Sensitivity	Specificity	PPV	NPV	AUROC
Schwarz-Dose 2010	FDG-PET	neo-adjuvant treatment	89	newly diagnosed breast cancer	SUV threshold 2.0: 32.9% SUV threshold 1.5: 57.5%	SUV threshold 2.0: 87.5% SUV threshold 1.5: 62.5%	SUV threshold 2.0: 92.3% threshold SUV of 1.5: 87.5,%	SUV threshold 2.0: 22.2% threshold SUV of 1.5: 24.4%	
Prati 2009	FDG-PET	neo-adjuvant treatment	45	newly diagnosed breast cancer	16%	88%	66.6%	40%	
McDermott 2007	FDG-PET	neo-adjuvant treatment	67	newly diagnosed breast cancer	100%	68%			0.91 threshold: -76% fixed to have 100% sensibility

Primary studies

Author, year	Schwarz-Dose2010
Technology	FDG-PET
Disease	breast cancer
Objective	to assess response to neo-adjuvant treatment (pre-operative chemotherapy)
Patients characteristics	99 patients with newly diagnosed locally advanced (stage III) or large (≥3 cm) non inflammatory breast cancer; mean age: 50 years (range 30-66) and had at least one imaging procedure after chemotherapy
Index test	FDG-PET
Comparator	MRI, mammography, US, physical examination
Reference standard	histopathology (all women underwent surgery)
Country	Germany
Outcomes considered	sensitivity and specificity for detecting residual disease MRD: no residual invasive tumor or few scattered foci of microscopic residual invasive tumor; GRD: gross residual disease: macroscopic residual tumor or extensive residual tumor infiltration
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
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 (89 patients): threshold SUV of 2.0 sensitivity: 32.9 specificity: 87.5 PPV: 92.3 NPV: 22.2 FDG-PET: threshold SUV of 1.5 sensitivity: 57.5 specificity: 62.5 PPV: 87.5 NPV: 24.4 MRI (46 patients) sensitivity: 97.6 specificity: 40 PPV: 93 NPV: 66.7 US (58 patients) sensitivity: 92 specificity 37.5 PPV: 90.2 NPV: 42.9 mammography (47 patients) sensitivity 92.5 specificity: 57.2 PPV: 92.5 NPV: 57.1 physical examination (99 patients) sensitivity: 91.5 specificity: 52.9 PPV: 90.4 NPV: 56.3
Authors recommendations and conclusions	FDG-PET does not allow for an accurate assessment of residual tumor after primary chemotherapy. Magnetic resonance imaging offers the highest sensitivity, bur all imaging modalities have distinct limitation in the assessment of residual tumor tissue when compared with histopathology.

Author, year	McDermott 2007
Technology	FDG-PET
Disease	breast cancer
Objective	to assess response to neo-adjuvant treatment (pre-operative chemotherapy)
Patients characteristics	96 patients with newly diagnosed locally advanced (stage III) or large (≥3 cm) non inflammatory breast cancer; mean age: 51 years
Index test	FDG-PET performed at and of first cycle, midpoint, end of chemotherapy
Comparator	
Reference standard	histopathology; tumor response graded according to the 1-5 Scale established by Miller Payne (responders: 4-5) non responders (1-3)
Country	UK
Outcomes considered	sensitivity, specificity and AUC for predicting histological response
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	yes
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	change in mean SUV uptake FDG-PET at the end of treatment (67 patients) sensitivity: 100% specificity: 68% AUROC: 0.91 threshold: -76% fixed to have 100% sens FDG-PET at midtherapy (58 patients) sensitivity: 100% specificity: 77% AUROC: 0.93 FDG-PET after the first cycle (75 patients) sensitivity: 100% specificity: 66% AUROC: 0.88
Authors recommendations and conclusions	FDG-PET is an effective technique for predicting the pathological response of breast tumor tissue and findings here and in the research literature indicate it will outperform conventional clinical methods in most circumstances. Therefore, a large-scale multi-centre clinical trial for FDG-PET response monitoring of primary breast cancers should be considered, such that definitive guidelines for its correct application in the clinical setting can be established.

