HTA REPORT

FDG-PET/CT for cancer staging

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PET-CT for cancer staging

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Foreword

This year Agenas has produced a HTA report on the use of PET-CT for cancer staging on behalf of the Italian Ministry of Health. Such report comes from a collaboration with some of Italian regions participating in the RITHA network (Rete Italiana di Health Technology Assessment) and from a long and laborious process of consultation with experts, reviewers (internal and external) and other stakeholders.

The HTA report is developed to answer the question: "Based on available evidence, is it possible to provide guidance on the appropriate and efficient use of PET-CT for cancer staging within the Italian NHS"?

The latest evidence on accuracy and clinical effectiveness has been synthesised by a systematic review of literature while, to describe the patterns of use and expected expenditure of PET-CT we performed a contextual analysis in the regions which took part in the assessment.

The findings suggest that the evidence on FDG-PET/CT is mainly limited to diagnostic accuracy studies. Few of these studies report a change in management and even fewer report patient outcomes. Future good quality research aimed at demonstrating the impact of FDG-PET/CT on clinical outcomes is necessary to develop clinical recommendations.

Fulvio Moirano

Executive Director of Agenas

Prefazione

Quest'anno Agenas ha prodotto, su mandato del Ministero della Salute, un report di HTA sull'utilizzo della FDG-PET/CT per la stadiazione dei tumori. Il report è stato prodotto con la collaborazione tra Agenas e alcune Regioni Italiane partecipanti alla RIHTA (Rete Italiana di Health Technology Assessment) ed è come sempre frutto di un lungo e laborioso processo di consultazione con esperti, revisori (interni ed esterni), produttori e altri stakeholder.

Il report è stato sviluppato a partire dal seguente quesito: "Sulla base delle prove disponibili è possibile fornire indicazioni sull'utilizzo appropriato ed efficiente della PET-CT per la stadiazione dei tumori all'interno del SSN?

Le prove di efficacia clinica ed accuratezza diagnostica sono state sintetizzate mediante revisione sistematica della letteratura mentre, per la descrizione dell'utilizzo e il calcolo della spesa attesa per PET-CT abbiamo condotto un'analisi di contesto nelle regioni che hanno preso parte al processo di valutazione.

I risultati suggeriscono che le prove di efficacia ed accuratezza sulla FDG-PET/CT sono limitate principalmente agli studi di accuratezza diagnostica. Pochi studi riportano un cambiamento nel management e gli esiti sui pazienti.

Per lo sviluppo di raccomandazioni cliniche sarà necessario, in futuro, avere a disposizione ricerche di buona qualità circa l'impatto della FDG-PET/CT sugli esiti clinici.

Fulvio Moirano

Executive Director of Agenas

Executive summary

One-liner

We assessed the diagnostic accuracy and the clinical effectiveness of PET-CT for cancer staging.

Background

After cardiovascular diseases, tumors are the main cause of death in industrialized countries, causing 27% of deaths. Although the Italian data from the Cancer Observatory show an overall reduction in the mortality rates as well as in the incidence rates over the last 10 years, the prevalence is still rising. This means that the impact of tumors on health care services is growing in terms of both diagnostics services and therapeutic needs. In particular, among the diagnostic services, hybrid Positron Emission Tomography- Computed Tomography (PET-CT) technology was recently introduced as a diagnostics technology available to clinicians. PET-CT is a non invasive nuclear medicine technique which produces images representative of different biochemical, functional and morphological processes in the human body, describing also the alterations induced by different pathologies.

The clinical use of PET-CT is strictly influenced by the type of cancer investigated as well as the indication for the use itself (first staging, re-staging, follow-up, etc) and the diagnostic protocol in which it is included. Modelling is often necessary to take into account all the above variables. Changes in resources (inputs) necessary to deliver the service in terms of cancer staging in comparison with resources employed using alternative technologies, a consequent change in the estimate of the costs related to the clinical outcome have to be taken into account. The complexity of PET-CT for cancer staging requires an assessment that takes into account the clinical and economic impact of this technology. Furthermore, accurate tumour staging represents a crucial decision-point within the clinical pathway of cancer patients to make decision on further therapy.

Objective

To assess the diagnostic accuracy, the clinical effectiveness of PET-CT for cancer staging and the economic and organisational aspects of its use for cancer staging. We also describe the pattern of use of PET/CT scan and to estimate the expected number of FDG-PET/CT scans for cancer staging.

Methods

We updated the results from the most recent good quality HTA reports on FDG-PET for any kind of cancer. A selection of the most recent good quality HTA reports on the use of FDG-PET or FDG-PET/CT in oncology was performed through an extensive search of HTA agency websites and appraisal of their quality. The results were appraised and conclusions on appropriateness of the use of FDG-PET or FDG-PET/CT were synthesised for single cancers. A systematic review of literature published after the date of HTA report searches was performed. Results from the systematic review were integrated with HTA reports' conclusions to formulate conclusions of appropriateness of FDG-PET/CT for any cancer. To describe the pattern of use of PET/CT scan and to estimate the expected number of FDG-PET/CT scans for cancer staging a methodology was developed by the ASSR-Regione Emilia-Romagna and applied to the context of all participant regions.

Results

We assessed diagnostic accuracy and the clinical effectiveness of FDG-PET/CT for the staging of the following cancers: brain tumours, head and neck cancer, non-small cell lung cancer, small cell lung cancer, malignant pleural mesothelioma, breast cancer, esophageal cancer, stomach cancer, pancreatic cancer, colorectal cancer, renal cancer, bladder cancer, uterine cancer, cervical cancer, testicular cancer, prostate cancer, penile cancer, melanoma, Hodgkin's lymphoma, aggressive non-Hodgkin's lymphoma.

The evidence of the effects of FDG-PET/CT is mainly limited to diagnostic accuracy studies. Few of these studies report a change in management and even fewer report patient outcomes. Overall the quality of studies reporting diagnostic accuracy is not good, with the majority studies being at high risk of biases (such as verification bias and spectrum bias). The vast amount of research and published literature allowed the identification of diseases for which diagnostic accuracy of FDG-PET/CT can be considered sufficiently reliable. These are the staging for Head & Neck cancer, Non Small Lung cancer, Hodgkin's and aggressive Non-Hodgkin's lymphoma; M staging of melanoma, esophageal and colorectal cancer. Further evidence is needed to establish diagnostic accuracy of FDG-PET/CT in staging of Small Cell Lung cancer, N Staging of esophageal cancer, M staging of breast cancer.

Context analysis, based on the use of FDG-PET/CT only in the clinical indications for which there is evidence in support of its diagnostic accuracy. for patients undergoing initial staging for cancer produced the following results: for Emilia-Romagna region the number of PET-CT scans was 5,562 (expected expenditure €7,152,732). For Sicilia region the number of PET-CT scan was 3,738 (expected expenditure e€4,807,068). For Puglia region the number of PET-CT scan was 2,250 (expected expenditure €2,784,375).

Conclusions

The conclusions on FDG-PET/CT diagnostic accuracy provided by this systematic review should represent the starting point for working panels to discuss its appropriate clinical use, by positioning the test in the clinical pathway and linking its results to specific therapeutic options.

Future good quality research aimed at demonstrating the impact of FDG-PET/CT on clinical outcomes is necessary to develop clinical recommendations.

Synthesis

Clinical problem and target population

After cardiovascular diseases, tumors are the main cause of death in industrialized countries, causing 27% of deaths. Although the Italian data from the Cancer Observatory show an overall reduction in the mortality rates as well as in the incidence rates over the last 10 years, the prevalence is still rising. This means that the impact of tumors on health care services is growing in terms of both diagnostics services and therapeutic needs. In particular, among the diagnostic services, hybrid Positron Emission Tomography- Computed Tomography (PET-CT) technology was recently introduced as a diagnostics technology available to clinicians.The clinical use of PET-CT is strictly influenced by the type of cancer investigated as well as the indication for the use itself (first staging, re-staging, follow-up, etc) and the diagnostic protocol in which it is included. Thus, for an exhaustive assessment, modelling is often necessary to take into account all the above variables. Furthermore changes in resources (inputs) necessary to deliver the service in terms of cancer staging in comparison with resources employed using alternative technologies, a consequent change in the estimate of the costs related to the clinical outcome have to be taken into account. The complexity of PET-CT for cancer staging requires an assessment that takes into account the clinical and economic impact of this technology.

Description of the technology

Positron Emission Tomography (PET), became operational in 1998, is a non-invasive molecular imaging technique that uses radiopharmaceuticals, which are compounds labelled with short-lived beta-emitter radioisotopes. The most used radiopharmaceutical is the glucose analogue fluorine 18 fluorodeoxyglucose (FDG). Such radiopharmaceuticals are used as tracers because of their characteristic of being attracted by specific biochemical processes in a different way according to the metabolic differences between tissues, thus depicting the functional status of a suspicious lesion. Due to its characteristic, PET imaging is considered to be a form of functional imaging. Since biochemical changes caused by disease usually precede changes in size or structure of a particular organ or tissue, PET is capable of identifying abnormal tissues earlier than anatomical imaging techniques.

PET is a relatively recent addition to the medical technology for imaging of cancer, and FDG PET complements the more conventional anatomic imaging modalities of computed tomography (CT) and magnetic resonance imaging (MRI). In the integrated PET/CT, CT provides accurate localization and/or

characterization of organs and lesions, while PET maps both normal and abnormal tissue function. When combined, the two modalities can help to both identify and localize functional abnormalities.

Objectives

Objectives of this HTA report were : i) to assess the diagnostic accuracy of PET-CT for cancer staging; ii) to evaluate the clinical effectiveness of PET-CT in cancer staging; iii) to analyse the marketing status and the clinical use of PET-CT in Italy; iv) to carry out an economic and organizational evaluation on the use of PET-CT for cancer staging.

Methods

To assess the diagnostic accuracy and evaluate clinical effectiveness of PET-CT we updated the results from the most recent good quality HTA reports on FDG-PET for any kind of cancer. A selection of the most recent good quality HTA reports on the use of FDG-PET or FDG-PET/CT in oncology was performed through an extensive search of HTA agency websites and appraisal of their quality. The most recent good quality HTA reports were included. Their results were appraised and conclusions on appropriateness of the use of FDG-PET or FDG-PET/CT were synthetised for single cancers. A systematic review of literature published after the HTA report update was performed. We carried out a further literature search starting from the latest search date, to March 2012.

The following electronic databases were searched:

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

Results from the systematic review were integrated with HTA reports' conclusions to formulate conclusions of appropriateness of FDG-PET/CT for any cancer.

To describe the pattern of use of PET/CT scan and to estimate the expected number of FDG-PET/CT scans for cancer staging a methodology was developed by the ASSR-Regione Emilia-Romagna and applied to the context of all participant regions.

Results

Systematic review

The results of the systematic review are reported for each cancer from paragraph 4.5 to paragraph 4.24. Conclusions for each cancer are summarised in the Summary of Findings table reported in paragraph 4.3.

Context Analysis

Context analysis produced the following results: assuming the use of FDG-PET/CT only in the clinical indications for which there is evidence in support of its diagnostic accuracy the expected volumes of FDG-PET/CT scans for patients undergoing initial staging for cancer is estimated to be for:

- Emilia-Romagna region: 5,562 scans corresponding to an expected expenditure of € 7,152,732.
- Sicilia region: 3,738 scans corresponding to an expected expenditure of € 4,807,068.
- Puglia region: 2,250 scans corresponding to an expected expenditure of € 2,784,375.
- Lazio region: only the expected volumes of FDG-PET/CT scans for patients for the staging of Lung cancer was quantify – NSCLC and Colorectal cancer in favour of FDG-PET/CT is estimated to be 3,147, corresponding to an expected expenditure of € 3,372,271.

Discussion

The present report is limited to the use of PET/CT in cancer staging, as accurate tumour staging represents a crucial decision-point within the clinical pathway of cancer patients informing the choices for further therapy.

Diagnostic tests have a potential clinical benefit if they are sufficiently reliable to induce appropriate treatment decisions and if they influence patients' management, outcomes and well-being. For this reason our systematic review was aimed at retrieving and appraising studies on diagnostic accuracy and on impact on clinical outcomes of FDG-PET/CT.

However, the evidence on FDG-PET/CT is mainly limited to diagnostic accuracy studies. Few of these studies report a change in management and even fewer report patient outcomes. Overall the quality of studies reporting diagnostic accuracy is not good, with majority studies being flawed with serious biases (such as verification bias and spectrum bias). Nevertheless the vast amount of research and published literature allowed the identification of diseases for which diagnostic accuracy of FDG-PET/CT can be considered sufficiently reliable. These are the staging for Head & Neck cancer, Non Small Cell Lung cancer, Hodgkin's and aggressive Non-Hodgkin's lymphoma; M staging of melanoma, esophageal and colorectal cancer. Further evidence is needed to establish diagnostic accuracy of FDG-PET/CT in staging of Small Cell Lung cancer, N Staging of esophageal cancer, M staging of breast cancer.

As FDG-PET/CT represents an important step to identify or exclude metastasis, it is clear that the test results could trigger a potential change in the initial diagnosis resulting in the patient being up-staged by

PET/CT scan results. Its appropriate use is therefore very much dependent on the availability of therapeutic options and the decision to act according to the test's results.

The conclusions on FDG-PET/CT's diagnostic accuracy provided by this systematic review should represent the starting point for working panels to discuss its appropriate clinical use, by positioning the test in the clinical pathway and linking its results to specific therapeutic options.

Future good quality research aimed at demonstrating the impact of FDG-PET/CT on clinical outcomes is necessary to develop clinical recommendations.

Regarding context analysis the effect on expenses should not be interpreted as budget impact due to the different role of FDG-PET/CT in the diagnostic pathways of the various tumours, sometimes representing a new test some others provided in substitution of conventional imaging or of further more invasive diagnostic procedures. This means that for a structured budget impact analysis a detailed diagnostic pathway for each tumour is needed.

Finally, these estimates should not be considered to represent the overall expected volumes of FDG-PET/CT scans, as there are other clinical indications reported in the literature, such as re-staging or evaluation of response to therapy, which have not been considered in the present report and in this analysis.

Recommendations

We recommend that:

- evidence for the effects of PET/CT be sought following ethical protocols for cancers which have so far not been assessed: breast, cervix, kidney, mesothelioma, pancreas, gastric adenocarcinoma, bladder, uterine, testicular and penile cancers.

- recommendations for the clinical use of FDG PET/CT be linked to its clinical use and predetermined outcomes which the operators want to achieve.

Sintesi

Problema clinico e popolazione target

Le patologie oncologiche rappresentano, dopo le malattie cardiovascolari, la principale causa di morte nei paesi industrializzati, essendo responsabili del 27% dei decessi. Nonostante i dati italiani dell'Osservatorio Tumori mostrino complessivamente una diminuzione della mortalità e dell'incidenza negli ultimi 10 anni, la prevalenza è in aumento.

Questo significa che l'impatto dei tumori sui servizi sanitari è in crescita in termini sia di prestazioni diagnostiche che terapeutiche.

In particolare, tra le tecnologie diagnostiche a disposizione dei clinici, negli ultimi anni è stata introdotta la tecnologia ibrida PET-CT. L'utilizzo clinico della PET-CT è strettamente influenzata dal tipo di tumore investigato nonché dalle indicazioni (prima stadiazione, ristadiazione, follow-up, etc.) e dal tipo di protocollo diagnostico nel quale viene inclusa.

L'utilizzo di un modello è spesso necessario per prendere in considerazione tutte le caratteristiche descritte.

Inoltre devono essere presi in considerazione le variazioni nell'ammontare delle risorse (input) necessarie per la stadiazione del tumore comparate con le risorse impiegate utilizzando tecnologie alternative e il conseguente cambiamento nella stima dei costi correlate al risultato clinico.

La complessità dell'utilizzo della PET-CT per la stadiazione dei tumori richiede una valutazione che comprenda sia gli aspetti clinici che gli aspetti economici.

Descrizione della tecnologia

La Tomografia ad emissione di positroni (PET), diventata operative a fine anni 90', è una tecnica non invasiva di imaging molecolare che prevede l'utilizzo di radiofarmaci (composti marcati con radioisotopi a breve emivita e beta-emettenti) .

Il radiofarmaco più utilizzato è il fluoro 18 fluorodesossiglucosio (FDG) un analogo del glucosio. I radiofarmaci sono usati come traccianti per la loro caratteristica di essere attratti, in diversi modi, da specifici processi biochimici a seconda delle differenze metaboliche tra tessuti, così da raffigurare lo stato funzionale di una lesione sospetta. Grazie alla sua caratteristica, l'imaging PET è considerata una forma di imaging funzionale. Dal momento che i cambiamenti biochimici causati dalla malattia di solito precedono cambiamenti nella dimensione o nella struttura di un particolare organo o tessuto, la PET è in grado di identificare le lesioni prima di altre tecniche di imaging anatomico.

La PET si è aggiunta relativamente di recente nel panorama delle tecniche di imaging per la diagnosi dei tumori. L'FDG PET, inoltre, integra le modalità più convenzionali di imaging anatomico quali la tomografia computerizzata (TC) e la risonanza magnetica (MRI). Nei sistemi integrati PET/TC, che oggi hanno completamente sostiuito il solo tomografo PET, la TC fornisce la localizzazione accurata e/o la caratterizzazione degli organi e delle lesioni, mentre la PET fornisce sia la funzione normale che anormale del tessuto. L'utilizzo combinato delle PET/TC può aiutare sia l'identificazione che la localizzazione delle anomalie funzionali.

Obiettivi

Obiettivi del presente report sono stati: i) valutare l'accuratezza diagnostica della PET-CT per la stadiazione dei tumori; ii) valutare l'efficacia clinica della PET-CT per la stadiazione dei tumori; iii) analizzare il mercato e l'utilizzo clinico della PET-CT in Italia; iv) condurre un'analisi economico organizzativa sull'utilizzo della PET-CT per la stadiazione dei tumori.

Metodi

Per valutare l'accuratezza diagnostica e l'efficacia clinica della PET-CT abbiamo aggiornato i risultati di recenti report di buona qualità sulla FDG PET per tutti i tipi di tumore. L'individuazione dei più recenti report di HTA sull'utilizzo della FDG-PET o FDG-PET/CT in oncologia è stata effettuata mediante un'ampia ricerca sui siti delle agenzie di HTA e ne abbiamo valutato la loro qualità includendo solo i più recenti di qualità buona.

I risultati di tali report sono stati valutati e le conclusioni sull'appropriatezza nell'utilizzo della PET-CT o della FDG-PET/CT sono stati sintetizzati per singolo tumore.

Abbiamo condotto una revisione sistematica della letteratura pubblicata a partire dall'aggiornamento dei report di HTA. Abbiamo condotto una ulteriore ricerca della letteratura a partire dall'ultima data riportata nei report fino a marzo 2012.

I data base utilizzati sono stati i seguenti:

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

I risultati della revisione sistematica sono stati integrati con le conclusioni dei report di HTA e sono state formulate le conclusioni finali di appropriatezza della FDG-PET/CT per tutti i tipi di tumore.

Per la descrizione dei pattern di utilizzo della PET/CT e per la stima del volume atteso di scansioni di FDG-PET/CT per la stadiazione dei tumori è stata sviluppata una metodologia dalla Regione Emilia Romagna (partecipante al processo di valutazione) e applicata successivamente a tutte le regioni partecipanti (Sicilia, P.A. Trento, Puglia, ASP Lazio, Umbria).

Risultati

Revisione sistematica

I risultati della revisione sistematica sono stati riportati per singolo tumore da paragrafo 4.5 a paragrafo 4.24. Le conclusioni per ciascun tipo di tumore sono riportate nella "Summary of Findings table" nel paragrafo 4.3.

Analisi di contesto

Assumendo l'utilizzo della FDG-PET/CT solo per le indicazioni cliniche supportate da prove di accuratezza diagnostica i volumi attesi di scansioni con FDG-PET/CT per pazienti sottoposti a prima stadiazione sono stimati come segue:

Emilia-Romagna: il numero di scansioni PET-CT è risultato pari a 5.562 (spesa attesa pari a €7.152.732).

Regione siciliana: il numero di scansioni PET-CT è risultato pari a 3.738 (spesa attesa pari a €4.807.068).

Puglia: il numero di PET-CT è risultato pari a 2.250 (pari a una spesa attesa di €2.784.375).

Discussione

Il report di HTA prodotto è limitato all'utilizzo della PET/CT per la stadiazione dei tumori, poiché un'accurata stadiazione rappresenta un nodo cruciale per stabilire il percorso dei pazienti oncologici e la scelta della terapia da seguire.

I test diagnostici rappresentano utili strumenti clinici qualora siano in grado di indurre decisioni appropriate circa il trattamento e se riescono ad influenzare la gestione, gli esiti e il benessere dei pazienti oncologici. Per tale motive la nostra revisione sugli esiti clinici sulla FDG-PET/CT.

Tuttavia, le prove sugli effetti della FDG-PET/CT trovate, sono limitate principalmente agli studi di accuratezza diagnostica. Pochi di questi studi evidenziano un cambiamento nel managment e ancora meno studi riportano outcome sui pazienti.

La qualità complessiva degli studi di accuratezza diagnostica non è buona, e la maggior parte degli studi presentano un elevato rischio di bias (verification bias e spectrum bias).

La grande quantità di letteratura pubblicata ha permesso l'identificazione di patologie per le quali l'accuratezza diagnostica della FDG-PET/CT può essere considerata sufficientemente affidabile.

Questo risultato vale per la stadiazione del tumore testa e collo, per il carcinoma polmonare non a piccole cellule, linfoma di Hodgkin e linfoma di Hodgkin aggressivo; stadiazione M del melanoma, cancro

dell'esofago e del colon retto. Ulteriori prove scientifiche sono necessarie per stabilire l'accuratezza diagnostica della stadiazione per i seguenti tumori: tumore polmonare a piccole cellule; stadiazione N del cancro esofageo, Stadiazione M del carcinoma mammario.

Poiché l'utilizzo della FDG-PET/CT rappresenta uno step importante nell'identificazione od esclusione delle metastasi, risulta chiaro che il test possa comportare dei potenziali cambiamenti nella diagnosi iniziale nei pazienti che siano stati stadiati correttamente dalla PET/CT.

L'uso appropriato di tale tecnologia è pertanto strettamente legato alla disponibilità di trattamenti terapeutici e alle decisioni prese in accordo ai risultati del test.

Le conclusioni sull'accuratezza diagnostica della FDG-PET/CT fornite dalla revisione sistematica della letteratura dovrebbero rappresentare il punto di partenza per un panel di discussione sul suo utilizzo clinico appropriato, collocando l'effettuazione dell'esame in un percorso clinico e correlando i risultati a specifiche opzioni terapeutiche.

Per lo sviluppo di raccomandazioni cliniche sarà necessario, in futuro, avere a disposizione ricerche di buona qualità circa l'impatto della FDG-PET/CT sugli esiti clinici.

Con riferimento all'analisi di contesto l'effetto sulla spesa non deve essere interpretata come budget impact a causa del diverso ruolo della FDG-PET/TC nei percorsi diagnostici dei vari tumori, talvolta rappresentando un nuovo test altre volte fornito in sostituzione di immagini convenzionali o di ulteriori procedure diagnostiche più invasive. Ciò significa che per un'analisi strutturata di impatto sul bilancio è necessaria un percorso diagnostico dettagliato per ciascun tumore è indagato.

Infine, le stime trovate non dovrebbero essere considerate come rappresentative dei volume attesi totali di scansioni con FDG-PET/CT, poichè esitono alter indicazioni cliniche riportate in letteratura, come la ristadiazione o la valutazione nelle risposte terapiche, non considerate nel presente report.

Raccomandazioni

Si raccomanda:

- la produzione di prove sugli effetti della FDG PET/CT seguiti da protocolli etici per quei tumori che non sono stati finora valutati: mammella, cervice uterina, rene, mesotelioma, pancreas, adenocarcinoma gastrico, vescica, utero, tumori del testicolo e del pene;

- raccomandazioni circa l'utilizzo clinico di FDG-PET/CT correlati al suo utilizzo clinico e agli esiti che gli operatori vogliono raggiungere.

1. Background

1.1 PET-CT for cancer staging: indication and clinical problems

After cardiovascular disease, tumors are the main cause of death in industrialized countries, causing 27% of deaths [www.epicentro.it]. In Italy, they represent a priority for the Ministry of Health and the National Health Service (SSN). Consequently the 2010/2012 National Cancer Plan lays down policy with respect to these pathologies. Such a priority is justified not only by the high number of new cases occurring annually (254,196 cases in 2008), but also by the number of existing cases (more than 1.8 million people affected). Although the Italian data from the Cancer Observatory show an overall reduction in the mortality rates as well as in the incidence rates over the last 10 years, the prevalence is still rising [www.tumori.net]. This means that the impact of tumors on health care services is growing in terms of both diagnostics services and therapeutic needs. In particular, among the diagnostic services, hybrid Positron Emission Tomography- Computed Tomography (PET-CT) technology was recently introduced as a diagnostics technology available to clinicians. PET-CT is a non invasive nuclear medicine technique which produces images representative of different biochemical, functional and morphological processes in the human body, describing also the alterations induced by different pathologies [Townsend DW, 2008; Poeppel TD, 2008]. PET-CT differs from other diagnostic technologies such as Ultrasound (US), CT and Magnetic Resonance Imaging (MRI) that usually provide morphological information about the anatomical district analyzed. The use of this technology in the Oncology field is based on the fact that cancer tissues present a different metabolism compared to healthy tissue enabling metabolic characterization of lesions identified morphologically with the traditional methods (US and CT in particular). Functional type alterations, at the biological-molecular level, often precede morphological type alterations and may be detected relatively earlier with PET through the use of appropriate radioactive agents (called radiopharmaceuticals), with a different type of distribution and accumulation depending on the type of tissue involved [Hicks RJ, 2006]. The clinical use of PET-CT is strictly influenced by the type of cancer investigated as well as the indication for the use itself (first staging, re-staging, follow-up, etc) and the diagnostic protocol in which it is included. Thus, for an exhaustive assessment, modeling is often necessary to take into account all the above variables. Furthermore changes in resources (inputs) necessary to deliver the service in terms of cancer staging in comparison with resources employed using alternative technologies, a consequent change in the estimate of the costs related to the clinical outcome has to be taken into account. The complexity of PET-CT for cancer staging requires an assessment that takes into account the clinical and economic impact of this technology.

1.2 Epidemiological data and population

Epidemiological data on tumours in Italy come from the Cancer Registry which, to date, cover only the 32% of the whole population. All cancer data collected by each accredited registry are sent to the AIRTUM database of the Higher Institute of Health (ISS) and then elaborated by the Cancer Epidemiology Department of CNESPS at ISS (whose data is updated to 2005 [www.tumori. net]).

The AIRTUM database currently provides regional and national estimates relative to six cancer sites with projections through to 2010. The incidence, prevalence and mortality estimates for all tumours in Italy, updated to May 2008, are described in Table 1.

Table 1. Incidence, prevalence and mortality data for all tumours (ICD-9 140-208 excluded 173). Italy, age 0-84. Year 2008

	Males			**Females**		
Incidence	*Cases*	*Gross rate*	*Std rate*	*Cases*	*Gross rate*	*Std rate*
Italy	**132141**	**483**	**336**	**122052**	**431**	**274**
Prevalence	*Prevalent cases*	*Rough prop*	*Std. Prop*	*Prevalent cases*	*Rough prop*	*Std. Prop*
Italy	**806103**	**2944**	**2054**	**1034820**	**3655**	**2365**
Mortality	*Deaths*	*Gross rate*	*Std rate*	*Deaths*	*Gross rate*	*Std rate*
Italy	**73355**	**268**	**177**	**50925**	**180**	**101**

Source: CNESPS, ISS
Notes: **Gross rate**: calculated as the deaths per population ratio, per 100,000
Standardised rate (std): mortality rate corrected by age using the European population as standard.
Rough prop = rough proportion.

The 2009 Cancer Report provides data on the incidence and mortality trends for cancers in the period 1998-2005. Overall 818,017 incident cases and 342,444 deaths were reported in the period considered. The trend is expressed with the APC (Annual Percent Change), which indicates the mean variation in the incidence or mortality rate with respect to the previous year. In the period considered there was an overall reduction in mortality from all cancers in both sexes, in particular for colorectal cancer, stomach cancer, liver cancer and non Hodgkins lymphomas. In males, mortality decreased for smoking related cancers, prostrate cancer and for leukaemia. In the female population, mortality significantly fell down also for colon cancer, bone cancer and uterine cancer not better specified.

There is a decreasing incidence trend in the period 1998-2005 for stomach cancer and Kaposi's sarcoma in both genders. In particular, in males the incidence of smoking related cancers, leukaemia and myelomas decreased, while in females there were significant less new cases for cancers of the gall bladder, the uterine cervix and the ovaries.

By contrast there was a rise in the incidence of thyroid cancer and melanomas in both genders. In females there was an increase in new cases of lung cancer and Hodgkin's lymphoma, while in the male population the overall incidence of cancer pathologies increased, in particular for cancer of the colon, testicles and soft tissues.

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2. Description of PET-CT technology

2.1 The technology

Positron Emission Tomography (PET), is a non-invasive molecular imaging technique that uses radiopharmaceuticals, which are compounds labelled with short-lived beta-emitter radioisotopes. The most used radiopharmaceutical is the glucose analogue fluorine 18 fluorodeoxyglucose (FDG). Such radiopharmaceuticals are used as tracers because of their characteristic of being attracted by specific biochemical processes in a different way according to the metabolic differences between tissues, thus depicting the functional status of a suspicious lesion. Due to its characteristic, PET imaging is considered to be a form of functional imaging. Since biochemical changes caused by disease usually precede changes in size or structure of a particular organ or tissue, PET is capable of identifying abnormal tissues earlier than anatomical imaging techniques [Brush et al. 2011].

PET is a relatively recent addition to the medical technology for imaging of cancer, and FDG PET complements the more conventional anatomic imaging modalities of computed tomography (CT) and magnetic resonance imaging (MRI). In the integrated PET/CT, CT provides accurate localization and/or characterization of organs and lesions, while PET maps both normal and abnormal tissue function. When combined, the two modalities can help to both identify and localize functional abnormalities [Blodgett et al., 2007].

PET was developed in the early 1970s and the first prototype of a PET/CT scanner became operational in 1998 [Blodgett et al., 2007].

Prior to the introduction of PET/CT, the attenuation correction in PET was typically based on transmission measurements made with one or more rotating positron (typically 68 Ge) or single photon (typically 137 Cs) emitting sources prior to the PET emission scan [IAEA 2009]. Attenuation correction of data is necessary for accurate qualitative (i.e. visually normal, increased, or decreased) and quantitative (i.e. standardized uptake values or SUVs) measurements of radiopharmaceutical activity. In PET/CT x-rays from a CT scan are used to construct an attenuation map of density differences throughout the body that can then be used to correct for the absorption of the photons emitted from radiopharmaceutical decay.

The advantages of PET/CT are that the transmission data can be acquired very quickly in a spiral CT scan, thus improving patient comfort and throughput.

One of the most important limitations of PET is that most anatomic structures are not depicted, thus making it difficult to localize tumor lesions precisely. Furthermore, radiopharmaceuticals accumulate in various normal tissues, such as the brain, muscles, salivary glands, thyroid gland, myocardium, gastrointestinal tract, and the urinary tract. It is, therefore, at times difficult to interpret the images when pathological lesions are located near an organ with physiological radiopharmaceutical uptake.

Consequently, in order to interpret the PET images correctly, the clinician can correlate them with CT images.

Moreover, diagnostic quality CT can be acquired after contrast media intravenous injection [Wasif Saif, 2010].

Stand-alone PET scanners have effectively disappeared from the market. Today, almost all manufacturers only offer PET in combination with CT. They are exclusively constructed from the state-of-the-art PET scanners and multidetector spiral CT scanners [IAEA, 2008].

The design incorporated a spiral CT scanner with PET detectors mounted on the rear of the rotating CT assembly.

Accurately aligned clinical-quality CT and PET images could, therefore, be acquired in a single examination without moving the patient from the bed. Two- and three-dimensional image reconstruction may be rendered as a function of a common software and control system.

In the past few years, spiral CT technology has progressed from single to dual-slice, to 4, 8, 16 and, most recently 128 slices, CT rotation times have decrease to less than 0.4s resulting in very rapid scanning protocols. Advances in PET technology have been equally dramatic with the introduction of new faster detectors such as gadolinium oxyorthosilicate (GSO) and lutetium oxyorthosilicate (LSO) and and lutetium yttrium orthosilicate (LYSO).

In recent years, Time-of-Flight (TOF) PET scanners have been introduced. TOF is a technique that measures the different arrival time of coincident photons, allowing a estimate of the location of the annihilation event and, in turn, increasing the signal-to-noise ratio (SNR) [Murray, 2010]. Higher SNR leads to the possibility to reduce the amount of the radiopharmaceutical needed for the examination, lowering the total effective dose (E) absorbed by the patient.

Radiopharmaceutical

The ensemble of a tracer and its radioactive label is called radiopharmaceutical. Radiopharmaceuticals are characterized by a behaviour similar to the original non-labelled drug when inserted into the human body. The administration of radiopharmaceuticals can follow either a systemic or a local approach, depending on the specific distribution and fixation mechanism of the radiopharmaceutical. Radiopharmaceuticals follow complexbiokinetic pathways that determine their concentration across the different structures of the organism as well as the excretion

Radiopharmaceuticals are built keeping into account determined requirements, in order to optimize the contrast between target tissues and other tissues with the lowest dose possible.

The radioisotopes used in PET, which include rubidium-82 (82Rb), fluorine-18 (18F), oxygen-15 (15O), nitrogen- 13 (13N), and carbon-11 (11C), are made into radiopharmaceuticals (also called labeled tracers) by a generator or a cyclotron, a fixed-energy accelerator that adds a positive charge to stable isotopes by high-energy proton or deuteron bombardment. The most commonly used PET radiopharmaceutical, 18F in the form of fluorine-18-deoxyglucose (FDG)—also called fluorodeoxyglucose or fludeoxyglucose— which is

obtained substituting a hydroxyl with an atom of 18F (half-life 110 mins) and is produced using a cyclotron and a tracer processing system. FDG is a glucose analogue that has the same cellular uptake as glucose but is metabolically trapped within the cell after enzymatic phosphorylation to FDG-6-phosphate. Therefore, FDG is used to quantify glucose metabolic rates in cells that use glucose as metabolic substrate [Murray et al., 2010].

An advantage of PET radioisotopes, compared those used in conventional nuclear medicine, is their short half-lives (75 seconds to 110 minutes), which makes radiation protection easier; it also shortens the delay required before another imaging procedure. Although short half-lives may make PET radioisotopes more manageable in some respects, this also makes time management a more important issue. Also, due to the higher energy states of PET radioisotopes, increased radiation shielding is necessary [ECRI, 2012].

2.2 The procedure

Combined PET/CT scanners using standard FDG allow scans to be acquired within approximately 30–40 minutes. During a PET/CT exam, a CT image is acquired first, and then a PET scan is performed. CT scanners produce thin cross-sectional images of the human body for a wide variety of diagnostic procedures.

2.3 Safety of the PET-CT

The radioactive isotopes which are used to label the tracers entail a radiological risk for both patients and operators. Detriment due to radiological exposure has been extensively studied since the dropping of the two bombs in Hiroshima and Nagasaki. Nonetheless, there are no epidemiological data to confirm a relationship between radiation dose and probability of stochastic damage for low radiation doses, such as those due to FDG PET/CT examinations. It is therefore common to preventively assume a linear relationship without inferior threshold (Linear-non-threshold hypothesis, LNT) when managing the radioprotection (i.e. protection from ionizing radiations) of both patients and operators. Radioprotection is organized in 3 subsequent pillars in order to reduce to a minimum the risks related to radiation exposure, these three being the justification, the optimization and the limitation of the exposure of both patients and operators. Following such pillars, radioprotection agencies and commissions (NCRP, ICRP) identified sets of strict rules, regularly updated according to possible new evidence and acting on both structural and organizational aspects.

In Italy, radioprotection is codified and reinforced by law (DL 230, 17 March 1995 and subsequent additions and DL 187, 26 May 2000, DL 241, 26 May 2000, DL 257, 9 May 2001), following specific directives (89/618/Euratom, 90/641/Euratom, 92/3/Euratom, 96/29/Euratom and 97/43/Euratom) issued by the European Atomic Energy Community (EURATOM).

Respect of the law as well as appropriate patient selection guarantees an adequate management of the radiological risk. However, there are some groups of patients for whom FDG is not advised: pregnant or

lactating women should avoid FDG unless the benefits outweigh the risks. Nursing mothers are advised that breastfeeding should be stopped for 12 hours, and close contact between mother and infant is discouraged within 12 hours of the injection.

2.4 The marketing status of PET-CT and current reimbursement arrangements for cancer staging in Italy

Using the "Repertorio generale dei Dispositivi Medici" (RDM), the national database concerning all registered medical devices available in Italian market, three pruducers of PET/CT systems are identified: Ge Medical Systems, Philips Medical Systems and Siemens Medical Solutions. Each manufacturer has a wide range of PET/CTs differing in quality of the crystals (e.g. energy resolution), number of slides (e.g. 2,4,16, 64, 128) related to the CT system and the availability of the TOF. In accordance with the Italian Directive all medical devices must bear a CE-mark to be sold and used.

Most of the examinations with PET-CT are performed on an outpatient basis. According to the Ministerial Decree (12th July 2006) "Provision of specialist ambulatory care deliverable within the NHS and related fees" is determined a cost of €1.263,00 for a total body PET (Ministerial code 92.18.6), €1.071,65 for brain PET (Ministerial code 92.11.7). In the Ministerial Decree is not differentiate the technology used PET alone or PET-CT. As Regions can change Ministerial fees total body Pet (Ministerial code 92.18.6) has a range of minimum of €1.058,57 to maximum of €1.708,90 with a mean of €1.154,30; brain PET (Ministerial code 92.11.7) has a range of a minimum €1.058,57 to a maximum of €1.538,40 has a mean of €1.155,99. Same Regions introduced new extra codes as (www.agenas.it):

Region	Regional Code	Description	Tariff (€)
PA Trento	92.18.7	Tomografia ad emissioni di positroni (PET) con correlazione TAC: globale corporea	1.281,00
PA Trento	92.19.7	Tomoscintigrafia segmentaria (PET)	1.100,00
PA Trento	92.19.8	Tomografia ad emissione di positroni (PET) con correlazione TAC: segmentaria	1.100,00
Veneto	92.12.9	Tomoscintigrafia totale (PET). PET totale corporea, qualitative o quantitative, PET segmentaria, quantitativa	1.139,55
Veneto	92.24.6	PET-CT da codificare in aggiunta alle prestazioni 92.12.9 Tomoscintigrafia totale (PET), 92.18.6 Tomoscintigrafia globale corporea (PET) se le indagini sono eseguite con apparecchiatura PET-CT	156,00
Friuli VG	92.19.7	Tomoscintigrafia corporea (PET) senza estremità	1.321,00
Friuli VG	92.19.8	Tomografia ad emission di positroni (PET) con correlazione TAC: corporea senza estremità	1.441,40
Emilia-Romagna	92.18.6	PET total body	1.286,00

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Glossary

The effective dose (E) is a measure of the stochastic (i.e., probabilistic) effect on a whole organism due to ionizing radiation delivered non-uniformly to part(s) of its body.

SUV, Standardized Uptake Value, is often used in PET imaging for a simple semi-quantitative analysis.

3. Objectives, policy and research questions

The objectives of this report were:

1. to assess the diagnostic accuracy of PET-CT for cancer staging
2. to evaluate the clinical effectiveness of PET-CT in cancer staging
3. to analyse the marketing status and the clinical use of PET-CT in Italy
4. to carry out an economic and organizational evaluation on the use of PET-CT for cancer staging

Policy question

Based on available evidence, is it possible to provide guidance on the appropriateness and efficiency use of PET-CT for cancer staging within the Italian NHS?

Research questions

1. What is the evidence of diagnostic accuracy of PET-CT versus alternative imaging technologies for cancer staging?
2. What is the evidence of clinical effectiveness of PET-CT for cancer staging?
3. What is the level of adoption and use of the technology by healthcare providers of the Italian NHS?
4. What is the economic and organizational impact of using the technology versus the standard diagnostic procedures?

4. Assessing the evidence from clinical studies: Systematic review

4.1 Objectives of the systematic review

The objective of this systematic review was to assess the diagnostic accuracy and the clinical effectiveness of FDG-PET/CT for the staging of the following cancers: brain tumours, head and neck cancer, non-small cell lung cancer, small cell lung cancer, malignant pleural mesothelioma, breast cancer, esophageal cancer, stomach cancer, pancreatic cancer, colorectal cancer, renal cancer, bladder cancer, uterine cancer, cervical cancer, testicular cancer, prostate cancer, penile cancer, melanoma, Hodgkin's lymphoma, aggressive non-Hodgkin's lymphoma.

4.2 Methods for the systematic review of diagnostic accuracy and clinical effectiveness

This is an update of results from the most recent good quality HTA reports on FDG-PET for any kind of cancer. A selection of the most recent good quality HTA reports on the use of FDG-PET or FDG-PET/CT in oncology was performed through an extensive search of HTA agency websites and appraisal of their quality. The most recent good quality HTA reports were included, namely KCE 2009, ASSR 2011a, ASSR 2011b, ASSR 2011c, ASSR 2012a, ASSR 2012b, ASSR 2012c. Their results were appraised and conclusions on appropriateness of the use of FDG-PET or FDG-PET/CT were synthetised for single cancers. A systematic review of literature published after the HTA report update was performed. Results from the systematic review were integrated with HTA reports' conclusions to formulate conclusions of appropriateness of FDG-PET/CT for any cancer.

Inclusion criteria

Type of studies

We included both systematic reviews and primary studies assessing the diagnostic accuracy and clinical effectiveness of the index test. We included only studies in full reports.

Diagnostic accuracy studies

1. Systematic reviews including prospective or retrospective primary studies, using either FDG-PET or FDG-PET/CT reporting patient-based estimates of diagnostic accuracy (sensitivity, specificity, likelihood ratios). Due to differences in FDG-PET/CT technology before and after 2005 we included only systematic reviews published after that year.

2. Primary studies, published after the possible systematic reviews, using FDG-PET/CT reporting patient based estimates of diagnostic accuracy (sensitivity , specificity, likelihood ratios) and with one of the following designs:

1. randomized controlled trials (RCTs)
2. non-randomized controlled clinical trials (CCTs)
3. prospective cross sectional diagnostic studies
4. prospective cohort and case series

Diagnostic case-control studies with healthy controls were excluded. Studies with less than 10 participants were excluded.

Clinical effectiveness

We included systematic reviews including RCTs or CCTs, using either FDG-PET or FDG-PET/CT where one of the study arms had FDG-PET or FDG-PET/CT applied to the diagnostic pathway while the other arm did not have FDG-PET/FDG-PET/CT. Due to differences in FDG-PET/CT technology before and after 2005 we included only systematic reviews published after that year.

We included RCTs and CCTs, published after the possible systematic reviews, where one of the study arms had FDG-PET/CT included into the diagnostic pathway while the other arm did not have FDG-PET/CT.

Participants

We included studies considering patients with one of the following cancers:

- Brain tumours
- Head and neck cancer
- Non-small cell lung cancer
- Small cell lung cancer
- Malignant pleural mesothelioma
- Breast cancer
- Esophageal cancer
- Stomach cancer
- Pancreatic cancer
- Colorectal cancer
- Renal cancer
- Bladder cancer
- Uterine cancer
- Cervical cancer
- Testicular cancer

- Prostate cancer
- Penile cancer
- Melanoma
- Hodgkin's lymphoma
- Aggressive non-Hodgkin's lymphoma

Participants must have a confirmed diagnosis of primary cancer at initial staging.
We excluded studies evaluating patients evaluated at the end of treatment (restaging) and patients with recurrence. However studies with mixed population (staging of primary cancer and staging of recurrence) were included only if less than 20% of participants had staging of recurrence.

Results are organized in chapters for each specific cancer type.

Index test (diagnostic accuracy studies) / intervention (clinical effectiveness studies)
We assessed

1. primary studies considering FDG-PET/CT

2. systematic reviews including studies assessing FDG-PET or FDG-PET/CT

Only studies using FDG as the radioactive tracer were included. Studies using both contrast enhanced and non-contrast enhanced CT were included.

Comparator
We considered any kind of diagnostic imaging test used in standard practice of any specific cancer as comparator test.

Reference standard (for diagnostic accuracy studies)
Diagnostic studies were included if the reference standard used to define the true disease status was histological diagnosis and/or long-term clinical follow-up.

Target conditions (for diagnostic accuracy studies)
Target conditions were pre-treatment assessment of metastatic lymph nodes (N staging) and distant metastases (M staging) in primary cancer, or overall staging, depending on the type of cancer (i.e. breast cancer versus lymphomas).

Outcomes and measure of outcomes

1. Diagnostic accuracy: sensitivity and specificity, positive and negative likelihood ratios calculated on a per-patient basis. Studies providing diagnostic accuracy estimates calculated only on a per-lesion basis were excluded.

2. Clinical effectiveness studies: quality of life, adverse events, time to recurrence, local, locoregional and distant recurrence, disease free survival, disease survival, overall survival evaluated by RCTs or CCTs, comparing FDG-PET/CT arm with non-FDG-PET/CT arm.

Literature search

We included the latest good quality HTA reports (KCE 2009, ASSR 2011a, ASSR 2011b, ASSR 2011c, ASSR 2012a, ASSR 2012b, ASSR 2012c).
To update the above HTA reports we carried out a further literature search starting from the latest search date, to March 2012.
The following electronic databases were searched:
- Cochrane Database of Systematic Reviews (CDSR - The Cochrane Library);
- Database of Abstracts of Reviews of Effects (DARE - Centre for Reviews and Dissemination);
- Health Technology Assessment Database (HTA Database - Centre for Reviews and Dissemination);
- Cochrane Central Register of Controlled Trials (CENTRAL - The Cochrane Library);
- National Library of Medicine's Medline database (PubMed);
- Elsevier's Embase;

The key words described the participants' disease and the index test (see appendices for details of single cancer strategy). Only documents in English, Italian, French and Spanish were included.
Reference lists of identified articles were checked for additional references.

Study selection
Selection of the studies followed these steps:

1. exclusion on the basis of title and abstract;

2. full text retrieving of the potentially interesting studies;

3. reading of the selected articles and application of the inclusion criteria.

We used Reference Manager programme (version 10) to manage the references.
Selection of studies was performed by one reviewer.

Data extraction
Studies on diagnostic accuracy
From systematic reviews on diagnostic accuracy the following data were extracted and displayed in the 'Characteristics of included studies' table:
- country
- summary information on study design (prospective and retrospective studies, consecutive recruitment)
- summary information on participants (overall number of participants, median sample size [with range], type of cancer, tumor stage at entry [frequency of studies with early cancer, locally advanced cancer, or both], when appropriate)
- summary information on index test
- summary information on comparators
- summary information on reference standard (including length of follow up when appropriate)
- summary of diagnostic accuracy estimates when appropriate (meta-analytic estimates of sensitivity and specificity, area under the ROC curves, heterogeneity, median and range of estimates)
- summary information of quality of evidence provided by the review (if possible according to QUADAS 2 categories)

From primary studies on diagnostic accuracy the following data were extracted and displayed in the 'Characteristics of included studies' table
- country
- information on study design (prospective and retrospective studies, consecutive recruitment)
- information on participants (number of participants, mean age, gender, type of cancer, tumor stage at entry [according to the categories of early cancer, locally advanced cancer], when appropriate)

- information on index test
- information on comparators
- information on reference standard (including length of follow up when appropriate)
- diagnostic accuracy estimates (estimates of sensitivity and specificity, likelihood ratios, area under the ROC curves)

Studies on effectiveness

The following data were extracted and displayed in the 'Characteristics of included studies' table:

- country
- information on study design
- information on participants (number of participants, mean age, gender, type of cancer, tumor stage at entry [according to the categories of early cancer, locally advanced cancer], when appropriate)
- information on intervention
- information on comparators
- estimates of outcomes

Data extraction from included studies was carried out using single study tables of evidence. Extraction was performed by one reviewer.

Methodological quality assessment

Quality of evidence of primary studies included into the systematic reviews and primary studies published after them were assessed according to the QUADAS 2 checklist (Whiting 2011) or criteria suggested by the Cochrane Handbook (Higgins 2011), synthesised according to GRADE method (Guyatt 2008) and reported in the Summary of Findings.

In particular randomized controlled trials and prospective diagnostic studies including consecutive 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):

1. Risk of bias (serious/very serious)

    a. diagnostic accuracy studies: the following methodological domains (Whiting 2011) were assessed: patient selection (consecutive series or not consecutive recruitment of the sample of patients); blinding of index test and reference standard; flow and timing (appropriate interval between the index test and reference standard; all patients with the same reference standard; all patients included in the analysis).

    b. clinical effectiveness studies: the following methodological domains were assessed (Higgins 2011): sequence generation and allocation sequence concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective outcome reporting.

2. Indirectness of results (serious/very serious)

a. diagnostic accuracy studies: the following methodological domains (Whiting 2011) were assessed: characteristics of patients and settings (in particular studies with mixed population - i.e. staging of primary cancer and staging of recurrence - underwent a downgrading of quality of evidence for indirectness), conduction and interpretation of index test and reference standard;

b. clinical effectiveness studies: the following methodological domains were assessed (Higgins 2011): characteristics of the target population, baseline prevalence of the health problem of interest.

3. Inconsistency of results (heterogeneity or variability in results due to unexplained inconsistency in sensitivity, specificity).

4. Imprecision of results (if results come from sparse data, i.e. from few studies - less than two - or an overall small number of patients - less than 200).

5. Reporting BIAS: a formal assessment of reporting bias was not undertaken as there are yet no accepted methods to do this (Brazzeli 2009)

Systematic reviews of diagnostic studies were also assessed for descriptive purposes only with the following four criteria (from the AMSTAR checklist [Shea 2007]): comprehensive bibliographic search (at least two databases searched); characteristics of included studies clearly reported in tables; methodological quality of primary studies assessed with reported criteria; meta-analysis performed with appropriate statistical methods (including heterogeneity evaluation).

Analysis and synthesis

The following quantitative data were extracted from the included studies: estimates of diagnostic accuracy (sensitivity and specificity) of FDG-PET/CT 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 range were calculated.

Findings for each questions were synthesized from studies into the Summary of Findings. The following domains were reported for each systematic review and for the entire body of primary studies published after systematic reviews:

1. References;
2. Number of studies and overall number of patients included
3. Study design
4. Risk of bias
5. Indirectness
6. Inconsistency

7. Imprecision
8. Diagnostic accuracy estimates for FDG-PET/CT and comparators (diagnostic accuracy studies) or clinical outcomes estimates for FDG-PET/CT arm and no FDG-PET/CT arm
9. Quality of evidence

Interpretation of results

Interpretation of the studies' results were carried out in terms of numerosity, quality and consistency of results and summarized according to each specific cancer type.

4.3 Results of the systematic review

The results of the systematic review are reported for each cancer from paragraph 4.5 to paragraph 4.24. Conclusions for each cancer are summerised in the following Summary of Findings table.

Summary of Findings

Tumour	target condition	Target population	Systematic Review Conclusions
Brain tumours	Any	all	There is no rationale for the use of FDG-PET/CT in staging of brain tumours. The KCE report (KCE 2009) concluded that FDG-PET scanning is insufficiently accurate to be recommended for staging of brain tumours. No studies were retrieved by our update. Therefore the use of FDG-PET/CT in staging of brain tumours would not be appropriate.
Head & neck cancer	N staging	all	Accurate N staging of patients with head and neck cancer is very important and there is a rationale in support of the use of FDG-PET/CT for patients with equivocal results following conventional imaging. The HTA document (ASSR 2012) judged the quality of appraised evidence as moderate and concluded that the use of FDG-PET for N staging of patients with primary head and neck cancer and with unclear results with conventional imaging (CT, MRI, ultrasound) is appropriate. The only study retrieved through our update and judged to be of low quality does not challenge the above conclusions.
Head & neck cancer	M staging	locally advanced disease	Accurate M staging of patients with head and neck cancer is important and there is a rationale in support of the use of FDG-PET/CT in locally advanced disease patients eligible to curative treatment. The HTA document (ASSR 2012) judged the quality of appraised evidence as moderate and concluded that the use of FDG-PET for M

			staging of patients with advanced head and neck cancer is appropriate. Evidence from the studies retrieved through our update and judged to be of moderate quality confirms the above conclusions.
Non-small cell lung cancer	Any staging	resectable cancer	Accurate staging - both mediastinal N staging and M staging - of patients with non-small cell lung cancer is very important and there is a rationale in support of the use of FDG-PET/CT for patients with potentially resectable cancer. The HTA document (ASSR 2012) judged the quality of appraised evidence as moderate and concluded that the use of FDG-PET/CT for staging of patients with non-small cell lung cancer is appropriate. Evidence from the studies retrieved through our update – both on diagnostic accuracy and on impact on clinical outcomes and judged to be of low to moderate quality - confirms the above conclusions.
Small cell lung cancer	Any	limited cancer	Accurate staging - both mediastinal N staging and M staging - of patients with small cell lung cancer is important and there is a rationale in support of the use of FDG-PET/CT for patients with limited disease. The HTA document (ASSR 2012b) judged the quality of appraised evidence as very low and concluded that the role of FDG-PET in staging of small cell lung cancer is uncertain. Evidence from the studies retrieved through our update – only on diagnostic accuracy of M staging and judged to be of low quality - confirms the above conclusions.
Pleural malignant mesotheli oma	Any	resectable cancer	Accurate overall staging (T, N and M staging) of patients with malignant pleural mesothelioma is important and there is a rationale in support of the use of FDG-PET/CT for patients considered for multimodality treatment. The HTA document (KCE 2009) concluded that there is uncertainty regarding the use of PET/CT for mesothelioma as available evidence is limited. Evidence from the studies retrieved through our update and judged to be of low/very low quality suggests that the use of FDG-PET/CT for patients would be inappropriate.
Breast cancer	N staging	all	The HTA document (ASSR-RER 2011a) judged the quality of appraised evidence as very low and concluded that the use of FDG-PET for N staging of patients with breast cancer is inappropriate. Evidence from the studies retrieved through our update and judged to be of very low to moderate quality confirms the above conclusions.

Breast cancer	M staging	locally advanced disease	Accurate M staging of patients with breast cancer is important and there is a rationale in support of the use of FDG-PET/CT in patients with locally advanced (T3-N1 disease) breast cancer eligible to curative treatment. The HTA document (ASSR-RER 2011a) judged the quality of appraised evidence as low and concluded that the use of FDG-PET for M staging of patients with locally advanced breast cancer is uncertain. The low quality evidence from the studies retrieved through our update does not challenge the above conclusions.
Esophageal cancer	N staging	resectable cancer	Accurate N staging of patients with primary esophageal cancer is very important and there is a rationale in support of the use of FDG-PET/CT for patients eligible to curative treatment. The HTA document (ASSR 2011b) judged the quality of appraised evidence as very low and concluded that the use of FDG-PET in staging patients with esophageal cancer for regional lymph nodes is uncertain. The only one study retrieved through our update and judged to be of low quality does not challenge the above conclusions.
Esophageal cancer	M staging	resectable cancer	Accurate M staging of patients with primary esophageal cancer is very important and there is a rationale in support of the use of FDG-PET/CT for patients eligible to curative treatment. The HTA document (ASSR 2011b) judged the quality of appraised evidence as moderate and concluded that the use of FDG-PET in staging patients with esophageal cancer for distant metastasis is appropriate. No additional evidence was retrieved through our update thus the above conclusions are not challenged.
Stomach cancer	N staging	all	The rationale in support of the use of FDG-PET/CT for N staging of patients with gastric adenocarcinoma is weak. The HTA document (KCE 2009) did not find any studies. Evidence from the studies retrieved through our update and judged to be of very low quality suggests that the use of FDG-PET/CT in staging patients with gastric adenocarcinoma for regional lymph nodes would be inappropriate.
Stomach cancer	M staging	locally advanced disease	The rationale in support of the use of FDG-PET/CT for M staging (liver and peritoneal metastases) of patients with gastric adenocarcinoma is weak. The HTA document (KCE 2009) did not find any studies. Evidence from the studies retrieved through our update and judged to be of low to very low quality suggests that the use of FDG-PET/CT in staging patients with gastric adenocarcinoma for distant metastasis

			would be inappropriate.
Pancreatic cancer	Any staging	all	Accurate staging of patients with pancreatic cancer is very important. There is reasonable rationale in support of the use of FDG-PET/CT for patients with equivocal results following conventional imaging. The HTA document (KCE 2009) did not find any studies. No evidence was retrieved through our update thus the use of FDG-PET/CT in staging patients with pancreatic cancer would be inappropriate.
Colorectal cancer	N staging	all	The HTA document (ASSR 2011c) judged the quality of appraised evidence as moderate and concluded that the use of FDG-PET for N staging of patients with primary colorectal cancer is inappropriate. Evidence from the studies retrieved through our update and judged to be of low quality confirms the above conclusions.
Colorectal cancer	M staging	locally advanced disease	Accurate M staging of patients with colorectal cancer is important and there is a rationale in support of the use of FDG-PET/CT in patients with locally advanced disease eligible to curative treatment. The HTA document (ASSR 2011c) judged the quality of appraised evidence as moderate and concluded that the use of FDG-PET for M staging of patients with locally advanced colorectal cancer is appropriate No additional evidence was retrieved through our update thus the above conclusions are not challenged.
Renal cancer	Any	all	KCE report (KCE 2009) concluded that the evidence on initial diagnosis and staging is limited to small studies of low quality reporting wide confidence intervals. No additional evidence was retrieved through our update thus the use of FDG-PET/CT in staging patients with renal cancer would be inappropriate.
Bladder cancer	Any	all	There is a rationale in support of the use of FDG-PET/CT for staging of patients with bladder cancer. HTA document (KCE 2009) concluded that the evidence on the use of PET/CT is too limited to base recommendations on. Evidence on the use of PET/CT retrieved through our update and judged to be of low/very low quality does not challenge the above conclusions.
Uterine cancer	Any	all	The HTA document (KCE 2009) concluded that the evidence on the use of PET and PET/CT is too limited to base recommendations on. Evidence from the studies retrieved through our update and judged to be of low quality suggests that the use of PET/CT would be inappropriate.
Cervical cancer	N staging	all	The rationale in support of the use of FDG-PET/CT for N staging of patients with cervical cancer is unclear.

			HTA report (KCE 2009) reported that the standard practice for N staging (sentinel-node biopsy) of patients with cervical cancer is superior than FDG-PET/CT. Evidence from the only one study retrieved through our update and judged to be of moderate quality confirms the above conclusions thus the use of FDG-PET/CT would be inappropriate.
Cervical cancer	M staging	all	It appears there is no rationale in support of the use of FDG-PET/CT for M staging of patients with cervical cancer and no studies were retrieved. Thus the use of FDG-PET/CT for staging of cervical cancer would be inappropriate.
Testicular cancer	Any	all	HTA report (KCE 2009) concluded that evidence is inconclusive to draw any conclusion on FDG-PET/CT for staging of patients with testicular cancer. Evidence from the only one study retrieved through our update and judged to be of very low quality does not challenge the above conclusions thus the use of FDG-PET/CT would be inappropriate.
Prostate cancer	Any	all	There is no rationale for the use of FDG-PET/CT in staging of prostate cancer. No evidence was found by the HTA document (KCE 2009). No studies are retrieved by our update. Therefore the use of FDG-PET/CT in staging of prostate cancer would be inappropriate.
Penile cancer	N staging	all	There is a rationale on the use of FDG-PET/CT for N staging (inguinal lymph node) of patients with penile cancer. There is no evidence from HTA report (KCE 2009). Evidence from studies retrieved through our update - judged to be of low quality- shows inconsistent diagnostic accuracy estimates, thus the use of FDG-PET/CT for N staging of patients with penile cancer would be inappropriate
Penile cancer	M staging	all	No evidence is available. The use of FDG-PET/CT would be inappropriate
Melanoma	N staging	all	HTA report (KCE 2009) concluded that the evidence consistently shows a low sensitivity for the detection of lymph node metastasis in clinically node negative melanomas Evidence from studies retrieved through our update and judged to be of low quality confirms the above conclusions, therefore the use of FDG-PET/CT would be inappropriate.
Melanoma	M staging	locally advanced disease	There is a rationale in support of the use of FDG-PET/CT for M staging of patients with higher stages of disease. HTA report (KCE 2009) concluded that there is a good diagnostic accuracy in advanced stages for the detection of distant metastasis in

			patients with primary melanoma. Evidence from studies retrieved through our update and judged to be of low quality confirms the above conclusions. Therefore FDG-PET/CT for M staging of patients with melanoma with higher stages of disease would be appropriate.
Hodgkin's lymphoma	any	all	Accurate staging of patients with Hodgkin's lymphoma is very important and there is a rationale in support of the use of FDG-PET/CT for patients at first diagnosis. HTA document (ASSR 2012c) judged the quality of appraised evidence as moderate and concluded that the use of FDG-PET for staging of patients with Hodgkin's lymphoma is appropriate. Evidence from studies retrieved through our update - judged to be of very low quality – does not challenge the above conclusions.
Aggressive non-Hodgkin's lymphoma	any	all	Accurate staging of patients with aggressive non-Hodgkin's lymphoma is very important and there is a rationale in support of the use of FDG-PET/CT for patients at first diagnosis. HTA document (ASSR 2012c) judged the quality of appraised evidence as moderate and concluded that the use of FDG-PET for staging of patients with aggressive non-Hodgkin's lymphoma is appropriate. Evidence from studies retrieved through our update - judged to be of low / very low quality – does not challenge the above conclusions

4.4 Discussion

Positron Emission Tomography is an important diagnostic technology which allows non-invasive imaging through the study of metabolic processes and their alterations caused by a number of diseases. In oncology, the potential indications for PET and PET/CT cover the entire disease process, ranging from diagnosis to staging to follow-up. Numerous technology assessment reports have evaluated the quality and relevance of published clinical trials to define PET/CT's effectiveness.

The present report is limited to the use of PET/CT in cancer staging, as accurate tumour staging represents a crucial decision-point within the clinical pathway of cancer patients determining further therapy. By *staging* we mean the evaluation of the extent of the disease in patients with a confirmed tumour before any treatment. Within the staging process, nodal staging (N-staging) and distant staging (M-staging) are separate processes.

Our choice of tracer (FDG) was based on the universal availability of the tracer, but excluded some important tumours, such as prostate cancer.

Diagnostic tests have a potential clinical benefit if they are sufficiently reliable to induce appropriate treatment decisions and if they influence patients' management, outcomes and well-being. For this reason our systematic review was aimed at retrieving and appraising studies on diagnostic accuracy and on impact on clinical outcomes of FDG-PET/CT.

However, the evidence on FDG-PET/CT is mainly limited to diagnostic accuracy studies. Few of these studies report a change in management and even fewer report on patients' outcomes. Overall the quality of studies reporting diagnostic accuracy is far from good, with majority studies being flawed with serious bias (verification bias, spectrum bias etc.). Nevertheless the vast amount of research and published literature allowed the identification of diseases for which diagnostic accuracy of FDG-PET/CT can be considered sufficiently reliable. These are the staging for Head & Neck cancer, Non Small Lung cancer, Hodgkin's and aggressive Non-Hodgkin's lymphoma; M staging of melanoma, esophageal and colorectal cancer. Further evidence is needed to establish diagnostic accuracy of FDG-PET/CT in staging of Small Cell Lung cancer, N Staging of esophageal cancer, M staging of breast cancer.

As FDG-PET/CT represents an important step to identify or exclude metastasis, it is clear that the test results could trigger a potential change in the initial diagnosis resulting in the patient being up-staged by PET/CT scan results. Its appropriate use is therefore very much dependent on the availability of therapeutic options and the decision to act according to the test's results.

The conclusions on FDG-PET/CT's diagnostic accuracy provided by this systematic review should represent the starting point for working panels to discuss its appropriate clinical use, by positioning the test in the clinical pathway and linking its results to specific therapeutic options.

Future good quality research aimed at demonstrating the impact of FDG-PET/CT on clinical outcomes is necessary to develop clinical recommendations.

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4.5 FDG-PET/CT for staging of brain tumours

Background

The mainstay of staging of brain tumors is magnetic resonance (MRI) (ESMO 2010) thanks to the range of sequences that can explore differences in the biophysical properties of the brain tissue and tumors. As the brain has a physiologically intense uptake of FDG, small malignant lesions are very difficult to detect with FDG-PET. In fact they may be masked by the hyper metabolic background and do not show significant increase of metabolic activity on FDG-PET imaging (Caroli 2010).

To confirm the hypothesis of an absence of rationale for staging of brain tumours with PDG-PET/CT we performed a new systematic search about this clinical question in case new evidence had emerged.

Results

The 2009 KCE report conclusions for brain tumours staging (KCE 2009) is based on the AHRQ 2008 report. It identified two studies using PET to stage patients with suspected primary glioma and one study to stage patients with primary astrocytomas. All studies used histology/biopsy as reference standard. In the 2 studies sensitivity was 63% and 75% and specificity was 100% and 0%. KCE report concluded that FDG-PET scanning is insufficiently accurate to be recommended for staging of brain cancer.

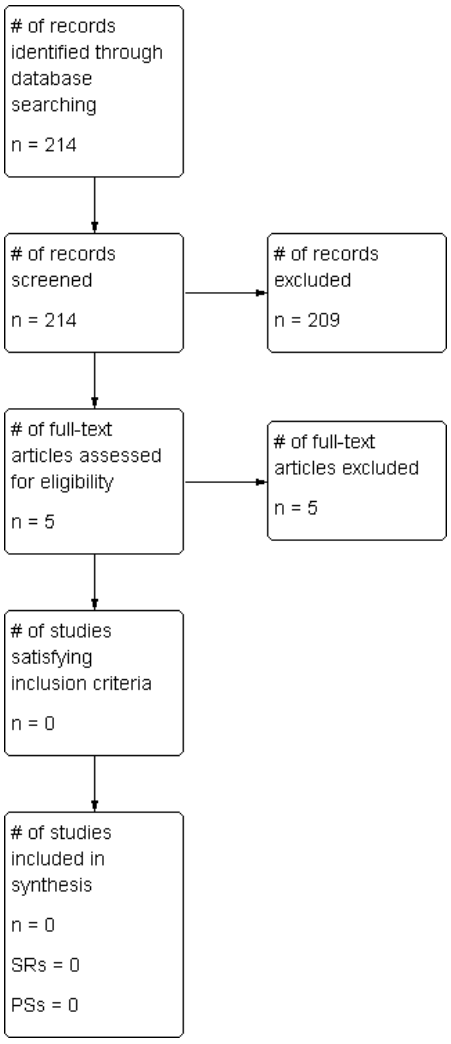
Results of the search

Identification and selection of studies

Our searches identified 214 titles possibly fitting inclusion criteria. After screening of titles and abstracts, 5 studies were retrieved and read by one of us (SP). All studies were excluded for various reasons (see Excluded studies in Appendix 1: De Wever 2010; Dunet 2010; Giovacchini 2009; Jora 2011; Li 2012).

The study selection process is summarized in the PRISMA flow diagram (Moher 2009; see Figure 1).

Figure 1: Brain tumors: study selection according to PRISMA flow diagram (Moher 2009).



Findings

No study retrieved.

Authors' conclusions

There is no rationale for the use of FDG-PET/CT in staging of brain tumours.

KCE report (KCE 2009) concluded that FDG-PET scanning is insufficiently accurate to be recommended for staging of brain tumours. No studies were retrieved by our update.

Therefore the use of FDG-PET/CT in staging of brain cancer would be inappropriate.

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KCE 2009

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4.6 FDG-PET/CT for staging of head and neck cancer

Background

The term head and neck cancer includes squamous cell tissue carcinomas from different sites of the upper respiratory and digestive tract (tongue, oral cavity, oropharynx, nasopharynx, hypopharynx, larynx). In Italy during the period 2003-2005, it represented 4.2% of all the cancers among males and 1.3% among females, corresponding to a crude incidence of 29.2 per 100,000 person/year in males and 6.9 per 100,000 person/year in females (Registri tumori). The most frequent site among males is larynx (16.8 cases/year per 100,000 men; Registri tumori). Five-year survival ranges from 29% (CI 95% 26-32%) for hypopharynx cancer to 69% (CI 95% 66-72%) for lip cancer, across all stages of disease (Registri tumori).

Target condition being diagnosed

Target conditions are: a) disease involvement of regional lymph nodes, both in term of number and topographical neck's level (SIGN 2006), identified through N staging, and b) presence of distant metastases, identified through M staging. The latter includes also the search of synchronous second malignant tumours (SIGN 2006), the so-called "second primary tumours".

Index test(s)

FDG-PET/CT

The majority of the most recent guidelines (AIOM 2009; HAS 2009; NCCN 2011; SEOM 2010) recommends use of FDG-PET/CT for M staging of patients with high risk of distant metastases (locally advanced cancer). Two guidelines (AIOM 2009; SIGN 2006) consider FDG-PET/CT as useful for N staging when results with conventional imaging are equivocal.

Alternative test(s)

Routine pre surgical N staging includes physical examination, CT and MRI, from skull base to sternoclavicular joints (AIOM 2009; SIGN 2006). CT is more accurate in detecting infrahyoid node metastasis and MRI is more accurate in detecting perivisceral nodal involvement

Routine M staging is carried out with CT of the thorax in high risk patients (SIGN 2006). For the investigation of synchronous second primary cancer esophagoscopy or bronchoscopy can be added (SIGN 2006). In the case of nasopharyngeal cancer, skeleton is the most frequent site of metastasis and scintigraphy is added to the diagnostic work up.

Reference standard for N staging is histopathology following resection or fine niddle aspiration; reference standard for M staging is histopathology of metastases, follow-up with imaging techniques (SR - Xu 2011a).

Rationale

Role of staging. Accurate pre surgical N staging is necessary to correctly classify patients into early or advanced disease. Higher numbers and inferior neck's levels of lymph nodes involved are adversely related to prognosis as is extracapsular nodal spread (microscopic or macroscopic) (SIGN 2006). Some clinically node negative patients have a high risk of occult nodal metastases. The probability of occult nodal metastases depends mainly on the extension (T category) and the site of the primary tumor (from less than 20% in glottic laryngeal tumors to more than 50% in oropharyngeal and hypopharyngeal tumors) (AIOM 2009; SIGN 2006). M staging and research of synchronous second primary cancer have a role in identifying and selecting patients candidate to curative treatment.

Treatment options. Curative treatment strategies mainly depend on the stage of disease. In early disease (stage I-II, i.e. node negative patients), either conservative surgery or radiotherapy (external radiotherapy or brachytherapy) give similar loco-regional control (AIOM 2009; EHNS–ESMO–ESTRO 2010). In node negative patients with a risk of micro metastases higher than 20% prophylactic treatment of the neck (either by appropriate selective or modified radical neck dissection or by external beam radiotherapy) is proposed (NCCN 2011; SEOM 2010; SIGN 2006) as data from retrospective studies suggest that in patients who do not have prophylactic therapy of the clinically node negative neck there is a higher risk of disease recurrence (SIGN 2006). Standard options for locally advanced stage III and IV tumors are surgery (primary tumor and neck dissection) plus postoperative radiotherapy or chemo-radiotherapy (with single-agent platinum) in case of high-risk features of local recurrence (nodal extracapsular extension and/or R1 resection) (AIOM 2009; EHNS–ESMO–ESTRO 2010). Patients with advanced larynx and hypopharynx cancer - requiring total laryngectomy - can undergo induction chemotherapy followed by radiotherapy in order to preserve the organ. The expected local recurrence and 5-year survival rate after curative treatment in each stage class depend on the site of cancer. The incidence of postoperative moderate to severe complications ranges between 13 and 24%; the risk of death is about 1-3% (Mendenhall 2002). Palliative treatment is the treatment of choice for patients with distant and not resectable metastases (NCCN 2011; SEOM 2010; SIGN 2006). Palliation - which might involve chemotherapy, radiotherapy or surgery - aims at debulking tumor mass and reducing symptoms (pain, bleeding, breathing problems) associated with tumor expansion.

Objectives

The objective of this review was to examine the diagnostic accuracy and the clinical effectiveness of FDG-PET/CT for N staging and M staging of patients diagnosed with head and neck cancer compared to conventional imaging examination.

Search methods for identification of studies

Evidence is based on a) the conclusion of the most recent HTA report on head and neck cancer (ASSR 2012) which was of good quality and had an electronic search updated to March 2011; b) a further search of studies published between January 2011 and March 2012. The key words described the participants' disease and the index test. See appendix 2 for details of strategy.

Results

The HTA document (ASSR 2012) concluded that

- the use of FDG-PET for N staging of patients with primary head and neck cancer and with unclear results with conventional imaging (CT, MRI, ultrasound) is appropriate. Level of evidence for diagnostic accuracy of FDG-PET has been judged moderate, with estimates for sensitivity and specificity slightly higher than those of conventional imaging.
- the use of FDG-PET for M staging of advanced head and neck cancer in patients with negative or equivocal results from conventional imaging is appropriate. Level of evidence for diagnostic accuracy of FDG-PET was judged moderate with estimates for sensitivity higher than conventional imaging.

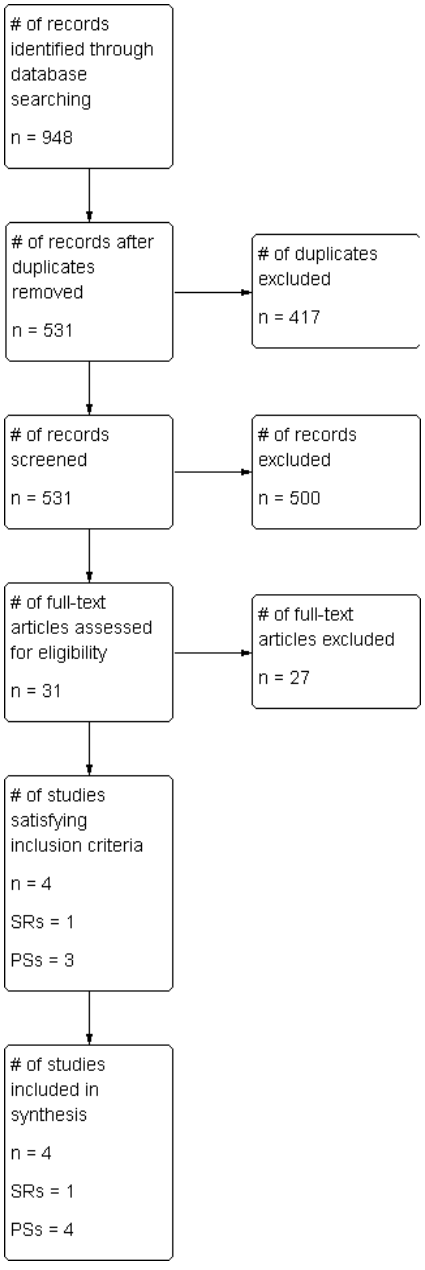
Results of the search

Identification and selection of studies.

The electronic search identified 948 records; 917 have been excluded because duplicates, or after checking the abstract, for not meeting the inclusion criteria. Full text has been acquired for the remaining potentially eligible 31 records, from which 27 studies have been excluded on the basis of inclusion criteria (see below excluded studies). Four studies have been finally included (PS - Chan 2011; PS - Fried 2012; PS - Liao 2011; SR - Xu 2011a).

The study selection process is summarized in the PRISMA flow diagram (Moher 2009; see Figure 1).

Figure 1: Head and neck cancer: study selection according to PRISMA flow diagram (Moher 2009).



Description of included studies.

Three studies evaluate diagnostic accuracy of FDG-PET/CT (PS - Chan 2011; PS - Liao 2011; SR - Xu 2011a); 1 further study (PS - Fried 2012) assesses the impact of FDG-PET/CT on clinical outcomes.

Diagnostic accuracy - N staging

Systematic reviews
None retrieved.

Primary studies

One study (473 participants) evaluating diagnostic accuracy of FDG-PET/CT for regional lymph node staging has been included (PS - Liao 2011). This study includes participants with oropharyngeal or hypopharyngeal squamous cell carcinoma (57% clinically negative neck patients). Reference standard is the postoperative pathologic N staging.

Diagnostic accuracy - M staging

Systematic reviews

One systematic review has been included (SR - Xu 2011a). This review assesses and compares the diagnostic accuracy of FDG-PET/CT for M staging (including second primary cancer). Eight studies include a total of 824 patients. Reference standard is histopathologic analysis or clinical and imaging follow-up for at least 6 months. No data are reported about cancer extension of patients at entry.

Primary studies

One study (103 participants) evaluating diagnostic accuracy of FDG-PET/CT for M staging published after the above reported systematic review has been included (PS - Chan 2011). Participants have oropharyngeal or hypopharyngeal carcinoma, mainly locally advanced (about 75% of included patients). Reference standard is pathological proof or evidence of progression at follow-up.

Impact on clinical outcomes - Any staging

Systematic reviews
None retrieved.

Primary studies

One retrospective matched cohort study (116 participants) evaluating impact on clinical outcomes of FDG-PET/CT for staging is included (PS - Fried 2012). From a retrospective chart review, 249 patients that

received definitive radiotherapy alone or chemoradiotherapy have been retrieved. One hundred patients (40%) have a pretreatment FDG-PET or FDG-PET/CT for staging. Patients who had undergone FDG-PET (PET cohort) have been matched to those who did not (No PET cohort). From this matching process 116 patients have been identified, 58 in each cohort. Patients are matched for T classification, N classification (according to CT), primary site (nasopharynx, oral cavity, oropharynx, larynx, or hypopharynx), and smoking status. The outcomes of interest are local control, regional control, freedom from distant metastasis, cause-specific survival, overall survival. The study includes mixed stage patients. Participants have been followed up for at least 24 months.

Methodological quality of included studies

Diagnostic accuracy - N staging

Systematic reviews
None retrieved.

Primary studies
Consecutive enrollment of participants is unclear and reference standard has an unclear risk of bias (PS - Liao 2011).

Quality assessment results for the included studies is provided in Figure 2.

Diagnostic accuracy - M staging

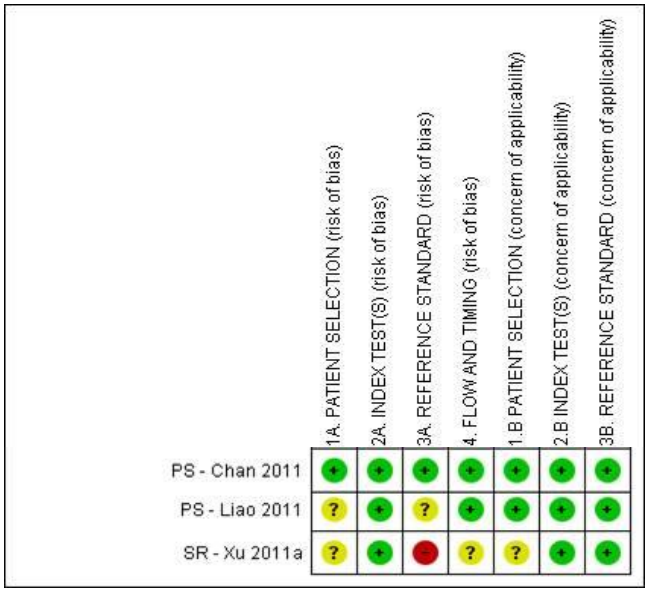
Systematic reviews
The systematic review by Xu et al. (SR - Xu 2011a) has a comprehnsive bibliographic search method, the methodological quality of included studies appropriately assessed and the statistic analysis performed. The characteristics of included studies are only partially reported.

The primary studies included into the systematic review (SR - Xu 2011a; Figure 2) could be prone to possible spectrum bias (50% with retrospective design) and 100% of studies have reference standard results interpreted with unclear or absence of blinding of index test.

Primary studies
The only included study (PS - Chan 2011) has a low risk of bias.

Quality assessment results for the included studies is provided in Figure 2.

Figure 2: Methodological quality summary: review authors' judgements about each methodological quality item for diagnostic accuracy studies.



Impact on clinical outcomes - Any staging

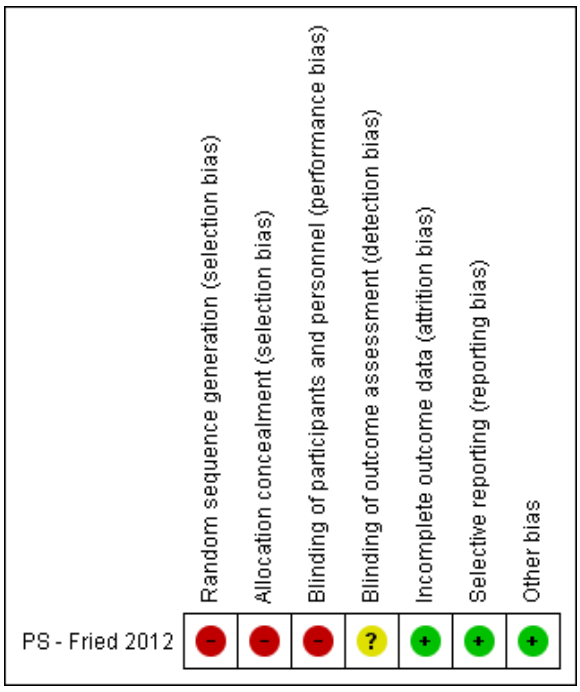
Systematic reviews
None retrieved.

Primary studies

The only included study (PS - Fried 2012) has a retrospective matched cohort design thus is limited by an incomplete control of confounders, an open design and the unclear blinding of assessment of outcomes.

Quality assessment results for the included studies is provided in Figure 3 .

Figure 3 Methodological quality summary: review authors' judgements about each methodological quality item for studies evaluating impact on clinical outcomes.



Findings

Diagnostic accuracy - N staging

Detailed results are reported below in the table Summary of Findings 1.

Systematic reviews
None retrieved.

Primary studies
The only study included reports for FDG-PET/CT a sensitivity of 77.7% and a specificity of 58.0% (PS - Liao 2011).

Diagnostic accuracy - M staging

Detailed results are reported below in the table Summary of Findings 2.

Systematic reviews
The systematic review by Xu et al. (SR - Xu 2011a) reports pooled estimates of diagnostic accuracy for FDG-PET/CT. Pooled sensitivity is 88.2% (CI 95% 79.8-93.9%), pooled specificity 95.1% (CI 95% 93.2-96.5%).

Primary studies
Only one study reports data for FDG-PET/CT (PS - Chan 2011); both estimates fall within the confidence interval of pooled estimates reported in the systematic review.

Impact on clinical outcomes - Any staging

Detailed results are reported below in the table Summary of Findings 3.

Systematic reviews
None.

Primary studies

The only study retrieved (PS - Fried 2012) does not find differences for any of the outcomes considered between the PET cohort and the no-PET cohort.

Comments on Findings

N staging

Only one study of *low quality* was retrieved. As no data on comparators are provided no conclusion can be drawn on FDG-PET/CT for N staging.

M staging

The data on diagnostic accuracy of FDG/PET-CT are of *moderate quality.* However, as only sparse data on comparators (whole body MRI) are available, it is not possible to make comparisons of diagnostic accuracy between different tests.

Any staging: impact on clinical outcomes

One comparative non-randomised study on impact of FDG-PET/CT on clinical outcomes for any staging is available. However data are sparse and it is not possible to draw any conclusion.

Summary of Findings 1: Diagnostic accuracy of FDG-PET/CT for N staging in patients with head and neck cancer

Patients/population: oropharyngeal or hypopharyngeal squamous cell carcinoma (57% clinically negative neck patients)
Target condition: N staging
Index test: FDG-PET/CT
Comparators: none
Reference standard: histopathology following resection, biopsy after fine niddle aspiration, follow-up with imaging techniques

Ref.	No. of studies	Study design	Risk of Bias	Indirectness	Inconsistency	Imprecision	Diagnostic Accuracy FDG-PET/CT	Diagnostic Accuracy Comparators	Quality of Evidence
Primary studies	1 (473 participants)	diagnostic accuracy studies with prospective recruitment	Serious[1]	No	No	Serious	Sensitivity 77.7% Specificity 58.0%		Low

1. possible spectrum bias and unclear bias for reference standard

Summary of Findings 2: Diagnostic accuracy of FDG-PET for M staging in patients with head and neck cancer

Patients/population: head and neck cancer (locally advanced disease)
Target condition: M staging
Index test: FDG-PET/CT
Comparators: WB-MRI
Reference standard: histopathology following resection, biopsy or fine niddle aspiration, follow-up with imaging techniques

Ref.	No. of studies	Study design	Risk of Bias	Indirectness	Inconsistency	Imprecision	Diagnostic Accuracy FDG-PET	Diagnostic Accuracy Comparators	Quality of Evidence
Xu 2011	FDG-PET/CT 8 (824 participants)	Systematic review	Serious[1]	No	No	No	Sensitivity (pooled): 88.2% (CI 95% 79.8-93.9%) Specificity: 95.1% (CI 95% 93.2-96.5%)	not applicable	Moderate
Primary studies	FDG-PET/CT and WB-MRI 1 (103 participants)	diagnostic accuracy studies with prospective recruitment (consecutive)	No	No	not applicable	Serious	sensitivity: 83.3% (CI 95% 58.6–96.4%) specificity: 95.3% (CI 95% 88.4–98.7%)	WB-MRI sensitivity: 66.7% (CI 95% 41.0–86.7%) specificity: 96.5% (CI 95% 90.0–99.3%)	Moderate

1. About 50% of studies with possible spectrum bias (retrospective design); 100% of studies with unclear or absence of blinding of index test

Summary of Findings 3: Impact on clinical outcomes of FDG-PET or FDG-PET/CT for staging in patients with head and neck cancer

Patients/population: head and neck cancer (locally advanced disease)
Intervention: FDG-PET or FDG-PET/CT for initial staging
Comparators: no FDG-PET
Outcomes: local control, regional control, freedom from distant metastasis, cause-specific survival, overall survival; 2-year endpoint

Ref.	No. of studies	Study design	Risk of Bias	Indirectness	Inconsistency	Imprecision	FDG-PET % (CI 95%)	No FDG-PET	Quality of Evidence
local control									
Primary studies	1 (116 patients)	retrospective matched cohort design	Serious[1]	No	No	Serious	75.6 (65–88)	70.1 (58–84)	Very low
regional control									
Primary studies	1 (116 patients)	retrospective matched cohort design	Serious[1]	No	No	Serious	81.0 (72–93)	76.0 (65–89)	Very low
freedom from distant metastasis									
Primary studies	1 (116 patients)	retrospective matched cohort design	Serious[1]	No	No	Serious	82.4 (72–94)	84.6 (75–96)	Very low
cause-specific serviva									
Primary studies	1 (116 patients)	retrospective matched cohort design	Serious[1]	No	No	Serious	70.8 (59–85)	66.4 (54–82)	Very low
overall serviva									
Primary studies	1 (116 patients)	retrospective matched cohort design	Serious[1]	No	No	Serious	68.1 (56–83)	63.5 (51–79)	Very low

1. incomplete control of confounders, open design, unclear blinding of assessment of outcomes

Authors' conclusions

N staging

Accurate N staging of patients with head and neck cancer is very important and there is a rationale in support of the use of FDG-PET/CT for patients with equivocal results following conventional imaging.

The HTA document (ASSR 2012) judged the quality of appraised evidence as moderate and concluded that the use of FDG-PET for N staging of patients with primary head and neck cancer and with unclear results with conventional imaging (CT, MRI, ultrasound) is appropriate.

The only one study retrieved through our update and judged to be of low quality does not challenge the above conclusions.

M staging

Accurate M staging of patients with head and neck cancer is important and there is a rationale in support of the use of FDG-PET/CT in locally advanced disease patients eligible to curative treatment.

The HTA document (ASSR 2012) judged the quality of appraised evidence as moderate and concluded that the use of FDG-PET for M staging of patients with advanced head and neck cancer is appropriate.

Evidence from the studies retrieved through our update and judged to be of moderate quality confirms the above conclusions.

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4.7 FDG-PET/CT for staging of non-small cell lung cancer

Background

Lung cancer is the leading cause of cancer mortality worldwide (ESMO 2010). In Italy during the period 1998-2004, it represented 14.2% of all the cancers among males and 4.6% among females, corresponding to a crude incidence of 111.5 per 100,000 person/year in males and 27.9 per 100,000 person/year in females (Registri Tumori). Five-year survival is 11% (CI 95% 10-11%), across all stages of disease and histologic subtypes (Registri Tumori). Non-small cell lung cancer - the argument of this chapter - is the main histologic category (the other is the small cell lung cancer) and represents - subdivided in three histologic subtypes (squamous cell carcinoma, adenocarcinoma, large cell carcinoma) - about 85% of all cancers (AIOM 2009).

Target condition being diagnosed

Target conditions are: a) disease involvement of mediastinal lymph nodes, identified through N staging, and b) presence of distant metastases, identified through M staging.

Index test(s)

FDG-PET/CT.

The most recent guidelines (AIOM 2009; ESMO 2010; HAS 2009; NCCN 2012; NICE 2011) agree in recommending the use of FDG-PET/CT for mediastinal lymph node staging and M staging of patients suitable for curative intent. At the same time FDG-PET/CT-positive mediastinal nodes must be evaluated by mediastinal sampling for pathologic confirmation (AIOM 2009; NCCN 2012; NICE 2011).

Alternative test(s)

CT is the initial imaging modality of choice for N and M staging of lung cancer, and serves as a tool for triage that determines the most appropriate further investigation.

Reference standard for N staging is histopathology following thoracotomy or mediastinoscopy (Alongi 2006); reference standard for M staging is histopathology of metastases, follow-up with imaging techniques.

Rationale

Role of staging. Staging is the assessment of the extent of disease and is performed for prognostic and therapeutic purposes. The selection of patients for radical treatment (surgery, radical chemotherapy/radiotherapy) requires an investigation pathway directed towards as much diagnostic and staging information as possible. Involvement of the mediastinal lymph nodes and metastatic disease should be thoroughly investigated and evaluated, before excluding patients from radical treatment (AIOM 2009; ESMO 2010; HAS 2009; NCCN 2012; NICE 2011).

Treatment options. Surgery is the most recommended treatment for early stage non-small cell lung cancer (AIOM 2009; ESMO 2010; HAS 2009; NCCN 2012; NICE 2011) and five-year survival of stage I patients is over 50% (73% in stage IA, 58% in stage IB), with much room for improvement with systemic adjuvant approaches

in stages II and III (ESMO 2010). In patients with unresectable stage III or stage IV disease chemotherapy and/or following or concurrent radiotherapy is the standard of care.

Objectives

The objective of this review was to examine the diagnostic accuracy and the clinical effectiveness of FDG-PET/CT for N staging and M staging of patients diagnosed with non-small cell lung cancer compared to conventional imaging examination.

Search methods for identification of studies

Evidence is based on a) the conclusion of the most recent HTA report on non-small cell lung cancer (ASSR 2012) which was of good quality and had an electronic search updated to September 2010; b) a further search of studies published between January 2010 and March 2012. The key words described the participants' disease and the index test. See appendix 3 for details of strategy.

Results

The HTA document (ASSR 2012) concluded that

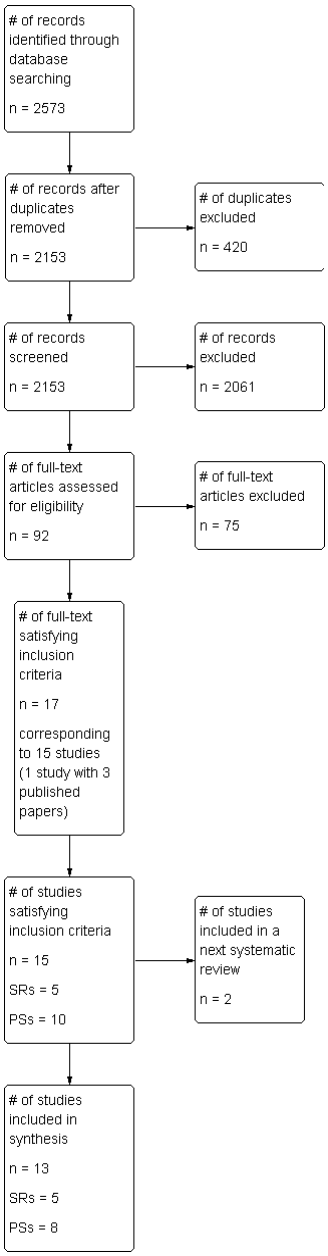
- the use of FDG-PET for staging of patients with non-small cell lung cancer is appropriate. The level of evidence for diagnostic accuracy of FDG-PET has been judged moderate.

Results of the search

Identification and selection of studies. The electronic search identified 2573 records; 2481 have been excluded because duplicates, or, after checking the abstract, for not meeting the inclusion criteria. Full text has been acquired for the remaining potentially eligible 92 records, from which 75 have been excluded on the basis of inclusion criteria (see below excluded studies). Two more papers (Darling 2011; Li 2011) are included in a next systematic review. Thirteen studies (15 papers) have been finally included (PS - Fischer 2009; PS - Fontaine 2011; PS - Gunluoglu 2011; PS - Kruger 2011; PS - Maziak 2009; PS - Ohnishi 2011; PS - Ohno 2011; PS - Sivrikoz 2011; SR - Chang 2012; SR - Liu 2011; SR - Lv 2011; SR - Qu 2011; SR - Zhao 2011).

The study selection process is summarized in the PRISMA flow diagram (Moher 2009; see Figure 1).

Figure 1: Non-small cell lung cancer: study selection according to PRISMA flow diagram (Moher 2009).



Description of included studies

Eleven studies evaluate diagnostic accuracy of FDG-PET/CT for N staging (PS - Fischer 2009; PS - Gunluoglu 2011; PS - Ohnishi 2011; PS - Ohno 2011; PS - Sivrikoz 2011; SR - Lv 2011; SR - Zhao 2011) or M staging (PS - Kruger 2011; SR - Chang 2012; SR - Liu 2011; SR - Qu 2011); 3 studies (PS - Fischer 2009; PS - Fontaine 2011; PS - Maziak 2009) assess the impact of FDG-PET/CT on clinical outcomes.

Diagnostic accuracy - N staging

Systematic reviews

Two systematic reviews have been included (SR - Lv 2011; SR - Zhao 2011). These reviews assess the diagnostic accuracy of FDG-PET/CT for mediastinal lymph nodes staging in patient with non-small cell lung cancer before any treatment.

The review by Lv et al. (SR - Lv 2011) includes 14 primary studies (11 studies with patient as unit of analysis; 9 studies with nodes as unit of analysis) for a total of 2550 participants (2191 in studies with patient as unit of analysis). Reference standard is histological examination of lymph nodes by surgery or biopsy. No data are reported about any comparator. No data are reported about cancer extension of patients at entry.

The review by Zhao et al. (SR - Zhao 2011) includes 20 primary studies (14 studies with patient as unit of analysis; 14 studies with nodes as unit of analysis) for a total of 3028 participants (2087 in studies with patient as unit of analysis). Reference standard is histological examination of lymph nodes by surgery or biopsy. No data are reported about any comparator. No data are reported about cancer extension of patients at entry.

Primary studies

Five studies (795 participants) evaluating diagnostic accuracy of FDG-PET/CT for regional lymph node staging published after the above reported systematic reviews have been included (PS - Fischer 2009; PS - Gunluoglu 2011; PS - Ohnishi 2011; PS - Ohno 2011; PS - Sivrikoz 2011). All studies compare results of FDG-PET/CT with one or more comparators: mediastinoscopy (PS - Gunluoglu 2011; PS - Sivrikoz 2011), conventional staging (PS - Fischer 2009: clinical data, initial CT scanning, bronchoscopy), diagnostic pathway recommended by a guideline (PS - Gunluoglu 2011), MRI (PS - Ohno 2011), ultrasound-guided transbronchial needle aspiration or transesophageal endoscopic ultrasound-guided fine-needle aspiration (PS - Ohnishi 2011). All studies included patients with suspected potentially resectable non-small cell lung cancer. Reference standard is histological examination of lymph nodes by surgery or biopsy.

Diagnostic accuracy - M staging

Systematic reviews

Three systematic reviews have been included (SR - Chang 2012; SR - Liu 2011; SR - Qu 2011). All assess diagnostic accuracy of FDG-PET/CT for bone metastasis in patients with undefined clinical phase (prabably both patients at staging and with suspected metastatic recurrence) and compared results with those of bone scintigraphy (SR - Chang 2012; SR - Liu 2011; SR - Qu 2011) or MRI (SR - Liu 2011; SR - Qu 2011). No systematic review has been found assessing diagnostic accuracy of FDG-PET/CT for complete M staging.

Considering only studies using patient as unit of analysis, the systematic review by Chang et al. (SR - Chang 2012), includes 6 studies for a total of 1746 patients, the systematic review by Liu et al. (SR - Liu 2011) includes 22 studies for a total of 2446 patients, the systematic review by Qu et al. (SR - Qu 2011), includes 7 studies for a total of 1644 patients. For all reviews reference standard is histological examination of lymph nodes by surgery or biopsy. No data are reported about cancer extension of patients at entry.

Primary studies

One study (104 participants) evaluating diagnostic accuracy of FDG-PET/CT for diagnosis of brain metastasis, published after the above reported systematic reviews, has been included (PS - Kruger 2011). Participants - undergoing at initial staging procedures without suspected brain metastasis - have either non-small cell lung cancer (82) or small cell lung cancer (22). Reference standard is MRI.

Impact on clinical outcomes - Any staging

Systematic reviews

None retrieved.

Primary studies
Three studies - 2 open randomised controlled trials and 1 cohort study - evaluating impact on clinical outcomes of FDG-PET/CT for staging are included (PS - Fischer 2009; PS - Fontaine 2011; PS - Maziak 2009).

In an open randomised controlled trial (PS - Fischer 2009) 189 patients - newly diagnosed or highly suspected for non-small cell lung-cancer and operable disease after conventional-staging procedures (i.e., medical history, physical examination, blood test, contrast-enhanced CT scan of the chest and upper abdomen, and bronchoscopy) - have been randomly assigned to conventional staging and PET–CT, followed by further invasive diagnostic procedures such as mediastinoscopy and endoscopic or endobronchial ultrasonography (the PET–CT group = 98 participants), or to conventional staging and invasive diagnostic procedures alone (the conventional-staging group = 91 participants). The primary end point is the frequency of futile thoracotomies (a benign lung lesion, pathologically proven mediastinal lymph-node involvement – i.e. stage IIIA, stage IIIB or IV disease, inoperable T3 or T4 disease, or recurrent disease or death from any cause within 1 year after randomization). Other clinical outcomeas are median survival and death at 12 months.

In an open randomised controlled trial (PS - Maziak 2009) 337 patients - with non-small cell lung-cancer and operable disease (I, II, or IIIA disease) after staging procedures with chest CT – have been randomly assigned to PET–CT, followed by further invasive diagnostic procedures such as mediastinoscopy and endoscopic or endobronchial ultrasonography (the PET–CT group = 170 participants), or to conventional staging and invasive diagnostic procedures (the conventional-staging group = 167 participants). The primary end point is the frequency of correct upstaging of cancer (true-positive results) where the imaging strategy identified a patient as having metastatic disease (stage IV) or locally advanced lung cancer (stage IIIB), thereby avoiding stage inappropriate surgery. Other clinical outcomes include incorrect upstaging (false positive results) and incorrect understaging (false-negative results).

In a cohort study (PS - Fontaine 2011) 1999 patients have undergone lung resection for proven or suspected non-small-cell lung cancer. Staging has been defined as pathological staging to eliminate bias by 'better' pre operative staging due to multislice computed tomography (CT) and PET/CT scanning. Mediastinsocopy has been used in all patients who have mediastinal lymph nodes enlarged by CT criteria, or who have undergone PET scanning and thought to have positive N2 nodes. Overall survival has been compared between patients who had a PET/CT scan pre operatively (= 934) and patients who had not undergone PET/CT scanning (= 1065) prior to surgical resection, at the end of follow up (median of 1.5 years in the PET/CT group and 3.7 years in the non-PET/CT group).

Methodological quality of included studies

Diagnostic accuracy - N staging

Systematic reviews
The systematic review by Lv et al. (SR - Lv 2011) assesses methodological quality of included studies, has a comprehensive bibliographic search method, and a well perforemed meta-analysis; the characteristics of included studies are only partially reported. The systematic review by Zhao et al. (SR - Zhao 2011) has a comprehensive bibliographic search method and a well perforemed meta-analysis, however the characteristics of included studies and their methodological quality are only partially reported.

The primary studies included into the systematic review by Lv et al. (SR - Lv 2011; Figure 2) could be prone to possible spectrum bias (50% with retrospective design) and about 40% of studies could be subjected to biased evaluation of reference standard due to have an unclear or absence of blinding of index test. The primary studies included into the systematic review by Zhao et al. (SR - Zhao 2011; Figure 2) have an unclear methodological quality profile.

Primary studies
In all included studies (PS - Fischer 2009; PS - Gunluoglu 2011; PS - Ohnishi 2011; PS - Ohno 2011; PS - Sivrikoz 2011) reference standard has an unclear risk of bias. Consecutive enrollment of participants is unclear for one study (PS - Gunluoglu 2011).

Quality assessment results for the included N staging studies is provided in Figure 2.

Diagnostic accuracy - M staging

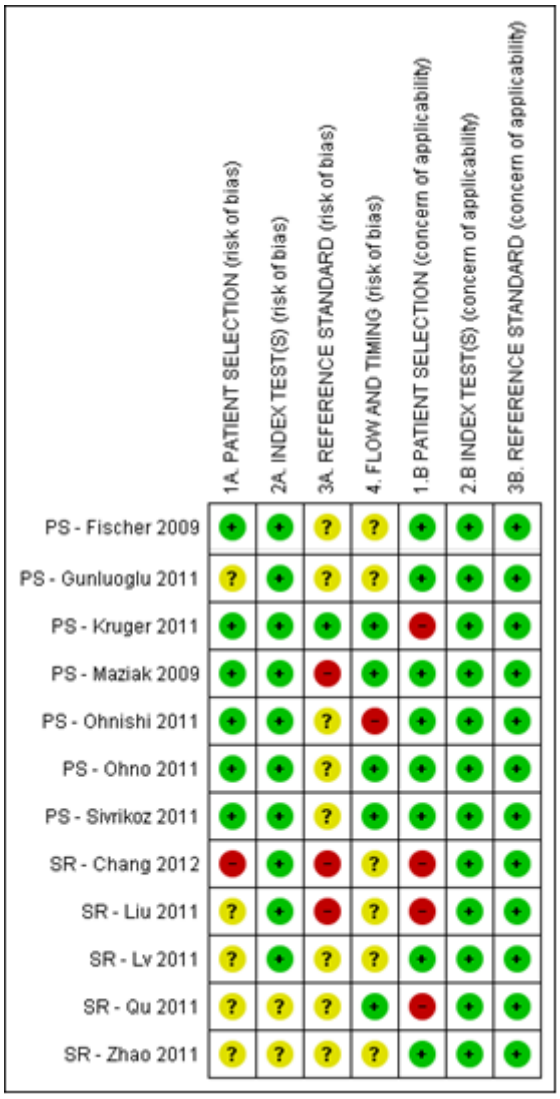
Systematic reviews
All systematic reviews (SR - Chang 2012; SR - Liu 2011; SR - Qu 2011) have a comprehensive bibliographic search method, assess methodological quality of included studies, and have a well perforemed meta-analysis; however the characteristics of included studies are only partially reported in all of them.