Author, year	**Prati 2009**
Technology	FDG-PET
Disease	breast cancer
Objective	to assess response to neo-adjuvant treatment (pre-operative chemotherapy)
Patients characteristics	45 patients with T3 or T4 breast cancer who received chemotherapy before surgery; median age 50 years (range 29-68)
Index test	FDG-PET
Comparator	physical examination
Reference standard	histopathology (all women underwent surgery)
Country	USA
Outcomes considered	sensitivity and specificity for detecting positive lymph node after chemotherapy
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
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	yes

Results	FDG-PET sensitivity: 16% specificity: 88% PPV: 66.6% NPV: 40% physical examination sensitivity: 11% specificity: 94% PPV: 75% NPV: 41.6%
Authors recommendations and conclusions	PE and FDG-PET after neo-adjuvant chemotherapy are highly specific, but poor for sensitivity; lymph node staging is still necessary even when PE and FDG-PET are negative.

CHAPTER 9.
Follow up in patients with no suspicion of recurrence

Diagnostic accuracy

Systematic reviews

Author, year	Iagaru 2007
Technology	FDG-PET/CT
Disease	breast cancer
Objective	to assess the utility of FDG-PET/CT for follow up in asymptomatic patients
Patients characteristics	15 women followed up after surgery; mean age: 52 (range 38-76)
Index test	FDG-PET/CT performed at an average time of 51.3 days after surgery (range 4-175 days)
Comparator	MRI performed at an average time of 51.3 days after surgery (range 4-175 days)
Reference standard	histology or follow up
Country	USA
Outcomes considered	sensitivity, specificity, change in management
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 for histology; not applicable for follow
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 17 patients and follow up for 4 patients)

Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	unclear
Withdrawals from the study explained	no withdrawn
Results	FDG PET/CT sensitivity: 33.3% for breast disease 100% for metastatic disease specificity: 91.7% for breast disease 90% for metastatic disease change in management: 28% of patients MRI sensitivity: 88.9% (95% CI 56.5-98) specificity: 83.3% (95% CI 43.6-96.9)
Authors recommendations and conclusions	MRI is more sensitive in detecting breast disease, while FDG-PET is important for identifying disease outside of the breast and axilla. FDG PET/CT and breast MRI should be considered as complimentary imaging tools in the pre- and postoperative work-up of patients diagnosed with breast cancer and at high risk due to tumor histology or symptomatology.

CHAPTER 10.
Diagnosis and staging of suspect distant recurrence

Diagnostic accuracy

Systematic reviews

Author, year	Shie 2008
Technology	FDG-PET
Disease	breast cancer
Objective	to assess M staging: bone metastases
Inclusion criteria	P female breast cancer patients of all ages in any stages regardless of treatment status I FDG-PET C bone scintigraphy R CT, MRI or bone biopsy with clinical follow up longer than 6 months O diagnostic accuracy for staging S diagnostic accuracy studies where FDG-PET and BS were performed within 3 months of one another
Years covered by the search	from 1995 to November 2006
Study selection data abstraction, quality assessment performed by two authors independently	yes
Comprehensive bibliographic search: at least two databases searched	Yes Medline, Cinahl, EBM reviews
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	yes (only reference lists)
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	yes (reason given: yes; references reported: no)
Characteristics of included studies clearly reported in tables	yes
Methodological quality of primary studies assessed; criteria reported	yes: quality assessed but criteria not reported

Results of quality assessment used to formulate results and conclusions	no; results of quality assessment not reported and not used
Meta-analysis performed with appropriate statistic methods	yes
Publication bias assessed	no
N. of included studies Study design	6 studies cross sectional diagnostic accuracy studies, 4 with prospective recruitment, 2 with retrospective recruitment
Characteristic of included patients	not reported
N. of included patients	301, median 47.5, range 15-89
Reference standard	CT, MRI or bone biopsy with clinical follow up longer than 6 months
Comparator	bone scintigraphy
Performance results	<u>patient based</u> FDG-PET sensitivity: 81% (95% CI 70-89) specificity: 93% (95% CI 84-81) bone scintigraphy sensitivity: 78% (95% CI 67-86) specificity 79% (95% CI 40-95) <u>lesion based</u> FDG-PET sensitivity: 69% (95% CI 28-93) specificity: 98% (95% CI 87-100) bone scintigraphy sensitivity: 88% (95% CI 82-92) specificity 87% (95% CI 29-99)
Authors recommendations and conclusions	Patients based versus lesions based assessment demonstrated notables differences in sensitivities between FDG-PET and bone scan. It remains unclear whether FDG-PET should supersede conventional imaging, including bone scan as the primary diagnostic modality in patients with suspected osseous metastatic breast cancer. Further research is needed to determine the most efficacious modality in detecting bone metastasis of breast cancer.