For all systematic reviews, included primary studies are in majority prone to possible spectrum bias - due to retrospective design - and possible biased evaluation of reference standard due to an unclear or absence of blinding of index test.

Primary studies
The only included study (PS - Kruger 2011) has a low risk of bias.

Quality assessment results for the included M staging studies is provided in Figure 2.

Figure 2: Methodological quality summary: review authors' judgements about each methodological quality item for included diagnostic accuracy studies.



Impact on clinical outcomes - Any staging

Systematic reviews
None retrieved.

Primary studies
The two randomised controlled trials (PS - Fischer 2009; PS - Maziak 2009), due to the open design, have an high risk of performance and detection bias. The cohort study (PS - Fontaine 2011) has an high risk of selection bias, with incomplete control of confounders, and an unclear risk of performance and detection bias.

Quality assessment results for the included M staging studies is provided in Figure 3.

Figure 3: Methodological quality summary: review authors' judgements about each methodological quality item for included clinical outcome studies.

Findings

Diagnostic accuracy - N staging

Detailed results are reported below in the table Summary of Findings 1.

Systematic reviews
The systematic reviews (SR - Lv 2011; SR - Zhao 2011) report similar estimates of sensitivity (76% vs 72%) and specificity (88% vs 90%) for FDG-PET/CT. However no data are available on comparators.

Primary studies
The five included studies report a quite wide range of accuracy estimates for FDG-PET/CT: from 47.4% to 75.0% for sensitivity and from 75.0 to 100% for specificity. However median estimates are similar to pooled estimates from systematic reviews. Two studies reports better diagnostic estimates for mediastinoscopy than for FDG-PET/CT (PS - Gunluoglu 2011; PS - Sivrikoz 2011). Data on other comparators are sparse.

Diagnostic accuracy - M staging

Detailed results are reported below in the table Summary of Findings 2.

Systematic reviews
No data are available on diagnostic accuracy of FDG-PET/CT for complete M staging .

The systematic reviews (SR - Chang 2012; SR - Liu 2011; SR - Qu 2011) - considering only bone metastasis as target condition - report similar pooled estimates of sensitivity (ranging from 92.0% to 94.6%) and specificity (ranging from 95.0% to 98.0%) for FDG-PET/CT. These values are consistently higher than those of comparators (bone scintigraphy, MRI).

Primary studies
No data are available on diagnostic accuracy of FDG-PET/CT for complete M staging.

Only one study (PS - Kruger 2011) - considering only brain metastasis as target condition - reports data for FDG-PET/CT. Sensitivity is very low (27.3%) compared with reference standard (brain MRI) .

Impact on clinical outcomes - Any staging

Detailed results are reported below in the table Summary of Findings 3.

Systematic reviews
None.

Primary studies
Two studies disclose better results in FDG-PET/CT group compared to no FDG-PET/CT group according to futile thoracotomy (lower rate), correct upstaging (higher rate) and incorrect understanging (lower rate) (PS - Fischer 2009; PS - Maziak 2009). One of them finds also a higher rate of incorrect upstaging in favour of the no FDG-PET/CT group. Inconsistent results are observed about death rate/overall survival.

Comments on Findings

N staging

Both moderate and *low quality* data on diagnostic accuracy of FDG-PET/CT were found. However, only *low quality* data compare FDG-PET/CT with another diagnostic tool (mediastinoscopy). Diagnostic accuracy estimates seem to be better for mediastinoscopy. Only sparse data on other comparators are available.

M staging

No data are available on diagnostic accuracy of FDG-PET/CT for whole body M staging. For the detection of bone metastasis, according to data of *low quality*, FDG-PET/CT seems to have higher sensitivity and specificity compared to other imaging methods (bone scintigraphy, MRI). For the detection of brain metastasis, according to data of *low quality*, FDG-PET/CT seems to have a worse diagnostic accuracy compared to MRI.

Any staging: impact on clinical outcomes

According to *moderate quality* data, FDG-PET/CT seems to reduce the risk of futile thoracotomy compared to conventional staging without FDG-PET/CT.

According to *moderate quality* data, FDG-PET/CT compared to conventional staging without FDG-PET/CT seems to perform better in terms of higher correct upstaging, and lower incorrect understaging. However - in the same time - FDG-PET/CT seems to produce slightly more incorrect upstaging.

The data on impact to death rate/overall survival - of *very low/low quality* - are inconsistent.

Summary of Findings 1: Diagnostic accuracy of FDG-PET/CT for mediastinal N staging in patients with non-small cell lung cancer

Patients/population: non-small cell lung cancer (patients with potentially resectable cancer)
Target condition: mediastinal N staging
Index test: FDG-PET/CT
Comparators: mediastinoscopy; conventional staging without FDG-PET/CT (medical history, physical examination, blood test, contrast-enhanced CT scan of the chest and upper abdomen, and bronchoscopy); MRI ((short inversion time inversion recovery STIR turbo spin-echo SE; diffusion-weighted DW); ultrasound-guided transbronchial needle aspiration (EBUS–TBNA) and transesophageal endoscopic ultrasound-guided fine-needle aspiration (EUS–FNA)
Reference standard: histological examination of lymph nodes by surgery or biopsy

Ref.	No. of studies	Study design	Risk of Bias	Indirectness	Inconsistency	Imprecision	Diagnostic Accuracy FDG-PET/CT	Diagnostic Accuracy Comparators	Quality of Evidence
Lv 2011	11 (2191 participants)	Systematic review	Serious[1]	No	No	No	pooled weighted sensitivity 76% (95% CI 65–84%) pooled weighted specificity 88% (95% CI 82–92%)	none	Moderate
Zhao 2011	14 (2087 participants)	Systematic review	Serious[2]	No	No	No	pooled sensitivity 72% (95% CI: 68–75%) pooled specificity 90% (95% CI: 88–91%)	none	Moderate
Primary studies	5 (704 participants) 2 studies (236 participants) for mediastinoscopy 1 study each: conventional staging (91 participants), MRI (250 participants), EBUS–	1 randomised controlled trial and 4 diagnostic accuracy studies with prospective recruitment	Serious[3]	No	Serius[4]	No	sensitivity (median) 71.0% (range 47.4-75.0%) specificity (median)	mediastinoscopy sensitivity (range) 81.8-84.0% specificity (range) 100% EBUS–TBNA/EUS–	Low

	TBNA/EUS–FNA (120 participants)						92.4% (range 75.0-100%)	FNA sensitivity 71.8% specificity 100% MRI sensitivity 71.0-77.4% specificity 88.5-89.8% conventional staging sensitivity 59.0% specificity 98.0%		

1. possible spectrum bias (50% of studies with retrospective design) and possible biased evaluation of reference standard (40% of studies with an unclear or absence of blinding of index test)
2. Not reported data on quality of studies
3. All studies with unclear risk of bias of reference standard; 1 study with possible spectrum bias (unclear if consecutive enrollment)
4. Inconsistent diagnostic estimates among included studies

Summary of Findings 2: Diagnostic accuracy of FDG-PET or FDG-PET/CT for M staging in patients with non-small cell lung cancer

Patients/population: non-small cell lung cancer (in majority of studies unclear if patients at staging or with suspect of recurrence or both)
Target condition: bone metastasis (3 systematic reviews); brain metastasis (1 primary study)
Index test: FDG-PET, FDG-PET/CT
Comparators: bone scintigraphy, MRI
Reference standard: histopathologic analysis and/or close clinical and imaging follow-up and/or radiographic confirmation by multiple imaging modalities

Ref.	No. of studies	Study design	Risk of Bias	Indirectness	Inconsistency	Imprecision	Diagnostic Accuracy FDG-PET, FDG-PET/CT	Diagnostic Accuracy Comparators	Quality of Evidence
Chang 2012	6 (1746 participants)	Systematic review	Serious[1]	Serious[2]	No	No	Sensitivity (pooled) 93% (95% CI 88–96%) Specificity (pooled) 95% (95% CI: 91–98%)	bone scintigraphy Sensitivity (pooled) 87% (95% CI 79–93%) Specificity (pooled) 82% (95% CI: 62–92%)	Low
Liu 2011	5 (No. of participants not reported) for FDG-PET/CT 11 (1537 participants) for bone scintigraphy 3 (258 participants) for MRI	Systematic review	Serious[1]	Serious[2]	No	No	Sensitivity (pooled) 94.6% (95% CI 91.1–97.0%) Specificity (pooled) 97.5% (95% CI 96.6–98.3%)	bone scintigraphy Sensitivity (pooled) 91.8% (95% CI 89.1–94.1%) Specificity (pooled) 68.8% (95% CI 65.8–71.6%) MRI Sensitivity (pooled) 80.0% (95% CI 67.0–89.6%) Specificity (pooled) 90.6% (95% CI 85.8–94.3%)	Low
Qu 2011	7 (1644 participants) for FDG-PET/CT 12 (1640 participants) for bone scintigraphy	Systematic review	Serious[1]	Serious[2]	No	No	Sensitivity (pooled) 92.0% (95% CI 88.0–95.0%) Specificity	bone scintigraphy Sensitivity (pooled) 85.0% (95% CI 80.0–89.0%) Specificity (pooled)	Low

	3 (252 participants) for MRI						(pooled) 98.0% (95% CI 97.0–99.0%)	93.0% (95% CI 91.0–94.0%) MRI Sensitivity (pooled) 77.0% (95% CI 65.0–87.0%) Specificity (pooled) 92.0% (95% CI 88.0–95.0%)		
Primary studies	1 (104 participants)	diagnostic accuracy studies with prospective recruitment (consecutive)	No	Serious[3]	not applicable	Serious	Sensitivity 27.3% Specificity 97.6%	none	Low	

1. Majority of included primary studies prone to possible spectrum bias and possible biased evaluation of reference standard due to an unclear or absence of blinding of index test
2. Only studies assessing bone metastasis in patients including patients with unclear clinical phase (prabably both patients at staging and with suspected metastatic recurrence)
3. The study includes also a group of patients with small cell lung cancer (No. 22); the target condition is brain metastasis

Summary of Findings 3: Impact on clinical outcomes of FDG-PET/CT for staging in patients with non-small cell lung cancer

Patients/population: non-small cell lung cancer (patients with potentially resectable cancer)
Intervention: FDG-PET/CT
Comparators: no FDG-PET
Outcomes: futile thoracotomy, correct upstaging, incorrect upstaging, incorrect understaging, death rate, overall survival; 12/22 months of follow up

Ref.	No. of studies	Study design	Risk of Bias	Indirectness	Inconsistency	Imprecision	FDG-PET/CT	No FDG-PET/CT	P	Quality of Evidence
futile thoracotomy										
Primary studies	1 (189 participants)	randomised controlled trial	Serious[1]	No	No	No	35%	52%	0.05	Moderate
correct upstaging										
Primary studies	1 (337 participants)	randomised controlled trial	Serious[1]	No	No	No	13.8%	6.8%	0.046	Moderate
incorrect upstaging										
Primary studies	1 (337 participants)	randomised controlled trial	Serious[1]	No	No	No	4.8%	0.6%	0.037	Moderate
incorrect understaging										
Primary studies	1 (337 participants)	randomised controlled trial	Serious[1]	No	No	No	14.9%	29.6%	0.002	Moderate
death rate										
Primary studies	2 (526 participants)	randomised controlled trials	Serious[1]	No	Serious	No	61% 52%	51% 57%	0.15 <0.05	Low
overall survival										
Primary studies	1 (1999 participants)	cohort study	Serious[2]	No	No	No	61%	53%	0.04	Very low

1. open design
2. risk of selection bias, incomplete control of confounders, unclear blinding of assessment of outcomes

Authors' conclusions

Accurate staging - both mediastinal N staging and M staging - of patients with non-small cell lung cancer is very important and there is a rationale in support of the use of FDG-PET/CT for patients with potentially resectable cancer.

The HTA document (ASSR 2012) judged the quality of appraised evidence as moderate and concluded that the use of FDG-PET/CT for staging of patients with non-small cell lung cancer is appropriate.

Evidence from the studies retrieved through our update – both on diagnostic accuracy and on impact on clinical outcomes, of low to moderate quality - confirms the above conclusions.

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4.8 FDG-PET/CT for staging of small cell lung cancer

Background

Lung cancer is the leading cause of cancer mortality worldwide (ESMO 2010). In Italy during the period 1998-2004, it represented 14.2% of all the cancers among males and 4.6% among females, corresponding to a crude incidence of 111.5 per 100,000 person/year in males and 27.9 per 100,000 person/year in females (Registri Tumori). Small cell lung cancer - the argument of this chapter - accounts for about 15% of lung cancers (AIOM 2009; ESMO 2010). Patients with limited disease have a 5-year survival rate of between 20% and 25%. The prognosis for extensive disease is poor with a median survival of 10 months and a 2-year survival rate of 10% (ESMO 2010).

Target condition being diagnosed

Target conditions are: a) disease involvement of mediastinal lymph nodes, identified through N staging, and b) presence of distant metastases, identified through M staging.

Index test(s)

FDG-PET/CT.

Among the most recent guidelines only NCCN recommends the use of FDG-PET/CT for N staging and M staging of patients with suspected limited disease and thus suitable for curative intent (NCCN 2012). Another group of guidelines (AIOM 2009; HAS 2009; NICE 2011) do not distinguish staging procedures for small cell lung cancer from those for non-small cell lung cancer. According to two further guidelines (BTS 2010 cancer; ESMO 2010) the role of FDG-PET/CT is yet to be completely defined.

Alternative test(s)

CT is the initial imaging modality of choice for N and M staging of lung cancer, and serves as a tool for triage that determines the most appropriate further investigation.

Reference standard for N staging is histopathology following thoracotomy or mediastinoscopy (Alongi 2006); reference standard for M staging is histopathology of metastases, follow-up with imaging techniques.

Rationale

Role of staging. Staging is the assessment of the extent of disease and is performed for prognostic and therapeutic purposes. The selection of patients for curative treatment requires an investigation pathway directed towards as much diagnostic and staging information as possible. Pre-treatment staging is necessary to differentiate between limited disease - defined as tumour tissue that could be encompassed in a single radiation port - and extended disease - any tumour that extended beyond the boundaries of a single radiation port (BTS 2010; ESMO 2010).

Treatment options. Limited disease is eligible for concurrent chemotherapy and radiotherapy; extended disease is treated with chemotherapy alone (BTS 2010; ESMO 2010). Clinical trials have reported better 5 year-survival rate (between 20% and 25%) in patients randomized to concurrent chemo-radiotherapy compared to patients treated with sequential chemo-radiotherapy (BTS 2010; ESMO 2010).

Objectives

The objective of this review was to examine the diagnostic accuracy and the clinical effectiveness of FDG-PET/CT for N staging and M staging of patients diagnosed with small cell lung cancer compared to conventional imaging examination.

Search methods for identification of studies

Evidence is based on a) the conclusion the most recent HTA report on small cell lung cancer (ASSR 2012) which was of good quality and had an electronic search updated to September 2010; b) a further search of studies published between January 2010 and March 2012. The key words described the participants' disease and the index test. See appendix 4 for details of strategy.

Results

The HTA document (ASSR 2012) concluded that

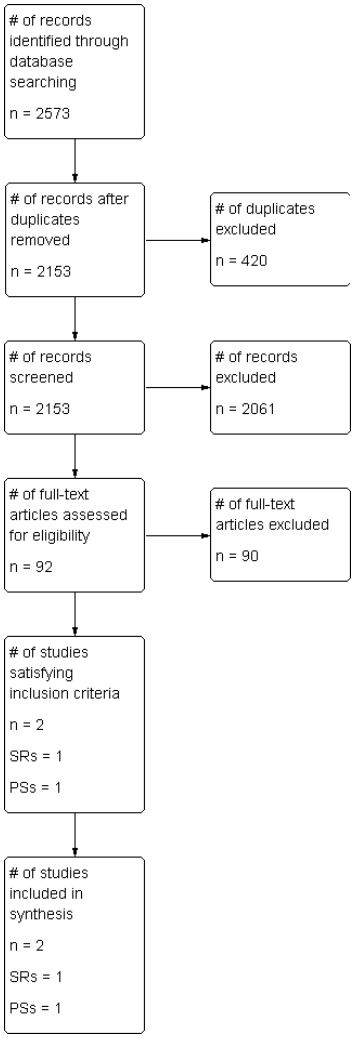
- the available data on FDG-PET accuracy in discriminating limited from extended SCLC are sparse and the level of evidence is *very low*. The role of FDG-PET in staging SCLC is uncertain.

Results of the search

Identification and selection of studies. The updated electronic search identified 2573 records; 2481 have been excluded because duplicates, or, after checking the abstract, for not meeting the inclusion criteria. Full text has been acquired for the remaining potentially eligible 92 records, from which 90 have been excluded on the basis of inclusion criteria (see below excluded studies). Two studies have been finally included (PS - Kruger 2011; SR - Qu 2011).

The study selection process is summarized in the PRISMA flow diagram (Moher 2009; see Figure 1).

Figure 1: Small cell lung cancer: study selection according to PRISMA flow diagram (Moher 2009).



Description of included studies.

No studies evaluate diagnostic accuracy of FDG-PET/CT for N staging. Two studies evaluate diagnostic accuracy of FDG-PET/CT for M staging (PS - Kruger 2011; SR - Qu 2011). No studies assess the impact of FDG-PET/CT on clinical outcomes.

Diagnostic accuracy - N staging

Systematic reviews
None retrieved.

Primary studies
None retrieved.

Diagnostic accuracy - M staging

Systematic reviews
One systematic review (SR - Qu 2011) assesses diagnostic accuracy of FDG-PET/CT for bone metastasis in patients with undefined clinical phase (prabably both patients at staging and with suspected metastatic recurrence) and compared results with those of bone scintigraphy. No systematic review assessing diagnostic accuracy of FDG-PET/CT for complete M staging was found.

Considering only studies using patient as unit of analysis, the systematic review includes 7 studies for a total of 1644 patients. The reference standard is histological examination of lymph nodes by surgery or biopsy. No data are reported about cancer extension of patients at entry.

Primary studies
One study (104 participants) evaluating diagnostic accuracy of FDG-PET/CT for diagnosis of brain metastasis, published after the above reported systematic reviews, has been included (PS - Kruger 2011). Participants - undergoing at initial staging procedures without suspected brain metastasis - have either non-small cell lung cancer (82) or small cell lung cancer (22). The reference standard was MRI.

Impact on clinical outcomes - Any staging

Systematic reviews
None retrieved.

Primary studies
None retrieved.

Methodological quality of included studies

Diagnostic accuracy - N staging

Systematic reviews
None retrieved.

Primary studies
None retrieved.

Diagnostic accuracy - M staging

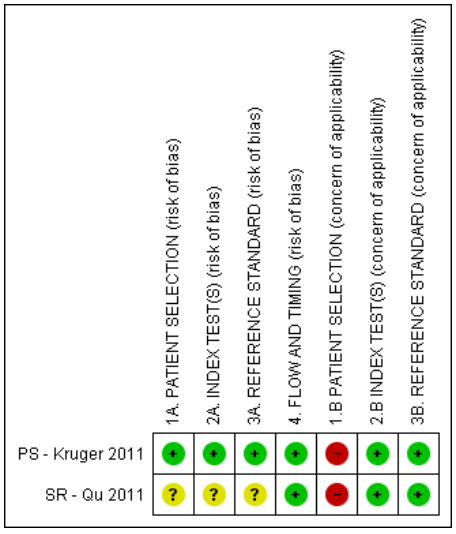
Systematic reviews
The systematic review (SR - Qu 2011) has a comprehensive bibliographic search method, assesses methodological quality of included studies, and has a well perforemed meta-analysis; however characteristics of included studies are only partially reported.

Included primary studies are in majority prone to possible spectrum bias - due to retrospective design - and possible biased evaluation of reference standard due to an unclear or absence of blinding of index test.

Primary studies
The only included study (PS - Kruger 2011) has a low risk of bias.

Quality assessment results for the included M staging studies is provided in Figure 2.

Figure 2: Methodological quality summary: review authors' judgements about each methodological quality item for included diagnostic accuracy studies



Impact on clinical outcomes - Any staging

Systematic reviews
None retrieved.

Primary studies
None retrieved.

Findings

Diagnostic accuracy - N staging

No data are avilable.

Diagnostic accuracy - M staging

Detailed results are reported below in the table Summary of Findings 1.

Systematic reviews
No data are available on diagnostic accuracy of FDG-PET/CT for complete M staging.

The systematic review (SR - Qu 2011) - considering only bone metastasis as target condition - reports higher pooled estimates of sensitivity (90.0%) and specificity (95.0%) for FDG-PET/CT those of bone scintigraphy (sensitivity 88.0%, specificity 74.0%).

Primary studies
No data are available on diagnostic accuracy of FDG-PET/CT for whole body M staging.

One study PS - Kruger 2011) - considering only brain metastasis as target condition - reports data for FDG-PET/CT. Sensitivity is very low (27.3%) compared with reference standard (brain MRI) .

Impact on clinical outcomes - Any staging

Systematic reviews
None retrieved.

Primary studies
None retrieved.

Comments on Findings

N staging

No data are available on diagnostic accuracy of FDG-PET/CT for N staging.

M staging

No data are available on diagnostic accuracy of FDG-PET/CT for complete M staging. According to data of *low quality*, FDG-PET/CT seems to have higher sensitivity and specificity compared to bone scintigraphy for the detection of bone metastasis. According to data of *low quality*, FDG-PET/CT seems to have a worse diagnostic accuracy compared to MRI for the detection of brain metastasis.

Any staging: impact on clinical outcomes

No data are available on impact of of FDG-PET/CT on clinical outcomes.

Summary of Findings 1: Diagnostic accuracy of FDG-PET or FDG-PET/CT for M staging in patients with small cell lung cancer

Patients/population: small cell lung cancer (in majority of studies unclear if patients at staging or with suspect of recurrence or both)
Target condition: bone metastasis (1 systematic review); brain metastasis (1 primary study)
Index test: FDG-PET/CT
Comparators: bone scintigraphy
Reference standard: histopathologic analysis and/or close clinical and imaging follow-up and/or radiographic confirmation by multiple imaging modalities

Ref.	No. of studies	Study design	Risk of Bias	Indirectness	Inconsistency	Imprecision	Diagnostic Accuracy FDG-PET, FDG-PET/CT	Diagnostic Accuracy Comparators	Quality of Evidence	
Qu 2011	2 (211 participants) for FDG-PET/CT 4 (645 participants) for bone scintigraphy	Systematic review	Serious[1]	Serious[2]	No	No	Sensitivity (pooled) 90.0% (95% CI 76.0–97.0%) Specificity (pooled) 95.0% (95% CI 90.0–98.0%)	bone scintigraphy Sensitivity (pooled) 88.0% (95% CI 81.0–93.0%) Specificity (pooled) 74.0% (95% CI 70.0–77.0%)	Low	
Primary studies	1 (104 participants)	diagnostic accuracy studies with prospective recruitment (consecutive)	No	Serious[3]	not applicable	Serious	Sensitivity 27.3% Specificity 97.6%	none	Low	

1. Majority of included primary studies prone to possible spectrum bias and possible biased evaluation of reference standard due to an unclear or absence of blinding of index test
2. Only studies assessing bone metastasis in patients including patients with unclear clinical phase (prabably both patients at staging and with suspected metastatic recurrence)
3. The study includes also a group of patients with non-small cell lung cancer (No. 82); the target condition is brain metastasis

Authors' conclusions

Accurate staging - both mediastinal N staging and M staging - of patients with small cell lung cancer is important and there is a rationale in support of the use of FDG-PET/CT for patients with limited disease.

The HTA document (ASSR 2012) judged the quality of appraised evidence as very low and concluded that the role of FDG-PET in staging of small cell lung cancer is uncertain.

Evidence from the studies retrieved through our update – only on diagnostic accuracy of M staging and of low quality - confirms the above conclusions.

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4.9 FDG-PET/CT for staging of malignant pleural mesothelioma

Background

Malignant pleural mesothelioma is a rare cancer for which exposure to asbestos is a well-established etiological factor, being occupational exposure documented in 70%–80% of those affected (ESMO 2010). In Italy during the period 1998-2002, it represented 0.4% of all the cancers among males and 0.2% among females, corresponding to a crude incidence of 3.4 per 100,000 person/year in males and 1.1 per 100,000 person/year in females (Registri Tumori). Five-year survival is 7% (CI 95% 6-8%), across all stages of disease (Registri Tumori).

Target condition being diagnosed

Target conditions are: a) disease involvement of mediastinal lymph nodes, identified through N staging, and b) presence of distant metastases, identified through M staging.

Index test(s)

FDG-PET/CT.

Among the most recent guidelines, only NCCN guidelines (NCCN 2012) recommends the use of FDG-PET/CT for staging of patients suitable for mutimodality therapy including surgical resection. According to the rest of guidelines (BTS 2007; ERS/ESTS 2010; ESMO 2010; HAS 2009) the role of FDG-PET/CT is yet to be completely defined or limited to selected patients.

Alternative test(s)

CT of chest and upper abdomen (ERS/ESTS 2010; ESMO 2010) is the initial imaging modality of choice for N and M staging of malignant pleural mesothelioma, and serves as a tool for triage that determines the most appropriate further investigation.

Reference standard for N staging is histopathology following surgery or mediastinoscopy (PS - Sorensen 2008); reference standard for M staging is histopathology of metastases, follow-up with imaging techniques.

Rationale

Role of staging. T, N and M staging is necessary to provide both prognostic information and guidance on the most appropriate therapeutic options. In particular patients with clinical stages I-III and good performance condition are eligible for therapy with a curative intent (multimodality therapy) (ESMO 2010; NCCN 2012).

Treatment options. The median survival of patients with mesothelioma is between 6 and 18 months, and 85% to 90% of patients present with unresectable disease at diagnosis; such patients rely on palliative treatment (Pinto 2011). However, selected patients with localized disease who receive aggressive multimodality therapy (surgery, radiation theraphy, chemotherapy) may be long term survivors (Sterman 2012).

Objectives

The objective of this review was to examine the diagnostic accuracy and the clinical effectiveness of FDG-PET/CT for T staging, N staging and M staging of patients diagnosed with malignant pleural mesothelioma compared to conventional imaging examination.

Search methods for identification of studies

Evidence is based on a) the conclusion of the most recent HTA report on malignant pleural mesothelioma (KCE 2009) which was of good quality and had an electronic search updated to January 2009; b) a further search of studies published between January 2009 and March 2012. The key words described the participants' disease and the index test. See appendix 5 for details of strategy.

Results

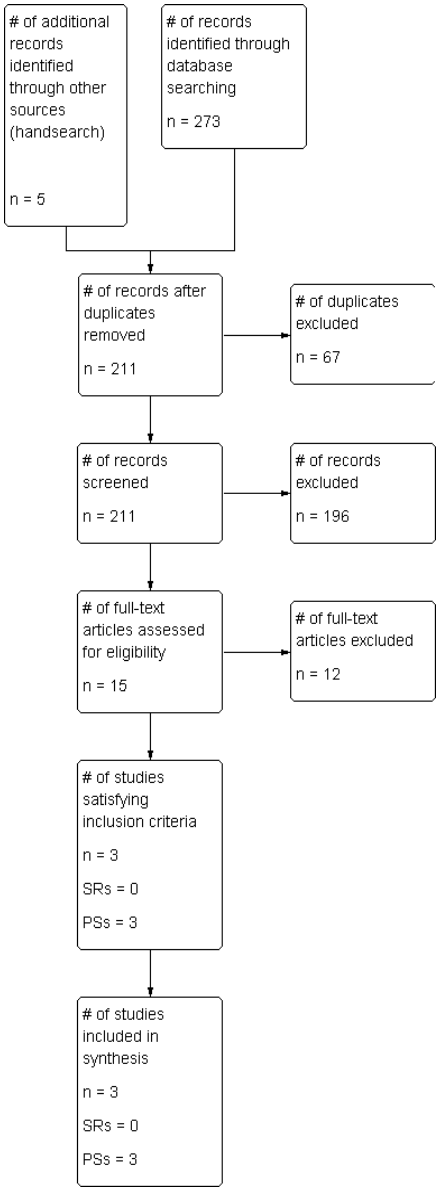
The HTA document (KCE 2009) concluded that the evidence is limited to one primary study on the prognostic value of FDG-PET in 137 patients with mesothelioma and does not allow the formulation of any firm conclusion.

Results of the search

Identification and selection of studies. The updated search identified 278 records; 263 have been excluded because duplicates, or, after checking the abstract, for not meeting the inclusion criteria. Full text has been acquired for the remaining potentially eligible 15 records, from which 12 have been excluded on the basis of inclusion criteria (see below excluded studies). Three studies have been finally included (PS - Erasmus 2005; PS - Pilling 2010; PS - Sorensen 2008).

The study selection process is summarized in the PRISMA flow diagram (Moher 2009; see Figure 1).

Figure 1 Malignant pleural mesothelioma: study selection according to PRISMA flow diagram (Moher 2009).



Description of included studies

Three studies evaluate diagnostic accuracy of FDG-PET/CT for T staging, N staging and any staging. No studies evaluate diagnostic accuracy of FDG-PET/CT for M staging. No studies assess the impact of FDG-PET/CT on clinical outcomes.

Diagnostic accuracy - T and N staging

Systematic reviews
None retrieved.

Primary studies
Three studies (91 participants) evaluating diagnostic accuracy of FDG-PET/CT for local T staging have been included (PS - Erasmus 2005; PS - Pilling 2010; PS - Sorensen 2008). All studies do not compare results of FDG-PET/CT with any comparator. All studies included patients considered for or undergone to extrapleural pneumonectomy. Reference standard is histopathology following surgery or mediastinoscopy.

Diagnostic accuracy - M staging

Systematic reviews
None retrieved.

Primary studies
None retrieved.

Diagnostic accuracy - Any staging

Systematic reviews
None retrieved.

Primary studies
One study (29 participants) evaluating diagnostic accuracy of FDG-PET/CT in assigning the overal stage has been included (PS - Erasmus 2005). Participants are patients considered for extrapleural pneumonectomy: stage I to III patients are considered for extrapleural pneumonectomy, stage IV are excluded from extrapleural pneumonectomy. The reference standard is histopathology following surgery or mediastinoscopy and/or results of further radiologic evaluation or follow-up.

Methodological quality of included studies

Diagnostic accuracy - T and N staging

Systematic reviews
None retrieved.

Primary studies
In all studies (PS - Erasmus 2005; PS - Pilling 2010; PS - Sorensen 2008) reference standard has an unclear risk of bias. Two studies (PS - Pilling 2010; PS - Sorensen 2008) have an high risk of bias due to an unclear or too long interval between index test and reference standard. Consecutive enrollment of participants is unclear for one study (PS - Erasmus 2005).

Quality assessment results for the included T and N staging studies is provided in Figure 2.

Figure 2 Methodological quality summary: review authors' judgements about each methodological quality item for each included diagnostic accuracy study.

Diagnostic accuracy - M staging

Systematic reviews

None retrieved.

Primary studies
None retrieved.

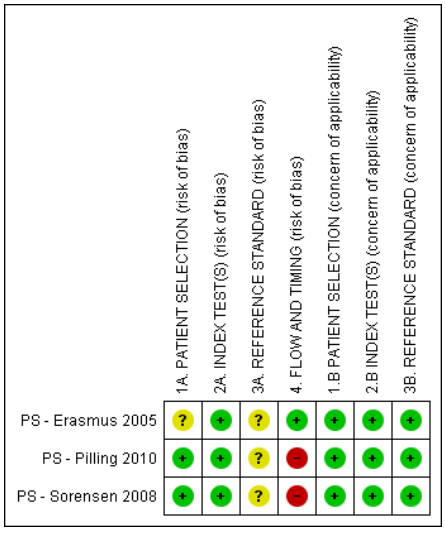
Diagnostic accuracy - Any staging

Systematic reviews
None retrieved.

Primary studies

In the only included study (PS - Erasmus 2005) consecutive enrollment of participants is unclear and reference standard has an unclear risk of bias.

Quality assessment results for the included M staging studies is provided in Figure 2.



Findings

Diagnostic accuracy - T and N staging

Primary studies
The three included studies report a very wide range of sensitivity estimates of FDG-PET/CT (from 0 to 75.0%) for T staging and a very low sensitivity for N staging (range 11.1-50.0%). Data on comparators are not available.

Detailed results are reported below in the table Summary of Findings 1 and 2

Diagnostic accuracy - Any staging

Primary studies

Only one study (PS - Erasmus 2005) reports data for FDG-PET/CT. Data on comparators are not available.

Detailed results are reported below in the table Summary of Findings 3.

Comments on Findings

Any staging: diagnostic accuracy
Available data on diagnostic accuracy of FDG-PET/CT are of *low/very low quality*. No data are available on diagnostic accuracy of comparators. Due to these limitation any conclusion cannot be drawn.

Any staging: impact on clinical outcomes
No data are available on impact of of FDG-PET/CT on clinical outcomes.

Summary of Findings 1: Diagnostic accuracy of FDG-PET/CT for T staging in malignant pleural mesothelioma

Patients/population: patients with malignant pleural mesothelioma considered for or undergone to extrapleural pneumonectomy
Target condition: T4 stage versus T1-T3 stages
Index test: FDG-PET/CT
Comparators: none
Reference standard: histopathology following surgery or mediastinoscopy.

Ref.	No. of studies	Study design	Risk of Bias	Indirectness	Inconsistency	Imprecision	Diagnostic Accuracy FDG-PET/CT	Diagnostic Accuracy Comparators	Quality of Evidence
Primary studies	3 (73 participants)	diagnostic accuracy studies with prospective recruitment	Serious[1]	No	Serious	Serious	Sensitivity (range) 0-75.0% Specificity (range) 93.0-100%	none	Very low

1. All studies prone to possible biased evaluation of reference standard due to an unclear or absence of blinding of index test; two studies with unclear or too long interval between index test and reference standard; one study with unclear consecutive enrollment

Summary of Findings 2: Diagnostic accuracy of FDG-PET/CT for N staging in malignant pleural mesothelioma

Patients/population: patients with malignant pleural mesothelioma considered for or undergone to extrapleural pneumonectomy
Target condition: N2-N3 stages versus N0-N1 stages
Index test: FDG-PET/CT
Comparators: none
Reference standard: histopathology following surgery or mediastinoscopy.

Ref.	No. of studies	Study design	Risk of Bias	Indirectness	Inconsistency	Imprecision	Diagnostic Accuracy FDG-PET/CT	Diagnostic Accuracy Comparators	Quality of Evidence
Primary studies	3 (67 participants)	diagnostic accuracy studies with prospective recruitment	Serious[1]	No	No	Serious	Sensitivity (range) 11.1-50.0% Specificity (range) 75.0-93.3%	none	Low

1. All studies prone to possible biased evaluation of reference standard due to an unclear or absence of blinding of index test; two studies with unclear or too long interval between index test and reference standard; one study with unclear consecutive enrollment

Summary of Findings 3: Diagnostic accuracy of FDG-PET/CT for any staging in malignant pleural mesothelioma (eligibility to extrapleural pneumonectomy)

Patients/population: patients with malignant pleural mesothelioma considered for extrapleural pneumonectomy
Target condition: eligibility to extrapleural pneumonectomy (stage I to III = considered for extrapleural pneumonectomy, stage IV = not considered for extrapleural pneumonectomy)
Index test: FDG-PET/CT
Comparators: none
Reference standard: histopathology and/or results of further radiologic evaluation or follow-up

Ref.	No. of studies	Study design	Risk of Bias	Indirectness	Inconsistency	Imprecision	Diagnostic Accuracy FDG-PET/CT	Diagnostic Accuracy Comparators	Quality of Evidence	
Primary studies	1 (29 participants)	diagnostic accuracy studies with prospective recruitment	Serious[1]	No	not applicable	Serious	Sensitivity 85.7% Specificity 73.3%	none	Low	

1. Unclear consecutive enrollment and possible biased evaluation of reference standard due to an unclear blinding of index test

Authors' conclusions

Accurate overall staging (T, N and M staging) of patients with malignant pleural mesothelioma is important and there is a rationale in support of the use of FDG-PET/CT for patients considered for multimodality treatment.

The HTA document (KCE 2009) concluded that there is uncertainty regarding the use of PET/CT for mesothelioma as available evidence is limited.

Evidence from the studies retrieved through our update and judged to be of low/very low quality suggests that the use of FDG-PET/CT for patients would be inappropriate.

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4.10 FDG-PET/CT for staging of breast cancer

Background

Breast cancer is is the most frequent cancer diagnosed among females in Italy; during 1998-2002, it represented 24.9% of all cancers among females, corresponding to a crude incidence of 152.0 per 100,000 person/year (Registri Tumori). Five-year survival is around 77% (CI 95% 76-77%), across all stages of disease (Registri Tumori).

Target condition being diagnosed

Target conditions are: a) disease involvement of regional (axillary) lymph nodes identified through N staging, and b) presence of any distant metastasis, identified through M staging (ESMO 2011).

Index test(s)

FDG-PET/CT.

Among the most recent guidelines only NCCN guidelines (NCCN 2012) recommends use of FDG-PET/CT for M staging of patients with locally advanced (T3-N1 disease). Other guidelines do not consider FDG-PET/CT at all (AIOM 2010; ESMO 2011; HAS 2010; NICE 2009) or judge data as inconclusive (NZGG 2009).

Alternative test(s)

Sentinel lymph node biopsy (SLNB) is the standard of care for axillary N staging in early breast cancer, unless axillary node involvement is suspected clinically or on ultrasound (ESMO 2011).

M staging includes X-ray, abdominal ultrasound or CT scan and bone scintigraphy (AIOM 2010; ESMO 2011).

Reference standard for N staging is histopathology following axillary lymph node dissection or sentinel lymph node biopsy (SR - Cooper 2011); reference standard for M staging is histopathology of metastases and/or follow-up with imaging techniques (SR - Brennan 2012).

Rationale

Role of staging. Regional (axillary) lymph node status remains the strongest predictor of long-term prognosis in primary breast cancer, and sentinel lymph node biopsy is the standard care to decide for axillary lymph node dissection (ESMO 2011; NICE 2009). In fact the presence of macrometastatic spread in the sentinel node mandates conventional axillary lymph node dissection (ESMO 2011). M staging is considered only if neaoadjuvant systemic therapy is planned or when patients have relevant risk of metastatic spread (clinically positive axillary nodes; large tumors; signs, symptoms or laboratory values indicating the presence of metastasis) (AIOM 2010; ESMO 2011).

Treatment options. Surgery (breast conservation surgery or mastectomy) is the core treatment for ductal carcinoma in situ and invasive breast cancer and is the proposed first treatment option (NICE 2009). Axillary lymph node dissection is recommended for patients with confirmed or suspect axillary node involvement (ESMO 2011; NICE 2009). Presence of locally invasive disease, axillary or systemic metastatic spread determine the use of other treatment tools (endocrine therapy, chemotherapy, radiation therapy).

Objectives

The objective of this review was to examine the diagnostic accuracy and the clinical effectiveness of FDG-PET/CT for N staging and M staging of patients diagnosed with breast cancer compared to conventional imaging examination.

Search methods for identification of studies

Evidence is based on a) the conclusion of the most recent HTA report on breast cancer (ASSR 2011) which was of good quality and had an electronic search updated to July 2010; b) a further search of studies published between January 2010 and March 2012. The key words described the participants' disease and the index test. See appendix 6 for details of strategy.

Results

The HTA document (ASSR 2011) concluded that

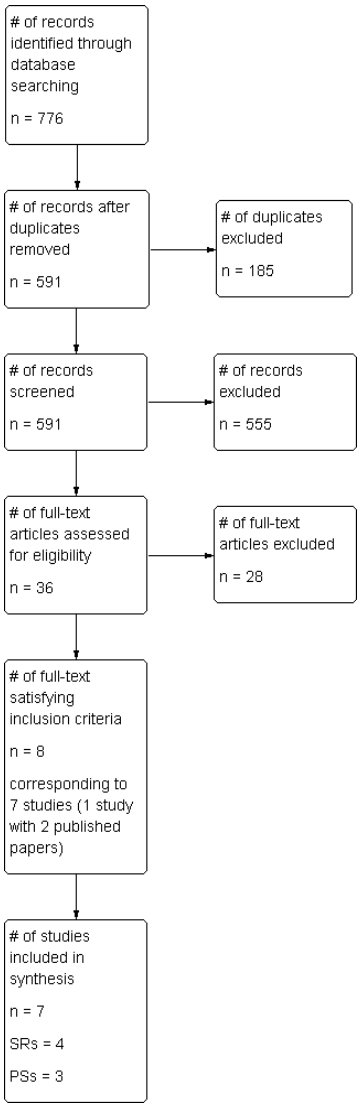
- the use of FDG-PET for N staging of patients with primary breast cancer is inappropriate. Level of evidence for diagnostic accuracy of FDG-PET resulted very low, due to the great variability in the estimates both of sensitivity and specificity.
- the use of FDG-PET for M staging of patients with locally advanced breast cancer is uncertain. Level of evidence for diagnostic accuracy of FDG-PET resulted low, due to the variability in the estimates of specificity.

Results of the search

Identification and selection of studies. The updated electronic search identified 776 records; 740 have been excluded because duplicates, or, after checking the abstract, for not meeting the inclusion criteria. Full text has been acquired for the remaining potentially eligible 36 records, from which 28 have been excluded on the basis of inclusion criteria (see below excluded studies). Seven studies (8 papers) have been finally included (PS - Heudel 2010; PS - Koolen 2012; PS - Pritchard 2012; SR - Brennan 2012; SR - Cooper 2011; SR - Peare 2010; SR - Warning 2011).

The study selection process is summarized in the PRISMA flow diagram (Moher 2009; see Figure 1)

Figure 1 Breast cancer: study selection according to PRISMA flow diagram (Moher 2009).



Description of included studies.

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

N staging

Systematic reviews

Three systematic reviews have been included (SR - Cooper 2011; SR - Peare 2010; SR - Warning 2011). These reviews assess the diagnostic accuracy of FDG-PET or FDG-PET/CT for axillary lymph nodes staging in women with breast cancer before any treatment.

The review by Cooper et al. (SR - Cooper 2011) includes 19 studies assessing FDG-PET, 7 FDG-PET/CT, 9 MRI for a total of 1729 participants for FDG-PET, 862 for FDG-PET/CT, 307 for MRI. Reference standard is

histopathology following axillary lymph node dissection or sentinel lymph node biopsy. Women included are newly diagnosed patients with early-stage breast cancer (stage I, II, IIIA).

The review by Peare et al. (SR - Peare 2010) includes 25 primary studies assessing FDG-PET or FDG-PET/CT for a total of 2460 participants. Reference standard is histopathology following axillary lymph node dissection or sentinel lymph node biopsy. Comparators considered are clinical examination (7 studies), ultrasound (4 studies), mammography (2 studies), MRI (1 study), MIBI (1 study). No data are reported about cancer extension of patients at entry.

The review by Warning et al. (SR - Warning 2011) includes 25 studies assessing FDG-PET, 9 FDG-PET/CT for a total of 2236 participants for FDG-PET, 859 for FDG-PET/CT. No data are reported about any comparator, reference standard, cancer extension of patients at entry.

Primary studies
Two studies (370 participants) evaluating diagnostic accuracy of FDG-PET/CT for axillary lymph node staging published after the above reported systematic reviews have been included (PS - Heudel 2010; PS - Pritchard 2012). Participants are women with breast cancer eligible for surgical resection. Reference standard is histopathology following axillary lymph node dissection or sentinel lymph node biopsy.

M staging

Systematic reviews
Two systematic reviews have been included (SR - Brennan 2012; SR - Warning 2011). These reviews assess the diagnostic accuracy of FDG-PET or FDG-PET/CT for M staging (distant metastases) in women with breast cancer before any treatment.

The review by Brennan et al. (SR - Brennan 2012) includes 8 studies assessing only FDG-PET and/or FDG-PET/CT (476 participants), 5 studies both conventional imaging and FDG-PET and/or FDG-PET/CT (488 participants), 9 studies only conventional imaging (abdominal ultrasound, chest X-ray, bone scan, CT, bone scintigraphy: 13860 participants). The 6 studies assessing FDG-PET/CT counted for 495 participants. Reference standard is clinical or imaging follow up, biopsy of positive lesions. Women included mixed population of stages and presentations at staging.

The review by Warning et al. (SR - Warning 2011) includes 6 studies assessing FDG-PET or FDG-PET/CT for a total of 296 participants. No data are reported about any comparator, reference standard, cancer extension of patients at entry.

Primary studies
Two studies (479 participants) evaluating diagnostic accuracy of FDG-PET/CT for M staging published after the above reported systematic reviews have been included (PS - Koolen 2012; PS - Pritchard 2012). Participants are women with stage I or II breast cancer (PS - Pritchard 2012), or with stage II or III breast cancer (eligible for neoadjuvant chemotherapy), without clinical evidence of metastasis. Reference standard is confirmation of suspect lesions obtained by cytological or histological verification or, if not available or possible, with additional imaging studies or by prolonged follow-up. One study (PS - Koolen 2012) considers conventional imaging techniques (bone scintigraphy, ultrasound of the liver, and chest radiography) as comparator.

Methodological quality of included studies

N staging

Systematic reviews
The systematic review by Cooper et al. (SR - Cooper 2011) has a comprehensive bibliographic search method, a

complete reporting of included studies, the methodological quality appropriately assessed and the statistical analysis well performed. The systematic review by Peare et al. (SR - Peare 2010) has an incomplete bibliographic search method, and a statistical analysis that does not considered the heterogeneity; reporting of included studies is complete, and methodological quality is appropriately assessed. The systematic review by Warning et al. (SR - Warning 2011) does not fulfil any of the dimensions of methodological quality.

Primary studies included into the systematic reviews (SR - Cooper 2011; SR - Peare 2010) could be prone to spectrum bias (retrospective design) and could have a biased evaluation of reference standard due to unclear or absence of blinding of index test when interpreting reference standard.

Primary studies
Blinding of the results either of the reference standard or of the index test is unclear for the two included studies (PS - Heudel 2010; PS - Pritchard 2012). Consecutive enrollment of participants is unclear for one of them studies (PS - Heudel 2010).

Quality assessment results for the included studies is provided in Figure 2.

M staging

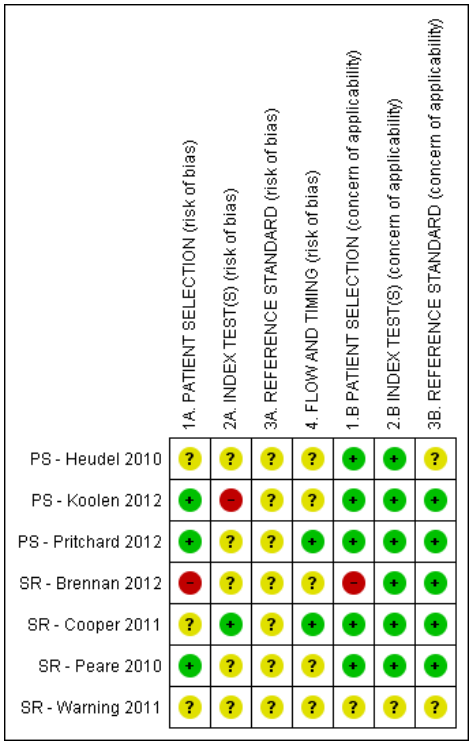
Systematic reviews
The systematic review by Brennan et al. (SR - Brennan 2012) has a complete reporting of included studies, the methodological quality appropriately assessed and the statistical analysis well performed; however the bibliographic search method is incomplete. The systematic review by Warning et al. (SR - Warning 2011) does not fulfil any of the dimensions of methodological quality.

Primary studies included into the systematic review (SR - Brennan 2012) could be prone to spectrum bias (retrospective design) and could have a biased evaluation of reference standard due to unclear or absence of blinding of index test when interpreting reference standard. Authors do not performed meta-analysis due to the heterogeneity of clinical parameters across studies (mixed populations for clinical features and pre-test probabilities of distant metastasis).

Primary studies
Blinding of the results either of the reference standard or of the index test is unclear or absent for the two included studies (PS - Koolen 2012; PS - Pritchard 2012).

Quality assessment results for the included studies is provided in Figure 2.

Figure 2 Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Findings

N staging

Detailed results are reported below in the table for Summary of Findings 1.

Systematic reviews
Only one systematic review (SR - Cooper 2011) reports pooled estimates of diagnostic accuracy for FDG-PET/CT and a comparator (MRI). Pooled sensitivity of FDG-PET/CT is 56.0% (CI 95% 44.0-67.0%), pooled specificity 96.0% (CI 95% 90.0-99.0%). Pooled sensitivity of MRI is 90.0% (CI 95% 78.0-96.0%), pooled specificity 90% (95% CI 75.0-96.0%).

Primary studies
Sensitivity ranges from 23.7% to 52.0% and specificity from 99.6% to 100%.

M staging

Detailed results are reported below in the table for Summary of Findings 2 .

Only one systematic review (SR - Brennan 2012) reports median estimates of diagnostic accuracy for FDG-PET/CT and comparators (combined conventional imaging, chest and/or abdomen CT). Median sensitivity of FDG-PET/CT is 100% (range 95.7-100%), median specificity 98.1% (range 91.2-100%). Median sensitivity of combined conventional imagingis 78.0% (range 33.3-100%), median specifiticy 91.4% (range 67.3-97.9%). Median sensitivity of CT is 100% (range 87.0-100%), median specificity 93.1% (range 85.7-97.6%).

Primary studies
For FDG-PET/CT sensitivity is 100% and specificity ranges from 96.0% to 96.8%. For conventional imaging sensitivity is 38.9% and specificity 88.2%.

Comments on Findings

N staging

Only evidence on diagnostic accuracy of FDG-PET/CT and comparators is available. There is no evidence of impact of FDG-PET/CT or comparators on clinical outcomes.
According to data of *moderate quality*, FDG/PET-CT seems to have: a lower sensitivity than the standard practice (sentinel lymph node biopsy or axillary lymph node dissection) and than MRI as comparator.

M staging

Only evidence on diagnostic accuracy of FDG-PET/CT and comparators is available. There is no evidence of impact of FDG-PET/CT and comparators on clinical outcomes.
According to data of *low quality*, FDG/PET-CT seems to have: similar sensitivity and slightly higher specificity compared to the best available comparator (CT).

Summary of Findings 1: Diagnostic accuracy of FDG-PET/CT for N staging (axillary nodes) in patients with breast cancer

Patients/population: brest cancer (early-stage: stage I, II, IIIA)
Target condition: N staging (axillary nodes)
Index test: FDG-PET, FDG-PET/CT
Comparators: MRI, ultrasound
Reference standard: histopathology following axillary lymph node dissection or sentinel lymph node biopsy

Ref.	No. of studies	Study design	Risk of Bias	Indirectness	Inconsistency	Imprecision	Diagnostic Accuracy FDG-PET	Diagnostic Accuracy Comparators	Quality of Evidence	
Cooper 2011	FDG-PET/CT: 7 (862 participants) MRI: 9 (307 participants)	Systematic review	Serious[1]	No	No	No	Sensitivity (pooled) 56.0% (95% CI 44.0-67.0%) Specificity (pooled) 96.0% (95% CI 90.0-99.0%)	MRI Sensitivity (pooled) 90% (95% CI 78.0-96.0%) Specificity (pooled) 90% (95% CI 75.0-96.0%)	Moderate	
Peare 2010	FDG-PET and/or FDG-PET/CT 25 (2460) Ultrasound 4 (not reported n. of participants)	Systematic review	Serious[2]	No	Serious	No	Sensitivity (range) 20.0-100% Specificity (range) 66.0-100%	Ultrasound Sensitivity (range) 52.0-100% Specificity (range) 83.0-100%	Low	
Warning 2011	FDG-PET/CT: 7 (859 participants)	Systematic review	Serious[3]	Serious[3]	Serious	No	Sensitivity (range) 20.0-98.0% Specificity (range) 84.0-100%		Very low	
Primary studies	FDG-PET/CT: 2 (370 participants)	diagnostic accuracy studies with prospective recruitment (consecutive or not consecutive)	Serious[4]	No	No	No	Sensitivity: (range) 23.7-52.0% Specificity: (range) 99.6-100%		Moderate	

1. About 40% of studies with possible spectrum bias (retrospective design); almost all studies with unclear or absence of blinding of index test to reference standard 2. About 24% of studies with possible spectrum bias (retrospective design); 28% of studies with unclear or absence of blinding of index test to reference standard 3. All dimensions of internal and external validity of included primary studies are unclear due to poor reporting 4. One study unclear if consecutive enrollment; all studies with unclear blinding of index test or reference standard

Summary of Findings 2: Diagnostic accuracy of FDG-PET/CT for M staging in patients with breast cancer.

Patients/population: breast cancer (all stages)
Target condition: M staging (distant metastases)
Index test: FDG-PET, FDG-PET/CT
Comparators: combined conventional imaging (abdomen ultrasound, chest X-ray, bone scintigraphy), chest and/or abdomen CT (lung and liver metastases)
Reference standard: clinical or imaging follow up, biopsy of positive lesions

Ref.	No. of studies	Study design	Risk of Bias	Indirectness	Inconsistency	Imprecision	Diagnostic Accuracy FDG-PET	Diagnostic Accuracy Comparators	Quality of Evidence	
Brennan 2012	FDG-PET/CT 6 (495 participants) combined conventional imaging 7 (1299 participants) CT 5 (1470 participants)	Systematic review	Serious[1]	Serious[2]	No	No	Sensitivity (median): 100% (range 95.7-100%) Specificity (median): 98.1% (range 91.2-100%)	combined conventional imaging Sensitivity (median): 78.0% (range 33.3-100%) Specificity (median): 91.4% (range 67.3-97.9%) CT Sensitivity (median): 100% (range 87.0-100%) Specificity (median): 93.1% (range 85.7-97.6%)	Low	
Warning 2011	FDG-PET or FDG-PET/CT 6 (296 participants)	Systematic review	Serious[3]	Serious[3]	No	No	Sensitivity (range) 80.0-100% Specificity (range) 75.0-100%		Low	
Primary	FDG-PET/CT: 2	diagnostic accuracy	Serious[4]	Serious[5]	No	No	Sensitivity:	conventional	Low	

studies	(479 participants) conventional imaging 1 (154 participants)	studies with prospective recruitment (consecutive)					(range) 100% Specificity: (range) 96.0-96.8%	imaging Sensitivity 38.9% Specificity 88.2%		

1. About 64% of studies with possible spectrum bias (retrospective design); all studies with unclear blinding of index test and reference standard
2. Authors did not performed meta-analysis due to the heterogeneity of clinical parameters across studies (mixed populations for clinical features and pre-test probabilities of distant metastasis)
3. All dimensions of internal and external validity of included primary studies are unclear due to poor reporting
4. Unclear or no blinding of index test and reference standard
5. One study with stage I or II disease

Authors' conclusions

N staging

The HTA document (ASSR 2011) judged the quality of appraised evidence as very low and concluded that the use of FDG-PET for N staging of patients with breast cancer is inappropriate.

Evidence from the studies retrieved through our update - ranging from very low to moderate quality - confirms the above conclusions.

M staging

Accurate M staging of patients with breast cancer is important and there is a rationale in support of the use of FDG-PET/CT in patients with locally advanced (T3-N1 disease) breast cancer eligible to curative treatment.

The HTA document (ASSR 2011) judged the quality of appraised evidence as low and concluded that the use of FDG-PET for M staging of patients with locally advanced breast cancer is uncertain.

The low quality evidence from the studies retrieved through our update does not challenge the above conclusions.

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PS - Heudel 2010

Heudel P, Cimarelli S, Montella A, Bouteille C, Mognetti T. Value of PET-FDG in primary breast cancer based on histopathological and immunohistochemical prognostic factors. Int.J Clin.Oncol. 2010;15:588-93.

PS - Koolen 2012

Koolen BB, Vrancken Peeters MJ, Aukema TS, Vogel WV, Oldenburg HS, van der Hage JA, et al. 18F-FDG PET/CT as a staging procedure in primary stage II and III breast cancer: comparison with conventional imaging techniques. Breast Cancer Research and Treatment 2012;131:117-26.

PS - Pritchard 2012

Pritchard KI, Julian JA, Holloway CM, McCready D, Gulenchyn KY, George R, et al. Prospective Study of 2-[18F]Fluorodeoxyglucose Positron Emission Tomography in the Assessment of Regional Nodal Spread of Disease in Patients With Breast Cancer: An Ontario Clinical Oncology Group Study. J Clin.Oncol. 2012;(1527-7755 (Electronic), 0732-183X (Linking)).

SR - Brennan 2012

Brennan ME, Houssami N. Evaluation of the evidence on staging imaging for detection of asymptomatic distant metastases in newly diagnosed breast cancer. Breast 2012;21:112-23.

SR - Cooper 2011

Cooper KL, Harnan S, Meng Y, Ward SE, Fitzgerald P, Papaioannou D, et al. Positron emission tomography (PET) for assessment of axillary lymph node status in early breast cancer: A systematic review and meta-analysis. Eur.J Surg.Oncol. 2011;37:187-98.

Cooper KL, Meng Y, Harnan S, Ward SE, Fitzgerald P, Papaioannou D, et al. Positron emission tomography (PET) and magnetic resonance imaging (MRI) for the assessment of axillary lymph node metastases in early breast cancer: systematic review and economic evaluation. Health Technology Assessment 2011;15:iii-134.

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Excluded studies

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Bruening 2012

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4.11 FDG-PET/CT for staging of esophageal cancer

Background

Esophageal cancer is relatively rare in Italy; during 2003-2005, it represented 1.0% of all cancers among males and 0.4% among females, corresponding to a crude incidence of 6.7 per 100,000 person/year in males and 2.2 per 100,000 person/year in females (Registri Tumori). Five-year survival is around 10% (CI 95% 9-11%), across all stages of disease (Registri Tumori). The two main esophageal cancers (each accounting for approximately 50% of all cases) are squamous cell carcinoma and adenocarcinoma (AIOM 2010; ESMO 2010; NCCN 2011).

Target condition being diagnosed

Target conditions are: a) disease involvement of regional lymph nodes (those in the esophgeal drainage area including coeliac axis nodes and paraesophageal nodes in the neck but not supraclavicular nodes) identified through N staging, and b) presence of any distant metastasis, identified through M staging (ESMO 2010).

Index test(s)

FDG-PET/CT.

Among recent guidelines only NCCN guidelines (NCCN 2011) recommends use of FDG-PET/CT for staging of patients with negative results of metastatic disease from conventional imaging tests. Other guidelines (AIOM 2010; ESMO 2010; SIGN 2006) consider FDG-PET/CT as potentially useful for staging but not routinely indicated.

Alternative test(s)

Routine N and M staging includes CT scan of chest and abdomen. In patients candidate for surgical resection endoscopic ultrasound is used in order to evaluate the T and N stage of the tumor ((AIOM 2010 - Esophageal cancer; ESMO 2010 - Esophageal cancer; SIGN 2006 - Esophageal cancer).

Reference standard for N staging is histopathology following resection or fine niddle aspiration, follow-up with imaging techniques; reference standard for M staging is histopathology of metastases, follow-up with imaging techniques (SR - van Vliet 2008).

Rationale

Role of staging. Tumor stage at diagnosis and comorbidity are strong predictors of outcome and determinants of survival. Moreover accurate pre-operative staging is necessary to correctly direct patients to curative surgery, non curative surgery or non surgical therapy (combined chemoradiation). N staging can be used to decide on extension of surgical resection and need for neoadjuvant treatment (Saltzman 2011). M staging has a role in identifying and selecting patients candidate to curative surgery (AIOM 2010; ESMO 2010; NCCN 2011; SIGN 2006).

Treatment options. Surgical treatment is the therapy of choice for all patients with potentially curable esophageal cancer and who are fit for major surgery (AIOM 2010; ESMO 2010; NCCN 2011; SIGN 2006). Pre-operative chemoradiation is recommended as neoadjuvant treatment in patients with locally advanced cancer to obtain mass reduction and allow less invasive surgery (AIOM 2010; ESMO 2010; NCCN 2011). Only palliative treatment (non curative surgery or non surgical therapy with combined chemoradiation) is available for

metastatic esophageal cancer, aimed at improving quality of life.The expected 2-year survival after curative surgical treatment (without neoadjuvant chemoradiotherapy) ranges between 20 and 50%. However in presence of regional lymph node involvement long-term survival does not exceed 25%. In patients with locally advanced cancer pre-operative chemoradiotherapy seems to improve the 2-year survival by 13% (absolute difference) compared to surgical treatment only (Gebski 2007).

Objectives

The objective of this review was to examine the diagnostic accuracy and the clinical effectiveness of FDG-PET/CT for N staging and M staging of patients diagnosed with esophageal cancer compared to conventional imaging examination.

Search methods for identification of studies

Evidence is based on a) the conclusion of the most recent HTA report on head and neck cancer (ASSR 2011) which was of good quality and had an electronic search updated to July 2010; b) a further search of studies published between January 2010 and March 2012. The key words described the participants' disease and the index test. See appendix 7 for details of strategy.

Results

The HTA document (ASSR 2011) concluded that

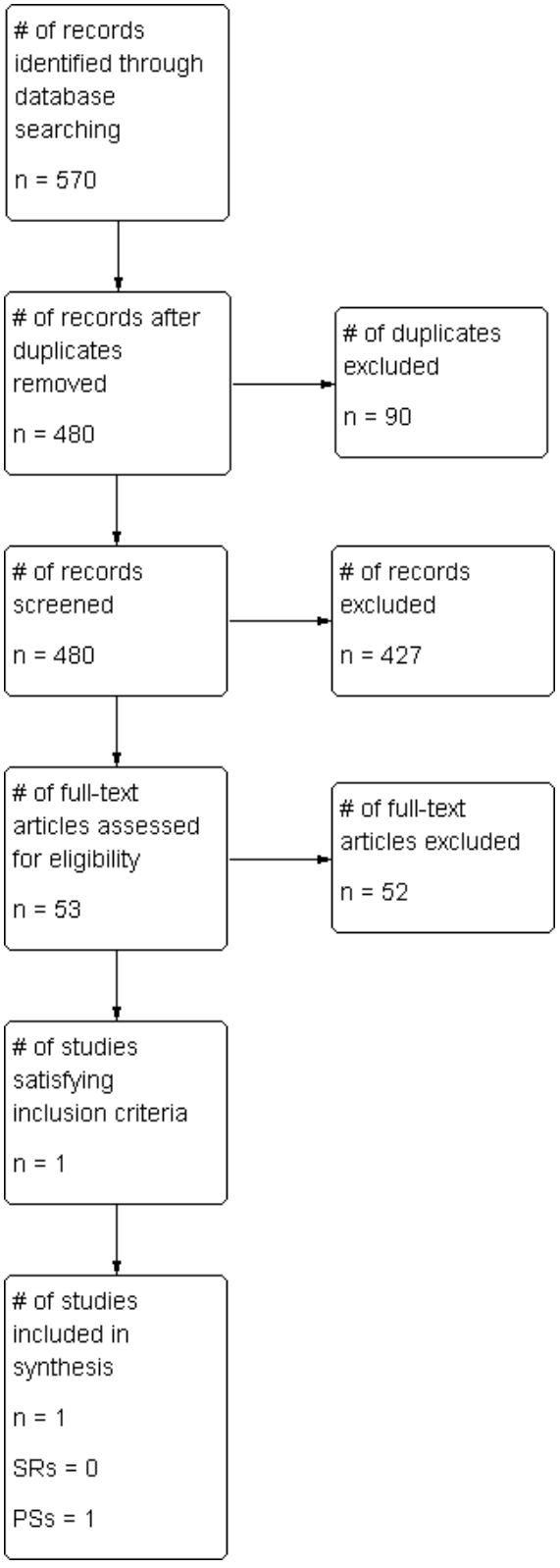
- the use of FDG-PET in staging patients with esophageal cancer for regional lymph nodes, in replacement of endoscopic ultrasonography is uncertain. The level of evidence for diagnostic accuracy of FDG-PET is *very low*, with heterogeneous estimates for both sensitivity and specificity.
- the use of FDG-PET in staging patients with esophageal cancer for distant metastasis is appropriate. Level of evidence for diagnostic accuracy of FDG-PET was judged *moderate* with FDG-PET performing better than CT.

Results of the search

Identification and selection of studies. The electronic search identified 570 records; 517 have been excluded because duplicates or, after checking the abstract, for not meeting the inclusion criteria. Full text has been acquired for the remaining potentially eligible 53 records, from which 52 studies have been excluded on the basis of inclusion criteria (see the list of excluded studies). Only one study has been finally included (PS - Hsu 2011).

The study selection process is summarized in the PRISMA flow diagram (Moher 2009; see Figure 1).

Figure 1 Esophageal cancer: study selection according to PRISMA flow diagram (Moher 2009).



Description of included studies

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

N staging

Systematic reviews
None retrieved.

Primary studies
One study (76 participants) evaluating diagnostic accuracy of FDG-PET/CT for regional lymph node staging has been included (PS - Hsu 2011). Participants are patients with squamous cell carcinoma, any tumour invasion depth (T1 to T4) and eligible for surgical resection. Referecence standard is the postoperative pathologic staging. No comparator is assessed.

M staging

Systematic reviews
None retrieved.

Primary studies
None retrieved.

Methodological quality of included studies

N staging

Systematic reviews
None retrieved.

Primary studies
The only included study has an unclear blinding of the results of index test when reference standard is interpreted and a relevant attrition of the sample (PS - Hsu 2011).

Quality assessment results for the included studies is provided in Figure 2.

M staging

Systematic reviews
None retrieved.

Primary studies
None retrieved.

Figure 2 Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

Findings

N staging

Detailed results are reported below in the table for Summary of Findings 1.

Systematic reviews
None retrieved.

Primary studies
The only included study (PS - Hsu 2011) reports a sensitivity of 52.4% and a specificity of 87.3%.

M staging

Systematic reviews
None retrieved.

Primary studies
None retrieved.

Comments on Findings

N staging

Only evidence on diagnostic accuracy of FDG-PET/CT is available. There is no evidence of impact of FDG-PET/CT or comparators on clinical outcomes
Due to data from only one study of *low quality*, no conclusion can be drawn on FDG/PET-CT for N staging.

M staging

There is no evidence on diagnostic accuracy and of impact of FDG-PET/CT or comparators on clinical outcomes.

Summary of Findings 1: Diagnostic accuracy of FDG-PET for N staging (regional lymph nodes) in patients with esophageal cancer

Patients/population: esophageal cancer
Target condition: N staging (regional lymph nodes)
Index test: FDG-PET/CT
Comparators: none
Reference standard: histopathology following resection, biopsy or fine niddle aspiration

Ref.	No. of studies	Study design	Risk of Bias	Indirectness	Inconsistency	Imprecision	Diagnostic Accuracy FDG-PET	Diagnostic Accuracy Comparators	Quality of Evidence	
Primary studies	1 (76 participants)	diagnostic accuracy study with prospective recruitment	Serious[1]	No	No	Serious	sensitivity 52.4% specificity 87.3%		Low	

1. possible attrition bias; unclear blinding of index test and reference standard

Authors' conclusions

N staging

Accurate N staging of patients with primary esophageal cancer is very important and there is a rationale in support of the use of FDG-PET/CT for patients eligible to curative treatment.

The HTA document (ASSR 2011) judged the quality of appraised evidence as very low and concluded that the use of FDG-PET in staging patients with esophageal cancer for regional lymph nodes is uncertain.

The only one study retrieved through our update and judged to be of low quality does not challenge the above conclusion.

M staging

Accurate M staging of patients with primary esophageal cancer is very important and there is a rationale in support of the use of FDG-PET/CT for patients eligible to curative treatment.

The HTA document (ASSR 2011) judged the quality of appraised evidence as moderate and concluded that the use of FDG-PET in staging patients with esophageal cancer for distant metastasis is appropriate.

No additional evidence was retrieved through our update thus the above conclusions are not challenged.

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4.12 FDG-PET/CT for staging of stomach cancer

Background

Despite the declining trend in both incidence and mortality worldwide (Bertuccio 2009), gastric cancer remains the fourth most common cancer with more than 980,000 cases occurring yearly and the second leading cause of cancer mortality (Jemal 2011). The incidence per 100.000 inhabitants in the developed world was 16.1 in males and 7.3 in females (Jemal 2011). In italy, between 2003-2005, gastric cancer was the 5th most common cancer for both sexes and among males accounted for 5.2% of total cancer incidence (females 4.6%), excluding non-melanoma skin cancers. The number of deaths attributable to gastric cancer accounted for 6.9% of male cancer mortality (female 6.8%), which made it the 4th most common cause of cancer death (females 5th) (AIRTUM 2009).

Target condition being diagnosed

Target conditions are: a) disease involvement of regional lymph nodes, identified through N staging, and b) presence of distant metastases, identified through M staging.

Index test(s)

FDG-PET/CT.

PET is not routinely indicated in the staging of oesophageal and gastric cancers according to SIGN guidelines (SIGN 2006).

Alternative test(s)

Endoscopic ultrasonography is the most accurate method in the preoperative T staging of the tumour (Kelly 2001). For nodal staging and evaluation of distant metastasis, spiral CT is currently the method of choice in the preoperative stage, (Kim 2011) though technology multislice CT systems are reported to give results as accurate as endoscopic.

Rationale

Role of staging. The optimal choice of the operative procedure depends on the stadium of a disease, the size and localization of the primary tumor, lymph node involvement and the general patient's condition. Also differentiation of intramural tumor extent and invasion beyond the gastric wall has considerable clinical importance, because the prognosis of the disease is directly related to the depth of invasion of the gastric wall and lymph node involvement. Lymph node involvement is the most important single factor, followed by T stage (Lerut 2004). The number of involved nodes and the ratio of involved to uninvolved nodes significantly influence long term outcome (Kim 2001).

Staging consists of physical examination, blood count and differential, liver and renal function tests, endoscopy and CT scan of the thorax, abdomen and pelvis. Endoscopic ultrasound (EUS) is helpful in determining the proximal and distal extent of the tumour as well as its T stage, although it is less useful in antral tumours. Laparoscopy with or without peritoneal washings for malignant cells is recommended in all those considered to be potentially resectable to exclude metastatic disease. In patients with gastric cancer CT scan of the chest and abdomen with intravenous contrast and gastric distension with oral contrast or water should be performed

routinely (SIGN 2006). PET scans, if available, may upstage patients with gastric cancer but can be negative, especially in patients with mucinous and diffuse tumours (Okines 2010).

Treatment options. The most essential aim of gastric cancer surgery is to completely remove the tumour with histologically confirmed tumour free (R0) surgical margins which usually requires proximal and distal margin clearance of at least 5-10 cm. To achieve this goal, the positions of the cancer and the tumor margin and stage have to be known which is the main determinant of survival. The aim of surgical resection is to achieve cure. The extent of resection must also take into account factors such as: site of tumour, submucosal spread as assessed by endoscopic ultrasonography, histological type of tumour, and presence of satellite nodules (SIGN 2006).

Objectives

The objective of this review was to examine the diagnostic accuracy and the clinical effectiveness of FDG-PET/CT for N staging and M staging of patients diagnosed with gastric cancer (adenocarcinoma) compared to conventional imaging examination.

Search methods for identification of studies

Evidence is based on a) the conclusion of the most recent HTA report on gastric cancer (KCE 2009) which was of good quality and had an electronic search updated to January 2009; b) a further search of studies published between January 2009 and March 2012. The key words described the participants' disease and the index test. See appendix 8 for details of strategy.

Results

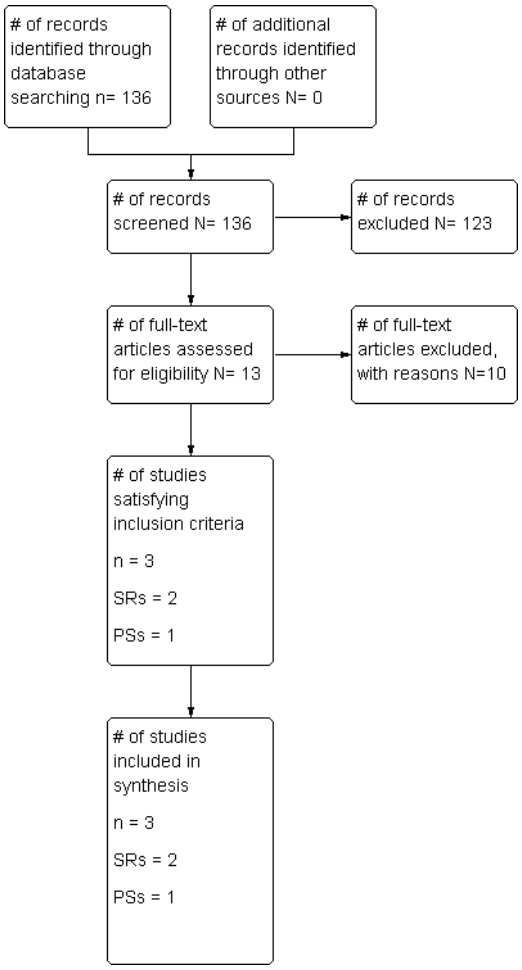
The HTA document (KCE 2009) concluded that

- no systematic reviews or primary studies were found regarding gastric cancer staging.

Results of the search

Identification and selection of studies. The updated electronic search identified 136 records; 123 have been excluded after checking the abstract, for not meeting the inclusion criteria. Full text has been acquired for the remaining potentially eligible 13 records. Three studies have been finally included (PS - Chung 2010; SR - Kwee 2009; SR - Wang 2011). The study selection process is summarized in the PRISMA flow diagram (Moher 2009; see Figure 1).

Figure 1 Study flow diagram.



Description of included studies

One study evaluates diagnostic accuracy of FDG-PET and FDG-PET/CT (SR - Kwee 2009) for N staging; for M staging, one study (SR - Wang 2011) assesses the diagnostic accuracy of FDG-PET and one study (PS - Chung 2010) that of FDG-PET/CT.

Diagnostic accuracy - N staging

Systematic reviews

One systematic review is included (SR - Kwee 2009). This review systematically assessed the current role of different imaging techniques involved in lymph node staging in gastric cancer: FDG-PET (4 studies), FDG-PET/CT (1 study), abdominal ultrasonography (AUS - 6 studies), endoscopic ultrasonography (EUS - 30 studies), multidetector-row computed tomography (MDCT - 10 studies), magnetic resonance imaging (MRI - 3 studies). For FDG-PET four studies were included with 183 patients and for FDG-PET/CT one study with 78 patients. The reference standard was histopathological examination after surgery or clinical follow-up.

Diagnostic accuracy - M staging

Systematic reviews

The review by Wang et al. (SR - Wang 2011) assessed the diagnostic accuracy of FDG-PET for detection of hepatic and peritoneal metastases (M staging). The aim of this study was to systematically review the current role of different imaging techinques: FDG-PET (5 studies), ultrasonography (US - 8 studies), endoscopic ultrasonography (EUS - 5 studies), computed tomography (CT - 22 studies), magnetic resonance imaging (MRI - 2 studies) in assessing hepatic and peritoneal metastases in gastric cancer. For FDG-PET five studies were included with 338 patients. The reference standard was histopathological examination after surgery or clinical follow-up.

Primary studies

One study (PS - Chung 2010) with 35 patients evaluating diagnostic accuracy of FDG-PET/CT for detecting solid organ metastases (lung, liver, bone, or adrenal gland) and, separately peritoneum or nonregional lymph node metastases (M Staging) was included; Comparators: CT, bone scintigraphy, magnetic resonance imaging. Reference standard: histologic confirmation or by contrast-enhanced CT and serial follow-up.

Impact on clinical outcomes - Any staging

None retrieved.

Methodological quality of included studies

Methodological quality summary for the included studies is provided in Figure 2

Diagnostic accuracy - N staging

Systematic reviews

The systematic review by Kwee et al. (SR - Kwee 2009;) reports bibliographic search restricted to MEDLINE and Embase databases and an assessement of methodological quality of included studies according to a modified QUADAS tool. The methodological quality of the included studies was assessed in terms of the potential for bias (internal validity) and lack of generalizability (external validity). For each of the included studies, 13 methodological quality items were assessed (maximum total score: 100%; a study was judged of high quality if score > 60%). For the FDG-PET studies, the total methodological quality score ranged from 46% to 62% (median, 58%). Two FDG-PET studies (Mukai 2006 and Yun 2005) were of high methodological quality. For the only FDG-PET/CT study (Yang 2008), the total methodological quality score was 54%.

High or unclear risk of bias regarded the following items: study design (ony one prospective study), avoidance of disease progression bias, avoidance of test review bias (blind interpretation of reference test without knowledge of index test) and avoidance of selection bias (consecutive series of patients or random selection of patients was performend in only one study).

Diagnostic accuracy - M staging

Systematic reviews

Wang et al. (SR - Wang 2011) report an assessement of methodological quality of included studies according to QUADAS tool. Bibliographic search method is comprehensive, and the characteristics of included studies are clearly reported; the methodological quality of included studies appropriately assessed and the statistical

analysis well conducted (meta-analysis). Primary studies included into the systematic review could be prone to selection bias and for most quality items the judgment is unclear.

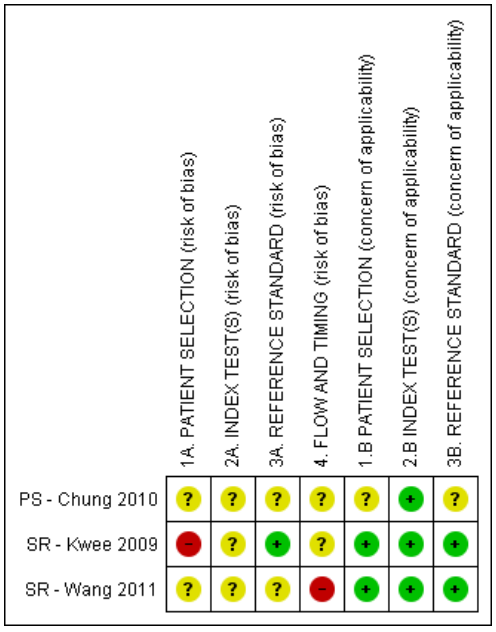
Primary studies

Chung et al. (PS - Chung 2010) enrolled 35 consecutive patients; all items of QUADAS-2 are assessed as having an unclear risk of bias with the exception of Index test (applicability concern).

Impact on clinical outcomes - Any staging

None retrieved.

Figure 2 Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Findings

Diagnostic accuracy - N staging

Detailed results are reported below in Summary of findings1.

Systematic reviews
The systematic review by Kwee et al. (SR - Kwee 2009; Summary of Findings 1) does not report pooled estimates of diagnostic accuracy for the different imaging techniques.

The sensitivity and specificity of FDG-PET varied between 33.3% and 64.6% (median 34.3%) and 85.7% and 97.0% (median 93.2%) respectively. There was no significant difference between the mean sensitivity of FDG-PET studies with high and low methodological quality (34.3% vs 49.0%; P = 0.515). There also was no significant difference between the mean specificity of studies with high and low methodological quality (96.7%

vs 87.9%; P = 0.131). The sensitivity and specificity of the only one FDG-PET/CT study included were 54.7% and 92.2%, respectively.

The sensitivity of AUS varied between 12.2% and 80.0% (median 39.9%), specificity between 56.3% and 100% (median 81.8%). The sensitivity of EUS varied between 16.7% and 96.8% (median 70.8%), specificity between 48.4% and 100% (median 84.6%). The sensitivity of MDCT varied between 62.5% and 91.9% (median 80.0%), specificity between 50.0% and 87.9% (median 77.8%). The sensitivity of MRI varied between 54.6% and 85.3% (median 68.8%), specificity between 50.0% and 100% (median 75.0%).

Diagnostic accuracy - M staging

Detailed results are reported below in Summary of Findings 2 (Systematic reviews) and in Summary of Findings 3 (Primary studies).

Systematic reviews

The systematic review by Wang et al. (SR - Wang 2011; Summary of Findings 2) reports pooled estimates of diagnostic accuracy of FDG-PET for M staging (liver and peritoneal metastases) compared with histopathological examination after surgery or clinical follow-up.

Liver metastases. FDG-PET pooled sensitivity was 70% (95% CI 36-90%), pooled specificity was 96% (95% CI 81-99%). US pooled sensitivity was 54% (95% CI 34-73%) and pooled specificity was 98% (95% CI 90-99%). CT pooled sensitivity was 74% (95% CI 59-85%) and pooled specificity 99% (95% CI 97-100%). Only two studies' data were sufficient for EUS and MRI, so pooled analysis was not conducted.

Peritoneal metastases. FDG-PET pooled sensitivity was 28% (95% CI 17-44%), pooled specificity was 97% (95% CI 83-100%). US pooled sensitivity was 9% (95% CI 3-21%), pooled specificity was 99% (95% CI 96-100%). EUS pooled sensitivity was 34% (95% CI 10-69%), pooled specificity was 96% (95% CI 87-99%). CT pooled sensitivity was 33% (95% CI 16-56%), pooled specificity was 99% (95% CI 98-100%).

Primary studies

The study included (PS - Chung 2010; Summary of findings 2) reports the following diagnostic accuracy estimates of FDG-PET/CT:

Solid organ metastases: sensitivity 95.2%, specificity: 100%

Peritoneal- only metastases: sensitivity: 66.7%, specificity:100%

Diagnostic accuracy - Any staging

None retrieved.

Impact on clinical outcomes - Any staging

None retrieved.

Comments on Findings

N staging

Only evidence on diagnostic accuracy of FDG-PET/CT and comparators is available. There is no evidence of impact of FDG-PET/CT or comparators on clinical outcomes
According to data of *very low quality*, FDG-PET/CT seems to have high specificity but very low sensitivity compared to AUS and CT .

M staging

Only evidence on diagnostic accuracy of FDG-PET/CT and comparators is available. There is no evidence of impact of FDG-PET/CT or comparators on clinical outcomes.
According to data of *low quality*, FDG-PET/CT seems to have a worse diagnostic accuracy than CT in detecting hepatic metastasis and than EUS in detecting peritoneal metastasis

***Summary of Findings 1**:* Diagnostic accuracy of FDG-PET and FDG-PET/CT for N staging of patients with gastric cancer (adenocarcinoma)

Patients/population: gastric cancer (adenocarcinoma)
Index test:FDG-PET and FDG-PET/CT.
Comparators: abdominal ultrasonography (AUS), endoscopic ultrasonography (EUS), multidetector-row computed tomography (MDCT), magnetic resonance imaging (MRI)
Reference standard: histopathological examination after surgery or clinical follow-up.

Ref.	N°studies	Study design	Risk of bias	indirectness	inconsistency	imprecision	Diagnostic accuracy FDG-PET and FDG-PET/CT	Diagnostic accuracy comparator	Quality of evidence
SR - Kwee 2009	4 diagnostic studies evaluating the accuracy (for N-staging) of FDG-PET and 1 study of FDG-PET/CT	Systematic review	serious[1]	no	serious[2]	serious[3]	FDG-PET Sensitivity median 34.3% (range 33.3-64.6%) Specificity median 93.2% (range 85.7-97.0%) FDG-PET/CT Sensitivity 54.7%, (95% CI 42.6-66.3%); Specificity 92.9% (95% CI 68.5-98.7%).	AUS Sensitivity median 39.9% (range 12.2- 80.0%) Specificity median 81.8% (range 56.3-100%) EUS Sensitivity median 70.8% (range 16.7-96.8%) Specificity median 84.6% (range 48.4-100%) MDCT Sensitivity median, 80.0% (range 62.5-91.9%) Specificity median 77.8% (range 50.0-87.9%) MRI Sensitivity median, 68.8% (range 54.6-85.3%) Specificity median 75.0% (range 50.0-100%)	Very Low

1. In only one study consecutive patients were enrolled. Blinding interpretation of index test was in 3 of 5 studies; there was no blinding interpretation of reference standard without knowledge of index test in all studies. Only one study was reported as prospective. 2. Because of the heterogeneity and moderate methodological quality of the included studies, no meta-analysis was performed. 3. Overall small number of patients (in FDG-PET and FDG-PET/CT)

Summary of Findings 2: *Diagnostic accuracy of FDG-PET for M (liver and peritoneal metastases) staging of patients with gastric cancer (adenocarcinoma)*

Patients/population: gastric cancer (adenocarcinoma)
Index test:FDG-PET
Comparators: US, EUS, CT, MR
Reference standard: histopathological examination after surgery or clinical follow-up; histologic confirmation or by contrast-enhanced CT and serial follow-up

Ref.	N°studies	Study design	Risk of bias	indirectness	inconsistency	imprecision	Diagnostic accuracy FDG-PET	Diagnostic accuracy comparator	Quality of evidence
SR - Wang 2011	5 diagnostic studies evaluating the accuracy (for M-staging: liver and peritoneal metastases) of FDG-PET	Systematic review	very serious[1]	no	no	no	Liver metastases Pooled sensitivity 70% (95% CI 36-90%) Pooled specificity 96% (95% CI 81-99%). Peritoneal metastases Pooled Sensitivity 28% (95% CI 17-44%). Pooled Specificity 97% (95% CI 83-100%).	Liver metastases US pooled sensitivity 54% (95% CI 34-73%) pooled specificity 98% (95% CI 90-99%) CT pooled sensitivity 74% (95% CI 59-85%) pooled specificity 99% (95% CI 97-100%) Peritoneal metastases US pooled sensitivity 9% (95% CI 3-21%)	Low

								pooled specificity 99% (95% CI 96-100%) EUS pooled sensitivity 34% (95% CI 10-69%) pooled specificity 96% (95% CI 87-99%) CT pooled sensitivity 33% (95% CI 16-56%) pooled specificity 99% (95% CI 98-100%)	
Primary studies	1 study	Primary study diagnostic accuracy measurement within a prognostic cohort study (for M-staging of FDG-PET/CT).	serious[1]	serious[2]	NA*	serious[3]	**Solid organ metastases** Sensitivity 95.2% Specificity 100% **Peritoneal-only metastases** Sensitivity 66.7% Specificity 100%	not reported	Very Low

1 Risk of bias items are judged no or unclear
2. Because of the conduction and interpretation of reference standard.
3. Small number of enrolled patients.
NA*: not applicable

Authors' conclusions

Diagnostic accuracy - N staging:

The rationale in support of the use of FDG-PET/CT for N staging of patients with gastric adenocarcinoma is weak.

The HTA document (KCE 2009) did not find any studies.

Evidence from the studies retrieved through our update and judged to be of very low quality suggests that the use of FDG-PET/CT in staging patients with gastric adenocarcinoma for regional lymph nodes would be inappropriate.

Diagnostic accuracy - M staging:

The rationale in support of the use of FDG-PET/CT for M staging (liver and peritoneal metastases) of patients with gastric adenocarcinoma is weak.

The HTA document (KCE 2009) did not find any studies.

Evidence from the studies retrieved through our update and judged to be of low to very low quality suggests that the use of FDG-PET/CT in staging patients with gastric adenocarcinoma for distant metastasis would be inappropriate.

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4.13 FDG-PET/CT for staging of pancreatic cancer

Background

In 2003-2005 pancreatic cancer was the 10th most frequent cancer in males and the eighth in females (2.5% and 3.6 of all tumors excluding cutaneous neoplasms), its incidence was just over 18 cases per 100,000 in both genders. In 2006 there were 4.756 deaths in males and 4.818 deaths in the female population. It is the sixth most frequent cause of cancer death for males and the fourth in females (Registri Tumori 2009). In last two decades the incidence trend of pancreatic cancer in Italy has increased while mortality rates have levelled off after a slight rise.

Target condition being diagnosed

Target conditions are: a) disease involvement of regional lymph nodes identified through N staging, and b) presence of distant metastases, identified through M staging.

Index test(s)

FDG-PET/CT.

FDG-PET/CT is not recommended as staging procedure according to ESMO guidelines (ESMO 2010).

Alternative test(s)

Standard imaging modalities are CT, Endoscopic Retrograde Cholangiopancreatography (ERCP), Endoscopic Ultrasonography (EUS). The reference test are either follow up or histology speciments.

Rationale

Role of staging. Pancreatic cancer is a solid tumor which is particularly difficult to diagnose early given the deep position of the organ in viscera and its late and aspecific presentation. Tumour size, nodal involvement and histological grade are strong prognostic factors (ESMO 2010). The prognosis of patients who have undergone radical resection for pancreatic adenocarcinoma depends mainly on presence of negative resection margins. The importance of staging is linked to the appropriateness of resection of both the primary and metastatic disease. FDG-PET/CT could have a role in the staging of patients with pancreatic cancer in case of a diagnostic conflict after conventional staging. However, these cases needed to be discussed on a one-one basis (KCE 2009).

Treatment options. The treatment of pancreatic cancer is undertaken with two different aims. The first is radical surgery for patients with early stage of disease, mainly stage I and some stage II. In all other cases, the aim of treatment is the palliation of the several distressing symptoms related to this cancer (ESMO 2010).

Objectives

The objective of this review was to examine the diagnostic accuracy and the clinical effectiveness FDG-PET/CT for staging of patients diagnosed with pancreatic cancer compared to conventional imaging examination.

Search methods for identification of studies

Evidence is based on a) the conclusion of the most recent HTA report on pancreatic cancer (KCE 2009) which was of good quality and had an electronic search updated to January 2009; b) a further search of studies published between January 2009 and March 2012. The key words described the participants' disease and the index test. See appendix 9 for details of strategy.

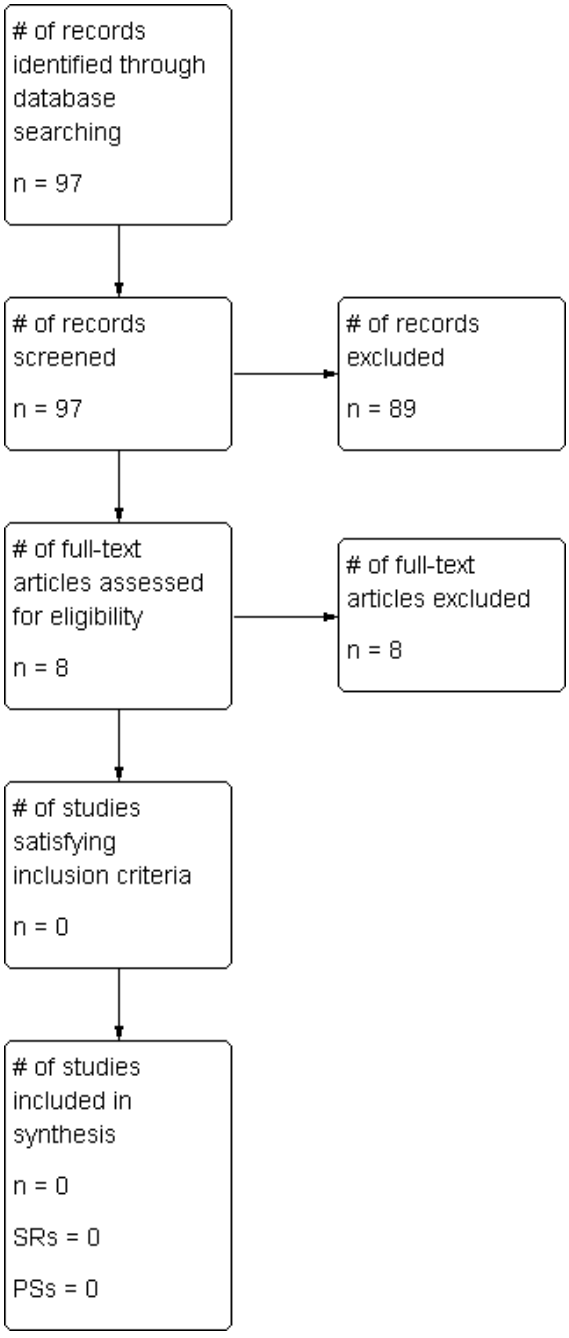
Results

The 2009 KCE report assessed the use of FDG-PET/CT and FDG-PET for diagnostic and staging purposes (KCE 2009). On the basis of 13 retrospective and prospective studies, KCE reported finding limited evidence of diagnostic utility and similarly limited evidence of sensitivity and specificity of the test for staging. For both indications it found no evidence of benefit compared to the currently available alternatives CT and EUS, US and ERCP. The conclusions were that the utility of FDG PET/CT for both diagnosis and staging needs confirmation from further larger studies. Therefore no firm conclusions can be made on the use of PET for staging of pancreatic cancer.

Results of the search

Identification and selection of studies.
Our searches identified 97 titles possibly fitting inclusion criteria. After screening of titles and abstracts, 8 studies were retrieved and read. All eight studies were excluded for various reasons (see Excluded studies: Abgral 2011; Buchs, 2011; Herrmann 2012; Kauhanen 2009; Kitajima 2010; Kuwatani 2009; Okano 2011; Tang 2011). The study selection process is summarized in the PRISMA flow diagram (Moher 2009; see Figure 1).

Figure 1 Pancreatic cancer: study selection according to PRISMA flow diagram (Moher 2009).



Description of included studies

Systematic reviews
None were included.

Primary studies

None were included.

Authors' conclusions

Accurate staging of patients with pancreatic cancer is very important. There is reasonable rationale in support of the use of FDG-PET/CT for patients with equivocal results following conventional imaging.

The HTA document (KCE 2009) did not find any studies.

No evidence was retrieved through our update thus the use of FDG-PET/CT in staging patients with pancreatic cancer would be inappropriate.

References

Inlcuded studies

KCE 2009

Vlayen J, Stordeur S, Van den Bruel A, Mambourg F, Eyssen M. Positron Emissie Tomografie: een update. Health Technology Assessment (HTA). Federaal Kenniscentrum voor de Gezondheidszorg (KCE) 2009;KCE reports 110A (D/2009/10.273/24). Last access 28th August 2012

Excluded studies

Abgral 2011

Abgral, R.; Leboulleux, S.; Deandreis, D.; Auperin, A.; Lumbroso, J.; Dromain, C.; Duvillard, P.; Elias, D.; De Baere, T.; Guigay, J.; Ducreux, M.; Schlumberger, M., Baudin, E. Performance of 18fluorodeoxyglucose-positron emission tomography and somatostatin receptor scintigraphy for high Ki67 ((greater-than or equal to)10%) well-differentiated endocrine carcinoma staging. J. Clin. Endocrinol. Metab 2011;96(3):665-671.

Buchs, 2011

Buchs, N. C.; Buhler, L.; Bucher, P.; Willi, J.-P.; Frossard, J.-L.; Roth, A. D.; Addeo, P.; Rosset, A.; Terraz, S.; Becker, C. D.; Ratib, O., Morel, P. Value of contrast-enhanced 18F-fluorodeoxyglucose positron emission tomography/computed tomography in detection and presurgical assessment of pancreatic cancer: A prospective study. J. Gastroenterol. Hepatol 2011;26(4):657-662.

Herrmann 2012

* Herrmann, K.; Erkan, M.; Dobritz, M.; Schuster, T.; Siveke, J. T.; Beer, A. J.; Wester, H. J.; Schmid, R. M.; Friess, H.; Schwaiger, M.; Kleeff, J., and Buck, A. K. Comparison of 3'-deoxy-3'-[18F]fluorothymidine positron emission tomography (FLT PET) and FDG PET/CT for the detection and characterization of pancreatic tumours. Eur. J. Nucl. Med. Mol. Imaging 2012. [DOI: 10.1007/s00259-012-2061-8]

Kauhanen 2009

Kauhanen, S. P.; Komar, G.; Seppanen, M. P.; Dean, K. I.; Minn, H. R.; Kajander, S. A.; Rinta-Kiikka, I.; Alanen, K.; Borra, R. J.; Puolakkainen, P. A.; Nuutila, P., and Ovaska, J. T. A prospective diagnostic accuracy study of 18F-fluorodeoxyglucose positron emission tomography/computed tomography, multidetector row computed tomography, and magnetic resonance imaging in primary diagnosis and staging of pancreatic cancer. Ann. Surg 2009;250(6):957-963.

Kitajima 2010

Kitajima, K.; Murakami, K.; Yamasaki, E.; Kaji, Y.; Shimoda, M.; Kubota, K.; Suganuma, N., Sugimura, K. Performance of integrated FDG-PET/contrast-enhanced CT in the diagnosis of recurrent pancreatic cancer: comparison with integrated FDG-PET/non-contrast-enhanced CT and enhanced CT. Mol Imaging Biol 2010;12(4):452-459.

Kuwatani 2009

Kuwatani, M.; Kawakami, H.; Eto, K.; Haba, S.; Shiga, T.; Tamaki, N., Asaka, M. Modalities for evaluating chemotherapeutic efficacy and survival time in patients with advanced pancreatic cancer: Comparison between FDG-PET, CT, and serum tumor markers. Intern. Med 2009;48(11):867-875.

Okano 2011

Okano, K.; Kakinoki, K.; Akamoto, S.; Hagiike, M.; Usuki, H.; Yamamoto, Y.; Nishiyama, Y., and Suzuki, Y. 18F-fluorodeoxyglucose positron emission tomography in the diagnosis of small pancreatic cancer. World J. Gastroenterol 2011;17(2):231-235.

Tang 2011

Tang, S.; Huang, G.; Liu, J.; Liu, T.; Treven, L.; Song, S.; Zhang, C.; Pan, L., Zhang, T. Usefulness of 18F-FDG PET, combined FDG-PET/CT and EUS in diagnosing primary pancreatic carcinoma: a meta-analysis. Eur J Radiol 2011;78(1):142-50.

Additional references

ESMO 2010

Cascinu S, Falconi M, Valentini V, Jelic S, on behalf of the ESMO Guidelines Working Group. Pancreatic cancer: ESMO Clinical Practice Guidelinesfor diagnosis, treatment and follow-up. Annals of Oncology 2010;21 (Supplement 5):v55–v58.

Registri Tumori 2009

www.registri-tumori.it/cms/?q=Rapp2009Indice. Accessed 10 May 2012.

4.14 FDG-PET/CT for staging of colorectal cancer

Background

In Italy colorectal cancer is the third most frequent cancer among males and second among females - during 2003-2005 it represented 13.4% and 13.8% of all cancers respectively. The crude incidence is 62.3 cases per 100,000 male-years and 51.3 cases per 100,000 female-years for colon cancer, and 30.2 per 100,000 male-years and 22.0 per 100,000 females-years for rectal cancer (Registri Tumori). It is the second commonest cause of death from cancer for both sexes; the 5-year survival is around 46% (CI 95% 46-47%), across all stages of disease (Registri Tumori).

Target condition being diagnosed

Target conditions are: a) disease involvement of regional lymph nodes identified through N staging, and b) presence of any distant metastasis, identified through M staging (ESMO 2010).

Index test(s)

FDG-PET/CT.

None of the recent guidelines recommend routinely the use of FDG-PET/CT for both N or M staging of patients diagnosed with colorectal cancer (AIOM 2010; ESMO 2010a; NCCN 2012a; b; NICE 2011; SIGN 2011). The same guidelines suggest the use of FDG-PET/CT - with different enphasis - only in patients with surgically curable metastatic disease (chiefly in the liver) in order to exclude other metastatic sites.

Alternative test(s)

Pre-surgical N staging with any imaging test is not a routine; post-surgical histopathological lymph node status is the standard practice (AIOM 2010; ESMO 2010a). M staging includes CT scan and ultrasonography of abdomen, and chest radiograph (AIOM 2010; ESMO 2010a).

Reference standard for N staging is intraoperative and pathological assessment of nodal spread of disease. For proper pathological N staging at least 12–14 nodes should be removed (ESMO 2010a). Reference standard for M staging is clinical and ultrasonography intraoperative assessment of liver metastases, biopsy of other distant metastases, follow-up with imaging techniques (ESMO 2010a).

Rationale

Role of staging. Pre-surgical N staging usually does not affect the initial treatment choice (AIOM 2010). Only post-surgical histopathological lymph node status is a predictor of long-term prognosis in colorectal cancer (ESMO 2010a).

Pre-operative M staging is important to differentiate localized from disseminated disease (AIOM 2010; ESMO 2010a). About 19% of patients with primary colorectal cancer have synchronous metastases (Mitry 2010); about 15% of patients have synchronous liver metastases (Manfredi 2006; Mantke 2012) and 2-4% synchronous lung metastases (Mitry 2010). The more advanced is the disease (in term of T and N staging) the higher the risk of distant metastases: about three-fold for N positive patients versus N negative patients and about 6-8 times for T3-T4 patients versus T1 patients (Mantke 2012). In the cancer of the rectal ampulla the risk of synchronous

lung metastases is about two-fold that of colon cancer (Mitry 2010). Thus pre-operative imaging of the liver and chest is required to detect possible metastases and to decide the general therapeutic strategy (AIOM 2010; ESMO 2010a); when patients present with synchronous liver metastases, resection of the primary cancer and liver can be done in a simultaneous or staged approach (NCCN 2012a).

Treatment options. Wide surgical resection of the involved segment of bowel together with removal of its lymphatic drainage is standard treatment (ESMO 2010a). Surgery of liver and lung metastases is reserved for selected patients with resectable lesions (10-20% of synchronous liver metastases and 2-4% of lung metastases; Mitry 2010; Penna 2002). Palliative surgery is indicated for patients with unresectable metastatic lesions. In locally advanced rectal cancer (T4) pre-operative chemoradiotherapy is recommended (ESMO 2010b). Five-year survival after surgical resection is 85%-95% for stage I, 60%-80% for stage II, 30%-60% for stage III, but 26% if more than 4 lymph nodes involved (Dynamed 2012). Patients undergoing surgical resection of resectable liver metastatic disease have a 5-year survival rates of 40% compared with no survival at 5 years for untreated patients (Geoghegan 1999). Unresectable liver metastases can be treated with ablation, although benefit is unclear (ESMO 2010c). Survival can also be improved by resection of lung mestastasis (SIGN 2011).

Objectives

The objective of this review was to examine the diagnostic accuracy and the clinical effectiveness of FDG-PET/CT for N staging and M staging of patients diagnosed with colorectal cancer compared to conventional imaging examination.

Search methods for identification of studies

Evidence is based on a) the conclusion of the most recent HTA report on colorectal cancer (ASSR 2011) which was of good quality and had an electronic search updated to September 2010; b) a further search of studies published between January 2010 and March 2012. The key words described the participants' disease and the index test. See appendix 10 for details of strategy.