Author, year	**Escalona 2010**
Technology	FDG-PET
Disease	breast cancer
Objective	to assess: ▪ primary diagnosis ▪ staging (before treatment): N axillary staging and M staging ▪ response to therapy (after treatment) ▪ diagnosis of suspected recurrence
Inclusion criteria	P patients with breast cancer I FDG-PET C all available R not specified O diagnostic accuracy for primary diagnosis, staging, re-staging after treatment, recurrence S retrospective and prospective studies
Years covered by the search	up to February 2007
Study selection data abstraction, quality assessment performed by two authors independently	not specified
Comprehensive bibliographic search: at least two databases searched	yes Medline, Embase, Cinahl, CancerLit, Pascal Biomed, DARE, Cochrane Library, HTA database
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	yes (only reference lists)
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	yes
Characteristics of included studies clearly reported in tables	yes
Methodological quality of primary studies assessed; criteria reported	yes (JAMA 2004)
Results of quality assessment used to formulate results and conclusions	yes: qualitative report in the result section

Meta-analysis performed with appropriate statistic methods	not performed
Publication bias assessed	no
N. of included studies Study design	19 cross sectional diagnostic accuracy studies, with prospective or retrospective recruitment
N. of included patients	960; median 44 (range 15-133)
Reference standard	histopathologic analysis and/or clinical follow
Comparator	conventional imaging
Pre-test probability	distant metastasis: median 68.5% (range 26.2%-93%) lung metastasis: 8%, 28% (3 studies) liver metastasis: 3%, 14% (2 studies)
Performance results	<u>sensitivity</u> FDG-PET distant metastasis (our calculation): median 93.5% (range 69-100%) lung metastasis: 78.6%, 83%, 85% (3 studies) liver metastasis: 85.7%, 100% (2 studies) conventional imaging distant metastasis (4 studies our calculation): median 79% (range 57%-84,8%) lung metastasis: 40%, 41.6%, 83% (3 studies) liver metastasis: 50%, 60% (2 studies) <u>specificity</u> FDG-PET distant metastasis (our calculation): median 80% (range 60%-97%) lung metastasis: 90%, 96%, 97.2% (3 studies) liver metastasis: 97.6%, 99% (2 studies) conventional imaging distant metastasis (4 studies our calculation): median 74.5% (range 62.5%-94%) lung metastasis: 85%, 96%, 100% (3 studies) liver metastasis: 94.7%, 95% (2 studies)
Recommendations and conclusions	none
Comments of ASSR reviewers	meta-analysis not performed

Author, year	**Pan 2010**
Technology	FDG-PET
Disease	breast cancer
Objective	to assess diagnosis of suspected recurrence
Inclusion criteria	P female breast cancer patients of all ages with suspected recurrence and metastases I FDG-PET C US, CT, MRI, SMM R histopathologic analysis and/or clinical follow up longer than 6 months O diagnostic accuracy S diagnostic accuracy studies with prospective or retrospective recruitment and at least 10 patients
Years covered by the search	from 1995 to August 2008
Study selection data abstraction, quality assessment performed by two authors independently	yes
Comprehensive bibliographic search: at least two databases searched	yes Medline, Embase, China bio-medicine databases, Cochrane Library, CancerLit, China National Knowledge Infrastructure database
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	yes (only reference lists)
Searched also unpublished studies	no
Language restriction	yes: English, Chinese
Overall number of references retrieved and n of included studies reported	yes
N. and references of excluded studies reported, reason given	yes (reason given: yes; references reported: no)
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; results of quality assessment reported
Meta-analysis performed with appropriate methods	yes
Publication bias assessed	yes