Results

The HTA document (ASSR 2011) concluded that

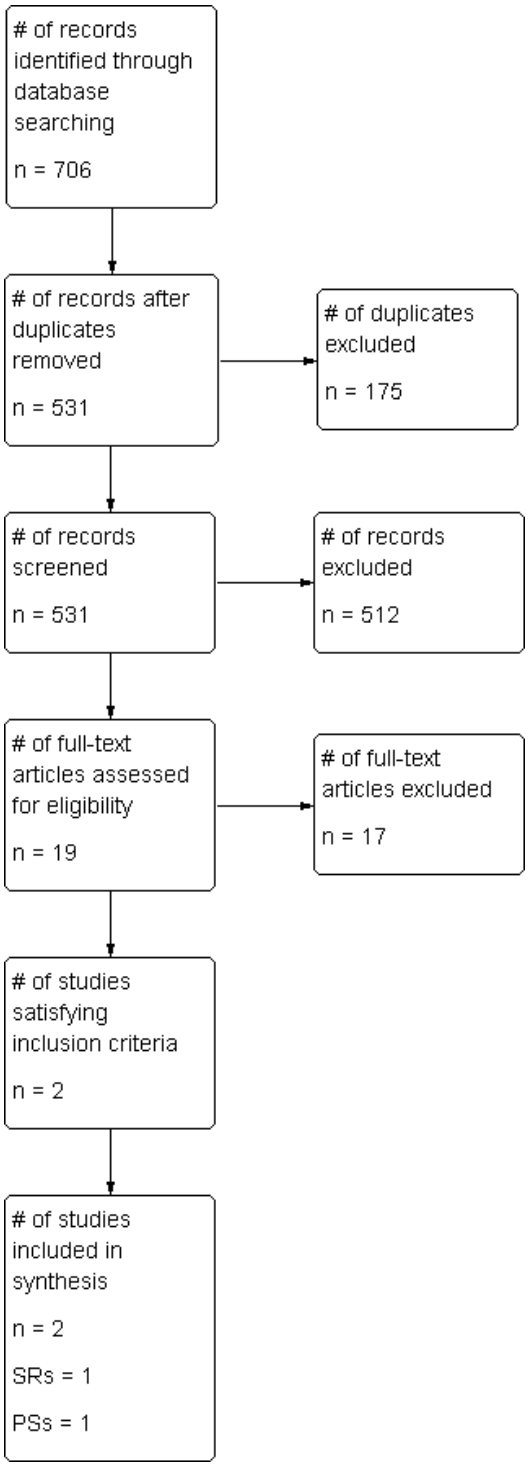
- the use of FDG-PET for N staging of patients with primary colorectal cancer is inappropriate due to absence of rationale for the diagnostic role of FDG-PET in this clinical indication
- the use of FDG-PET for M staging of patients with locally advanced colorectal cancer is appropriate when applied for discriminating between localized disease with resectable metastases and disseminated disease. Level of evidence for diagnostic accuracy of FDG-PET resulted *moderate*.

Results of the search

Identification and selection of studies. The updated electronic search identified 706 records; 687 have been excluded because duplicates or, after checking the abstract, for not meeting the inclusion criteria. Full text has been acquired for the remaining potentially eligible 19 records, from which 17 studies have been excluded on the basis of inclusion criteria (see the list of excluded studies). Two studies have been finally included (PS -

Mainenti 2011; SR - Brush 2011). The study selection process is summarized in the PRISMA flow diagram (Moher 2009; see Figure 1).

Figure 1 Colorectal cancer: study selection according to PRISMA flow diagram (Moher 2009).



Description of included studies

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

N staging

Systematic reviews

One systematic review has been included (SR - Brush 2011). This review assess the diagnostic accuracy of FDG-PET/CT for regional lymph nodes staging in patients with colorectal cancer before surgical treatment and includes 2 studies for a total of 141 participants. Reference standard is histopathology following surgical resection and regional lymph node dissection. Patients included are newly diagnosed patients with any stage cancer. No comparator is assessed in the included studies.

Primary studies

One study (34 participants) evaluating diagnostic accuracy of FDG-PET/CT for regional lymph node staging published after the above reported systematic review has been included (PS - Mainenti 2011). Participants have colorectal cancer eligible for surgical resection. Reference standard is surgical findings and histopathological analysis of the surgical specimens. No comparator is assessed in the included study.

M staging

Systematic reviews

None retrieved.

Primary studies

None retrieved.

Methodological quality of included studies

N staging

Systematic reviews

The systematic review by Brush et al. (SR - Brush 2011) has a comprehensive bibliographic search method, a complete reporting of included studies, the methodological quality appropriately assessed and the statistical analysis well performed. The primary studies included into the systematic review could be both prone to spectrum bias and a biased reference standard due to unclear blinding of index test.

Primary studies

Blinding of the results of index test is unclear for the included study (PS - Mainenti 2011).

Quality assessment results for the included studies is provided in Figure 2.

M staging

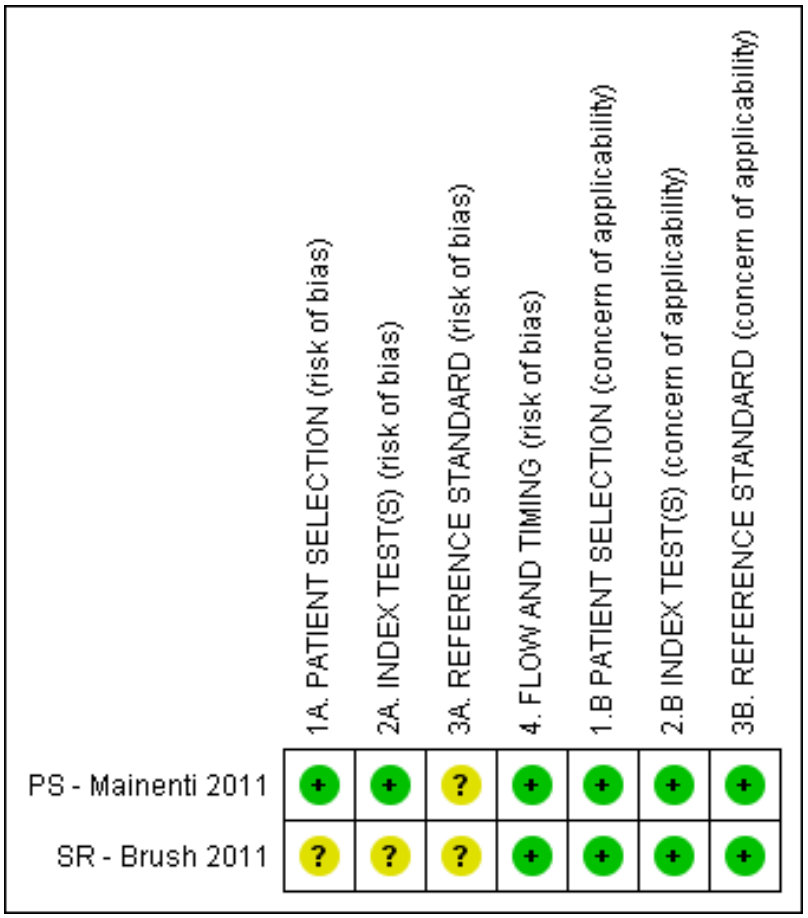
Systematic reviews

None retrieved.

Primary studies

None retrieved.

Figure 2 Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Findings

N staging

Detailed results are reported below in the table for Summary of Findings 1.

Systematic reviews
Due to the scarcity of data the systematic review by Brush et al. (SR - Brush 2011) does not calculate pooled estimates of diagnostic accuracy for FDG-PET/CT.

Primary studies
The only study included reports sensitivity of 75.0% and specificity of 83.3%.

M staging

Systematic reviews
None retrieved.

Primary studies
None retrieved.

Comments on Findings

N staging

According to data of *low quality*, FDG-PET/CT seems to have both unsatisfactory sensitivity and specificity estimates than the standard practice (post-surgical histopathological lymph node status).

M staging

There is no evidence of impact of FDG-PET/CT or comparators on diagnostic accuray and clinical outcomes

Summary of Findings 1: Diagnostic accuracy of FDG-PET for N staging in patients with colorectal cancer

Patients/population: colorectal cancer
Target condition: N staging
Index test: FDG-PET/CT, contrast-enhanced FDG-PET/CT
Comparators: none
Reference standard: histopathology following surgical resection and regional lymph node dissection

Ref.	No. of studies	Study design	Risk of Bias	Indirectness	Inconsistency	Imprecision	Diagnostic Accuracy FDG-PET	Diagnostic Accuracy Comparators	Quality of Evidence
Brush 2011	FDG-PET/CT: 2 (141 participants)	Systematic review	Serious[1]	No	No	Serious	1 study FDG-PET/CT Proximal node staging Sensitivity 51.0% (95% CI 36.0-66.0%) Specificity 85.0% (95% CI 72.0-92.0%) Distal node staging Sensitivity 62.0% (95% CI 30.0-86.0%) Specificity 92.0% (95% CI 84.0-96.0%) 1 study FDG-PET/CT Sensitivity 85.0% (95% CI 69.0-93.0%) Specificity 42.0% (95% CI 23.0-67.0%) contrast-enhanced FDG-		Low

							PET/CT Sensitivity 85.0% (95% CI 69.0-93.0%) Specificity 68.0% (95% CI 46.0-84.0%)			
Primary studies	FDG-PET/CT 1 (34 participants)	diagnostic accuracy studies with prospective recruitment (consecutive)	Serious[2]	No	No	Serious	Sensitivity: 75.0% Specificity: 85.3%		Low	

1. possible spectrum bias; unclear or absent blinding of index test and reference standard
2. unclear blinding of index test

Authors' conclusions

N staging

The HTA document (ASSR 2011) judged the quality of appraised evidence as moderate and concluded that the use of FDG-PET for N staging of patients with primary colorectal cancer is inappropriate.

Evidence from the studies retrieved through our update and judged to be of low quality confirms the above conclusions.

M staging

Accurate M staging of patients with colorectal cancer is important and there is a rationale in support of the use of FDG-PET/CT in patients with locally advanced disease eligible to curative treatment.

The HTA document (ASSR 2011) judged the quality of appraised evidence as moderate and concluded that the use of FDG-PET for M staging of patients with locally advanced colorectal cancer is appropriate

No additional evidence was retrieved through our update thus the above conclusions are not challenged.

References

Included studies

ASSR-RER 2011

Ballini L, Vignatelli L, Negro A, Maltoni S, Longo G. Criteria for appropriate use of FDG-PET in colorectal cancer. Dossier 211 - Agenzia sanitaria e sociale regionale, Regione Emilia-Romagna. Available from http://asr.regione.emilia-romagna.it/wcm/asr/collana_dossier/doss211.htm 2011. Last access 28th August 2012

PS - Mainenti 2011

Mainenti PP, Iodice D, Segreto S, Storto G, Magliulo M, De Palma GD, et al. Colorectal cancer and 18FDG-PET/CT: what about adding the T to the N parameter in loco-regional staging? World Journal of Gastroenterology 2011;17:1427-33.

SR - Brush 2011

Brush J, Boyd K, Chappell F, Crawford F, Dozier M, Fenwick E, et al. The value of FDG positron emission tomography/computerised tomography (PET/CT) in pre-operative staging of colorectal cancer: a systematic review and economic evaluation. Health Technology Assessment 2011;15:1-iv.

Excluded studies

Bamba 2011

Bamba Y, Itabashi M, Kameoka S. Value of PET/CT imaging for diagnosing pulmonary metastasis of colorectal cancer. Hepatogastroenterology 2011;58:1972-4.

Chan 2011

Chan K, Welch S, Walker-Dilks C, Raifu A. Evidence-based Guideline Recommendations on the use of Positron Emission Tomography Imaging in Colorectal Cancer. Clin.Oncol.(R.Coll.Radiol.) 2011;(1433-2981 (Electronic), 0936-6555 (Linking)).

Dirisamer 2010

Dirisamer A, Halpern BS, Flory D, Wolf F, Beheshti M, Mayerhoefer ME, et al. Performance of integrated FDG-PET/contrast-enhanced CT in the staging and restaging of colorectal cancer: comparison with PET and enhanced CT. European Journal of Radiology 2010;73:324-8.

Eglinton 2010

Eglinton T, Luck A, Bartholomeusz D, Varghese R, Lawrence M. Positron-emission tomography/computed tomography (PET/CT) in the initial staging of primary rectal cancer. Colorectal Disease 2010;12:667-73.

Floriani 2010

Floriani I, Torri V, Rulli E, Garavaglia D, Compagnoni A, Salvolini L, et al. Performance of imaging modalities in diagnosis of liver metastases from colorectal cancer: a systematic review and meta-analysis. J.Magn Reson.Imaging 2010;31:19-31.

Hunter 2011

Hunter CJ, Garant A, Vuong T, Artho G, Lisbona R, Tekkis P, et al. Adverse Features on Rectal MRI Identify a High-risk Group that May Benefit from More Intensive Preoperative Staging and Treatment. Annals of Surgical Oncology 2011;(1534-4681 (Electronic), 1068-9265 (Linking)).

Kim 2011

Kim DJ, Kim JH, Ryu YH, Jeon TJ, Yu JS, Chung JJ. Nodal staging of rectal cancer: high-resolution pelvic MRI versus (1)F-FDGPET/CT. J.Comput.Assist.Tomogr. 2011;35:531-4.

Kochhar 2010

Kochhar R, Liong S, Manoharan P. The role of FDG PET/CT in patients with colorectal cancer metastases. Cancer Biomark. 2010;7:235-48.

Mainenti 2010

Mainenti PP, Mancini M, Mainolfi C, Camera L, Maurea S, Manchia A, et al. Detection of colo-rectal liver metastases: prospective comparison of contrast enhanced US, multidetector CT, PET/CT, and 1.5 Tesla MR with extracellular and reticulo-endothelial cell specific contrast agents. Abdom Imaging 2010;35:511-21.

Niekel 2010

Niekel MC, Bipat S, Stoker J. Diagnostic imaging of colorectal liver metastases with CT, MR imaging, FDG PET, and/or FDG PET/CT: a meta-analysis of prospective studies including patients who have not previously undergone treatment. Radiology 2010;257:674-84.

Nozawa 2012

Nozawa H, Sunami E, Nakajima J, Nagawa H, Kitayama J. Synchronous and metachronous lung metastases in patients with colorectal cancer: A 20-year monocentric experience. Experimental and Therapeutic Medicine 2012;3:449-56.

Patel 2011

Patel S, McCall M, Ohinmaa A, Bigam D, Dryden DM. Positron emission tomography/computed tomographic scans compared to computed tomographic scans for detecting colorectal liver metastases: a systematic review. Annals of Surgery 2011;253:666-71.

Ramos 2011

Ramos E, Valls C, Martinez L, Llado L, Torras J, Ruiz S, et al. Preoperative staging of patients with liver metastases of colorectal carcinoma. Does PET/CT really add something to multidetector CT? Annals of Surgical Oncology 2011;18:2654-61.

Strasberg 2010

Strasberg SM, Dehdashti F. Role of FDG-PET staging in selecting the optimum patient for hepatic resection of metastatic colorectal cancer. Journal of Surgical Oncology 2010;102:955-9.

Van der Pas 2011

Van der Pas MHGM, Meijer S, Hoekstra OS, Riphagen II, De Vet HCW, Knol DL, et al. Sentinel-lymph-node procedure in colon and rectal cancer: A systematic review and meta-analysis. The Lancet Oncology 2011;12:540-50.

Wiering 2010

Wiering B, Adang EM, van der Sijp Jr, Roumen RM, de Jong KP, Comans EF, et al. Added value of positron emission tomography imaging in the surgical treatment of colorectal liver metastases. Nuclear Medicine Communications 2010;31:938-44.

Yu 2012

Yu L, Tian M, Gao X, Wang D, Qin Y, Geng J. The Method and Efficacy of (18)F-fluorodeoxyglucose Positron Emission Tomography/Computed Tomography for Diagnosing the Lymphatic Metastasis of Colorectal Carcinoma. Academic Radiology 2012.

Additional references

AIOM 2010

Linee Guida AIOM. Tumori del colon-retto. Available from http://www.aiom.it/Attivit%E0+Scientifica/Linee+guida/Archivio+2010/Tumori+del+Colon-Retto/1,4754,0, 2010, last access 18th May 2012

Dynamed 2012

Colorectal cancer. In DynaMed [database online]. Available from http://web.ebscohost.com/dynamed/detail?vid=3&hid=12&sid=71170faf-3324-4078-a397-7e5007d8f860%40sessionmgr15&bdata=JnNpdGU9ZHluYW1lZC1saXZlJnNjb3BlPXNpdGU%3d#db=dme&AN=113642 Updated 2012 Feb 26 2012, last access 18th May 2012

ESMO 2010a

Van Cutsem E, Nordlinger B, Cervantes A on behalf of the ESMO Guidelines Working Group. Advanced colorectal cancer: ESMO ClinicalPractice Guidelines for treatment. Annals of Oncology 2010;21 (Supplement 5):v93–v97.

ESMO 2010b

Labianca R, Nordlinger B, Beretta GD, Brouquet A, Cervantes A on behalf of the ESMO Guidelines Working Group. Primary colon cancer: ESMO Clinical Practice Guidelinesfor diagnosis, adjuvant treatment and follow-up. Annals of Oncology 2010;21 (Supplement 5):v70–v77.

ESMO 2010c

Glimelius B, Pahlman L, Cervantes A on behalf of the ESMO Guidelines Working Group. Rectal cancer: ESMO Clinical Practice Guidelines fordiagnosis, treatment and follow-up. Annals of Oncology 2010;21 (Supplement 5):v82–v86.

Geoghegan 1999

Geoghegan JG, Scheele J. Treatment of colorectal liver metastases. The British journal of surgery 1999;86:158-69.

Manfredi 2006

Manfredi S, Lepage C, Hatem C, Coatmeur O, Faivre J, Bouvier AM. Epidemiology and management of liver metastases from colorectal cancer. Annals of surgery 2006;244:254-9.

Mantke 2012

Mantke R, Schmidt U, Wolff S, Kube R, Lippert H. Incidence of synchronous liver metastases in patients with colorectal cancer in relationship to clinico-pathologic characteristics. Results of a German prospective multicentre observational study. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology 2012;38:259-65.

Mitry 2010

Mitry E, Guiu B, Cosconea S, Jooste V, Faivre J, Bouvier AM. Epidemiology, management and prognosis of colorectal cancer with lung metastases: a 30-year population-based study. Gut 2010;59:1383-8.

Moher 2009

Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. BMJ 2009;339:b2535.

NCCN 2012a

NCCN Clinical Practice Guidelines in Oncology. Colon cancer. Version 3.2012. Available from http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#colon 2012, last access 18th May 2012

NCCN 2012b

NCCN Clinical Practice Guidelines in Oncology. Rectal cancer. Version 3.2012. Available from http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#rectal 2012, last access 18th May 2012

NICE 2011

NICE clinical guideline 131. The diagnosis and management of colorectal cancer. Available from www.nice.org.uk/cg131 2011, last access 18th May 2012

Penna 2002

Penna C, Nordlinger B. Colorectal metastasis (liver and lung). The Surgical clinics of North America 2002;82:1075-90.

Registri Tumori

www.registri-tumori.it/cms/?q=sede_colon, last access 18th May 2012

SIGN 2011

Scottish Intercollegiate Guidelines Network (SIGN). Diagnosis and management of colorectal cancer.. SIGN publication no. 126. Available from http://www.sign.ac.uk 2011, last access 18th May 2012

4.15 FDG-PET/CT for staging of renal cancer

Background

During 1998-2002 (Registri Tumori), renal cancer (including also cancers of the renal pelvis, ureter, and urethra) represented 3.2% of all the cancer diagnoses among males and 2.1% among females. In Italy, incidence is about 25.2 per 100,000 males (21.0 kidney, 1.7 urethra, 1.2 pelvis, and 1.3 ureter) and 12.9 per 100,000 women (11.2 kidney, 0.7 urethra, 0.6 pelvis, and 0.4 ureter). Crude survival at 5 years is about 59%.

Target condition being diagnosed

Target conditions are: a) disease involvement of regional lymph nodes identified through N staging, and b) presence of distant metastases, identified through M staging.

Index test(s)

FDG-PET/CT.

FDG-PET/CT is not recommended as staging procedure according to ESMO guidelines (ESMO 2010).

Alternative test(s)

Diagnosis is usually suggested by ultrasonography, and confirmed by CT scan which allows for assessment of local invasiveness, lymph node involvement or other metastases (ESMO 2010).

Rationale

Role of staging. The main prognostic system do not include nodal involvement or metastatic disease at N and M staging as prognostic factors (ESMO 2010), however treatment depends on disease extension.

Treatment options. Nephrectomy is the standard of care of localized disease (ESMO 2010). Cytoreductive nephrectomy and adjuvant treatment benefit many patients with metastatic renal carcinoma.

Objectives

The objective of this review was to examine the diagnostic accuracy and the clinical effectiveness FDG-PET/CT for staging of patients diagnosed with renal cancer compared to conventional imaging examination.

Search methods for identification of studies

Evidence is based on a) the conclusion of the most recent HTA report on renal cancer (KCE 2009) which was of good quality and had an electronic search updated to January 2009; b) a further search of studies published between January 2009 and March 2012. The key words described the participants' disease and the index test. See appendix 11 for details of strategy.

Results

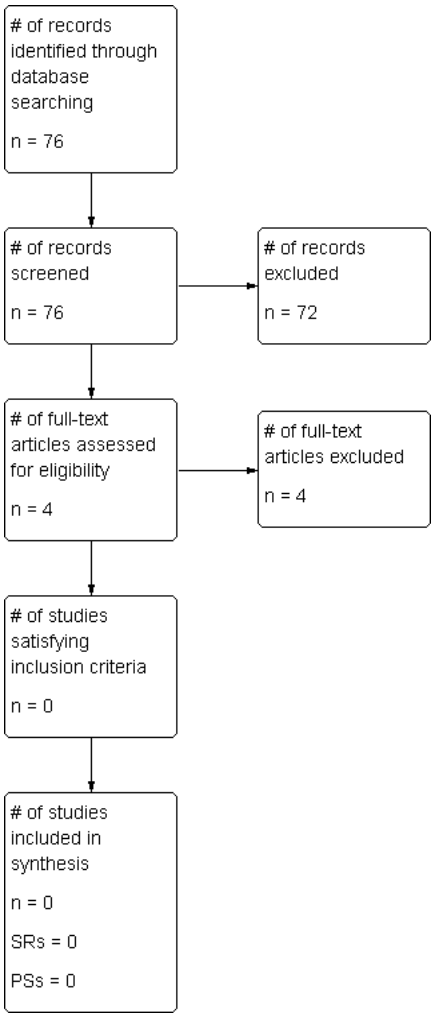
The 2009 KCE report conclusions for renal cancer staging are based on the AHRQ 2008 report (AHRQ 2008; KCE 2009). 2009 KCE report concluded that the evidences on staging are limited to small studies of low quality.

Results of the search

Identification and selection of studies

Our searches identified 76 titles possibly fitting inclusion criteria. After screening of titles and abstracts, 4 studies were retrieved and read. All studies were excluded for various reasons (see Excluded studies: Ansquer 2010; Lodde 2010; Ozulker 2011; Ye 2010).

Figure 1 Renal cancer: study selection according to PRISMA flow diagram (Moher 2009).



Description of included studies

Systematic reviews
None were included.

Primary studies

None were included.

Authors' conclusions

KCE report (KCE 2009) concluded that the evidence on initial diagnosis and staging is limited to small studies of low quality reporting wide confidence intervals.

No additional evidence was retrieved through our update thus the use of FDG-PET/CT in staging patients with renal cancer would be inappropriate.

References to studies

Included studies

KCE 2009

Vlayen J, Stordeur S, Van den Bruel A, Mambourg F, Eyssen M.. KCE reports 110A. Positron Emissie Tomografie: een update. Health Technology Assessment (HTA). Federaal Kenniscentrum voor de Gezondheidszorg (KCE) (D/2009/10.273/24) 2009. Last access 28th August 2012

Excluded studies

Ansquer 2010

Ansquer, C.; Scigliano, S.; Mirallie, E.; Taieb, D.; Brunaud, L.; Sebag, F.; Leux, C.; Drui, D.; Dupas, B.; Renaudin, K., and Kraeber-Bodere, F. 18F-FDG PET/CT in the characterization and surgical decision concerning adrenal masses: A prospective multicentre evaluation. Eur. J. Nucl. Med. Mol. Imaging. 2010; 37(9):1669-1678; ISSN: 1619-7070.

Lodde 2010

Lodde, M.; Lacombe, L.; Friede, J.; Morin, F.; Saourine, A., and Fradet, Y. Evaluation of fluorodeoxyglucose positron-emission tomography with computed tomography for staging of urothelial carcinoma. BJU Int. 2010; 106(5):658-663; ISSN: 1464-4096. 1464-410X.

Ozulker 2011

Ozulker, T.; Ozulker, F.; Ozbek, E., and Ozpacaci, T. A prospective diagnostic accuracy study of F-18 fluorodeoxyglucose-positron emission tomography/computed tomography in the evaluation of indeterminate renal masses. Nucl. Med. Commun. 2011; 32(4):265-272; ISSN: 0143-3636.

Ye 2010

Ye, X.-H.; Chen, L.-H.; Wu, H.-B.; Feng, J.; Zhou, W.-L.; Yang, R.-M.; Bu, Z.-B.; Ding, Y.; Guan, J., and Wang, Q.-S. 18F-FDG PET/CT evaluation of lymphoma with renal involvement: Comparison with renal carcinoma. South. Med. J. 2010; 103(7):642-649; ISSN: 0038-4348.

Additional references

AHRQ 2008

Agency for Healthcare Research and Quality. Positron Emission Tomography for Nine Cancers (Bladder, Brain, Cervical, Kidney, Ovarian, Pancreatic, Prostate, Small Cell Lung, Testicular). Rockville: AHRQ 2008.

ESMO 2010

Escudier B, Kataja V, on behalf of the ESMO Guidelines Working Group. Renal cell carcinoma: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol 2010; 21 (Supplement 5): v137-v139.

Moher 2009

Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. BMJ 2009;339:b2535.

Registri Tumori

www.registri-tumori.it/cms/?q=Rapp2009Indice. Accessed 23 June 2012.

4.16 FDG-PET/CT for staging of bladder cancer

Background

Bladder cancer is the most common malignancy of the urinary system and the ninth most common malignancy worldwide (Ploeg 2009; Jemal 2011). An estimated 386,300 new cases and 150,200 deaths from bladder cancer occurred in 2008 worldwide. The majority of bladder cancer occurs in males and there is a 14-fold variation in incidence internationally. The highest incidence rates are found in the countries of Europe, North America, and Northern Africa.

In the Italian Network of Cancer Registries area, between 2003 and 2005, the average annual crude incidence rate was 71.4 per 100,000 males and 16.0 per 100,000 females while mortality, in the same area in 2003-2005 was 16.8 deaths every 100,000 men and 4.6 every 100,000 women (AIRTUM 2009).

Urothelial (transitional cell) carcinoma is the predominant histologic type in the Western Europe, where it accounts for approximately 90 percent of bladder cancers. In other areas of the world, such as the Middle East, non-urothelial histologies are more frequent, at least in part to the prevalence of schistosomiasis. Numerous factors including cigarette smoking and various occupational exposures (i.e. cyclic chemicals, benzene derivatives, arylamines etc.) have been identified that may play an etiologic role in some cases of urothelial cancer.

Target condition being diagnosed

Target conditions are: a) disease involvement of regional lymph nodes (pelvic), identified through N staging, and b) presence of distant metastases, identified through M staging.

Index test(s)

FDG-PET/CT.

Recent guidelines do not recommend use of FDG-PET/CT for staging of patients with bladder cancer (EAU 2011; ESMO 2011).

Alternative test(s)

Once bladder cancer is diagnosed, accurate disease staging and grading are critical. Anatomical and functional information to help disease staging can be obtained using different imaging methods. N staging can be carried out with either computed tomography (CT) or magnetic resonance imaging (MRI). Both tests can be used to assess extravescial invasion but are unable to detect T3a disease (microscopic invasion of perivesical fat). Similarly both tests are useful to detect enlarged nodes—over 8 mm in the pelvic area and over 1 cm for abdominal nodes—and distant metastasis. For patients with muscle-invasive bladder cancer a chest CT should be undergone at the same time as the abdomino-pelvis CT for M staging . Additional diagnostic tests, such as bone scan, should be performed if clinically indicated (EAU 2011; ESMO 2011).

Rationale

Role of staging. Management of bladder cancer is based on the pathological findings of the biopsy, with attention to histology, grade and depth of invasion. Muscle-invasive bladder cancer should be staged according to the TNM system and grouped into categories. Accurate pre surgical N-M staging is necessary to correctly classify patients into early or advanced disease.

Treatment options. The aim of treatment for patients with bladder cancer is to prevent disease recurrence or progression to invasive disease, to avoid the loss of the bladder, and, ultimately, to enhance survival. The optimal choice of the operative procedure depends on the stadium of a disease, the size and localization of the primary tumor, lymph node involvement and the general patient's condition.

Radical cystectomy (consisting in removal of the bladder and neighbouring organs, such as the prostate and seminal vesicles in men and uterus and annexa in women) is considered the gold standard treatment for muscle-invasive bladder tumours. Although renewed interest in quality-of-life issues has increased interest in bladder preservation treatments, the primary indication for cystectomy is muscle-invasive bladder cancer T2-T4a, N0-NX, M0. Other indications are high-risk superficial tumours (T1 G3 and BCG-resistant Tis). Radio and chemotherapy too are used according to disesase staging or other situations as relapse, non-resectable tumours, metastatic disease, comorbidities (EAU 2011).

Objectives

The objective of this review was to examine the diagnostic accuracy and the clinical effectiveness of FDG-PET/CT for N staging and M staging of patients diagnosed with bladder cancer compared to conventional imaging examination.

Search methods for identification of studies

Evidence is based on a) the conclusion of the most recent HTA report on bladder cancer (KCE 2009) which was of good quality and had an electronic search updated to January 2009; b) a further search of studies published between January 2009 and March 2012. The key words described the participants' disease and the index test. See appendix 12 for details of strategy.

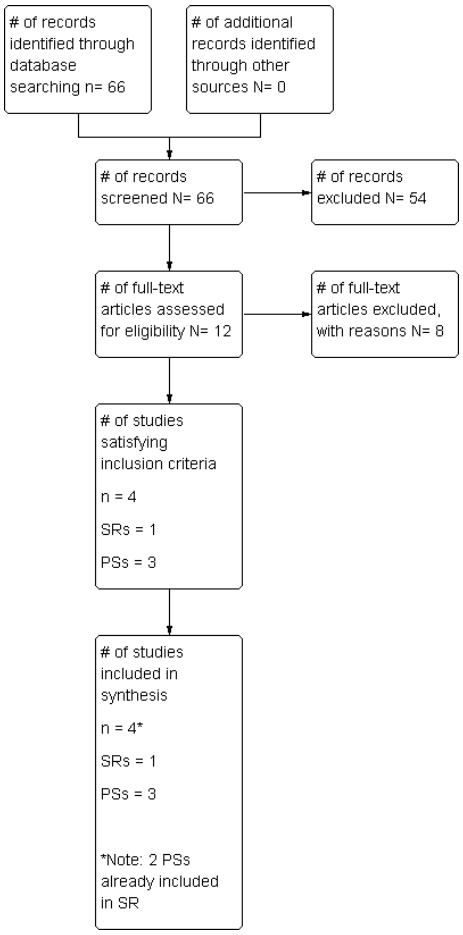
Results

The HTA document (KCE 2009) concluded that:

- the evidence on the use of PET/CT is too limited to base recommendations on.

Identification and selection of studies: the updated electronic search identified 66 records and no additional study by reference lists; 54 have been excluded after checking the abstract, for not meeting the inclusion criteria. Full text has been acquired for the remaining potentially eligible 12 records. Four studies have been finally included (PS - Swinnen 2009; SR - Lu 2011; Apolo 2010; Kibel 2009) but two of them (Apolo 2010; Kibel 2009) have not been evaluated because they are included in SR - Lu 2011. The study selection process is summarized in the PRISMA flow diagram (Moher 2009; see Figure 1).

Figure 1 Study flow diagram.



Results of the search

Description of included studies

Two studies evaluating the diagnostic accuracy of FDG-PET/CT for staging in bladder cancer matched our inclusion criteria: a systematic review (SR - Lu 2011) and a primary study (PS - Swinnen 2009).

Diagnostic accuracy - N staging

Systematic reviews

None retrieved.

Primary studies
One study (PS - Swinnen 2009) (51 patients) with initial diagnosis of bladder cancer and evaluating diagnostic accuracy of FDG-PET/CT for lymph node [paraaortic; paracaval; pelvic (right and left), including external and internal iliac; obturator fossa (right and left), and presacral] staging was included. Reference standard is the postoperative pathologic N staging following radical cystectomy with extended lymphadenectomy or follow-up. CT as comparative tests was used.

Diagnostic accuracy - M staging

None retrieved.

Diagnostic accuracy - Any staging

Systematic reviews

One systematic review has been included (SR - Lu 2011). Primary tumor detection, staging, tumor recurrence or restaging of bladder cancer were assessed. In particular this review assesses and compares the diagnostic accuracy of FDG-PET and FDG-PET/CT with pathological proof (biopsy or surgery) or evidence of progression at follow-up for lymph nodes and distant metastases (N-M) for staging/restaging in patient with bladder carcinoma.

The review by Lu et al. (SR - Lu 2011) includes six diagnostic studies (236 patients) with prospective or retrospective patients recruitment but only five of them, in total 219 patients, were considered to perform accuracy diagnostic test metanalysis for staging/restaging (three studies for staging with FDG-PET/CT as index test and one with FDG-PET as index test).

Primary studies

None retrieved.

Impact on clinical outcomes - Any staging

None retrieved.

Methodological quality of included studies

Diagnostic accuracy - N staging

Primary studies

PS - Swinnen 2009 enrolled 51 patients; Patient selection, Index test and Reference standard have an unclear risk of bias. The remaining items have a low risk of bias. No patients were excluded from analyses. Overall quality of evidence is low. Quality assessment results for the included studies is provided in Figure 2.

Diagnostic accuracy - Any staging

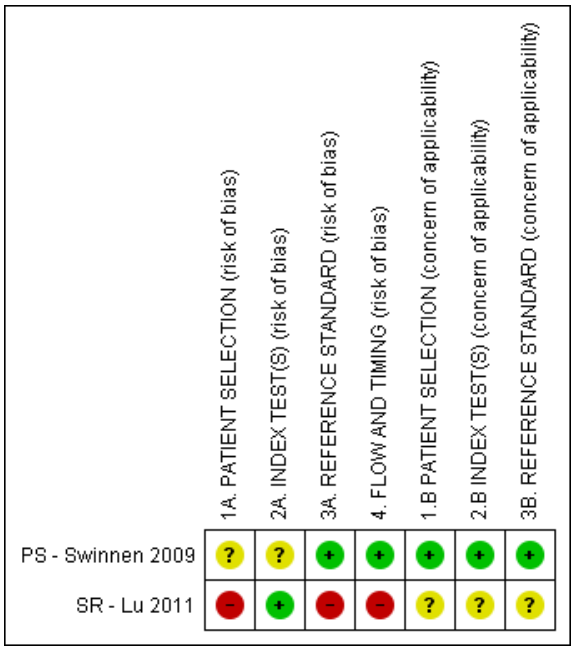
Systematic reviews
The systematic review by Lu et al. (SR - Lu 2011) reports an assessement of methodological quality of included studies according to Cochrane Methods Working Group on Systematic Review of Screening and Diagnostic Tests: Recommended Methods.
http://www.cochrane.org/cochrane/sadtdoc1.htm (accessed on June 6, 2012).

Authors did not perform subgroup analyses (meta-analyses) within included studies (staging vs restaging, N vs M metastases and FDG-PET vs FDG-PET/CT index test) and did not reported conventional comparators data (as CT). Bibliographic search is not properly exhaustive, the characteristics of included studies are clearly reported; the methodological quality of included studies appropriately assessed and the statistical analysis well conducted.

Five studies were considered to perform accuracy diagnostic test metanalysis for staging/restaging (three studies for staging with FDG-PET/CT as index test and one with FDG-PET as index test).

Two studies (40%) were prospective; the presence of clinical heterogeneity in the patient population, imaging techniques, study design, and quality in these selected studies affects the generalizability of the results. The retrospective design in three studies, as well as the interpretation of FDG PET with other available clinical information, further decreased the methodological quality. There was verification bias in four studies. This is because the reference test was assessed on patients selected by the index test results, which can lead to overestimation of the sensitivity. Thirty-three patients were excluded from analyses. Overall quality was judged very low.

Figure 2 Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Findings

Diagnostic accuracy - N staging

Primary studies
The study included (PS - Swinnen 2009) reports the following diagnostic accuracy estimates for FDG-PET/CT: sensitivity 46.2% (95% CI 22.4–71.3%) specificity 97.4% (95% CI 88.1–99.9%); and for CT: sensitivity 46.2% (95% CI 22.4–71.3%) specificity 92.1% (95% CI 80.9–97.8%).

Detailed results are reported below in the table Summary of Findings 1.

Diagnostic accuracy - Any staging

Systematic reviews
The systematic review by Lu et al. (SR - Lu 2011a) reports pooled estimates of diagnostic accuracy of FDG-PET/CT and FDG-PET compared with pathological proof (biopsy or surgery) and/or follow-up for staging and\or restaging of patients with bladder carcinoma. Pooled sensitivity 82% (95% CI 72–89%), I^2:79.6%; Pooled specificity 89% (95% CI 81–95%), I^2:65.6%.

Detailed results are reported below in the table Summary of Findings 2.

Comments on Findings

Only evidence on diagnostic accuracy of FDG-PET/CT and comparator is available.

According to data of *low quality*, FDG-PET/CT seems to have similar diagnostic accuracy of comparator (CT).

M staging

No evidence is availlable.

Any staging: diagnostic accuracy

Data available on FDG-PET/CT are based only on evidence of *very low quality* without diagnostic accuracy data on comparator, thus no conclusion can be drawn.

Summary of Findings 1: Diagnostic accuracy of FDG-PET/CT for N staging in patients with bladder carcinoma

Patients/population: bladder carcinoma
Index test:FDG-PET/CT.
Comparators:CT
Reference standard: pathology (from biopsy or surgery), or follow-up.

Ref.	N°studies	Study design	Risk of bias	indirectness	inconsistency	imprecision	Diagnostic accuracy FDG-PET/CT	Diagnostic accuracy comparator-CT	Quality of evidence
Primary studies	1 study (51 patients)	diagnostic cross sectional study with prospective recruitment	Serious	no	NA*	Serious	Sensitivity 46.2% (95% CI: 22.4–71.3) Specificity 97.4% (95% CI: 88.1–99.9)	Sensitivity 46.2% (95% CI: 22.4–71.3) Specificity 92.1% (95% CI: 80.9–97.8)	Low

*NA: not applicable

Summary of Findings 2: Diagnostic accuracy of FDG-PET and FDG-PET/CT for any staging in patients with bladder carcinoma

Patients/population: bladder carcinoma
Index test:FDG-PET and FDG-PET/CT.
Comparators:not reported
Reference standard: pathology (from biopsy or surgery), or follow-up.

Ref.	N°studies	Study design	Risk of bias	indirectness	inconsistency	imprecision	Diagnostic accuracy FDG-PET/CT	Diagnostic accuracy comparator-CT	Quality of evidence
SR - Lu 2011	6 diagnostic studies include of which 3 retrospective and 3 prospective; only 5 of them were used to perform accuracy diagnostic test metanalysis (staging/restaging) 236 patients (219 in meta-analysis)	Systematic review	serious[1]	serious[2]	serious[3]	no	sensitivity (pooled) 82% (95% CI: 72–89%) specificity (pooled) 89% (95% CI: 81–95%)		Very Low

[1]Only one studies investigated staging exclusively; staging + diagnosis; staging + restaging. Not all patients received the same reference standard and 33 were excluded from analysis.
[2] No study meets research question properly.
[3] Presence of clinical heterogeneity in the patient population, imaging techniques and study design.

Authors' conclusions

Any staging

There is a rationale in support of the use of FDG-PET/CT for staging of patients with bladder cancer.

The KCE HTA document (KCE 2009) concluded that the evidence on the use of PET/CT is too limited to base recommendations on.

Evidence on the use of PET/CT retrieved through our update and judged to be of low/very low quality does not challenge the above conclusions.

References to studies

Included studies

KCE 2009

Vlayen J, Stordeur S, Van den Bruel A, Mambourg F, Eyssen M.. KCE reports 110A. Positron Emissie Tomografie: een update. Health Technology Assessment (HTA). Federaal Kenniscentrum voor de Gezondheidszorg (KCE) (D/2009/10.273/24) 2009. Last access 28th August 2012

PS - Swinnen 2009

Swinnen G, Maes A, Pottel H, Vanneste A, Billiet I, Lesage K, et al. FDG-PET/CT for the Preoperative Lymph Node Staging of Invasive Bladder Cancer. Eur. Urol.57(4):641-7.

SR - Lu 2011

Lu YY, Chen JH, Liang JA, Wang HY, Lin CC, Lin WY, et al. Clinical value of FDG PET or PET/CT in urinary bladder cancer: A systemic review and meta-analysis. Eur. J. Radiol..

Excluded studies

Almuhaideb 2011

Almuhaideb A, Papathanasiou N, Bomanji J. 18F-FDG PET/CT imaging in oncology. Ann. Saudi Med.31(1):3-13.

Bostrom 2010

Bostrom PJ, van Rhijn BWG, Fleshner N, Finelli A, Jewett M, Thoms J, et al. Staging and Staging Errors in Bladder Cancer. Eur. Urol. Suppl.9(1):2-9.

Boujelbene 2011

Boujelbene N, Prior JO, Boubaker A, Azria D, Schaffer M, Gez E, et al. [Value of positron emission tomography and computer tomography (PET/CT) for urologic malignancies]. Cancer Radiother15(4):307-15.

Jensen 2011

Jensen TK, Holt P, Gerke O, Riehmann M, Svolgaard B, Marcussen N, et al. Preoperative lymph-node staging of invasive urothelial bladder cancer with 18F-fluorodeoxyglucose positron emission tomography/computed axial tomography and magnetic resonance imaging: Correlation with histopathology. Scand. J. Urol. Nephrol.45(2):122-8.

Lodde 2010

Lodde M, Lacombe L, Friede J, Morin F, Saourine A, Fradet Y. Evaluation of fluorodeoxyglucose positron-emission tomography with computed tomography for staging of urothelial carcinoma. BJU Int.106(5):658-63.

Moses 2011

Moses KA, Zhang J, Hricak H, Bochner BH. Bladder cancer imaging: an update. Curr Opin Urol21(5):393-7.

Rioja 2010

Rioja J, Rodriguez-Fraile M, Lima-Favaretto R, Rincon-Mayans A, Penuelas-Sanchez I, Zudaire-Bergera JJ, et al. Role of positron emission tomography in urological oncology. BJU Int.106(11):1578-93.

Zouhair 2010

Zouhair A, Ozsahin M, Schaffer M, Albrecht S, Camus F, Jichlinski P, et al. Positron emission tomography and computer tomography (PET/CT) in prostate, bladder, and testicular cancers. Curr Med Chem17(23):2492-502.

Additional references

AIRTUM 2009

Avaialble at http://www.registri-tumori.it/PDF/AIRTUM2009Trend/E&P33_4-5S1_78_vescica.pdf.

EAU 2011

Stenzl A, Witjes JA, Cowan NC, De Santis M, Kuczyk M, Lebret T, Merseburger AS, Ribal MJ, Sherif A. Guidelines on bladder cancer muscle-invasive and metastatic. European Association of Urology. Available from http://www.uroweb.org/gls/pdf/07_%20Bladder%20Cancer.pdf. [PubMed: 21632173]

ESMO 2011

J. Bellmunt, A. Orsola, T. Wiegel, M. Guix, M. De Santis & V. Kataja, On behalf of the ESMO Guidelines Working Group. Bladder cancer: ESMO Clinical Practice Guidelines fordiagnosis, treatment and follow-up. Annals of Oncology 2011;22((Supplement 6)):vi45–vi49.

Jemal 2011

Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA: a cancer journal for clinicians 2011;61(2):69-90. [PubMed: 21296855]

Moher 2009

Moher David, Liberati Alessandro, Tetzlaff Jennifer, Altman Douglas G, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009;6(7):e1000097-.

Ploeg 2009

Ploeg M, Aben KK, Kiemeney LA. The present and future burden of urinary bladder cancer in the world. World journal of urology 2009;27(3):289-93. [PubMed: 19219610]

4.17 FDG-PET/CT for staging of uterine cancer

Background

Endometrial cancer makes up more than 95% of uterine cancers. It develops from cells in the lining of the uterus, the endometrium. This cancer is also commonly called adenocarcinoma of the endometrium. Less common types of uterine cancer include carcinosarcoma and endometrial stromal sarcoma (Cancer.net).

Endometrial cancer is the most common gynecologic malignancy in the developed countries. In the United States almost 40,000 new cases of endometrial cancer have been diagnosed in 2007, with more than 7000 cancer-related deaths (Jemal 2009). In Italy the estimated new cases from endometrial cancer were on average 25.4 per 100,000 female between 2003 and 2005, while estimated cancer related deaths were 2,404 in 2006 (AIRTUM 2009).

An increased incidence of endometrial cancer has been found in association with prolonged, unopposed estrogen exposure (Ziel 1975). Conversely, combined estrogen and progesterone therapy appears to prevent the increase in risk of endometrial cancer associated with unopposed estrogen use (Jick 1993). In addition, use of tamoxifen seems to be associated with endometrial cancer, perhaps due to its to the estrogenic effect on the endometrium (van Leeuwen 1994).

Target condition being diagnosed

Target conditions are: a) disease involvement of regional lymph nodes (pelvic and paraaortic lymph node metastases), identified through N staging, and b) presence of distant metastases, identified through M staging.

Index test(s)

FDG-PET/CT.

FDG-PET/CT is not recommended as staging procedure according to most recente guidelines (ESMO 2011; NCCN 2012).

Alternative test(s)

Imaging tests are considered when cervical involvement or extrauterine disease extension are suspected (NCCN 2012). CT is commonly used in the assessment of advanced disease, ie, invasion of local structures, such as the bladder, rectum or side wall, as well as distant metastases. MRI provides the best one-stop approach for preoperative assessment of endometrial cancer because of excellent soft tissue contrast. Overall staging accuracy of MRI is 83% to 92%, which compares favorably with TransVaginal UltraSound-TVUS (60%-77%) and CT (61%-76%) (Barwick 2006). These modern imaging provides important tools in the accurate pre-treatment assessment of endometrial cancer and may optimize treatment planning. However, there is little consensus to date on imaging in the routine preoperative assessment of endometrial carcinoma and practice varies amongst many gynaecologists.

Rationale

Role of staging. Staging in endometrial cancer is surgical–pathological based on the FIGO (International Federation of Gynaecology and Obstetrics) system (Shepherd 1989). This is partly because most patients are treated surgically and also as clinical staging is inaccurate and often underestimates the extent of disease

(Creasman 1999). Since 1988, the FIGO classification has recommended systemic pelvic and para-aortic lymphadenectomy for complete staging of endometrial cancer (ASTEC 2009). Distant metastases including intra-abdominal and/or inguinal lymph nodes must be investigated too (Plataniotis 2010). TNM staging is also used (Sobin 1997).

Treatment options. Most patients (75%) with endometrial cancer are diagnosed with stage I disease, as a result of an early investigation of abnormal postmenopausal bleeding. In fact women with endometrial cancer with localized disease (stage I) can be cured with hysterectomy and bilateral salpingo-oophorectomy.

Two randomized trials on the use of adjuvant radiation therapy in patients with stage I disease did not show improved survival but did show reduced locoregional recurrence (3%–4% vs 12%–14% after 5–6 years' median follow-up, $P < .001$) with an increase in side effects (Creutzberg 2000; Keys 2004). Progestational agents have been evaluated as adjuvant therapy in a randomized clinical trial of stage I disease and have been shown to be of no benefit.

For stage II, if cervical involvement is documented, options include radical hysterectomy, bilateral salpingo-oophorectomy, and pelvic and para-aortic lymph node dissection; if the cervix is clinically uninvolved but extension to the cervix is documented on postoperative pathology, radiation therapy should be considered.

For stage III endometrial cancer patients are treated with surgery and radiation therapy. Patients with inoperable disease, caused by the tumor that extends to the pelvic wall, may be treated with radiation therapy. The usual approach is to use a combination of intracavitary and external-beam radiation therapy.

Treatment of patients with stage IV endometrial cancer is dictated by the site of metastatic disease and symptoms related to disease sites (Plataniotis 2010).

Objectives

The objective of this review was to examine the diagnostic accuracy and the clinical effectiveness of FDG-PET/CT for N staging and M staging of patients diagnosed with uterine cancer compared to conventional imaging examination.

Search methods for identification of studies

Evidence is based on a) the conclusion of the most recent HTA report on uterine cancer (KCE 2009) which was of good quality and had an electronic search updated to January 2009; b) a further search of studies published between January 2009 and March 2012. The key words described the participants' disease and the index test. See appendix 13 for details of strategy.

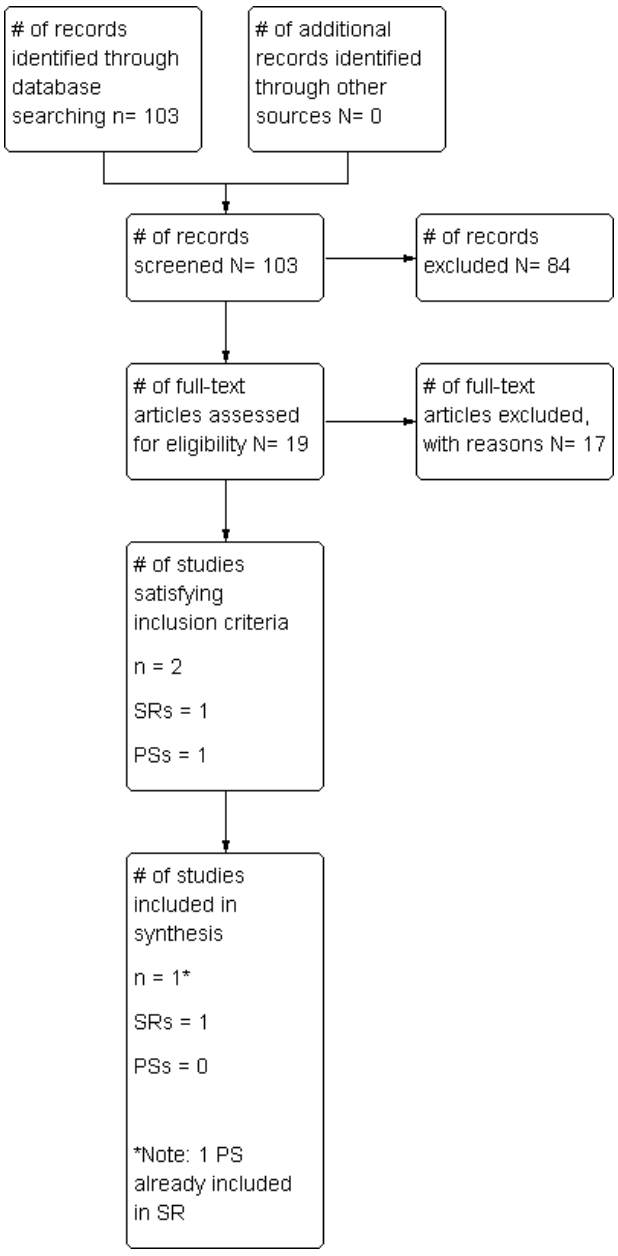
Results

The HTA document (KCE 2009) concluded that:

- the evidence on the use of PET and PET/CT is too limited to base recommendations on.

Identification and selection of studies: the updated electronic search identified 103 records and no additional study by reference lists; 84 have been excluded after checking the abstract, for not meeting the inclusion criteria. Full text has been acquired for the remaining potentially eligible 19 records. Two studies have been finally included (SR - Chang 2012; PS - Signorelli 2009) but one of them (PS - Signorelli 2009) has not been evaluated because it's included in SR - Chang 2012. The study selection process is summarized in the PRISMA flow diagram (Moher 2009; see Figure 1).

Figure 1 Study flow diagram.



Results of the search

Description of included studies.

Only one study evaluating the diagnostic accuracy of FDG-PET/CT for staging in uterine cancer was included in final analysis: a systematic review: SR - Chang 2012.

Diagnostic accuracy - N staging

Systematic reviews

One systematic review has been included (SR - Chang 2012). This review assesses the diagnostic accuracy of FDG-PET and FDG-PET/CT with pathological proof (pelvic and/or paraaortic lymph nodes) or evidence of progression at follow-up for N staging in patient with uterine cancer.

The review by Chang et al. (SR - Chang 2012) includes seven diagnostic studies (243 patients) with prospective or retrospective patients recruitment (two studies underwent as index test FDG-PET alone; four studies FDG-PET/CT and one study FDG-PET or FDG-PET/CT).

Diagnostic accuracy - M staging

None retrieved.

Impact on clinical outcomes - Any staging

None retrieved.

Methodological quality of included studies

Diagnostic accuracy - N - staging

Systematic reviews

The systematic review by Chang et al. (SR - Chang 2012) reports an assessement of methodological quality of included studies according to a modified QUADAS tool.

Authors did not perform subgroup analyses (meta-analyses) within included studies (FDG-PET vs FDG-PET/CT index test) and did not reported conventional comparators data (as CT). Bibliographic search is not exhaustive (only one database scanned: MEDLINE), the characteristics of included studies are clearly reported; the methodological quality of included studies appropriately assessed and the statistical analysis well conducted.

The prospective study design performed in only four studies (60%) as well as the fact that most of risk of bias items are judged at high or unclear risk of bias further decreased the methodological quality. Sensitivity and specificity did not demonstrate significant heterogeneity (I^2 < 50% and p > 0.05). Overall quality was judged Low.

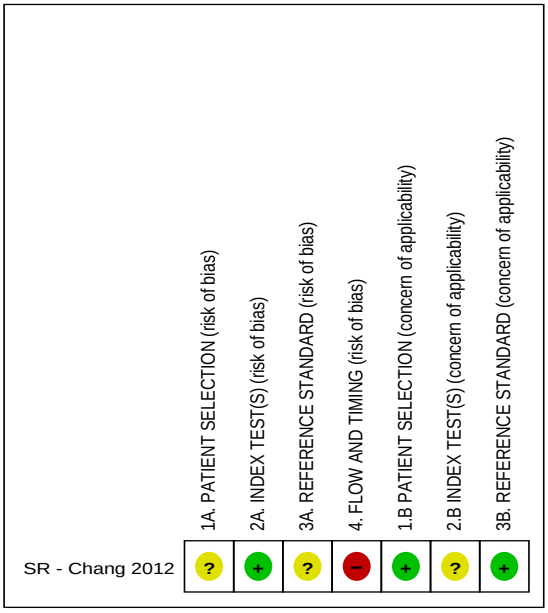
Diagnostic accuracy - M staging

None retrieved.

Impact on clinical outcomes - Any staging

None retrieved.

Figure 2 Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Findings

Diagnostic accuracy - N- staging

Systematic reviews
The systematic review by Chang et al. (SR - Chang 2012) reports pooled estimates of diagnostic accuracy of FDG-PET/CT and FDG-PET compared with pathological proof and/or follow-up for N staging of patients with uterine cancer. Pooled sensitivity : 63.0% (95% CI, 48.7–75.7%); pooled specificity : 94.7% (95% CI, 90.4–97.4%).

Detailed results are reported below in the Summary of results table 1.

Diagnostic accuracy - M staging

None retrieved.

Impact on clinical outcomes - Any staging

None retrieved.

Comments on Findings

N staging

Only evidence on diagnostic accuracy of FDG-PET/CT is available.
According to data of *low quality*, FDG-PET/CT seems to have a low sensitivity and high specificity estimates. However no data are available on diagnostic accuracy of comparators. The use of FDG-PET/CT (and FDG-PET) is supported by weak evidence. FDG/PET-CT (and FDG-PET) seem to have an good specificity 94.7% (95% CI, 90.4–97.4%) compared to reference standard (histological proof post pelvic-paraortic lymphadenectomy).

M staging

No evidence is availlable.

1 Summary of Findings: Diagnostic accuracy of FDG-PET and FDG-PET/CT for N staging in patients with uterine (endometrial) cancer

Patients/population: uterine cancer
Index test:FDG-PET and FDG-PET/CT.
Comparators:not reported
Reference standard: histological proof

Ref.	N°studies	Study design	Risk of bias	indirectness	inconsistency	imprecision	Diagnostic accuracy FDG-PET and FDG-PET/CT	Diagnostic accuracy comparator-CT	Quality of evidence
SR - Chang 2012	7 (243 patients) As index test FDG-PET/CT alone was used in four studies, FDG-PET alone in two and FDG-PET/CT or FDG-PET in one.	Systematic review	Very Serious[1,2]	no	no	no	**Pooled sensitivity** : 63.0% (95% CI, 48.7–75.7%) I^2 :48.3% (p=0.071) **Pooled specificity** : 94.7% (95% CI, 90.4–97.4%) $I^{2:}$ 45.7% (p=0.087)		Low

[1]All risk of bias items are judged at high risk of bias or unclear with the exception of "Index test".
[2]Lymphadenectomy was performed selectively (verification bias).

Authors' conclusions

Any staging

The HTA document (KCE 2009) concluded that the evidence on the use of PET and PET/CT in uterine cancer is too limited to base recommendations on.

Evidence from the studies retrieved through our update and judged to be of low quality suggests that the use of PET/CT would be inappropriate.

References

Included studies

KCE 2009

Vlayen J, Stordeur S, Van den Bruel A, Mambourg F, Eyssen M.. KCE reports 110A. Positron Emissie Tomografie: een update. Health Technology Assessment (HTA). Federaal Kenniscentrum voor de Gezondheidszorg (KCE) (D/2009/10.273/24) 2009. Last access 28th August 2012

SR - Chang 2012

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4.18 FDG-PET/CT for staging of cervical cancer

Background

In Italy in the period 2003-2005, cervical cancer accounted for 1.6% of new cancers and 0.6% of cancer mortality in females. In women up to the age of 44 cervical cancer ranked fourth among the most common cancers (4.8% of total female cancer incidence excluding non-melanoma skin cancer). The estimated incidence in the 2003-2005 period was 8.6 cases per 100,000 females. In 2006 there were 351 deaths from cervical cancer in Italy. There is a 20 year decreasing mortality and incidence trend, in part masked by the ageing population (Registri Tumori).

Target condition being diagnosed

Target conditions are: a) disease involvement of regional lymph nodes identified through N staging, and b) presence of distant metastases, identified through M staging.

Index test(s)

FDG-PET/CT.

The role of FDG-PET for staging is under evaluation according to ESMO guidelines (ESMO 2010). According to the SIGN guideline (SIGN 2008) staging is carried out using MRI, with PET reserved only for those with a contraindication to MRI. PET-based staging should be carried out on those who cannot undergo surgery.

Alternative test(s)

Clinical examination represents the basis for Federation Internationale de Gynecologie et d'Obstetrique (FIGO) classification, which is the most widely used classification. Staging classification (FIGO classification) is based on tumoral extension, assessed by clinical examination, depending on tumour size, vaginal and/or parametrial involvement, and bladder/rectum tumoral extension. FIGO classification requires also basic complementary examinations including chest X-ray and intravenous pyelogram. Nowadays, magnetic resonance imaging (MRI) is considered the reference complementary examination as it is superior to computed tomography (CT) scan for tumour extension assessment and equal to CT scan for nodal involvement assessment. MRI should be preferred to CT scan and include pelvic and abdominal imaging. A thoracic CT scan may be included for metastasis assessment (ESMO 2010).

Rationale

Role of staging. Tumour risk assessment includes tumour size, stage, nodal involvement, lymphovascular space involvement and histological subtype (ESMO 2010). Lymph node status is one of the most powerful prognostic factors in determining the administration of adjuvant therapies in surgically treated patients, and influencing survival rate of patients with early stage cervical cancer (PS - Signorelli 2011). The potential role of PET/CT therefore appears to be only the definition of staging especially in advanced cases to guide the therapeutic approach. However there does not appear to be a clear cut rationale for its use. The SIGN guideline states "Cervical cancer is clinically staged using the FIGO criteria (see Annex 5). FIGO staging does not take into account results of computerised tomography (CT), magnetic resonance imaging (MRI) or positron emission tomography (PET)".

Treatment options. The treatment approach is dictated by the general conditions of the patient and by the stage of the disease (0 to IVb) (SIGN 2008). According to the US National Cancer Institute (US NCI) there are three treatment options:
- Surgery may be used at times, either through a cone biopsy of the cervix (a procedure which is diagnotic/therapeutic in local cancers or by partial, total hysterectomy or by removing some of the uterine adnexa too or by other techniques such cryotherapy aimed at freezing the target parts).
- Radiation therapy (external or internal)
- Chemotherapy (regional or systemic).

Objectives

The objective of this review was to examine the diagnostic accuracy and the clinical effectiveness FDG-PET/CT for staging or N staging and M staging of patients diagnosed with cervical cancer compared to conventional imaging examination.

Search methods for identification of studies

Evidence is based on a) the conclusion of the most recent HTA report on cervical cancer (KCE 2009) which was of good quality and had an electronic search updated to January 2009; b) a further search of studies published between January 2009 and March 2012. The key words described the participants' disease and the index test. See appendix 14 for details of strategy.

Results

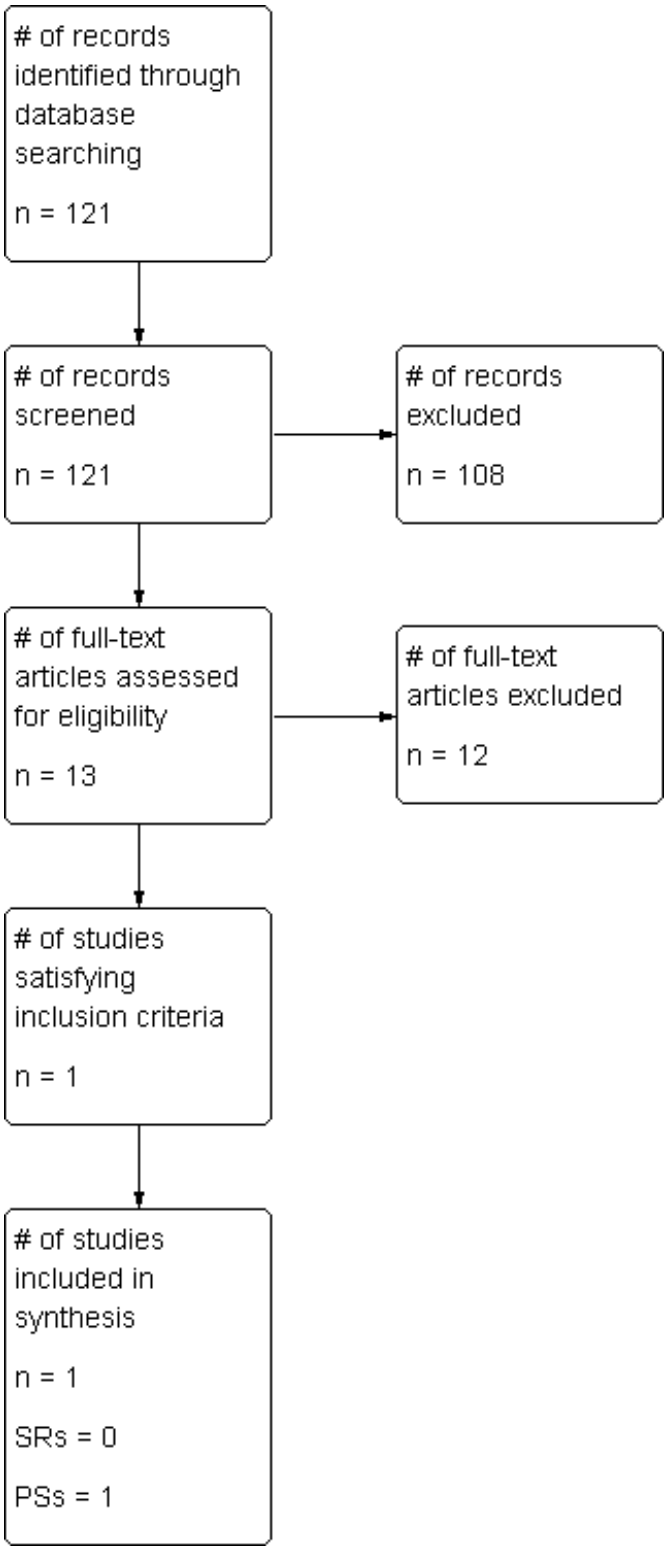
KCE concluded that a number of studies "reported a low sensitivity for pelvic lymph node staging, but a moderate sensitivity for extrapelvic lymph node staging. Specificity was consistently good across both lymph node regions (level 2). A good-quality systematic review found sentinel-node biopsy to be the most accurate technique for early-stage disease (level 2)" (KCE 2009).

Results of the search

Identification and selection of studies. Our searches identified 121 titles possibly fitting inclusion criteria. After screening of titles and abstracts 13 studies were retrieved and read by one of us (TJ). Twelve studies were excluded for various reasons (see Excluded studies: Ferrandina 2012; Kang 2010; Kitajima 2009; Lee 2011; Leseur 2011; Olsen 2011; Ozcan 2011; Rudmik 2011; Small 2010; Tatsumi 2009; Tsai 2010; Ylmaz 2010). One primary primary study was finally included (PS - Signorelli 2011).

The study selection process is summarized in the PRISMA flow diagram (Moher 2009; see Figure 1).

Figure 1 Cervical cancer: study selection according to PRISMA flow diagram (Moher 2009).



Description of included studies

N staging

Systematic reviews
None retrieved.

Primary studies
One study (159 women) evaluating diagnostic accuracy of FDG-PET/CT for regional lymph node staging has been included (PS - Signorelli 2011). Participants are women with Ib1–IIa < 4 cm cervical carcinoma and eligible for surgical treatment. Refererence standard is the postoperative pathologic staging. No comparator is assessed.

M staging

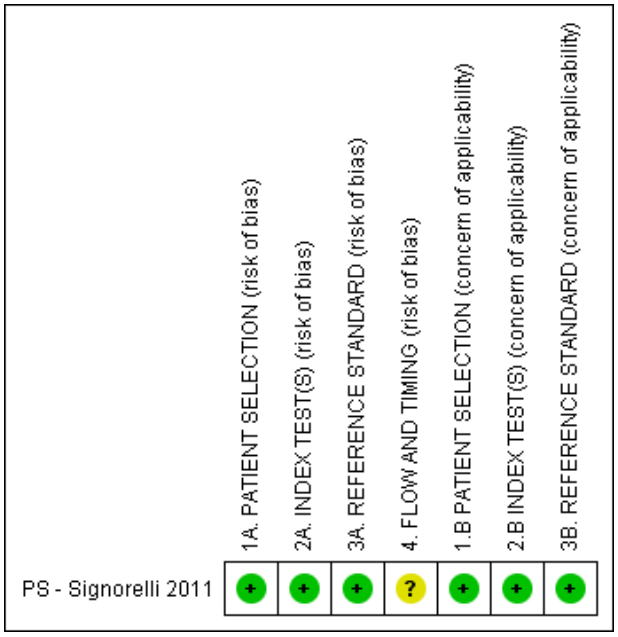
Systematic reviews
None retrieved.

Primary studies
None retrieved.

Methodological quality of included studies

The quality assessment results for the only study included can be found in Figure 2.

Figure 2 Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Findings

N staging

Primary studies Low sensitivity and relatively more acceptable specificity are confirmed by our additional study. See below the Summary of Findings table for details

Comments on Findings

Only evidence on diagnostic accuracy of FDG-PET/CT is available.
According to data considered to be of *moderate quality*, FDG/PET/CT seems to have very low sensitivity however data on comparators are not available, thus no conclusions can be drawn.

Summary of Findings: Diagnostic accuracy of FDG-PET for N staging of cervical cancer

Patients/population: cervical cancer (women with Ib1–IIa < 4 cm cervical carcinoma and eligible for surgical treatment)
Index test: FDG-PET/CT
Comparators: none
Reference standard: intraoperative histology

Primary studies	No. of studies (participants)	Study design	Risk of Bias	Indirectness	Inconsistency	Imprecision	Diagnostic Accuracy FDG-PET/CT	Diagnostic Accuracy Comparators	Quality of Evidence
Primary studies	1 (159 women)	Diagnostic accuracy studies with prospective recruitment	No	No	No	Serious	Sensitivity 32.1% Specificity 96.9%	not applicable	Moderate

Authors' conclusions

N staging

The rationale in support of the use of FDG-PET/CT for N staging of patients with cervical cancer is unclear.

HTA report (KCE 2009) reported that the standard practice for N staging (sentinel-node biopsy) of patients with cervical cancer is superior than FDG-PET/CT.

Evidence from the only one study retrieved through our update and judged to be of moderate quality confirms the above conclusions thus the use of FDG-PET/CT would be inappropriate.

M staging: diagnostic accuracy

It appears there is no rationale in support of the use of FDG-PET/CT for M staging of patients with cervical cancer and no studies were retrieved.

Thus the use of FDG-PET/CT for staging of cervical cancer would be inappropriate.

References

Included studies

KCE 2009

Vlayen J, Stordeur S, Van den Bruel A, Mambourg F, Eyssen M. Positron Emissie Tomografie: een update. Health Technology Assessment (HTA). Federaal Kenniscentrum voor de Gezondheidszorg (KCE) 2009;KCE reports 110A (D/2009/10.273/24). Last access 28th August 2012

PS - Signorelli 2011

Signorelli M, Guerra L, Montanelli L, Crivellaro C, Buda A, Dell'Anna T, Picchio M, Milani R, Fruscio R, Messa C. Preoperative staging of cervical cancer Is 18-FDG-PET/CT really effective in patients with early stage disease? Gynecol Oncol 2011;123(2):236-240.

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Kitajima 2009

Kitajima K, Murakami K, Yamasaki E, Kaji Y, Sugimura K. Accuracy of integrated FDG-PET/contrast-enhanced CT in detecting pelvic and paraaortic lymph node metastasis in patients with uterine cancer. Eur Radiol 2009;19(6):1529-36.

Lee 2011

Lee M, Lee Y, Hwang KH, Choe W, Park CY. Usefulness of F-18 FDG PET/CT in assessment of recurrence of cervical cancer after treatment. Nucl Med Mol Imaging 2011;45(2):111-116.

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Olsen J R, Dehdashti F, Siegel B A, Zighelboim I, Grigsby P W, Schwarz J K. Prognostic utility of squamous cell carcinoma antigen in carcinoma of the cervix: Association with pre- and posttreatment FDG-PET. Int J Radiat Oncol Biol Phys 2011;81(3):772-777.

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Tatsumi M, Cohade C, Bristow RE, Wahl R L. Imaging uterine cervical cancer with FDG-PET/CT: direct comparison with PET. Mol Imaging Biol 2009;11(4):229-35.

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Tsai C S, Lai C H, Chang T C, Yen T C, Ng K K, Hsueh S, Lee S P, Hong J H. A prospective randomized trial to study the impact of pretreatment FDG-PET for cervical cancer patients with MRI-detected positive pelvic but negative para-aortic lymphadenopathy. Int J Radiat Oncol Biol Phys 2010;76(2):477-84.

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Registri Tumori

www.registri-tumori.it/cms/?q=Rapp2009Indice. Accessed 10 May 2012.

SIGN 2008

Management of cervical cancer. A national clinical guideline. Scottish Intercollegiate Guidelines Network (SIGN). Available at http://www.sign.ac.uk/guidelines/fulltext/99/index.html 2008. Accessed 10 May 2012.

US NCI

Available at http://www.cancer.gov/cancertopics/pdq/treatment/cervical/Patient/page4 accessed 17 May 2012.

4.19 FDG-PET/CT for staging of testicular cancer

Background

Testicular cancer accounts for 1% to 2% of all cancers in men (Bosl 1997), and is the most prevalent cancer in otherwise healthy men 20 to 35 years of age (Garner 2005). The incidence of testicular cancer in Europe is rising, with doubling every 20 years. The current incidence is 6.3/100 000/ year, with the highest rate in Northern European countries (6.8/100 000/year). The death rate is very low (0.38 cases/ 100 000/year). Of testicular tumours, 40% are seminomas and 60% non-seminomas (Schmoll 2010b).

In Italy, testicular cancer is the most frequently diagnosed cancer among men in the 0-44 year age group after non-melanoma skin cancers. During 1998-2002, testis cancer represented 0.7% of all the diagnosed cancer among males; as regards mortality, it represented 0.1% of all cancer deaths among males. In the area of the Italian Network of Cancer Registries, there were on yearly average 5.4 new testicular cancers per 100,000 males. It has been estimated that every year there are 872 new testicular cancer diagnoses in Italy; as regards mortality, there were 95 deaths due to testis cancer in 2002 (Registri Tumori).

Survival for patients with metastatic germ-cell tumours varies according to prognosis, with 5-year overall survival rates for those with a good, intermediate and poor prognosis 92%, 80% and 48%, respectively (Feldman 2008).

Target condition being diagnosed

Target conditions are: a) disease involvement of retroperitoneal (or mediastinal) lymph nodes, identified through N staging; b) presence of distant metastases, identified through M staging according to TNM classification and International Germ Cell Consensus Classification (Sobin 2002; IGCCCG 1997; Krege 2008a).

Index test(s)

FDG-PET/CT.

None of the most recent guidelines recommends the use of FDG-PET/CT for staging of patients with testicular cancer (Albers 2011; NCCN 2012; Schmoll 2010a; Schmoll 2010b)

Alternative test(s)

Routine pre-treatment N - M staging includes computed tomography (CT) of the chest, abdomen, and pelvis. CT of the chest may be omitted for patients with testicular seminoma presenting without a retroperitoneal tumour mass (Krege 2008b); bone scans should be obtained in patients in whom bone metastases are clinically suspected. Imaging of the brain, by magnetic resonance tomography, is required in patients with clinical symptoms and signs indicating brain metastases, particularly when they occur in patients with advanced disease (Bokemeyer 1997).

Reference standard for N staging is histological examination following retroperitoneal lymph node dissection (RPLND), CT imaging for mediastinal lymph node or clinical follow up; reference standard for M staging is histopathology of metastases or follow-up with imaging techniques (Krege 2008a).

Rationale

Role of staging. Staging represents the cornerstone on which testicular cancer treatment is based; the nodal pathway, distant metastasis and half-life kinetics of serum tumour markers must be assessed to enable the most appropriate treatment (Krege 2008a).

To define the clinical stage of a patient with a gonadal germ cell tumour the TNM classification of the UICC should be used (Sobin 2002). In addition, most patients with metastatic disease are classified according to the classification of the International Germ Cell Cancer Collaborative Group (IGCCCG 1997) which is also incorporated into the TNM classification.

Treatment options. Treatment strategies mainly depend on the stage of disease. Surgery of the primary tumour (orchiectomy) should be performed before any further treatment, unless there is life-threatening metastatic disease and clear clinical diagnosis of germ cell tumour by marker elevation which requires immediate chemotherapy (Schmoll 2010a; Schmoll 2010b).

N and M metastases are treated with radio and/or chemotherapy depending on tumour staging (secondary surgery after chemotherapy or radiotherapy and salvage treatment are planned too)(Schmoll 2010a; Schmoll 2010b).

Objectives

The objective of this review was to examine the diagnostic accuracy and the clinical effectiveness of FDG-PET/CT for N staging and M staging of patients diagnosed with testicular cancer compared to conventional imaging examination.

Search methods for identification of studies

Evidence is based on a) the conclusion of the most recent HTA report on testicular cancer (KCE 2009) which was of good quality and had an electronic search updated to January 2009; b) a further search of studies published between January 2009 and March 2012. The key words described the participants' disease and the index test. See appendix 15 for details of strategy.

Results

The HTA document (KCE 2009) concluded that:

- evidence is inconclusive to draw any conclusion on FDG-PET/CT for staging of patients with testicular cancer

Results of the search

Identification and selection of studies. The updated search identified 76 records; 70 have been excluded after checking the abstract, for not meeting the inclusion criteria. Full text has been acquired for the remaining potentially eligible 6 records. Only one study has been finally included (PS - Sterbis 2010). The study selection process is summarized in the PRISMA flow diagram (Moher 2009; see Figure 1).

Figure 1 Study flow diagram.

Description of included studies

One study evaluates diagnostic accuracy of FDG-PET/CT (PS - Sterbis 2010).

Diagnostic accuracy - N staging

Primary studies
One study (PS - Sterbis 2010) (49 patients) with initial diagnosis of testicular cancer and evaluating diagnostic accuracy of FDG-PET/CT for regional retroperitoneal lymph node staging was included.

Reference standard is the postoperative pathologic N staging following retroperitoneal lymph node dissection. For the purposes of calculating sensitivity, specificity a true positive was confirmed by histology obtained at retroperitoneal lymph node dissection (RPLND) (n = 3) or either positive serum markers or positive CT size criteria (n = 11) in those patients that did not undergo RPLND. A true negative was defined by pathology when available (n = 15) or by negative follow-up accompanying a negative PET/CT (n = 18). False positives (n=1) and negatives (n=1) were defined either by pathologic findings or clinical follow up contrary to initial PET/CT results. Comparative tests as CT, chest radiographs and MRI were used.

Diagnostic accuracy - M staging

None retrieved.

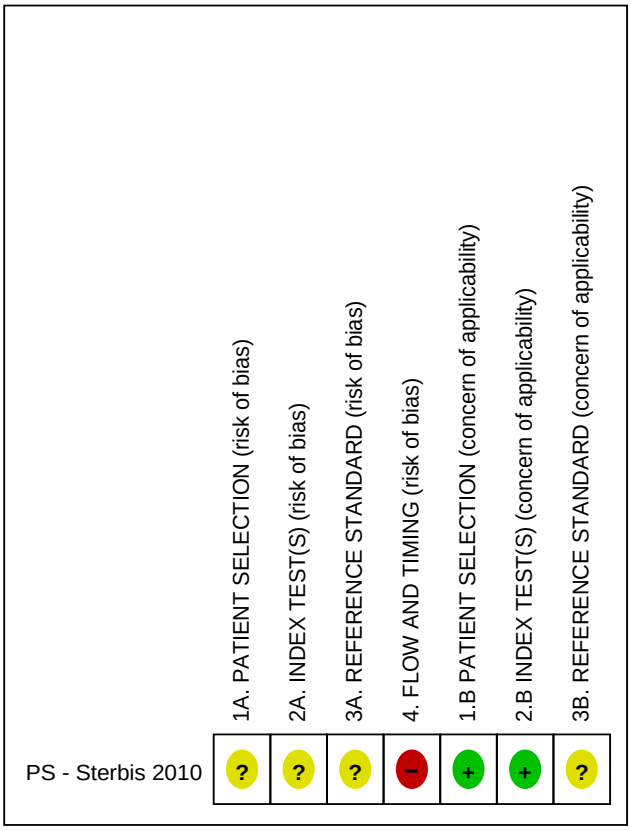
Methodological quality of included studies

Diagnostic accuracy - N staging

Primary studies

Sterbis et al. (PS - Sterbis 2010) enrolled 49 patients; Patient selection and Index test have an unclear risk of bias. Reference standard and Flow and timing has a high risk of bias. Overall quality of evidence is very low. Quality assessment results for the included studies is provided in Figure 2.

Figure 2 Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Diagnostic accuracy - M staging

None retrieved.

Impact on clinical outcomes - Any staging

None retrieved.

Findings

Diagnostic accuracy - N staging

Detailed results are reported below in the Summary of findings 1.

Primary studies
The study included (PS - Sterbis 2010) reports the following diagnostic accuracy estimates for FDG-PET/CT: sensitivity 93.3% (95% CI 66-99%) and specificity 97.0% (95% CI 83-99%).

FDG-PET-CT sensitivity and specificity were higher than that of CT (Sensitivity 60.0%, 95% CI 33-82%, and Specificity 82.3%, 95% CI 65-93%).

Comments on Findings

N staging

Data available on FDG-PET/CT are based only on evidence of *very low quality*, thus no conclusion can be drawn.

M staging

No evidence is available.

Summary of findings 1

Patients/population: seminomatous germ cell tumors (SGCT) and non-seminomatous germ cell tumors (NSGCT) of the testis **Index test**:FDG-PET/CT. **Comparators**:CT **Reference standard:** retroperitoneal lymph node dissection or clinical follow-up (or serum markers CT size criteria).									
Ref.	N°studies	Study design	Risk of bias	indirectness	inconsistency	imprecision	Diagnostic accuracy FDG-PET/CT	Diagnostic accuracy comparator-CT	Quality of evidence
Primary studies	1 study (49 patients)	diagnostic cross sectional study with prospective recruitment	serious	serious	NA*	serious	Sensitivity: 93.3% (95% CI 66-99%) Specificity: 97.0% (95% CI 83-99%)	Sensitivity: 60.0% (95% CI 33-82%) Specificity: 82.3% (95% CI 65-93%)	Very Low
*NA: not applicable									

Authors' conclusions

Any staging

The KCE HTA report (KCE 2009) concluded that evidence is inconclusive to draw any conclusion on FDG-PET/CT for staging of patients with testicular cancer.

Evidence from the only one study retrieved through our update and judged to be of very low quality does not challenge the above conclusions thus the use of FDG-PET/CT would be inappropriate.

References

Included studies

KCE 2009

Vlayen J, Stordeur S, Van den Bruel A, Mambourg F, Eyssen M.. KCE reports 110A. Positron Emissie Tomografie: een update. Health Technology Assessment (HTA). Federaal Kenniscentrum voor de Gezondheidszorg (KCE) (D/2009/10.273/24) 2009. Last access 28th August 2012

PS - Sterbis 2010

Sterbis JR, Rice KR, Javitt MC, Schenkman NS, Brassell SA. Fusion imaging: A novel staging modality in testis cancer. J. Cancer1(1):223-9.

Excluded studies

Boujelbene 2011

Boujelbene N, Prior JO, Boubaker A, Azria D, Schaffer M, Gez E, et al. [Value of positron emission tomography and computer tomography (PET/CT) for urologic malignancies]. Cancer Radiother15(4):307-15.

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Heidenreich A, Albers P, Classen J, Graefen M, Gschwend J, Kotzerke J, et al. Imaging studies in metastatic urogenital cancer patients undergoing systemic therapy: recommendations of a multidisciplinary consensus meeting of the Association of Urological Oncology of the German Cancer Society. Urol Int85(1):1-10.

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Zouhair 2010

Zouhair A, Ozsahin M, Schaffer M, Albrecht S, Camus F, Jichlinski P, et al. Positron emission tomography and computer tomography (PET/CT) in prostate, bladder, and testicular cancers. Curr Med Chem17(23):2492-502.

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Albers P, Albrecht W, Algaba F, Bokemeyer C, Cohn-Cedermark G, Fizazi K, et al. EAU guidelines on testicular cancer: 2011 update. European urology 2011;60(2):304-19.

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Bosl GJ, Motzer RJ. Testicular germ-cell cancer. The New England journal of medicine 1997;337(4):242-53.

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Garner MJ, Turner MC, Ghadirian P, Krewski D. Epidemiology of testicular cancer: an overview. International journal of cancer. Journal international du cancer 2005;116(3):331-9.

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Krege 2008b

Krege S. et al. European consensus conference on diagnosis and treatment of germ cell cancer: a report of the second meeting of the European Germ Cell Cancer Consensus group (EGCCCG): part II. Eur Urol 2008 Mar;53(3):497-513.

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Registri Tumori

http://www.registri-tumori.it, last access 5th June 2012

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Schmoll 2010b

H.-J. Schmoll, K. Jordan, R. Huddart, M. P. Laguna Pes, A. Horwich, K. Fizazi & V. Kataja. On behalf of the ESMO Guidelines Working Group. Testicular non-seminoma: ESMO Clinical Practice Guidelinesfor diagnosis, treatment and follow-up. Annals of Oncology 2010;21 (Supplement 5):v147–v154.

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4.20 FDG-PET/CT for staging of prostate cancer

Background

For several years it has been recognized that FDG-PET is not a useful test for the diagnostic pathway of prostate cancer because of instrinsic technical limitation of the FDG tracer (Fanti 2007). This is due, on one hand to the decreased metabolic dependance of prostate cancer upon glucose (reduced uptake and glycolysis), on the other hand to the metabolic pathway of FDG that, being excreted througout ureters and bladder, obscures prostate and closely related adjacent tissues (seminal vescicles) that can harbour local and regional metastases.

To confirm the hypothesis of an absence of rationale for staging of prostate cancer with PDG-PET/CT we performed a new systematic search about this clinical question in case new evidence had emerged.

Results

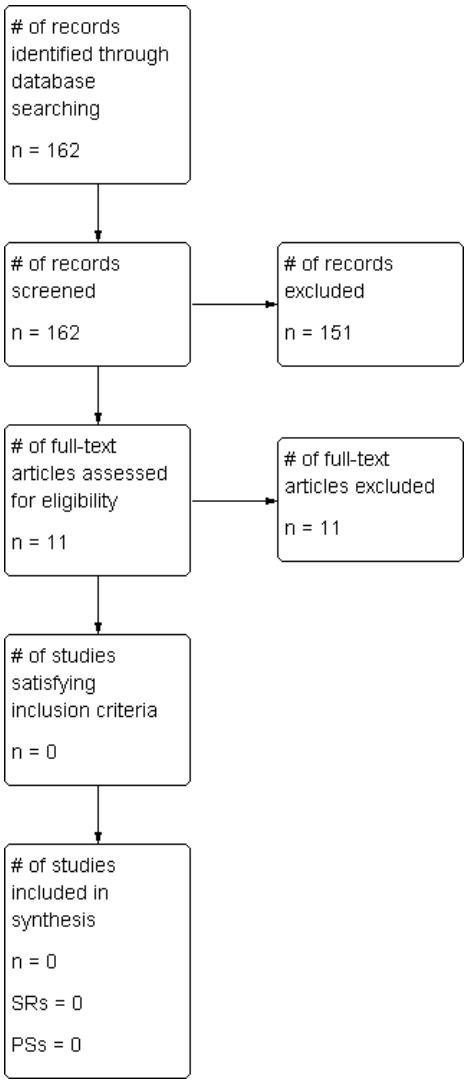
The HTA document (KCE 2009) concluded that:

- the evidence on the use of PET(/CT) is too limited to draw firm conclusions

Results of the search

Identification and selection of studies. Our searches identified 162 possible studies. After screening of title and abstract we retrieved 11 studies. None fulfilled our inclusion criteria (Figure 1).

Figure 1 Prostate cancer: study selection according to PRISMA flow diagram (Moher 2009).



Authors' conclusions

There is no rationale for the use of FDG-PET/CT in staging of prostate cancer.

No evidence was found by the KCE report (KCE 2009). No studies are retrieved by our update.

Therefore the use of FDG-PET/CT in staging of prostate cancer would be inappropriate.

References

Included studies

KCE 2009

Vlayen J, Stordeur S, Van den Bruel A, Mambourg F, Eyssen M. Positron Emissie Tomografie: een update. Health Technology Assessment (HTA). Federaal Kenniscentrum voor de Gezondheidszorg (KCE) 2009;KCE reports 110A (D/2009/10.273/24). Last access 28th August 2012

Excluded studies

Budiharto 2011

Budiharto T, Joniau S, Lerut E, Van Den Bergh L, Mottaghy F, Deroose CM, Oyen R, Ameye F, Bogaerts K, Haustermans K, Van Poppel H.. Prospective evaluation of 11C-choline positron emission tomography/computed tomography and diffusion-weighted magnetic resonance imaging for the nodal staging of prostate cancer with a high risk of lymph node metastases. Eur. Urol 2011;60(1):125-130.

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Contractor K, Challapalli A, Barwick T, Winkler M, Hellawell G, Hazell S, Tomasi G, Al-Nahhas A, Mapelli P, Kenny LM, Tadrous P, Coombes RC, Aboagye EO, Mangar S. Use of [11C]choline PET-CT as a noninvasive method for detecting pelvic lymph node status from prostate cancer and relationship with choline kinase expression. Clin. Cancer Res 2011;17(24):7673-7683.

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Garcia J R, Soler M, Blanch M A, Ramirez I, Riera E, Lozano P, Perez X, Delgado E, Carrio I, Lomena F. [PET/CT with (11)C-choline and (18)F-FDG in patients with elevated PSA after radical treatment of a prostate cancer]. Rev Esp Med Nucl 2009;28(3):95-100.

McCarthy 2011

McCarthy M, Siew T, Campbell A, Lenzo, N, Spry N, Vivian J, Morandeau L. (1)F-Fluoromethylcholine (FCH) PET imaging in patients with castration-resistant prostate cancer: prospective comparison with standard imaging. Eur J Nucl Med Mol Imaging 2011;38(1):14-22.

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Panebianco V, Sciarra A, Lisi D, Galati F, Buonocore V, Catalano C, Gentile V, Laghi A, Passariello R. Prostate cancer: 1HMRS-DCEMR at 3 T versus [(18)F]choline PET/CT in the detection of local prostate cancer recurrence in men with biochemical progression after radical retropubic prostatectomy (RRP). Eur J Radiol 2012;81(4):700-708.

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Steuber 2010

Steuber T, Schlomm T, Heinzer H, Zacharias M, Ahyai S, Chun KF, Haese A, Klutmann S, Kollermann J, Sauter G, Mester J, Mikecz P, Fisch M, Huland H, Graefen M, Salomon G. [F18]-fluoroethylcholine combined in-line PET-CT scan for detection of lymph-node metastasis in high risk prostate cancer patients prior to radical prostatectomy: Preliminary results from a prospective histology-based study. Eur. J. Cancer. 2010; 46(2):449-455. Eur. J. Cancer 2010;46(2):449-455.

Watanabe 2010

Watanabe H, Kanematsu M, Kondo H, Kako N, Yamamoto N, Yamada T, Goshima S, Hoshi H, Bae K. T. Preoperative detection of prostate cancer: a comparison with 11C-choline PET 18F-fluorodeoxyglucose PET and MR imaging. J Magn Reson Imaging 2010;31(5):1151-6.

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Withofs N, Grayet B, Tancredi T, Rorive A, Mella C, Giacomelli F, Mievis F, Aerts J, Waltregny D, Jerusalem G, Hustinx R. (1)F-fluoride PET/CT for assessing bone involvement in prostate and breast cancers. Nucl Med Commun 2011;32(3):168-76.

Wurschmidt 2011

Wurschmidt F, Petersen C, Wahl A, Dahle J,Kretschmer M. [18F]fluoroethylcholine-PET/CT imaging for radiation treatment planning of recurrent and primary prostate cancer with dose escalation to PET/CT-positive lymph nodes. Radiat. Oncol 2011;6(1):1748-757.

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4.21 FDG-PET/CT for staging of penile cancer

Background

Penile cancer is the growth of malignant cells on the external skin and in the tissues of the penis. It is a relatively rare squamous cell carcinoma with an incidence of 0.1–0.9 per 100,000 males in Europe and 0.7–0.9 per 100,000 males in the USA (Solsona 2004; Cancer.gov).

If we consider one of the most reliable cancer registries in Italy: Umbrian Population Cancer Registry (RTUP): we can estimate in the period 2004-2008 a crude incidence of 2.4 per 100.000 person/year for penile cancer (rtup.unipg.it).

Relative survival at 5 years is about 70% (AIRTUM Working Group 2006). Major prognostic factors of this disease are lymph node status (66% survival for patients with node-negative and 27% for those with positive lymph nodes) and the degree of differentiation of the tumor with perineural infiltration evaluation (Ornellas 2008; Velazquez 2008; Cubilla 2009).

At the initial presentation, clinically palpable inguinal lymph nodes are present in 28%-64% of patients with penile squamous cell carcinoma. In 47%-85% of these patients, lymphadenopathy is caused by metastatic invasion, and inflammatory reactions account for the remainder. Approximately 25% of patients with palpable inguinal metastases will have bilateral and 75% will have unilateral palpable nodes (Solsona 2004).

Distant metastases are uncommon in patients who present with penile cancer (3%-5% of cases), and these are generally accompanied by regional lymph node metastases (LNMs).The detection of pelvic metastases and of more distant metastases has a considerable impact on therapy and prognosis (Pizzocaro 2010; PS - Schlenker 2012).

Target condition being diagnosed

Target conditions are: a) disease involvement of inguinal and pelvic lymph nodes, identified through N staging; b) presence of distant metastases, identified through M staging according to European Association of Urology Penile Cancer Guidelines 2009 (Pizzocaro 2010) .

Index test(s)

FDG-PET/CT.

Among the most recent guidelines, NCCN guidelines (NCCN 2012 - Penile cancer) does not recommend use of FDG-PET/CT for staging, while EAU guidelines (Pizzocaro 2010) states that FDG-PET/CT could be used both for N and M staging .

Alternative test(s)

Routine pre-surgical N staging includes physical examination of the inguinal region, sentinel node biopsy, fine niddle aspiration cytology, ultrasonograhy, conventional CT-scan, or abdominopelvic MRI. Routine M staging is carried out with abdominal CT scan and chest x-ray, and in symptomatic M1 patients a bone scan is also advisable.

Reference standard for N staging is histological examination following radical lymph node dissection or clinical follow up; reference standard for M staging is histopathology of metastases or follow-up with imaging techniques (Pizzocaro 2010).

Rationale

Role of staging. The primary tumour and regional lymph nodes must be staged correctly to enable the most appropriate treatment. In fact curative treatment strategies mainly depend on the stage of disease. While the treatment of non-metastatic penile cancer is based on early local resection in later presentations, N and M staging are necessary to direct surgery, local metastatic treatment and furnish a baseline for possible later progression (Pizzocaro 2010).

Treatment options. Treatment strategies mainly depend on the stage of disease. In Stages Tis, Ta, and T1a only local resection of primary lesion is required with the following penis-sparing techniques: local excision with or without circumcision; laser therapy with carbon dioxide; Mohs micrographic surgery; photodynamic therapy ; topical therapy with 5-fluorouracil (5-FU). In stage T1b are currently used wide local (laser) excision, neoadjuvant chemotherapy; radiotherapy or glansectomy. Stage 3 and 4 require partial or total amputation (Pizzocaro 2010)

Lymphadenectomy (LAD) is the treatment of choice for patients with inguinal lymph node metastases; adjuvant chemotherapy is recommended in pN2–3 patients while adjuvant radiotherapy may improve locoregional control in patients with extensive metastases and/or extranodal spread (Pizzocaro 2010).

Objectives

The objective of this review was to examine the diagnostic accuracy and the clinical effectiveness of FDG-PET/CT for N staging and M staging of patients diagnosed with squamous cell carcinoma of the penis compared to conventional imaging examination.

Search methods for identification of studies

Evidence is based on a) the conclusion of the most recent HTA report on penile cancer (KCE 2009) which was of good quality and had an electronic search updated to January 2009; b) a further search of studies published between January 2009 and March 2012. The key words described the participants' disease and the index test. See appendix 17 for details of strategy.

Results

The HTA document (KCE 2009) concluded that

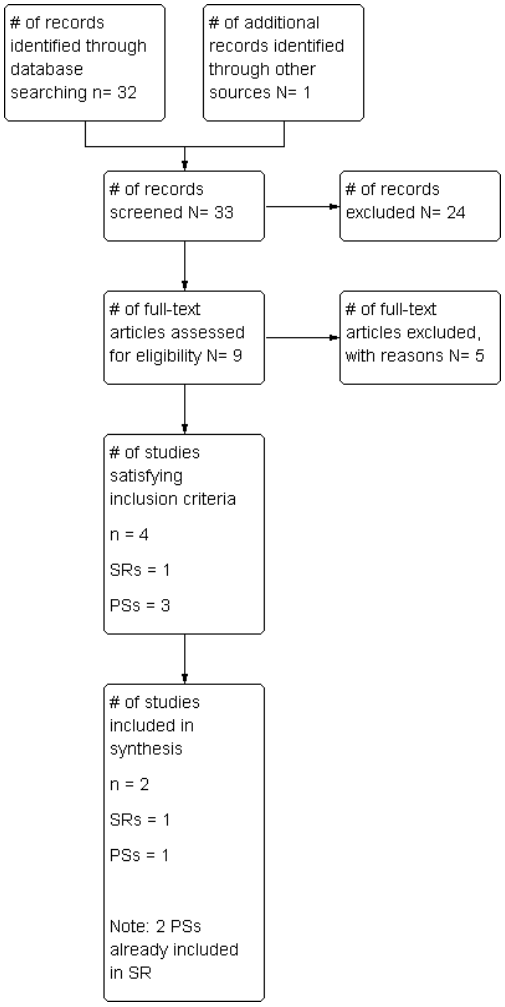
- no systematic reviews or primary studies were found regarding penile cancer.

Results of the search

Identification and selection of studies. The updated electronic search identified 32 records and an additional one by reference lists; 24 have been excluded after checking the abstract, for not meeting the

inclusion criteria. Full text has been acquired for the remaining potentially eligible 9 records. Four studies have been finally included (PS - Souillac 2012; Leijte 2009; Schlenker 2012; SR - Sadeghi 2012) but two of them (Leijte 2009; Schlenker 2012) have not been evaluated because they are included in SR - Sadeghi 2012. The study selection process is summarized in the PRISMA flow diagram (Moher 2009; see Figure 1).

Figure 1 Study flow diagram.



Description of included studies

Two studies evaluate diagnostic accuracy of FDG-PET/CT (PS - Souillac 2012; SR - Sadeghi 2012).

Systematic reviews
One systematic review has been included (SR - Sadeghi 2012). This review assesses and compares the diagnostic accuracy of FDG-PET/CT with pathological proof following inguinal dissection or evidence of progression at follow-up for regional inguinal lymph nodes staging in patient with penile carcinoma before any treatment.

The review by Sadeghi et al. (SR - Sadeghi 2012) includes 7 primary studies (one study had 2 separate subgroups of patients cN+ and cN0 patients - that were included in the meta-analysis separately - with a total of 115 patients (213 groins). Some studies assess also diagnostic accuracy of CT, MRI and ultrasonograaphy but the number of studies is not reported. Studies include mixed stage patients.

Primary studies
One study (PS - Souillac 2012) (30 patients and 60 inguinal groins) evaluating diagnostic accuracy of FDG-PET/CT for regional inguinal lymph node staging was included. Reference standard is the postoperative pathologic N staging following inguinal dissection. Comparative tests as clinical examination and CT were used.

Diagnostic accuracy - M staging

None retrieved.

Impact on clinical outcomes - Any staging

None retrieved.

Methodological quality of included studies

Diagnostic accuracy - N staging

Systematic reviews
The systematic review by Sadeghi et al. (SR - Sadeghi 2012) reports an assessement of methodological quality of included studies according to The Oxford Center for Evidence-Based Medicine checklist for diagnostic studies (http://www.cebm.net/index.aspx?o1025). Authors performed meta-analysis; bibliographic search method is comprehensive, and the characteristics of included studies are clearly reported; the methodological quality of included studies appropriately assessed and the statistical analysis well conducted. Primary studies (50%) included into the systematic review could be prone to possible spectrum bias (50% with retrospective or unclear design) and about 75% of studies have an unclear or absence of blind comparison between the index test and the reference standard.

Primary studies
Souillac et al. (PS - Souillac 2012) enrolled 30 consecutive patients. Index test and reference standard have an unclear risk of bias. Quality assessment results for the included studies is provided in Figure 2.

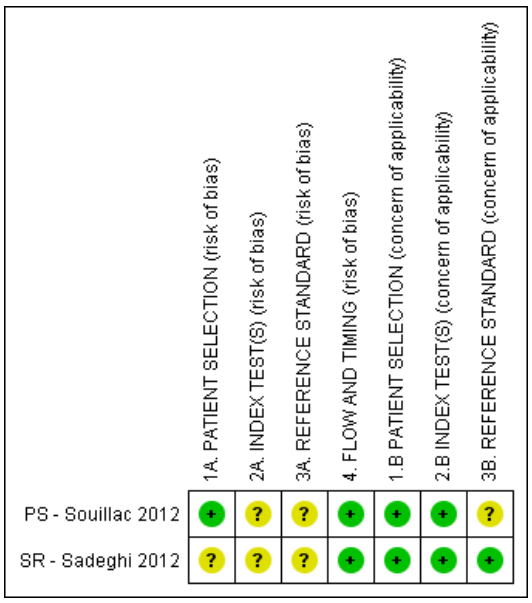
Diagnostic accuracy - M staging

None retrieved.

Impact on clinical outcomes - Any staging

None retrieved.

Figure 2 Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Findings

Diagnostic accuracy - N staging

Detailed results are reported below in the Summary of findings 1.

Systematic reviews
The systematic review by Sadeghi et al. (SR - Sadeghi 2012) reports pooled estimates of diagnostic accuracy for FDG-PET/CT compared with inguinal lymph node dissection (or sentinel node biopsy) and/or follow-up. Pooled sensitivity of FDG-PET/CT is 80.9% (95% CI: 69.5%–89.4%), pooled specificity 92.4% (95% CI: 86.8%–96.2%).

Diagnostic accuracy estimates in the subgroup of clinically negative inguinal limph node are noticeably lower for FDG-PET/CT (cN0 sensitivity : 56.5% (95% CI: 34.5%–76.8%);specificity : 85.9% (95% CI: 75.6%– 93.0%)) and higher in the subgroup of clinically positive inguinal limph node (cN+ sensitivity : 96.4% (95% CI: 81.7%–99.9%); specificity : 100% (95% CI: 83.9%–100%)).

Primary studies
The study included (PS - Souillac 2012) reports the following diagnostic accuracy estimates for FDG-PET/CT: all patients sensitivity 91%, specificity 89.8%; cN0 sensitivity 75%, specificity 87.5%; cN+ sensitivity 100%, specificity 100%. Different diagnostic accuracy estimates are found with CT imaging (alternative test): all patients sensitivity 91%, specificity 81.6%; cN0: sensitivity 100%, specificity 77.5%; cN+**:** sensitivity 85.7%, specificity 100%.

Comments on Findings

N staging

The systematic review retrieved by our update - of *low quality*- shows inconsistent diagnostic accuracy estimates. Very few data are available on diagnostic accuracy of comparators.