N. of included studies Study design	43 studies (US: 10, CT:8, MRI: 11, SPECT: 7, FDG-PET: 21) cross sectional diagnostic accuracy studies
Characteristic of included patients	not reported
N. of included patients	5 421, range 10-1 968
Reference standard	histopathologic analysis and/or clinical follow up longer than 6 months
Comparator	US, CT, MRI, SMM
Performance results	FDG-PET sensitivity: 95.3% (95% CI 93.7-96.5) specificity: 86.3%% (95% CI 82.4-89.5) AUROC: 0.9604 US sensitivity: 85.7% (95% CI 80.4-89.9) specificity 96.2% (95% CI 95.4-97) AUROC: 0.9251 CT sensitivity: 84.8% (95% CI 81.1-88.1) specificity: 75.3% (95% CI 69.2-80.7) AUROC: 0.8596 MRI sensitivity: 95% (95% CI 92.3-97) specificity 92.9% (95% CI 90.2-95) AUROC: 0.9718 SMM sensitivity: 90% (95% CI 85.3-93.7) specificity 79.8% (95% CI 71.5-86.6) AUROC: 0.9386
Impact on management	not assessed
Impact on clinical outcome	not assessed
Authors recommendations and conclusions	MRI seemed to be a more useful supplement to current surveillance techniques to assess patients with suspected recurrent and/or metastatic breast cancer. If MRI shows an indeterminate or benign lesion or MRI was not applicable (e.g., pacemaker), FDG-PET could be performed in addition

Author, year	**Pennant 2010**
Technology	FDG-PET
Disease	breast cancer
Objective	to assess diagnosis of suspected recurrence
Inclusion criteria	P female breast cancer patients of all ages with suspected recurrence and metastases I FDG-PET C conventional imaging tests R histopathologic analysis and/or long clinical follow up O diagnostic accuracy S diagnostic accuracy studies with prospective or retrospective recruitment
Years covered by the search	up to May 2009
Study selection data abstraction, quality assessment performed by two authors independently	yes
Comprehensive bibliographic search: at least two databases searched	yes: Medline, Embase
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	no
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	yes (reason given: yes; references reported: no)
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; results of quality assessment reported
Meta-analysis performed with appropriate methods	yes
Publication bias assessed	no
N. of included studies Study design	28 studies cross sectional diagnostic accuracy studies

Characteristic of included patients	The patient population was to be under investigation for suspicion of BC recurrence. Patients were to have had a previous diagnosis of BC and to have completed a course of primary treatment. The initial aim of this review was to include only studies in which patients had previously been cleared of BC. However, it soon became evident that, in many studies, the exact patient group was unclear. It was often not fully clear whether patients with history of BC had subsequently been cleared or if they had known BC and were having further imaging investigations in order to diagnose metastatic disease. Exclusion of these types of studies was likely to substantially limit the scope of this review and restrict its application. A decision was therefore made to include studies investigating the diagnosis of BC recurrence in patient groups that may have been cleared or not cleared of their original disease. All studies were to have been conducted in the context of secondary BC investigations, i.e. they did not form part of the initial BC diagnosis, BC staging or monitoring of response to primary BC treatment.
N. of included patients	1 679; median 44 (range 7-291)
Reference standard	histopathologic analysis and/or clinical follow up longer than 6 months
Comparator	This review included both studies with and without comparator groups. For studies including comparator groups, those using any diagnostic comparators were included but patients were also to have undergone FDG-PET or PET/CT and the reference standard.
Performance results	sensitivity FDG-PET (25 studies): 91% (95% CI 87-93) FDG-PET/CT (5 studies): 95% (95% CI 89-97) conventional imaging tests (11 studies): 81% (95% CI 73-87) specificity FDG-PET (25 studies): 86% (95% CI 79-91) FDG-PET/CT (5 studies): 89% (95% CI 76-96) conventional imaging tests (11 studies): 73% (95% CI 59-83)
Impact on clinical outcome	not assessed
Authors recommendations and conclusions	Available evidence suggests that for the detection of BC recurrence PET, in addition to conventional imaging techniques, may generally offer improved diagnostic accuracy compared with current standard practice. However, uncertainty remains around its use as a replacement for, rather than an add-on to, existing imaging technologies. In addition, PET/CT appeared to show clear advantage over CT and PET alone for the diagnosis of BC recurrence.