Summary of findings 1

Patients/population: squamous cell carcinoma of the penis. **Index test**:FDG-PET/CT. **Comparators**: clinical examination, CT. **Reference standard:** inguinal lymph node dissection (or sentinel node biopsy) and/or follow-up.									
Ref.	N°studies	Study design	Risk of bias	indirectness	inconsistency	imprecision	Diagnostic accuracy FDG-PET/CT	Diagnostic accuracy comparators	Quality of evidence
Sadeghi 2012	7 primary studies; one study had 2 separate subgroups of patients (cN and cN0 patients) that were included in the meta-analysis separately; 115 patients (213 groins)	Systematic review	no	no	serious	serious	All patients sensitivity : 80.9% (95% CI: 69.5%–89.4%) specificity : 92.4% (95% CI: 86.8%–96.2%) cN+ patients sensitivity : 96.4% (95% CI: 81.7%–99.9%). specificity : 100% (95% CI: 83.9%–100%) cN0 patients sensitivity : 56.5% (95% CI: 34.5%–76.8%). specificity : 85.9% (95% CI: 75.6%–93.0%)		Low
Primary studies	1 study; 30 patients with histologically proven penile carcinoma (60 groins)	diagnostic cross sectional study with prospective recruitment	no	no	NA*	very serious	All patients Sensitivity: 91% Specificity: 89.8% cN0 Sensitivity: 75% Specificity: 87.5% cN+ Sensitivity: 100%	All patients CT Sensitivity: 91% Specificity: 81.6% cN0 CT Sensitivity: 100% Specificity:	Low

							Specificity: 100%	77.5% cN+ CT Sensitivity: 85.7% Specificity: 100%	
*NA: not applicable									

Authors' conclusions

N staging: diagnostic accuracy

There is a rationale on the use of FDG-PET/CT for N staging (inguinal lymph node) of patients with penile cancer.

There is no evidence from HTA report (KCE 2009).

Evidence from studies retrieved through our update - judged to be of low quality - shows inconsistent diagnostic accuracy estimates, thus the use of FDG-PET/CT for N staging of patients with penile cancer would be inappropriate

M staging: diagnostic accuracy

No evidence is availlable. The use of FDG-PET/CT would be inappropriate.

References

Included studies

KCE 2009

Vlayen J, Stordeur S, Van den Bruel A, Mambourg F, Eyssen M.. KCE reports 110A. Positron Emissie Tomografie: een update. Health Technology Assessment (HTA). Federaal Kenniscentrum voor de Gezondheidszorg (KCE) (D/2009/10.273/24) 2009. Last access 28th August 2012

PS - Souillac 2012

Souillac I, Rigaud J, Ansquer C, Marconnet L, Bouchot O. Prospective evaluation of 18F-fluorodeoxyglucose positron emission tomography-computerized tomography to assess inguinal lymph node status in invasive squamous cell carcinoma of the penis. J. Urol.187(2):493-7.

SR - Sadeghi 2012

Sadeghi R, Gholami H, Zakavi SR, Kakhki VR, Horenblas S. Accuracy of 18F-FDG PET/CT for Diagnosing Inguinal Lymph Node Involvement in Penile Squamous Cell Carcinoma: Systematic Review and Meta-Analysis of the Literature. Clin Nucl Med37(5):436-41.

Excluded studies

Graafland 2009

Graafland NM, Leijte JAP, Valdes Olmos RA, Hoefnagel CA, Teertstra HJ, Horenblas S. Scanning with 18F-FDG-PET/CT for Detection of Pelvic Nodal Involvement in Inguinal Node-Positive Penile Carcinoma. Eur. Urol. 2009;56(2):339-45.

Hughes 2009

Hughes B, Leijte J, Shabbir M, Watkin N, Horenblas S. Non-invasive and minimally invasive staging of regional lymph nodes in penile cancer. World J Urol 2009;27(2):197-203.

Johnson 2009

Johnson MH, Brandes SB, Humphrey PA. Recurrent and metastatic malignant melanoma of the penis. J. Urol.187(4):1438-9.

Rosevear 2011

Rosevear HM, Williams H, Collins M, Lightfoot AJ, Coleman T, Brown JA. Utility of (18)F-FDG PET/CT in identifying penile squamous cell carcinoma metastatic lymph nodes. Urol Oncol article in press.

Scher 2005

Scher B et al. 18F-FDG PET/CT for Staging of Penile Cancer. THE JOURNAL OF NUCLEAR MEDICINE 2005;46(9):1460-65.

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http://www.cancer.gov/cancertopics/pdq/treatment/penile/healthprofessional/allpages, last access 1st June 2012

Cubilla 2009

Cubilla AL. The role of pathologic prognostic factors in squamous cell carcinoma of the penis. World journal of urology 2009;27(2):169-77.

Leijte 2009

SR - Leijte JAP, Graafland NM, Valdes Olmos RA, Van Boven HH, Hoefnagel CA, Horenblas S. Prospective evaluation of hybrid 18F-fluorodeoxyglucose positron emission tomography/computed tomography in staging clinically node-negative patients with penile carcinoma. BJU Int. 2009;104(5):640-4.

Moher 2009

Moher David, Liberati Alessandro, Tetzlaff Jennifer, Altman Douglas G, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009;6(7):e1000097-.

NCCN 2012

NCCN Clinical Practice Guidelines in Oncology. Penile cancer. Version 1.2012. Available from www.nccn.org/professionals/physician_gls/f_guidelines.asp 2012, last access 1st June 2012

Ornellas 2008

Ornellas AA, Nobrega BL, Wei Kin Chin E, Wisnescky A, da Silva PC, de Santos Schwindt AB. Prognostic factors in invasive squamous cell carcinoma of the penis: analysis of 196 patients treated at the Brazilian National Cancer Institute. The Journal of urology 2008;180(4):1354-9.

Pizzocaro 2010

Pizzocaro G, Algaba F, Horenblas S, Solsona E, Tana S, Van Der Poel H, et al. EAU penile cancer guidelines 2009. European urology 2010;57(6):1002-12.

RTUP.UNIPG

http://www.rtup.unipg.it/rtupWebSiteNew/index.php?lang=en

Schlenker 2012

Schlenker B, Scher B, Tiling R, Siegert S, Hungerhuber E, Gratzke C, et al. Detection of inguinal lymph node involvement in penile squamous cell carcinoma by 18F-fluorodeoxyglucose PET/CT: A prospective single-center study. Urol. Oncol. Semin. Orig. Invest.30(1):55-9.

Solsona 2004

Solsona E, Algaba F, Horenblas S, Pizzocaro G, Windahl T. EAU Guidelines on Penile Cancer. European urology 2004;46(1):1-8.

Velazquez 2008

Velazquez EF, Ayala G, Liu H, Chaux A, Zanotti M, Torres J, et al. Histologic grade and perineural invasion are more important than tumor thickness as predictor of nodal metastasis in penile squamous cell carcinoma invading 5 to 10 mm. The American journal of surgical pathology 2008;32(7):974-9.

4.22 FDG-PET/CT for staging of melanoma

Background

Skin melanoma ranked as the 3rd most incident tumor in Italy in the years 2003-05. It accounted for 2.1% of the total incidence in men and women with a rising incidence trend in the past 2 decades, partly explained by the ageing population. In 2006 skin melanoma caused 943 deaths in the male population and 635 in the female population (Registri Tumori).

Target condition being diagnosed

Target conditions are: a) disease involvement of regional lymph nodes, identified through N staging, and b) presence of distant metastases, identified through M staging.

Index test(s)

FDG-PET/CT

According to the Ontario Cancer guidelines (CCO 2009), the combination of FDG-PET and CT increased the sensitivity of the test beyond that of the single tests carried out on their own. This statement however is not valid for the imaging of brain metastases because of the relatively low uptake of FDG by brain cells. There appears to be evidence that FDG-PET/CT has inadequate sensitivity to detect sentinel lymph node metastases or uveal melanoma.

Alternative test(s)

Only physical examination (suspicious pigmented lesions, tumour satellites, in-transit metastases) is routine in low-risk melanomas (tumour thickness <1 mm). Sentinel lymph node biopsy in melanoma with a tumour thickness of >1 mm is necessary for precise staging, possibly with complete lymphadenectomy of regional lymph nodes, if the sentinel node was found positive for metastases. In higher stages standard imaging is recommended in order to allow proper staging (ESMO 2010).

Reference standard for N staging is sentinel lymph node biopsy with pathological confirmation; reference standard for M staging is histological analysis of suspected lesions with or without follow-up (SR - Xing 2011).

Rationale

Role of staging. The diagnosis of skin melanoma is based on history, examination, dermatoscopy and histological specimens from resected tissue. While the treatment of non-metastatic melanoma is based on early local resection in later presentations, N and M staging are necessary to direct surgery, local metastatic treatment and furnish a baseline for possible later progression (ACS 2012).

Treatment options. Treatment options depend on staging. In Stages 0 and I, only local resection is required. In stage II with lymph node involvement, adjuvant therapy (e.g. interferon) may be required. In stage III and IV with widespread disease detection of metastases is essential to guide local surgery or chemo or adjuvant therapy or palliation (ACS 2012).

Objectives

The objective of this review was to examine the diagnostic accuracy and the clinical effectiveness of FDG-PET/CT for N staging and M staging of patients diagnosed melanoma compared to conventional imaging examination.

Search methods for identification of studies

Evidence is based on a) the conclusion of the most recent HTA report on melanoma (KCE 2009) which was of good quality and had an electronic search updated to January 2009; b) a further search of studies published between January 2009 and March 2012. The key words described the participants' disease and the index test. See appendix 18 for details of strategy.

Results

The HTA document (KCE 2009) concluded that

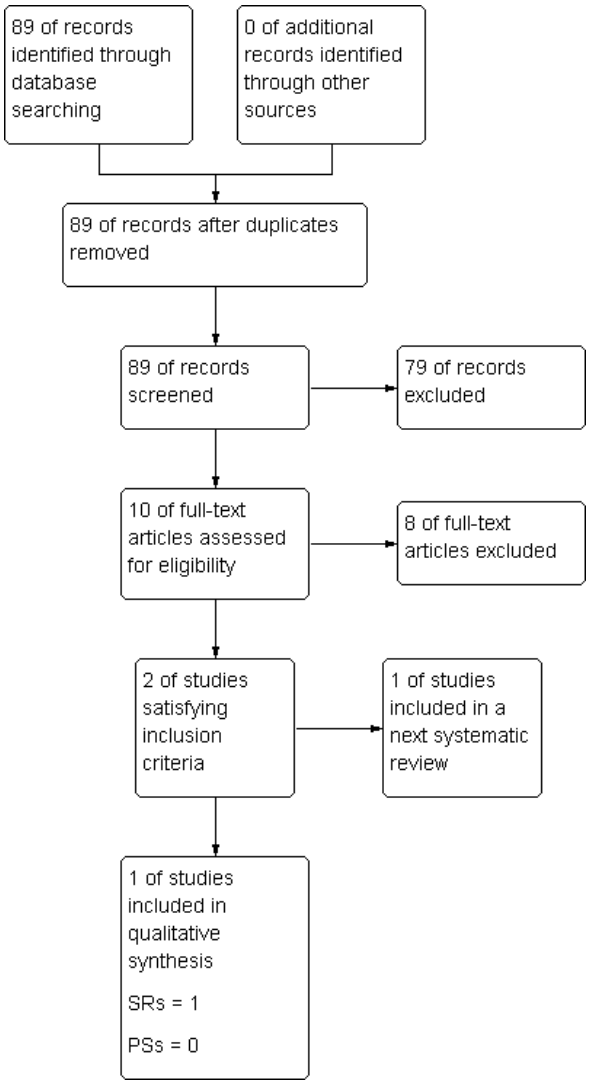
- the evidence consistently shows a low sensitivity for the detection of lymph node metastasis in cN0 melanomas (level 2)
- It also found that a good balance between sensitivity and specificity in advanced stages for the detection of distant metastasis in patients with primary and recurrent malignant melanoma (level 2).

Results of the search

Identification and selection of studies. Our searches identified 89 titles possibly fitting inclusion criteria. After screening of titles and abstracts 10 studies were retrieved and read. Eight studies were excluded for various reasons (see Excluded studies: Bastiaannet 2009; Bastiaannet 2011; Camargo Etchebehere 2010; Dellestable 2011; Heusner 2011; Jimenez-Requena 2010; Peric 2011; Ribas 2011). One more retrieved study (Veit-Haibach 2009) is included in a next systematic review (SR - Xing 2011) so finally one systematic review (SR - Xing 2011) was included.

The study selection process is summarized in the PRISMA flow diagram (Moher 2009; see Figure 1).

Figure 1 Melanoma: study selection according to PRISMA flow diagram (Moher 2009).



Description of included studies

One study evaluate diagnostic accuracy of FDG-PET/CT for N and M staging (SR - Xing 2011). No studies assess the impact of FDG-PET/CT on clinical outcomes.

Diagnostic accuracy - N staging

Systematic reviews
One systematic review has been included (SR - Xing 2011). This review assesses the diagnostic accuracy of FDG-PET/CT, FDG-PET, ultrasonography, CT for regional lymph nodes staging in patient with melanoma before any treatment and includes 74 primary studies (13 studies on FDG-PET/CT) . Patients were enrolled for the purposes of primary staging in 30 studies and surveillance in 34 studies. Reference standard is sentinel lymph node biopsy with pathological confirmation. No data are reported about cancer extension of patients at entry.

Primary studies
None retrieved.

Diagnostic accuracy - M staging

Systematic reviews
One systematic review has been included (SR - Xing 2011). This review assesses the diagnostic accuracy of FDG-PET/CT, FDG-PET, ultrasonography, CT for distant metastases staging in patient with melanoma before any treatment and includes 74 primary studies (13 studies on FDG-PET/CT). Reference standard is histological analysis of suspected lesions with or without follow-up. No data are reported about cancer extension of patients at entry.

Primary studies
None retrieved.

Impact on clinical outcomes - Any staging

Systematic reviews
None retrieved.

Primary studies
None retrieved.

Methodological quality of included studies

Diagnostic accuracy - N and M staging

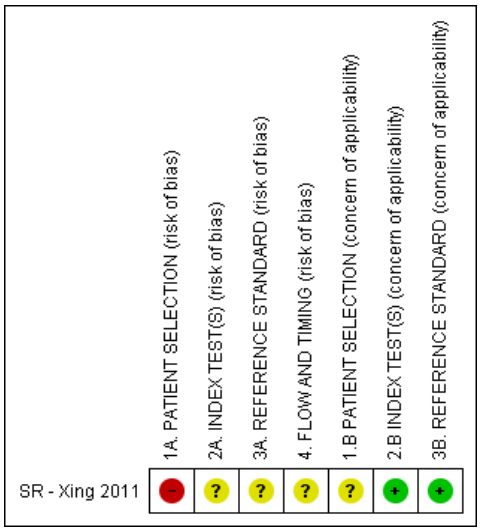
Systematic reviews

The systematic review by Xing et al is of acceptable quality, although the reporting of the quality assessment of included studies and subsequent sensitivity analyses are at times unclear.

Primary studies
None retrieved.

Quality assessment results for the included studies is provided in Figure 2.

Figure 2 Methodological quality summary: review authors' judgements about each methodological quality item for each included diagnostic accuracy study.



Findings

Diagnostic accuracy - N staging

Detailed results are reported below in the table Summary of Findings 1.

Systematic reviews
For the staging of regional lymph nodes ultrasonography shows higher sensitivity (60%, 95% CI 33-83%) and specificity (97%, 95% CI 88-99%) than FDG-PET/CT (11%, 95% CI 1-50%; 97%, 95% CI 78-100%).

Primary studies
None retrieved.

Diagnostic accuracy - M staging

Detailed results are reported below in the table Summary of Findings 2.

Systematic reviews
For the staging of distant metastases FDG-PET/CT has the highest sensitivity (80%, 95% CI 53-93%) and specificity (87%, 95% CI 54-97%) than other comparators.

Primary studies
None retrieved.

Impact on clinical outcomes - Any staging

Systematic reviews
None retrieved.

Primary studies
None retrieved.

Comments on Findings

N staging

Only evidence on diagnostic accuracy of FDG-PET/CT and comparators is available. There is no evidence of impact of FDG-PET/CT or comparators on clinical outcomes.
According to data of *low quality*, FDG/PET-CT seems to have: a greatly lower sensitivity compared to the standard practice (sentinel lymph node biopsy) and the best available comparator (ultrasonography).

M staging

Only evidence on diagnostic accuracy of FDG-PET/CT and comparators is available. There is no evidence of impact of FDG-PET/CT and comparators on clinical outcomes.
According to data of *low quality*, FDG/PET-CT seems to have higher sensitivity and specificity compared to the best available comparator (CT).

Summary of Findings 1: Diagnostic accuracy of FDG-PET/CT for regional N staging in patients with melanoma

Patients/population: melanoma
Target condition: regional N staging
Index test: FDG-PET/CT
Comparators: FDG-PET, ultrasonography, CT
Reference standard: sentinel lymph node biopsy with pathological confirmation

Ref.	No. of studies	Study design	Risk of Bias	Indirectness	Inconsistency	Imprecision	Diagnostic Accuracy FDG-PET/CT	Diagnostic Accuracy Comparators	Quality of Evidence
Xing 2011	30	Systematic review	Serious[1]	Serious[2]	No	No	(median) sensitivity 11% (95% CI 1-50%) specificity 97% (95% CI 78-100%)	ultrasonography (median) sensitivity 60% (95% CI 33-83%) specificity 97% (95% CI 88-99%) CT (median) sensitivity 9% (95% CI 1-52%) specificity 92% (95% CI 50-99%)	Low

1. possible spectrum bias due to retrospective design of majority of studies
2. Unclear clinical status of patients at enrollment

Summary of Findings 2: Diagnostic accuracy of FDG-PET/CT for M staging in patients with melanoma

Patients/population: melanoma
Target condition: M staging
Index test: FDG-PET/CT
Comparators: FDG-PET, CT
Reference standard: histological analysis of suspected lesions with or without follow-up

Ref.	No. of studies	Study design	Risk of Bias	Indirectness	Inconsistency	Imprecision	Diagnostic Accuracy FDG-PET/CT	Diagnostic Accuracy Comparators	Quality of Evidence
Xing 2011	30	Systematic review	Serious[1]	Serious[2]	No	No	(median) FDG-PET/CT sensitivity 80% (95% CI 53-93%) specificity 87% (95% CI 54-97%)	CT (median) sensitivity 51% (95% CI 24-76%) specificity 69% (95% CI 30-92%) FDG-PET (median) sensitivity 74% (95% CI 51-88%) specificity 75% (95% CI 45-91%)	Low

1. possible spectrum bias due to retrospective design of majority of studies
2. Unclear clinical status of patients at enrollment

Authors' conclusions

N staging

The KCE HTA report (KCE 2009) concluded that the evidence consistently shows a low sensitivity for the detection of lymph node metastasis in clinically node negative melanomas

Evidence from studies retrieved through our update and judged to be of low quality confirms the above conclusions, therefore the use of FDG-PET/CT would be inappropriate

M staging

There is a rationale in support of the use of FDG-PET/CT for M staging of patients with higher stages of disease.

The KCE HTA report (KCE 2009) concluded that there is a good diagnostic accuracy in advanced stages for the detection of distant metastasis in patients with primary melanoma.

Evidence from studies retrieved through our update and judged to be of low quality confirms the above conclusions. Therefore FDG-PET/CT for M staging of patients with melanoma with higher stages of disease would be appropriate.

References

Included studies

KCE 2009

Vlayen J, Stordeur S, Van den Bruel A, Mambourg F, Eyssen M.. KCE reports 110A. Positron Emissie Tomografie: een update. Health Technology Assessment (HTA). Federaal Kenniscentrum voor de Gezondheidszorg (KCE) (D/2009/10.273/24) 2009. Last access 28th August 2012

SR - Xing 2011

Xing Y, Bronstein Y, Ross MI, Askew RL, Lee JE, Gershenwald JE, Royal R, Cormier JN. Contemporary diagnostic imaging modalities for the staging and surveillance of melanoma patients: A meta-analysis. J Natl Cancer Inst 2011;103:129-142.

Excluded studies

Bastiaannet 2009

Bastiaannet, E.; Wobbes, T.; Hoekstra, O. S.; van der Jagt, E. J.; Brouwers, A. H.; Koelemij, R.; de Klerk, J. M.; Oyen, W. J.; Meijer, S., and Hoekstra, H. J. Prospective comparison of [18F]fluorodeoxyglucose positron emission tomography and computed tomography in patients with melanoma with palpable lymph node metastases: diagnostic accuracy and impact on treatment. J. Clin. Oncol 2009;27(28):4774-4780.

Bastiaannet 2011

Bastiaannet, E.; Uyl-de Groot, C. A.; Brouwers, A. H.; van der Jagt, E. J.; Hoekstra, O. S.; Oyen, W.; Verzijlbergen, F.; van Ooijen, B.; Thompson, J. F., and Hoekstra, H. J. Cost-effectiveness of adding FDG-PET or CT to the diagnostic work-up of patients with stage III melanoma. Ann Surg 2012;1528-1140.

Camargo Etchebehere 2010

Camargo Etchebehere, E. C. S.; Romanato, J. S.; Santos, A. O.; Buzaid, A. C., and Camargo, E. E. Impact of [F-18] FDG-PET/CT in the restaging and management of patients with malignant melanoma. Nucl. Med. Commun 2010;31(11):925-930.

Dellestable 2011

Dellestable, P.; Granel-Brocard, F.; Rat, A.-C.; Olivier, P.; Regent, D., and Schmutz, J.-L. Impact of whole body Magnetic Resonance Imaging (MRI) in the management of melanoma patients, in comparison with positron emission tomography/computed tomography (TEP/CT) and CT [Apport de l'imagerie en resonance magnetique (IRM) du corps entier dans la prise en charge du melanome: Comparaison avec la tomoscintigraphie par emission de positons couplee a la tomodensitometrie (TEP-TDM) et a la TDM seule]. Ann. Dermatol. Venereol 2011;138(5):377-383.

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Heusner, T.; Golitz, P.; Hamami, M.; Eberhardt, W.; Esser, S.; Forsting, M.; Bockisch, A., and Antoch, G. "One-stop-shop" staging: should we prefer FDG-PET/CT or MRI for the detection of bone metastases? Eur J Radiol 2011;78(3):430-5.

Jimenez-Requena 2010

Jimenez-Requena, F.; Delgado-Bolton, R. C.; Fernandez-Perez, C.; Gambhir, S. S.; Schwimmer, J.; Perez-Vazquez, J. M., and Carreras-Delgado, J. L. Meta-analysis of the performance of 18F-FDG PET in cutaneous melanoma. Eur. J. Nucl. Med. Mol. Imaging 2010;37(2):284-300.

Peric 2011

Peric, B.; Zagar, I.; Novakovic, S.; Zgajnar, J., and Hocevar, M. Role of serum S100B and PET-CT in follow-up of patients with cutaneous melanoma. BMC Cancer 2011;11.

Ribas 2011

Ribas, A.; Benz, M. R.; Allen-Auerbach, M. S.; Radu, C.; Chmielowski, B.; Seja, E.; Williams, J. L.; Gomez-Navarro, J.; McCarthy, T., and Czernin, J. Imaging of CTLA4 blockade-induced cell replication with (18)F-FLT PET in patients with advanced melanoma treated with tremelimumab. J Nucl Med 2010;51(3):340-6..

Additional references

ACS 2012

American cancer society. Melanoma Skin Cancer. Available from http://www.cancer.org/Cancer/SkinCancer-Melanoma/DetailedGuide/melanoma-skin-cancer-treating-by-stage. Accessed 10 May 2012 2012.

CCO 2009

Petrella T, Walker-Dilks C.. PET imaging in melanoma: recommendations. Toronto (ON): Cancer Care Ontario (CCO). Available from https://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=43131 2009. Accessed 10 May 2012

ESMO 2010

Dummer R, Hauschild A, Guggenheim A, Jost L, Pentheroudakis G, on behalf of the ESMO Guidelines Working Group. Melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 2010;21 (Supplement 5):v194–v197.

Moher 2009

Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. BMJ 2009;339:b2535.

Registri Tumori

www.registri-tumori.it/cms/?q=Rapp2009Indice. Accessed 10 May 2012

Veit-Haibach 2009

Veit-Haibach, P.; Vogt, F. M.; Jablonka, R.; Kuehl, H.; Bockisch, A.; Beyer, T.; Dahmen, G.; Rosenbaum, S., Antoch, G. Diagnostic accuracy of contrast-enhanced FDG-PET/CT in primary staging of cutaneous malignant melanoma. Eur. J. Nucl. Med. Mol. Imaging 2009;36(6):910-918.

4.23 FDG-PET/CT for staging of Hodgkin's lymphoma

Background

In Italy - period 1998-2002 - Hodgkin's lymphoma represented 0.5.% of all the cancers among males and females, corresponding to a crude incidence of 3.7 per 100,000 person/year in males and 3.0 per 100,000 person/year in females (Registri Tumori). Five-year survival is 79% (CI 95% 77-81%), across all stages of disease (Registri Tumori).

Target condition being diagnosed

Target condition is: the extension of disease defined as limited (I/II stages, i.e. single lymph node region / one extralymphatic site or two or more lymph node regions / local extralymphatic extensions on the same side of the diaphragm) or advanced disease (III/IV stages, i.e. lymph node regions on both sides of the diaphragm or diffuse involvement of one or more extralymphatic organs or sites) (ISH/ISEH/IGBMT 2009).

Index test(s)

FDG-PET/CT.

The most recent guidelines agree in recommending the use of FDG-PET/CT for staging of patients once the diagnosis has been established (AIOM 2009; ESMO 2011; ISH/ISEH/IGBMT; NCCN 2012).

Alternative test(s)

CT total body still forms the cornerstone of imaging for the assessment of disease status. Staging of lymphomas usually includes a bone marrow biopsy to judge bone marrow involvement (AIOM 2009; ESMO 2011; ISH/ISEH/IGBMT 2009; NCCN 2012).

Reference standard for staging is histopathology and/or clinical and imaging follow-up of at least 6 months (Kirby 2007).

Rationale

Role of staging. The accurate staging of dissemination is still a mainstay of the initial evaluation as it gives information on the prognosis, guides treatment management and predicts response to treatment and potential for cure (Namberger 2007). To define the extension of disease as limited (I/II stages) or advanced (III/IV stages) is important in order to decide between more and less aggressive treatment.

Treatment options. Therapeutic approach for Hodgkin's lymphoma is different according to the disease stage: patients in early stage (I and II) are usually treated with chemotherapy followed by radiation (involved-field radiation therapy). Patients with advanced stage disease (III and IV) are usually treated with a prolonged course of chemotherapy, radiotherapy being limited to patients with bulky disease and with large residual masses after chemotherapy (AIOM 2009 ; ESMO 2011; NCCN 2012).

Objectives

The objective of this review was to examine the diagnostic accuracy and the clinical effectiveness of FDG-PET/CT for staging of patients diagnosed with Hodgkin's lymphoma compared to conventional imaging examination.

Search methods for identification of studies

Evidence is based on a) the conclusion of the most recent HTA report on Hodgkin's lymphoma (ASSR 2012) which was of good quality and had an electronic search updated to February 2011; b) a further search of studies published between January 2011 and December 2011. The key words described the participants' disease and the index test. See appendix 19 for details of strategy.

Results

The HTA document (ASSR 2012) concluded that

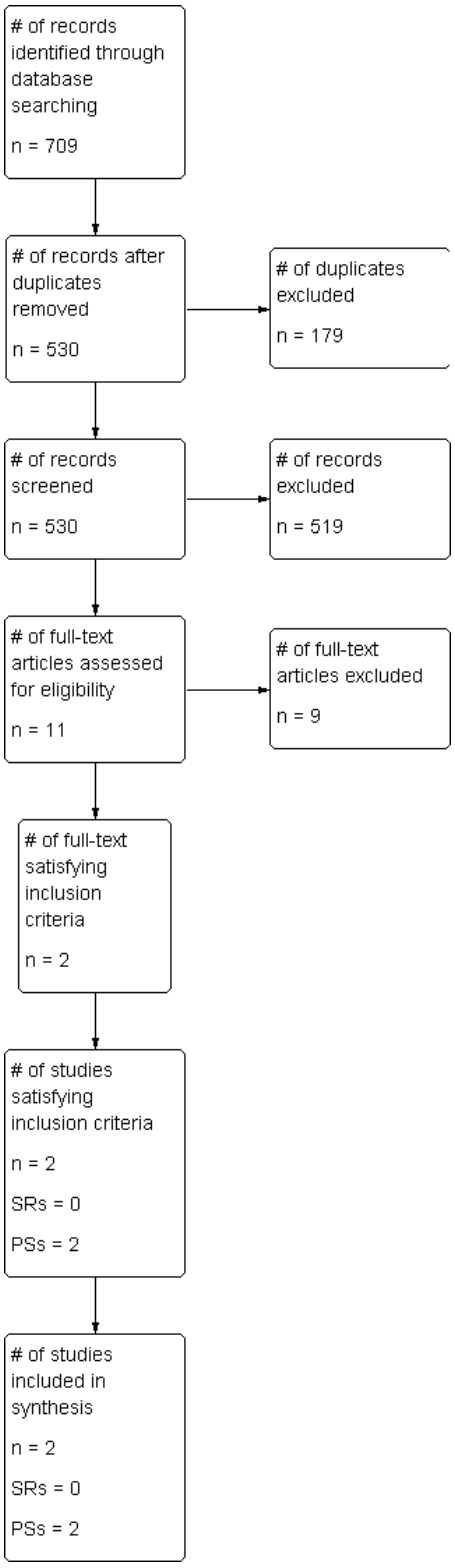
- the use of FDG-PET for staging patients with Hodgkin's lymphoma, in order to distinguish early, localised stage (I and II) from advanced, extended (stage III and IV) disease and direct patients to most appropriate treatment, is appropriate. The level of evidence for estimates of FDG-PET diagnostic accuracy was moderate, with FDG-PET performing better than comparator for detection of both linfonodal and extra-nodal involvement.

Results of the search

Identification and selection of studies. The updated electronic search identified 709 records; 698 have been excluded because duplicates, or, after checking the abstract, for not meeting the inclusion criteria. Full text has been acquired for the remaining potentially eligible 11 records, from which 9 have been excluded on the basis of inclusion criteria (see below excluded studies). Two studies have been finally included (PS - Pelosi 2011; PS - Purz 2011).

The study selection process is summarized in the PRISMA flow diagram (Moher 2009; see Figure 1).

Figure 1 Hodgkin's lymphoma: study selection according to PRISMA flow diagram (Moher 2009).



Description of included studies

Two studies evaluate diagnostic accuracy of FDG-PET/CT for staging.

Diagnostic accuracy - Staging

Systematic reviews
None retrieved.

Primary studies
Two studies (305 participants) evaluating diagnostic accuracy of FDG-PET/CT for bone marrow extension of disease at staging have been included (PS - Pelosi 2011; PS - Purz 2011). One study (PS - Pelosi 2011) includes patients of any age at first diagnosis, considers as comparator bone marrow biopsy and as composite reference standard bone marrow biopsy and imaging follow up (with FDG-PET/CT and /or MRI). Another study (PS - Purz 2011) includes pediatric patients with stage greater than IIA, does not consider any comparator and uses as reference standard bone marrow biopsy.

Methodological quality of included studies

Diagnostic accuracy - Staging

Systematic reviews
None retrieved

Primary studies
In both included studies (PS - Pelosi 2011; PS - Purz 2011) reference standard has an unclear or high risk of bias. Morever one study has a high risk of spectrum bias (PS - Purz 2011), and the other study a high risk of a biased index test (PS - Pelosi 2011). Finally both studies consider only one aspect of staging (bone marrow extension of disease).

Quality assessment results for the included staging studies is provided in Figure 2.

Figure 2 Methodological quality summary: review authors' judgements about each methodological quality item for each included diagnostic accuracy study.

Findings

Diagnostic accuracy - Staging

Detailed results are reported below in the table Summary of Findings 1.

Primary studies
The two included studies report inconsistent estimates of sensitivity and specificity.

Comments on Findings

Only evidence on diagnostic accuracy of FDG-PET/CT is available. There is no evidence of impact of FDG-PET/CT or comparators on clinical outcomes.
Due to data of *very low quality*, it is not possible to draw any conclusion on the role of FDG-PET/CT for detecting bone marrow disease extension.

Summary of Findings 1: Diagnostic accuracy of FDG-PET/CT for staging in patients with Hodgkin's lymphoma

Patients/population: Hodgkin's lymphoma
Target condition: bone marrow extension of disease
Index test: FDG-PET/CT
Comparators: bone marrow biopsy (1 study)
Reference standard: composite reference standard (1 study: bone marrow biopsy and imaging follow up - with FDG-PET/CT and /or MRI); bone marrow biopsy (1 study)

Ref.	No. of studies	Study design	Risk of Bias	Indirectness	Inconsistency	Imprecision	Diagnostic Accuracy FDG-PET/CT	Diagnostic Accuracy Comparators	Quality of Evidence
Primary studies	2 studies (305 participants) FDG-PET/CT 1 study (130 participants) bone marrow biopsy	diagnostic accuracy studies with prospective recruitment	Serious[1]	Serious[2]	Serious[3]	No	1 study sensitivity 78.6% specificity 100% 1 study sensitivity 100% specificity 77.3%	bone marrow biopsy 1 study sensitivity 42.9% specificity 100%	Very low

1. both studies with high or unclear risk of biased reference standard; 1 study high risk of spectrum bias; 1 study high risk of biased index test
2. bone marrow extension of disease as target condition is only a partial aspect of disease extension at staging
3. Inconsistent diagnostic estimates among included studies

Authors' conclusions

Staging

Accurate staging of patients with Hodgkin's lymphoma is very important and there is a rationale in support of the use of FDG-PET/CT for patients at first diagnosis.

HTA document (ASSR 2012) judged the quality of appraised evidence as moderate and concluded that the use of FDG-PET for staging of patients with Hodgkin's lymphoma is appropriate.

Evidence from studies retrieved through our update - judged to be of very low quality – does not challenge the above conclusions.

References

Included studies

ASSR 2012

Ballini L, Maltoni S, Vignatelli L, Negro A, Trimaglio F. Criteria for appropriate use of FDG-PET in lung cancer. Dossier 227 - Agenzia sanitaria e sociale regionale, Regione Emilia-Romagna. Available from http://asr.regione.emilia-romagna.it/wcm/asr/collana_dossier/doss227.htm 2012. Last access 28th August 2012

PS - Pelosi 2011

Pelosi E, Penna D, Douroukas A, Bello M, Amati A, Arena V, et al. Bone marrow disease detection with FDG-PET/CT and bone marrow biopsy during the staging of malignant lymphoma: Results from a large multicentre study. Quarterly Journal of Nuclear Medicine and Molecular Imaging 2011;55(4):469-75.

PS - Purz 2011

Purz S, Mauz-Korholz C, Korholz D, Hasenclever D, Krausse A, Sorge I, et al. [18F]fluorodeoxyglucose positron emission tomography for detection of bone marrow involvement in children and adolescents with Hodgkin's lymphoma. J Clin Oncology 2011;29:3523-28.

Excluded studies

Abdulqadhr 2011

Abdulqadhr G, Molin D, Astrom G, Suurkula M, Johansson L, Hagberg H, et al. Whole-body diffusion-weighted imaging compared with FDG-PET/CT in staging of lymphoma patients. Acta Radiol 2011;52:173-80.

Cerci 2011

Cerci JJ, Trindade E, Buccheri V, Fanti S, Coutinho AM, Zanoni L, et al. Consistency of FDG-PET accuracy and cost-effectiveness in initial staging of patients with Hodgkin lymphoma across jurisdictions. Clin Lymphoma Myeloma Leuk. 2011;11:314-20.

Cheng 2011

Cheng G, Chen W, Chamroonrat W, Torigian DA, Zhuang H, Alavi A. Biopsy versus FDG PET/CT in the initial evaluation of bone marrow involvement in pediatric lymphoma patients. European Journal of Nuclear Medicine and Molecular Imaging 2011;38(8):1469-76.

Gu 2011

Gu J, Chan T, Zhang J, Leung AYH, Kwong YL, Khong PL. Whole-body diffusion-weighted imaging: The added value to whole-body MRI at initial diagnosis of lymphoma. American Journal of Roentgenology 2011;197:W384-91.

Huang 2011

Huang YY, You DL, Liu MC, Tan TD, Lee PI, Lee MY. Underperformance of gallium-67 scan is greater in relapse than in initial staging, compared with FDG PET. Clinical Nuclear Medicine 2011;36:867-71.

Ilica 2011

Ilica AT, Kocacelebi K, Savas R, Ayan A. Imaging of extranodal lymphoma with PET/CT. Clinical Nuclear Medicine 2011;36:e127-38.

Mittal 2011

Mittal BR, Manohar K, Malhotra P, Das R, Kashyap R, Bhattacharya A, et al. Can fluorodeoxyglucose positron emission tomography/computed tomography avoid negative iliac crest biopsies in evaluation of marrow involvement by lymphoma at time of initial staging? Leukemia and Lymphoma 2011;52:2111-6.

Paulino 2011

Paulino AC, Margolin J, Dreyer Z, Teh BS, Chiang S. Impact of PET-CT on involved field radiotherapy design for pediatric Hodgkin lymphoma. Pediatr.Blood Cancer 2011;(1545-5017 (Electronic), 1545-5009 (Linking)).

van Ufford 2011

van Ufford HM, Kwee TC, Beek FJ, Van Leeuwen MS, Takahara T, Fijnheer R, et al. Newly diagnosed lymphoma: initial results with whole-body T1-weighted, STIR, and diffusion-weighted MRI compared with 18F-FDG PET/CT. AJR Am J Roentgenol 2011;196:662-9.

Additional references

AIOM 2009

Linee Guida AIOM. Linfomi. Available from http://www.aiom.it/Attivit%E0+Scientifica/Linee+guida/Linfomi/1,3493,0, 2009, last access 22th May 2012

ESMO 2011

Eichenauer DA, Engert A, Dreyling M, on behalf of the ESMO Guidelines Working Group. Hodgkin's lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 2011;22 (Supplement 6):vi55–vi58.

ISH/ISEH/IGBMT 2009

Brusamolino E, Bacigalupo A, Barosi G, Biti G, Gobbi PG, Levis A, et al. Classical Hodgkin's lymphoma in adults: guidelines of the Italian Society of Hematology, the Italian Society of Experimental Hematology, and the Italian Group for Bone Marrow Transplantation on initial work-up, management, and follow-up. Haematologica 2009;94:550-65.

Kirby 2007

Kirby AM, Mikhaeel NG. The role of FDG PET in the management of lymphoma: what is the evidence base? Nucl Med Commun 2007;28:335-54.

Moher 2009

Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. BMJ 2009;339:b2535.

Namberger 2007

Namberger K, Greil R. The role of imaging in malignant lymphoma: A critical view on PET scanning in current clinical practice. Imaging Decis MRI 2007;10:22-31.

NCCN 2012

NCCN Clinical Practice Guidelines in Oncology. Hodgkin lymphoma. Version 2.2012. Available from www.nccn.org/professionals/physician_gls/f_guidelines.asp 2012, last access 22th May 2012

Registri Tumori

http://www.registri-tumori.it/cms/?q=sede_linfomah, last access 22th May 2012

4.24 FDG-PET/CT for staging of aggressive non-Hodgkin's lymphoma

Background

In Italy - period 1998-2002 - non-Hodgkin's lymphomas represented 2.9% of all the cancers among males and 3.2% among females, corresponding to a crude incidence of 22.8 per 100,000 person/year in males and 19.8 per 100,000 person/year in females (Registri Tumori). Five-year survival is 51% (CI 95% 50-52%), across all stages of disease (Registri Tumori). Non-Hodgkin's lymphomas are a heterogeneous group of lymphoproliferative disorders - originating mostly (85% of cases) in B lymphocytes - classified as indolent (low grade), aggressive or highly aggressive (high grade), based on the morphology and the natural history of the disease (NCCN 2012). Aggressive non-Hodgkin's lymphomas are the object of this document.

The most recent guidelines (AIOM 2009; ESMO 2010; NCCN 2012) agree in recommending the use of FDG-PET/CT for staging of patients once the diagnosis has been established.

Target condition being diagnosed

Target condition is: the extension of disease defined as limited (I/II stages, i.e. single lymph node region / one extralymphatic site or two or more lymph node regions / local extralymphatic extensions on the same side of the diaphragm) or advanced disease (III/IV stages, i.e. lymph node regions on both sides of the diaphragm or diffuse involvement of one or more extralymphatic organs or sites) (NCCN 2012).

Index test(s)

FDG-PET/CT

Alternative test(s)

The stage of the disease is usually assessed by CT total body, to identify nodal and extra-nodal lesions. As bone marrow involvement occurs in approximately 20% to 40% patients with aggressive and highly aggressive non-Hodgkin's lymphoma, indicating a stage IV disease (Kwee 2008; Muslimani 2008; Wu 2012, NCCN 2012), a bone marrow biopsy is usually part of the staging assessment; however, being the bone marrow involvement usually patchy, false negatives results in bone marrow biopsy are not unusual (Muslimani 2008).

Reference standard for staging is histopathology and/or clinical and imaging follow-up of at least 6 months (Kirby 2007).

Rationale

Role of staging. The accurate staging of dissemination gives information on the prognosis, guides treatment management and predicts response to treatment and potential for cure. To define the extension of disease as limited (I/II stages) or advanced (III/IV stages) is important in order to decide between more and less aggressive treatment.

Treatment options. Effectiveness of treatment is extremely variable according to the lymphoma type, the disease stage and individual prognostic factors (AIOM 2009; NCCN 2012). Early, localised diffuse large B-cell lymphoma (stage I-II) may be amenable to 3-4 cycles of immunochemotherapy followed by consolidative involved-field radiotherapy whilst more advanced stages (stage III and IV) are usually treated with a longer immunochemotherapy treatment (AIOM 2009; ESMO 2010; NCCN 2012). Prognosis is extremely good for patients with limited disease and no adverse risk factors (NCCN 2012) in which therapy yields a 5-yr progression-free survival rate of around 80% and a 5-yr OS of around 82% (Shenkier 2002).

Objectives

The objective of this review was to examine the diagnostic accuracy and the clinical effectiveness of FDG-PET/CT for staging of patients diagnosed with non-Hodgkin's lymphoma compared to conventional imaging examination.

Search methods for identification of studies

Evidence is based on a) the conclusion of the most recent HTA report on Hodgkin's lymphoma (ASSR 2012) which was of good quality and had an electronic search updated to February 2011; b) a further search of studies published between January 2011 and December 2011. The key words described the participants' disease and the index test. See appendix 20 for details of strategy.

Results

The HTA document (ASSR 2012) concluded that

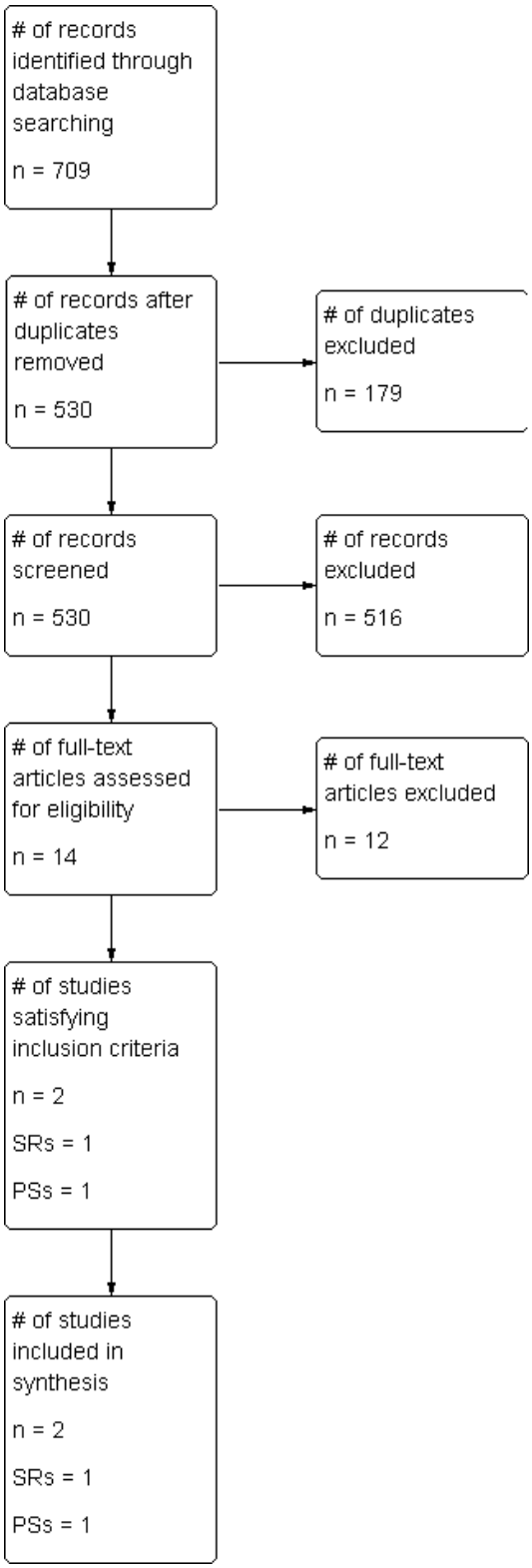
- the use of FDG-PET for staging patients with aggressive non-Hodgkin's lymphoma, to distinguish early, localised stage (I and II) from advanced, extended (stage III and IV) disease and direct patients to most appropriate treatment, is appropriate. The level of evidence for estimates of FDG-PET diagnostic accuracy was moderate, with FDG-PET performing better than comparators for detection of both linfonodal/extra-nodal involvement and bone marrow involvement.

Results of the search

Identification and selection of studies. The updated electronic search identified 709 records; 695 have been excluded because duplicates, or, after checking the abstract, for not meeting the inclusion criteria. Full text has been acquired for the remaining potentially eligible 14 records, from which 12 have been excluded on the basis of inclusion criteria (see below excluded studies). Two studies have been finally included (RS - Chen 2011; PS - Pelosi 2011).

The study selection process is summarized in the PRISMA flow diagram (Moher 2009; see Figure 1).

Figure 1 Aggressive non-Hodgkin's lymphoma: study selection according to PRISMA flow diagram (Moher 2009).



Description of included studies

Two studies evaluate diagnostic accuracy of FDG-PET/CT for staging.

Diagnostic accuracy - Staging

Systematic reviews
One systematic review has been included (RS - Chen 2011). This review assess the diagnostic accuracy of FDG/PET or FDG-PET/CT for bone marrow extension of disease at staging and includes 8 studies (6 on aggressive non-Hodgkin's lymphoma, and 3 on indolent non-Hodgkin's lymphoma). Reference standard is bone marrow biopsy. No data are reported on clinical status of patients. No comparator is assessed in the included studies.

Primary studies
One study (207 participants) evaluating diagnostic accuracy of FDG-PET/CT for bone marrow extension of disease at staging have been included (PS - Pelosi 2011). This study includes patients of any age at first diagnosis, it considers as comparator bone marrow biopsy and as composite reference standard bone marrow biopsy and imaging follow up (with FDG-PET/CT and /or MRI).

Methodological quality of included studies

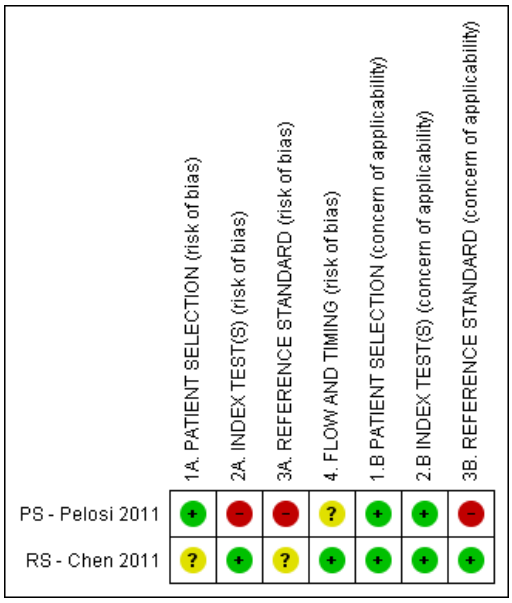
Diagnostic accuracy - Staging

Systematic reviews
The systematic review by Chen et al. (RS - Chen 2011) has a comprehensive bibliographic search method, the methodological quality appropriately assessed and the statistical analysis well performed; however the characteristics of included studies are not reported (Table 2). The primary studies included into the systematic review could be both prone to spectrum bias and a biased reference standard due to unclear blinding of index test when interpreted reference standard.

Primary studies
In the included study(PS - Pelosi 2011) reference standard and index test have a high risk of bias. Finally it considers only a partial aspect of staging (bone marrow extension of disease).

Quality assessment results for the included staging studies is provided in Figure 2.

Figure 2 Methodological quality summary: review authors' judgements about each methodological quality item for each included diagnostic accuracy study.



Findings

Diagnostic accuracy - Staging

Detailed results are reported below in the table Summary of Findings 1.

Systematic reviews
The included systematic review (RS - Chen 2011) reports data on diagnostic accuracy for FDG-PET/CT in studies with aggressive non-Hodgkin's lymphoma. Pooled estimates of sensitivity and specificity are 74.0% (95% CI 65.0-83.0%) and 80.0% (95% CI 74.0-87.0%) respectively.

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Primary studies
The included study reports low sensitivities both for FDG-PET/CT and bone marrow biopsy.

Comments on Findings

Only evidence on diagnostic accuracy of FDG-PET/CT is available. There is no evidence of impact of FDG-PET/CT or comparators on clinical outcomes.
Due to data of *low/ very low quality*, it is not possible to draw any conclusion on the role of FDG-PET/CT for detecting bone marrow disease extension.

Summary of Findings 1: Diagnostic accuracy of FDG-PET/CT for staging in patients with aggressive non-Hodgkin's lymphoma

Patients/population: aggressive non-Hodgkin's lymphoma
Target condition: bone marrow extension of disease
Index test: FDG-PET/CT
Comparators: bone marrow biopsy (1 study)
Reference standard: composite reference standard (1 study: bone marrow biopsy and imaging follow up - with FDG-PET/CT and /or MRI)

Ref.	No. of studies	Study design	Risk of Bias	Indirectness	Inconsistency	Imprecision	Diagnostic Accuracy FDG-PET/CT	Diagnostic Accuracy Comparators	Quality of Evidence
Chen 2011	6 studies (237 participants)	Systematic review	Serious[1]	Serious[2]	No	No	sensitivity (pooled) 74.0% (95% CI 65.0-83.0%) specificity (pooled) 80.0% (95% CI 74.0-87.0%)		Low
Primary studies	1 study (207 participants)	diagnostic accuracy study with prospective recruitment	Serious[3]	Serious[2]	No	Serious	sensitivity 64.4% specificity 100%	bone marrow biopsy sensitivity 67.8% specificity 100%	Very low

1. possible spectrum bias for 50% of studies; 37.5% of studies with unclear blinding of index test when interpreted reference standard
2. bone marrow extension of disease as target condition is a partial aspect of disease extension at staging
3. high risk of biased reference standard and index test

Authors' conclusions

Staging

Accurate staging of patients with aggressive non-Hodgkin's lymphoma is very important and there is a rationale in support of the use of FDG-PET/CT for patients at first diagnosis.

The HTA document (ASSR 2012) judged the quality of appraised evidence as moderate and concluded that the use of FDG-PET for staging of patients with aggressive non-Hodgkin's lymphoma is appropriate.

Evidence from studies retrieved through our update - of low / very low quality – does not challenge the above conclusions.

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5. Context analysis

Context analysis was important to determine the pattern of use and costs of FDG-PET/CT among the six regions (Emilia-Romagna, Puglia, Sicilia, Provincia Autonoma di Trento, Lazio, Umbria). The aim of this chapter was to describe the pattern of use of PET/CT scan and to estimate the expected number of FDG-PET/CT scans for cancer staging.

5.1 Methods for contextual analysis

The methodology was developed by the ASSR-Regione Emilia-Romagna and piloted in the Emilia Romagna region. Subsequently it was applied to the context of all participant regions. Each sub-chapter (pattern of use of FDG-PET/CT scan, patients submitted to PET/CT scan for oncologic disease and definition of target population and estimate of expected volumes of FDG-PET/CT scans in cancer staging) contains a common section (materials and methods), the results by region and a synthesis of the main results from the six regions. In the final paragraph estimates of expected volumes onf FDG-PET/CT in cancer staging, based on definition of target population, are provided for the six regions.