Synoptic table of primary studies on diagnosis and staging of suspect distant recurrence

Author, year	Technology	Patient number	Patient characteristics	Sensitivity	Specificity	PPV	NPV
Palomar Munoz 2010	FDG-PET/CT	70	suspicious of recurrence	87.8%	86.4%	85.2%	88.8%
Aukema 2010	FDG-PET/CT	56	diagnosed recurrence	97% *	92% *	94% *	96% *

* for detecting distant metastases

Primary studies

Author, year	Aukema 2010
Technology	FDG-PET/CT
Disease	breast cancer
Objective	to assess diagnostic accuracy for staging of recurrence and impact on management
Patients characteristics	56 patients with already diagnosed recurrence mean age 48 years (range 27-74)
Index test	FDG-PET/CT
Comparator	
Reference standard	histopathological confirmation or clinical follow up
Country	The Netherlands
Outcomes considered	sensitivity, specificity, PPV, NPV for detecting additional lesions besides locoregional recurrence, 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	no (histopathological confirmation for 14 patients, further imaging or follow up of a mean period of 13.4 months for other)
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	unclear
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	no withdrawals

Results	sensitivity: 97% specificity: 92% PPV: 94% NPV: 96% change in management: 48% of patients
Authors recommendations and conclusions	FDG PET/CT plays an important role in the staging of patients with confirmed locoregional breast cancer recurrence. FDG PET/CT could potentially replace conventional staging imaging in patients with a locoregional breast cancer recurrence, and thus spare a significant proportion extensive but futile local treatment.

Author, year	**Palomar Munoz 2010**
Technology	FDG-PET/CT
Disease	breast cancer
Objective	to assess diagnostic accuracy for suspected recurrence and impact on management
Patients characteristics	70 patients with suspicious of recurrence either because elevation of tumor markers, doubtful findings on other imaging techniques) and/or suspicious symptoms; mean age 61.3 years (range 34-84)
Index test	FDG-PET/CT
Comparator	
Reference standard	histopathological confirmation or clinical follow up for at least 6 months
Country	Spain
Outcomes considered	sensitivity, specificity, PPV, NPV for detecting recurrence 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	no (histopathological confirmation for 14 patients, further imaging or follow up of a mean period of 13.4 months for other)
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	unclear for histopathological confirmation, not applicable for clinical 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	no
Withdrawals from the study explained	no withdrawals

Results	sensitivity: 87.8% (95% CI 86.3-89.4) specificity: 86.4% (95% CI 85-87.9) PPV: 85.2% (95% CI 83.7-86.8) NPV: 88.8% (95% CI 87.4-90.3) change in management: 41.4% of patients
Authors recommendations and conclusions	FDG PET/CT is a technique with high diagnostic yield in patients with suspected recurrence

COLLANA DOSSIER

a cura dell'Agenzia sanitaria e sociale regionale

1990

1. Centrale a carbone "Rete 2": valutazione dei rischi. Bologna. **(*)**
2. Igiene e medicina del lavoro: componente della assistenza sanitaria di base. Servizi di igiene e medicina del lavoro. (Traduzione di rapporti OMS). Bologna. **(*)**
3. Il rumore nella ceramica: prevenzione e bonifica. Bologna. **(*)**
4. Catalogo collettivo dei periodici per la prevenzione. I edizione - 1990. Bologna. **(*)**
5. Catalogo delle biblioteche SEDI - CID - CEDOC e Servizio documentazione e informazione dell'ISPESL. Bologna. **(*)**

1991

6. Lavoratori immigrati e attività dei servizi di medicina preventiva e igiene del lavoro. Bologna. **(*)**
7. Radioattività naturale nelle abitazioni. Bologna. **(*)**
8. Educazione alimentare e tutela del consumatore "Seminario regionale Bologna 1-2 marzo 1990". Bologna. **(*)**

1992

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