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5.2 Use of FDG-PET/CT in cancer staging in six Italian regions: Emilia Romagna, Sicilia, Provincia Autonoma di Trento, Lazio, Puglia, Umbria

5.2.1 Pattern of use of FDG-PET/CT scan

Background

Emilia Romagna region (RER)

Emilia-Romagna, a northeast Italian region with 9 Provinces covers an area of over 22,446 km^2, has a resident population of 4,395,606 (update: 1st January 2010), 2,135,966 male and 2,259,640 female.

The Regional Health Service comprises: 11 Local Health Trusts, 4 University Hospital Trusts, 4 Research Hospitals (Istituto di Ricovero e Cura a Carattere Scientifico, IRCCS).

Currently in Emilia-Romagna there are 11 PET/CT scanners and 3 cyclotrons (Table 1, situation updated at June 2012) corresponding to 1 PET/CT scanners every 399,601 inhabitants and 1 cyclotron every 1,465,202 inhabitants.

Table 1. PET/CT scanners and cyclotrons in Emilia-Romagna Region

Hospital	Type of structure	N° PET/CT	Cyclotron
University Hospital Trust of Bologna	public	1 PET, 2 PET/CT	1
University Hospital Trust of Modena	public	1 PET/CT	
IRCCS S. Maria Nuova of Reggio Emilia	public	1 PET/CT	1
University Hospital Trust of Ferrara	public	1 mobile PET/CT	
Cesena Hospital	public	1 PET	
Forlì Hospital	public	1 PET/CT	
University Hospital Trust of Parma	public but the PET/CT scanners is located in a private centre	1 PET/CT	
IRCCS of Meldola	public	1 PET/CT	1
Villa Cecilia of Cotignola	private	1 PET/CT	
Total		**11 (9 PET/CT, 2 PET)**	**3**

Sicilia region (SR)

Sicilia, a south Italian region with 9 Provinces covers an area of over 25,711 km^2, has a resident population of 5,049,598 (ISTAT 30/09/2011), 2,438,955 male and 2,610,643 female.

The Regional Health Service comprises: 9 Provincial Health Trusts (ASP – Azienda Sanitaria Provinciale) , 5 Hospital Trusts (3 AO - Aziende Ospedaliere and 2 ARNAS - Aziende di Rilievo Nazionale e Alta Specializzazione), 3 University Hospital Trusts, 2 Research Hospitals (Istituti di Ricovero e Cura a Carattere Scientifico - IRCCS), 1

Religious Hospital (Ospedale Classificato) e 2 Trials Public/Private Management Hospitals (Sperimentazioni Gestionali).

Currently in Sicilia there are 17 PET–PET/CT scanners and 4 cyclotrons (Table 2, situation updated at may 2012) corresponding to 1 PET scanners every 297,035 inhabitants and 1 cyclotron every 1,262,399 inhabitants.

Table 2. PET–PET/CT scanners and cyclotrons in Sicilia Region

Hospital	Type of structure	N° PET–PET/CT	Cyclotron
ASP di Catania (Hospital "Gravina" – Caltagirone)	Public	1 PET/CT	
AO "Cannizzaro" - Catania	Public	1 PET, 1 PET/CT	1
AO "Garibaldi" – Catania	Public	1 PET/CT	
AO "Papardo-Piemonte" - Messina	Public	1 PET/CT	
AO "Ospedali Riuniti Villa Sofia-Cervello" Palermo	Public	1 PET/CT	1
Studio Diagnostico s.r.l. – Agrigento	Private	1 PET, 1 PET/CT	
Humanitas Centro Catanese di Oncologia - Catania	Private	1 PET/CT	
Clinical Isotopic medical Center – Catania	Private	1 PET	
Casa di Cura Villa SALUS S.A.S. – Messina	Private	1 PET/CT	
La Maddalena – Palermo	Private	1 PET, 1 PET/CT	1
Centro medicina Nucleare San Gaetano – Palermo	Private	1 PET	
Villa Santa Teresa – Bagheria (PA)	Private	1 PET, 1 PET/CT	1
Centro di Radiologia Medica – Trapani	Private	1 PET	
Total		**17 (10 PET/CT, 7 PET)**	**4**

Provincia Autonoma di Trento (PAT)

Provincia Autonoma di Trento is a northeast Italian autonomous province that covers an area of 6,212 km^2, has a resident population of 529,457 (update: 1st January 2011), 258,741 male (48,9%) and 270,716 female (51,1%).

The Provincial Health Service comprises 1 Main Hospital (Ospedale Santa Chiara, Trento) and 6 smaller local hospitals (Arco, Borgo Valsugana, Cavalese, Cles, Rovereto, Tione).

Currently in Provincia Autonoma di Trento there is a single PET/CT scanner located in Trento (Ospedale Santa Chiara) and no cyclotrons.

Lazio region (LR)

Lazio Region, a central Italian region with 5 Provinces covers an area of over 17,236 km^2, has a resident population of 5,681,868 (update: 1st January 2010), 2,731,425 male and 2,950,443 female.

The Regional Health Service comprises: 12 Local Health Trusts, 4 University Hospital Trusts, 7 Research Hospitals (Istituto di Ricovero e Cura a Carattere Scientifico, IRCCS).

Currently in Lazio there are 5 PET/CT scanners, active from the year 2005 and 2 cyclotrons (Table 3, situation updated at June 2011) corresponding to 1 PET/CT scanners every 1,136,374 inhabitants and 1 cyclotron every 2,840,934 inhabitants.

Table 3. PET/CT scanners and cyclotrons in Lazio Region

Hospital	Type of structure	N° PET/CT	Cyclotron
Poliambulatorio Ospedaliero-Latina	public	1	0
IRCCS - I.F.O. Regina Elena-Roma	public	1	0
Azienda ospedaliera S. Andrea-Roma	public	1	0
Policlinico Universitario Tor Vergata-Roma	public	1	1
Policlinico Universitario Gemelli-Roma	private	1	1
Total		**5**	**2**

Puglia region (PR)

Puglia, a southeast Italian region with 6 Provinces covers an area of over 19,358 km^2, has a resident population of 4,084,035 (update: 1st January 2010, ISTAT), of which 1,980,902 male and 2,103,133 female.

The Regional Health Service comprises: 6 Local Health Trusts, 2 University Hospital Trusts, 3 Research Hospitals (Istituto di Ricovero e Cura a Carattere Scientifico, IRCCS).

Currently in Puglia there are 7 PET/CT scanners and 1 cyclotrons (Table 4, situation updated at June 2012) corresponding to 1 PET/CT scanners every 583,434 inhabitants and 1 cyclotron every 4,084,035 inhabitants.

Table 4. PET/CT scanners and cyclotrons in Puglia Region

Hospital/	Type of structure	No. PET/CT	Cyclotron
A.O.U. Policlinico Bari	public	1 mobile PET/CT	
A.O.U. Ospedali Riuniti Foggia	public	1 mobile PET/CT *	
Ospedale Di Miccoli, Barletta, ASL BAT	public	1 PET/CT	
Ospedale Perrino, Brindisi, ASL BR	public	1 PET/CT	
Ospedale S.G. Moscati,	public	1 PET/CT	

Taranto, ASL TA			
Centro PET, Casa Sollievo della Sofferenza, San Giovanni Rotondo (FG)	private	1 PET/CT	
Centro di Medicina Nucleare Calabrese, Cavallino (LE)	private	1 PET/CT	
ITELPHARMA, division of ITEL Telecomunicazioni S.r.l., Ruvo di Puglia (BA)	private		1
Total		**7 PET/CT**	**1 Cyclotron**

* The call for tender to install a new PET/CT is on-going

Umbria region (UR)

Umbria, a central Italian region with 2 Provinces covers an area of over 8,456 km^2, has a resident population of 906,486 (update: 31st December 2010 - ISTAT), 436,259 male and 470,227 female.

The Regional Health Service comprises: 4 Local Health Trusts, 2 Hospital Trusts.

Currently in Umbria there are 2 PET/CT scanners and 1 cyclotrons (Table 5, situation updated at June 2012) corresponding to 1 PET/CT scanners every 453,243 inhabitants and 1 cyclotron every 906,486 inhabitants.

Table 5. PET/CT scanners and cyclotrons in Umbria Region

Hospital (Trust)	Type of structure	N° PET/CT	Cyclotron
Perugia Hospital (Hospital Trust)	public	1 (PET/CT)	1
Foligno Hospital (Local Health Trusts n°3)	public	1 (PET/CT)	0
Total		**2 (PET/CT)**	**1**

Synthesis-PET-CT scanners and cyclotron in the six italian regions

In Table 6 are reported by region, the number of inhabitants, the infrastructure of PET/CT and cyclotron and the number of inhabitants per PET/CT and cyclotron **.** The italian population is about 60 million of inhabitants and these six regions, with about 20 million of inhabitants, represented about a 33% of the italian population.

The range of number of inhabitants per PET/CT is between 297,035 of Sicilia region to 1,136,374 of Lazio region.

The range of number of inhabitants per cyclotron is between 906,486 of Umbria region to 4,084,035 of Puglia region.

Table 6. PET/CT scanners and cyclotron in the six italian regions

Region	N° of PET/CT	N° of cyclotron	Inhabitants	Number of inhabitants per PET/CT	Number of inhabitants per cyclotron
Emilia-Romagna	11	3	4,395,606	399,601	1,465,202
Sicilia	17	4	5,049,598	297,035	1,262,399
Provincia Autonoma di Trento	1	0	529,457	529,457	
Lazio	5	2	5,681,868	1,136,374	2,840,934
Puglia	7	1	4,084,035	583,434	4,084,035
Umbria	2	1	906,486	453,243	906,486

Objective

To describe patterns of use of PET/CT scan, in terms of PET/CT scans performed and healthcare mobility in six regions of Italy (Emilia-Romagna, Sicilia, Provincia Autonoma di Trento, Lazio, Puglia and Umbria).

Materials and Methods

Identification of PET/CT scans performed

The analysis of positron emission tomography's use in the six Italian regions was performed using administrative data of Regional Outpatient Database (ASA - Assistenza Specialistica Ambulatoriale) and Hospital Discharge Database (SDO - Schede Dimissione Ospedaliera) in the period 2004-2010. The type of radio-marker used for the PET/CT is not specified in administrative database but FDG is the most common PET tracer used for the study of neoplasms.

Codes used to select data are reported in Table 7.

Table 7. Selected ICD-9-CM codes for PET/CT scan

	ICD9-CM Procedure Codes	ICD9-CM Procedure Description
Outpatient Database (ASA) codes	92.11.6	Qualitative PET
	92.11.7	Quantitative PET
	92.18.6	PET Total Body
Hospital Discharge Database (SDO) codes	Combined codes 92.18-88.38	SPECT-Computed Tomography

Additional information on volumes of PET/CT scan performed in 2010 has been obtained through a survey for Emilia-Romagna, Puglia and Umbria regions . For Emilia-Romagna region in April 2012 the heads of the nuclear medicine centres were interviewed by telephone regarding the number of PET/CT scans performed in their centres from 1° January to 31 December 2010. In Puglia and Umbria regions, in June 2012, the same information was obtained through an official letter that was sent to the heads of the nuclear medicine centres.

Mobility for PET/CT scan

The mobility of patients was analyzed through the administrative database and the analysis was done at the regional and provincial level.
The indicators utilized for the regional level analysis are the passive regional mobility and the active regional mobility and were calculated as follow:

- Passive regional mobility= N° of PET-CT scans performed in other regions for patients resident in that region/N° of PET-CT scans performed for patients resident in that region
- Active regional mobility=N° of PET-CT scans performed in that region for patients resident in other regions/ N° of PET-CT scans performed in that region

The indicators utilized for the provincial level analysis are the passive inter-provincial mobility, the passive inter-regional mobility and the active provincial mobility and were calculated as follow:

- Passive inter-provincial mobility= N° of PET-CT scans performed in other provinces of that region for patients resident in province (X) /N° of PET-CT scans performed for patients resident in province (X)
- Passive provincial-regional mobility= N° of PET-CT scans performed in other regions for patients resident in province (X) / N° of PET-CT scans performed for patients resident in province (X)
- Active provincial mobility=N° of PET-CT scans performed in province (X) for patients resident in other regions / N° of PET-CT scans performed in province (X)

The data of Emilia-Romagna, Sicilia, Lazio and Umbria regions were analyzed using the SAS system for Windows software, release 9.1, 4.1 and 8,.2.
The data of Puglia region an Provincia Autonoma di Trento were analysed using Microsoft Excel 2010 and Microsoft Excel 2007.

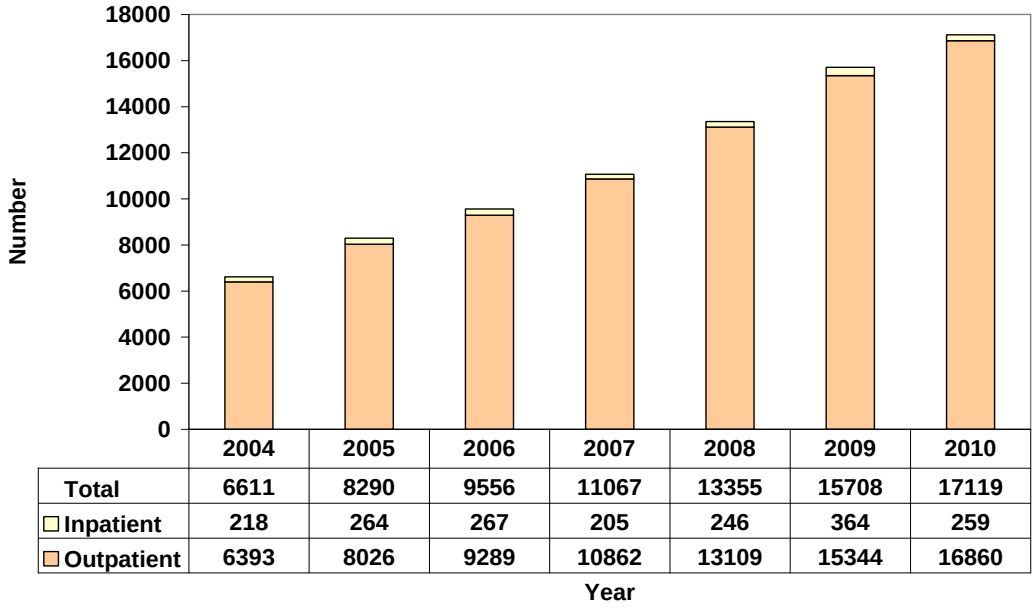
Results

Emilia-Romagna Region (RER)

Identification of PET/CT scans performed

Figure 1 reports the number of PET/CT scans performed between 2004 and 2010 in Emilia-Romagna region for all types of disease. There is a strong upward trend in the use of PET/CT between 2004 and 2010 with an increase of about 160% (from 6,661 scans in the 2004 to 17,119 scans in the 2010).

Figure 1. Volumes of PET/CT scans in in Emilia-Romagna region -2004-2010



In Table 8 are reported the results of the survey on PET/CT use. The comparison of survey data with administrative data shows how the latter systematically underestimates the number of PET/CT scans. Probably the underestimation of PET/CT is due to unregistered inpatients' scans in administrative data lack of a specific ICD9-CM procedure code for PET/CT in Hospital Discharge Database, and to the Diagnosis Related Group (DRG) system of remuneration.

Considering the administrative data limit the "real" volumes of PET/CT scans performed in RER is derived applying survey correction, giving a "corrected" number of exams in 2010 of about 22,618. A difference of 5,499 scans (24%) between the two data sources was detected.

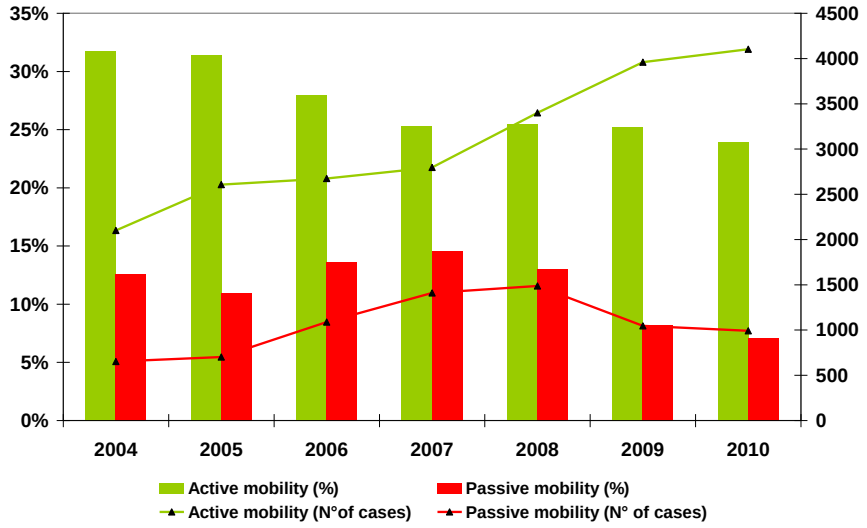
Table 8. Survey of volumes of PET/CT exams in Emilia-Romagna region by hospital trust- 2010

Hospital trust	Volumes (Administrative data)	Volumes (Survey Data)	Difference
	All exams N	All exams N	N (%)
AOSP Bologna	7,648	8,834	**1,186 (13%)**
AUSL Bologna	718	1,500	**782(52%)**
AOSP Reggio-Emilia	1,243	2,889	**1,646 (57%)**
AOSP Ferrara	167	700	**533 (76%)**
AOSP Modena	1,463	1,900	**437 (23%)**
AUSL Forlì	2,414	2,896	**482 (17%)**
AUSL Cesena	467	919	**452 (49%)**
AOSP Parma	2,217		
Other regional centre	782		
All	**17,119**	**22,618**	**5,499 (24%)**

Mobility for PET/CT scan

In Emilia-Romagna region the passive regional mobility increased in the first period (2004-2007) while in the last four years it has decreased from 13% to 7% (Figure 2), probably due to the increase in technology's availability, showing capacity to satisfy internal request of exams. In terms of percentage, active regional mobility shows a decreasing trend from 32% in 2004 to 24% in 2010 even if the absolute number of scans reflects the trend of volumes that has been increasing over time.

Figure 2. Emilia-Romagna Region exam based passive/ active mobility 2004-2010



Figures 3, Figure 4 and Figure 5 show the 2010 passive and active mobility at the province level. The provincial-regional passive mobility is very limited (Fig. 4) because need for PET scans from provinces without a PET/CT scanner is satisfied by other regional centres.

Figure 5 shows the active mobility and that the more attractive provinces for the patient coming from other region are Bologna and Ravenna (where there is a private centre).

Figure 3. Passive Inter-provincial mobility RER (%)-2010

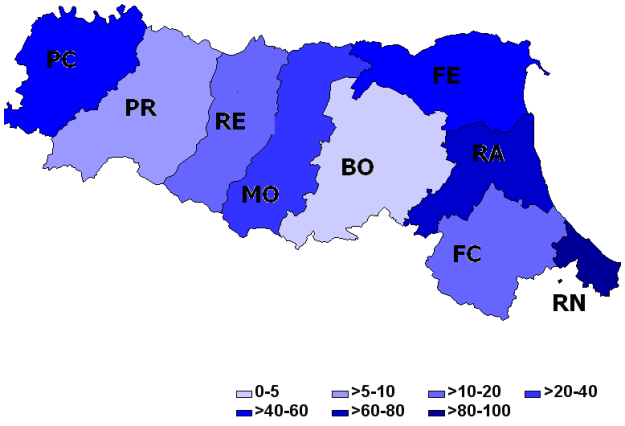


Figure 4. Passive provincial-regional mobility RER (%)-2010

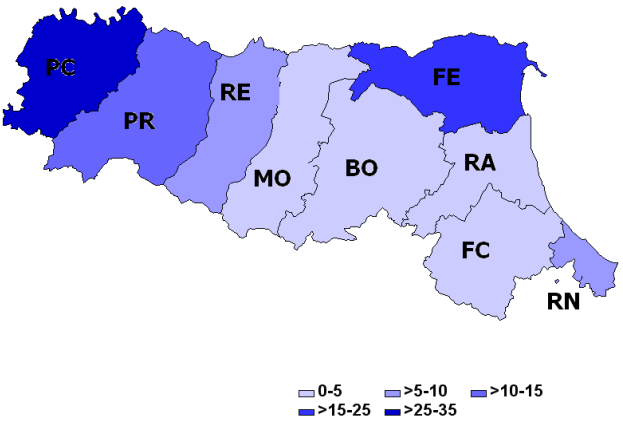
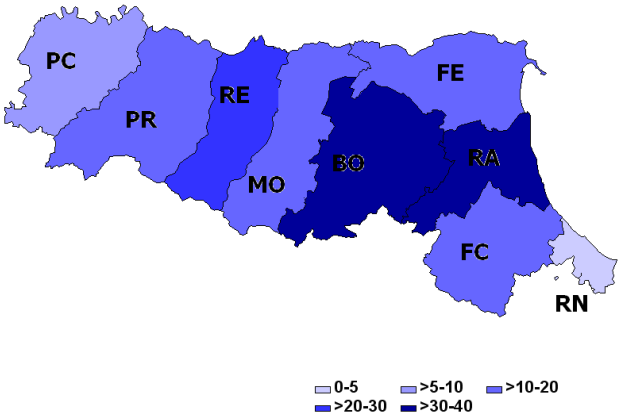


Figure 5. Active provincial mobility RER (%)-2010

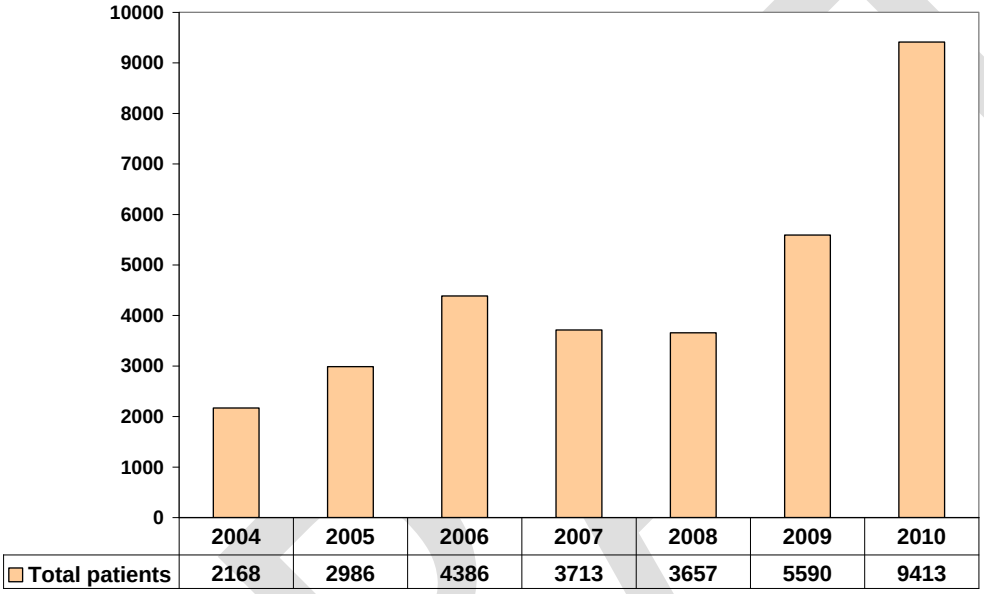


Sicilia region (SR)

Identification of PET/CT scans performed

Figure 6 reports the number of PET/CT scans performed between 2004 and 2010 in Sicilia region for all types of disease. There is a strong upward trend in the use of PET/CT between 2004 and 2010 with an increase of about 335 % (from 2,168 scans in the 2004 to 9,413 scans in the 2010).

Figure 6. Volumes of PET/CT scans in Sicilia region 2004-2010



In Table 9 are reported the results of the administrative data number on PET/CT use in the year 2010, by province.

Table 9. Volumes of PET/CT exams in Sicilia region by province – 2010

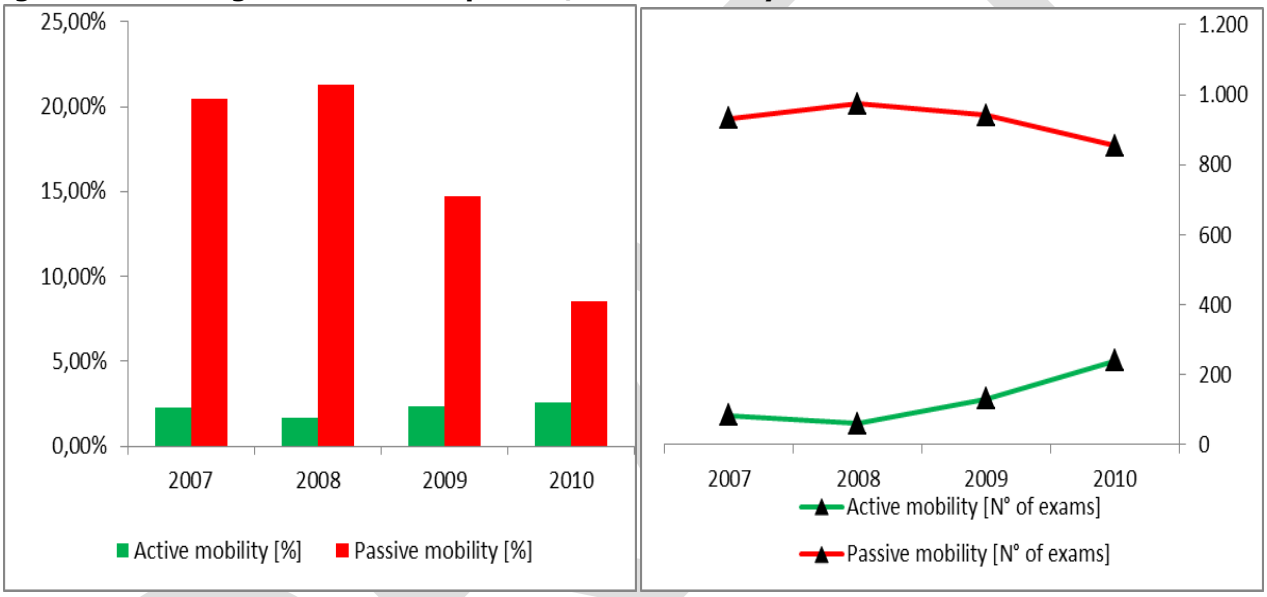
Province	Volumes (Adiministative data)
Agrigento	**267**
Caltanssetta	**488**
Catania	**2,948**
Enna	**206**
Messina	**1,323**
Palermo	**2,327**
Ragusa	**380**
Siracusa	**1,114**
Trapani	**360**
All	**9,413**

Mobility for PET/CT scan

In Sicilia region in the observed period (2007-2010) the passive regional mobility decreased both in term of percentage, from 20.5% to 8.5% (Figure 7), and in term of absolute number of scans performed, from 933 to 854. This is probably due to the increase in technology's availability, showing improved capacity to satisfy internal request of exams.

In terms of percentage, active regional mobility is stationary even if the absolute number of scans (from 84 to 240) reflects the trend of volumes that has been increasing over time.

Figure 7. Sicilia region exam based passive/active mobility 2007-2010



Figures 8, Figure 9 and Figure 10 show the 2010 passive and active mobility at the province level. Figure 8 shows that need for PET/CT scans is better satisfied in the metropolitan cities Palermo, Catania and Messina.

The results shown in Figure 8 could appear inconsistent with the data in Table 2, as the passive mobility for provinces without a PET/CT (Caltanissetta, Enna, Ragusa and Siracusa) is different from 100%.

This is because the data on passive mobility come from the hospital discharge database (SDO). These figures point out the hospital where the patients were nursed, while the PET/CT scan could have been performed in another hospital, also situated in another province.

Figure 8. Passive Inter-provincial mobility SR(%) 2010

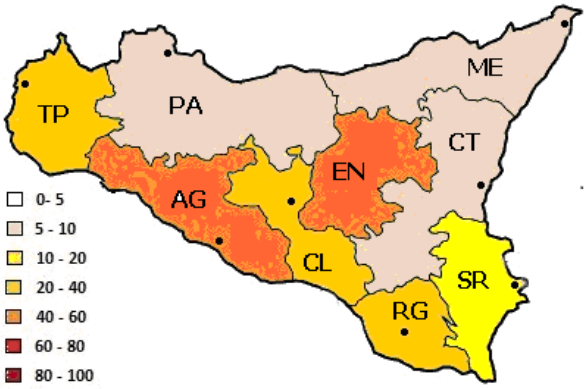


Figure 9. Passive provincial-regional mobility SR (%)-2010

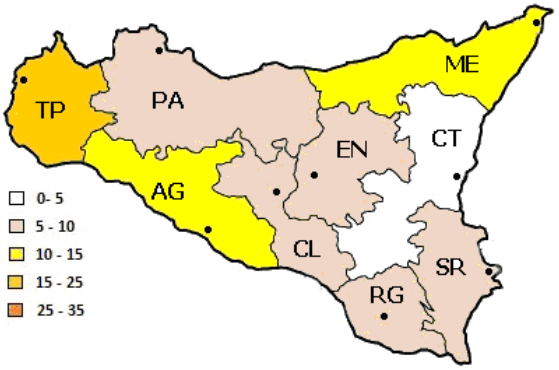
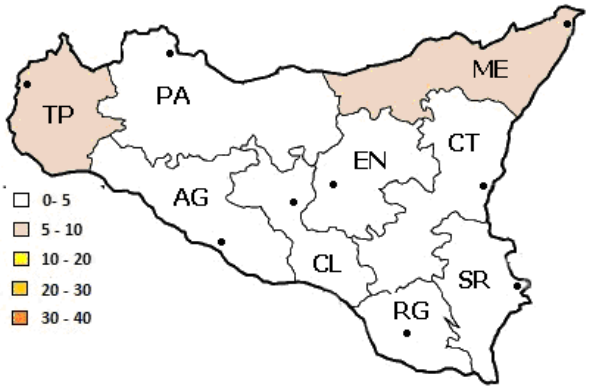


Figure 10. Active provincial mobility SR (%)-2010



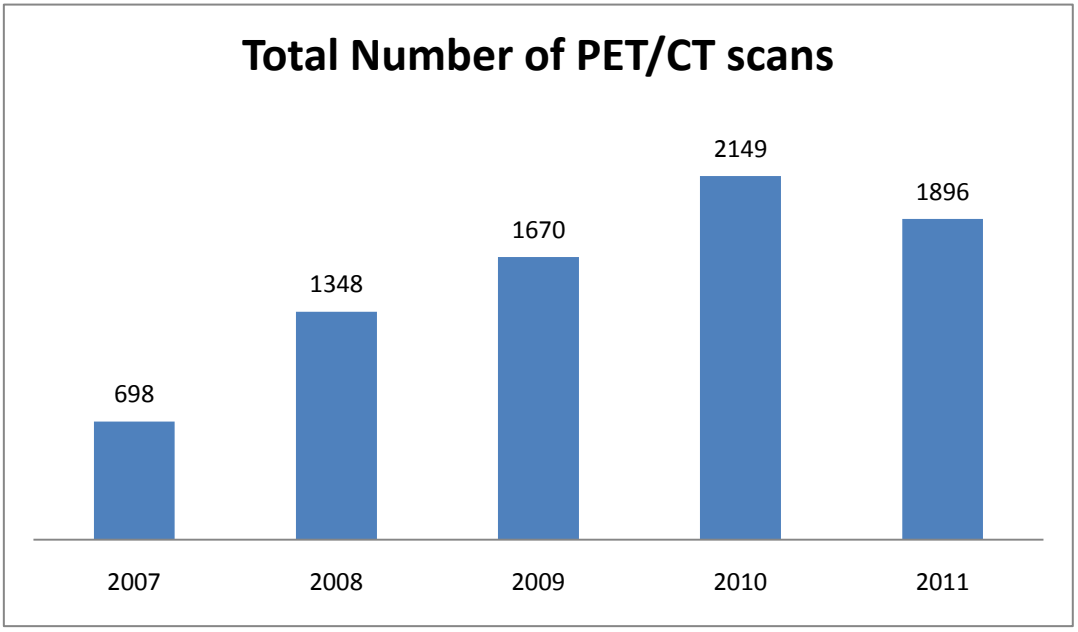
Provincia Autonoma di Trento (PAT)

Identification of PET/CT scans performed

The analysis of positron emission tomography's use in the nuclear medicine centre of Provincia Autonoma di Trento was performed searching the register of PET/CT scans adopted by the Nuclear Medicine Department in the period 2007-2011. The type of radio-marker used for the PET/CT is specified in the register, as well as the type of examination performed.

Figure 11 reports the number of PET/CT scans performed between 2007 and 2011 in Provincia Autonoma di Trento for all types of disease. There is an upward trend in the use of PET/CT between 2007 and 2010, with a following decrease in 2011 due to a need decrease.

Figure 11. Volumes of PET/CT scans in Provincia Autonoma di Trento -2007-2011



Mobility for PET/CT scan

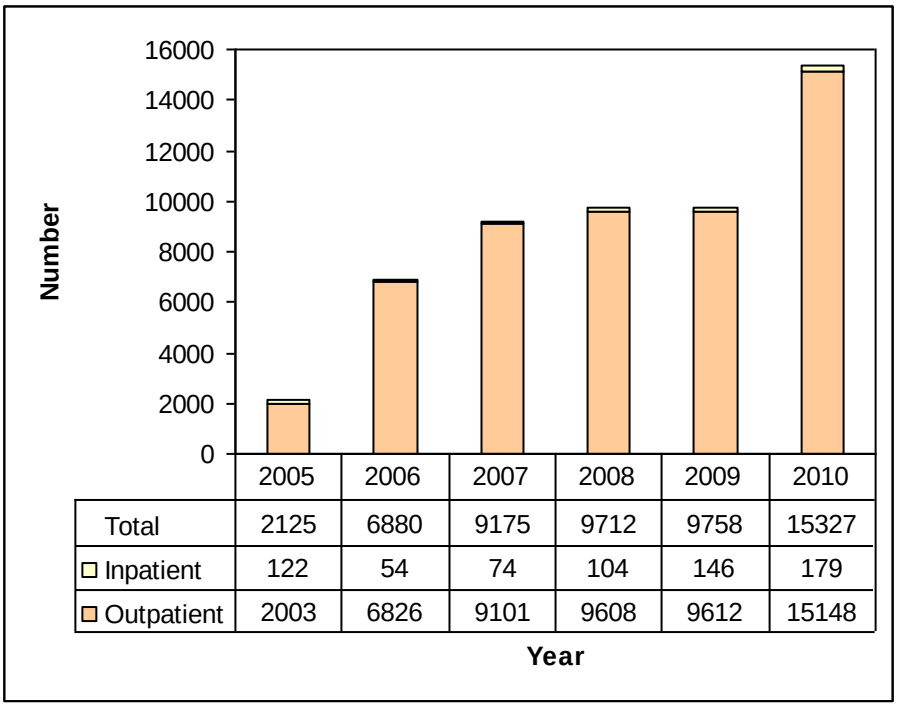
The mobility of patients was not analyzed, due to the nature of the register which does not allow such investigation.

Lazio region (LR)

Identification of PET/CT scans performed

Figure 12 reports the number of PET/CT scans performed between 2005 and 2010 in Lazio region for all types of disease. There is a strong upward trend in the use of PET/CT between 2005 and 2010 with an increase of about 620% (from 2,125 scans in the 2005 to 15,327 scans in the 2010).

Figure 12. Volumes of PET/CT scans in Lazio Region - 2005-2010



	2005	2006	2007	2008	2009	2010
Total	2125	6880	9175	9712	9758	15327
Inpatient	122	54	74	104	146	179
Outpatient	2003	6826	9101	9608	9612	15148

In Table 10 are reported the volumes of PET/CT scans by hospital trust. In Lazio region, all volumes of PET/CT scans performed are registered in the administrative data.

Table 10. Volumes of PET/CT exams in Lazio region by hospital trust- 2010

Hospital trust	Volumes (Administrative data)
	All exams
	N
Poliambulatorio Ospedaliero Latina	515
Policlinico Universitario Gemelli	6 828
IRCCS - I.F.O. Regina Elena	3 865
Azienda ospedaliera S. Andrea	1 658
Policlinico Universitario Tor Vergata	2 427
Other (data only from Hospital Discharges)	34
All	**15 327**

Mobility for PET/CT scan

In Lazio region the passive regional mobility decreased from 65% in 2005 to 23% in 2010 (Figure 13), probably due to the increase in technology's availability, showing capacity to satisfy internal request of exams. However, the number of exams performed out of the Region has increased, probably due to the attractive power of adjacent Regions such as Campania and Molise. In terms of percentage, active regional mobility shows a rather stable trend (13% in 2005 and in 2010), even if the absolute number of scans reflects the trend of volumes that has been increasing over time.

Figure 13. Lazio region exam based passive/ active mobility 2005-2010

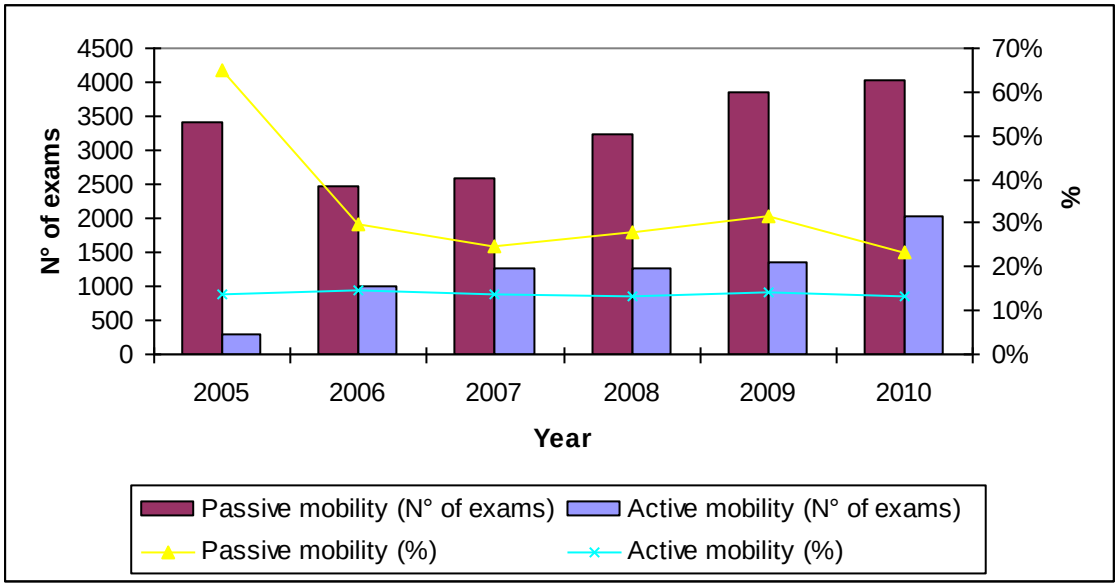


Table 11 and Table 12 show the 2010 passive and active mobility at the province level. Table 11 shows that need for PET scans is often satisfied by other regional centres, especially for provinces without a PET/CT scanner.

Table12 show the active mobility and that the more attractive province for the patient coming from other region is Rome.

Table 11. Passive provincial-regional mobility LR (%) – 2010

Province of residence	Passive provincial-regional mobility (%)
Viterbo	43.0
Rieti	54.1
Roma	17.0
Latina	38.2
Frosinone	49.0

Table 12. Active provincial mobility LR(%) – 2010

Province	Active provincial mobility (%)
Viterbo	0
Rieti	0
Roma	13.8
Latina	3.1
Frosinone	0

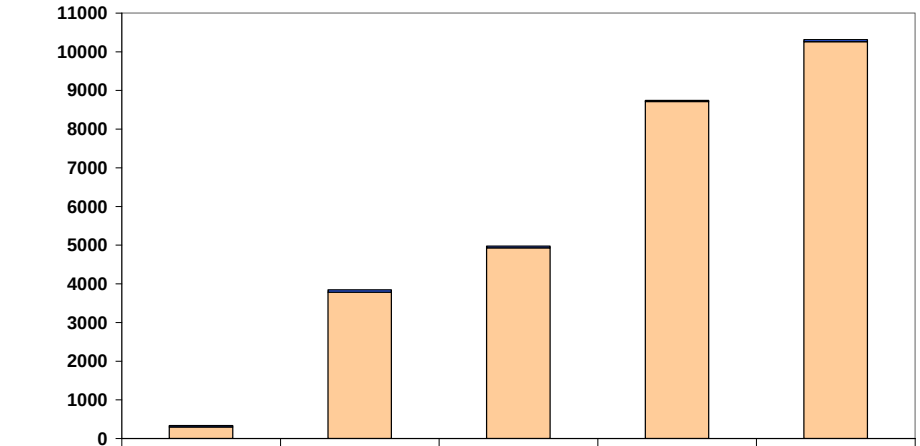
Since PET/CT scanners in Lazio region are concentrated in Rome (4 PET/CT), and the PET/CT scanner located in Latina is operating only starting from 2010, the passive inter-provincial mobility indicator has not been included in the results.

Puglia region (PR)

Identification of PET/CT scans performed

Figure 14 reports the number of PET/CT scans performed between 2006 and 2010 in Puglia region for all types of disease. There is an outstanding upward trend in the use of PET/CT between 2006 and 2010 with an increase of about 3,000% (from 332 scans in the 2006 to 10,311 scans in the 2010).

Figure 14. Volumes of PET/CT scans in Puglia region 2004-2010



	2006	2007	2008	2009	2010
Total	332	3842	4975	8742	10311
Inpatient	34	60	44	28	49
Outpatient	298	3782	4931	8714	10262

The results of the survey on PET/CT use are reported in Table 13. The comparison with administrative data shows differences that, according to the information taken from the users (Heads of the nuclear medicine centres), are probably due to technical problems in the Information Technology procedure of data exchange among the nuclear medicine centres and the central regional system. A total difference of 2,118 scans (17%) between the two data sources was detected, mainly related to the Centro di Medicina Nucleare Calabrese (+1,170, +100%), a private centre operating also with self-paying patients not registered in the administrative data.

Table 13. Survey of volumes of PET/CT exams in Puglia region by nuclear medicine centre - 2010

Nuclear medicine centres	Volumes (Administrative data)	Volumes (Survey Data)	Difference
	All exams N	All exams N	N (%)
A.O.U. Policlinico Bari	4,746	5,312	566 (11%)
A.O.U. Ospedali Riuniti Foggia	1,011	1,101	90 (8%)
Ospedale Di Miccoli, Barletta, ASL BAT (operating from March 2010)	799	711	-88 (-12%)
Ospedale Perrino, Brindisi, ASL BR (operating from June 2010)	1,025	1,081	56 (5%)
Ospedale S.G. Moscati, Taranto, ASL TA (operating from Oct. 2011)	-	-	-
Casa Sollievo della Sofferenza, San Giovanni Rotondo (FG)	2,729	3,053	324 (11%)
Centro di Medicina Nucleare Calabrese, Cavallino (LE) (operating from July 2010)	1	1,171	1,170 (100%)
All	**10,311**	**12,429**	**2,118 (17%)**

Mobility for PET/CT scan

In Puglia region, in 2010, a passive mobility for 4,187 PET/CT scans has been observed (30% of the total scans – 14,094 – required by patients resident in PR), in the same year the active mobility was equal to 405 PET/CT scans (3% of the scans performed in PR); data on passive mobility in the period 2004-2009 are not available. Foggia is the only PR province with two PET/CT scanners, one public and one private. The following tables 14, 15 and 16 and figure 15 show the 2010 passive and active mobility at the province level.

Table 14. Passive inter-provincial mobility PR (%) - 2010

		Patients moving to the province of (tot 14 094)						
		Bari	Barletta	Brindisi	Foggia	Lecce	Taranto	Out of PR
Patients coming from the province of	Bari	60%	5%	1%	15%	0%	0%	18%
	Barletta	21%	33%	0%	19%	0%	0%	27%
	Brindisi	17%	1%	35%	21%	0%	0%	26%
	Foggia	2%	1%	0%	76%	0%	0%	22%
	Lecce	19%	1%	9%	18%	0%	0%	52%
	Taranto	30%	1%	13%	10%	0%	0%	46%

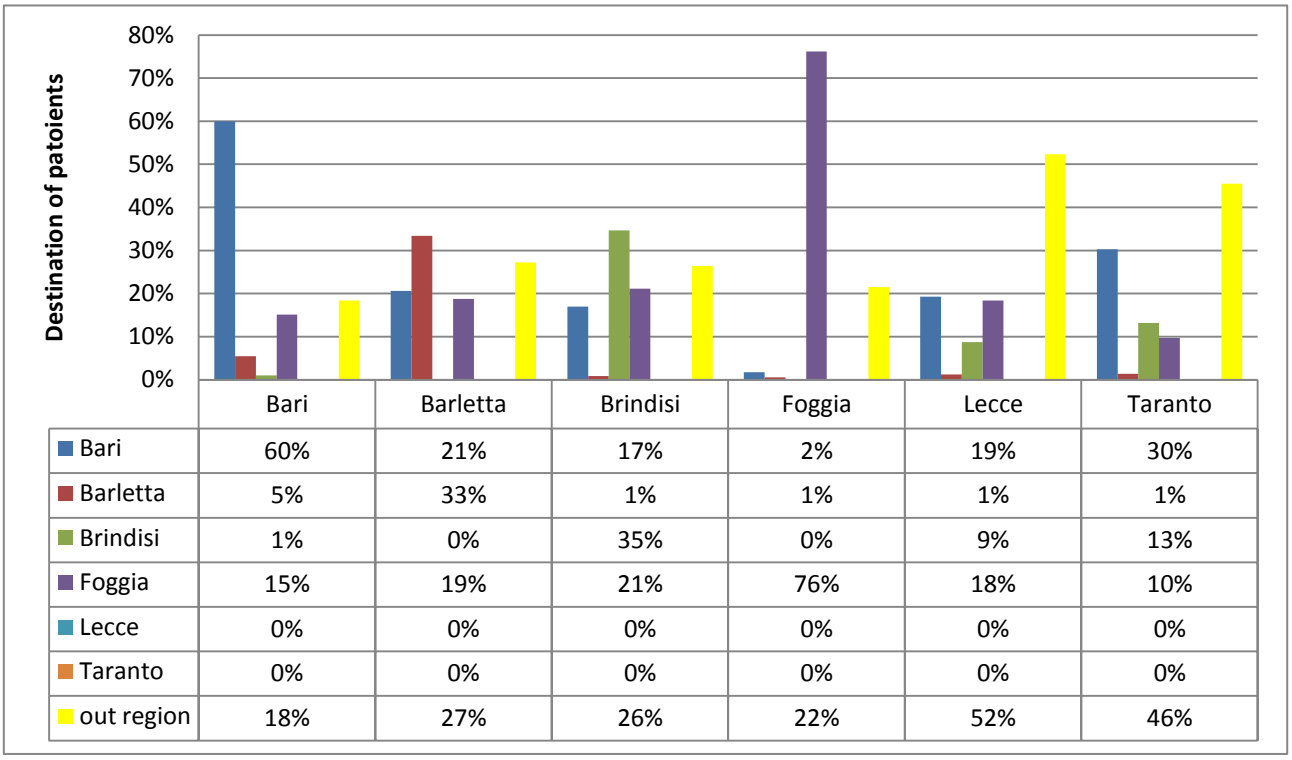
Table 15. Passive provincial-regional mobility PR (%) - 2010

		Patients moving to the region (tot 4 187)					
		Basilicata	Lombardia	Campania	Emilia R.	Lazio	other
Patients coming from the province of	Bari	20%	32%	31%	7%	4%	5%
	Barletta	13%	29%	42%	6%	5%	5%
	Brindisi	16%	33%	26%	11%	5%	10%
	Foggia	26%	25%	14%	21%	7%	7%
	Lecce	15%	28%	27%	15%	10%	5%
	Taranto	54%	15%	15%	6%	5%	5%
	not avail.	2%	0%	0%	0%	6%	92%

Table 16. Active provincial mobility (%) - 2010

		Patients coming from the region (tot 405)					
		Campania	Basilicata	Calabria	Abruzzo	Lazio	Other
Patients moving to the province of	Bari	1%	17%	6%	0%	0%	76%
	Barletta	0%	1%	1%	0%	1%	97%
	Brindisi	0%	0%	0%	0%	0%	99%
	Foggia	36%	7%	7%	12%	1%	37%
	Lecce	-	-	-	-	-	-
	Taranto	-	-	-	-	-	-

Figure 15. Mobility of patients resident in Puglia (%) – 2010



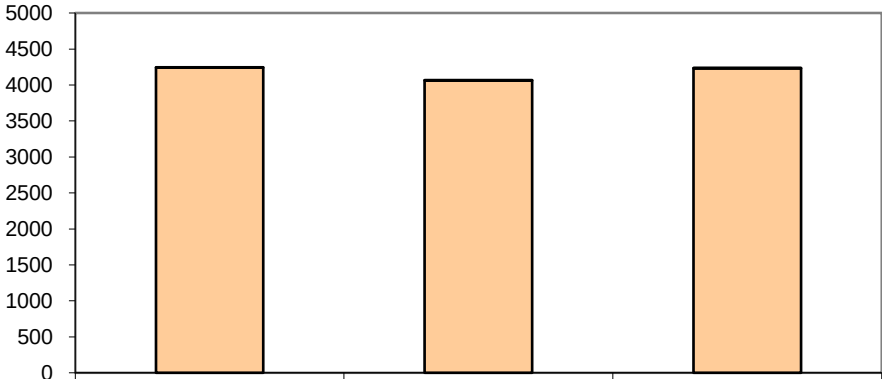
	Bari	Barletta	Brindisi	Foggia	Lecce	Taranto
Bari	60%	21%	17%	2%	19%	30%
Barletta	5%	33%	1%	1%	1%	1%
Brindisi	1%	0%	35%	0%	9%	13%
Foggia	15%	19%	21%	76%	18%	10%
Lecce	0%	0%	0%	0%	0%	0%
Taranto	0%	0%	0%	0%	0%	0%
out region	18%	27%	26%	22%	52%	46%

Umbria region (UR)

Identification of PET/CT scans performed

Figure 16 reports the number of PET/CT scans performed between 2008 and 2010 in Umbria region for all types of diseases (only data from administrative databases; see codes Table 2). We have found substantial invariance in the use of PET/CT scan from 2008 to 2010.

Figure 16. Volumes of PET/CT scans in Umbria (2008-2010)



	2008	2009	2010
Total	4241	4063	4234
Inpatient	1	1	4
Outpatient	4240	4062	4230

In Table 17 are reported the results of the survey on PET/CT use. The comparison of survey data with administrative data shows how the latter systematically underestimates the number of PET/CT scans. Probably the underestimation of PET/CT is due to unregistered inpatients' scans in administrative data lack of a specific ICD9-CM procedure code for PET/CT in Hospital Discharge Database, and to the Diagnosis Related Group (DRG) system of remuneration.

Considering the administrative data limit the "real" volumes of PET/CT scans performed in UR is derived applying survey correction, giving a "corrected" number of exams in 2010 of about 4,570. A difference of 340 scans (7.5%) between the two data sources was detected.

Table 17. Survey of volumes of PET/CT exams in Umbria Region - 2010

	Volumes (Administrative data) All exams (N)	Volumes (Survey Data) All exams (N)	Difference
Umbria Region	**4230**	**4570**	**340 (7.5%)**

Mobility for PET/CT scan in Umbria Region

In Umbria region, between 2008 and 2010, a slight decrease in active mobility (from 24% to 21%; Table 18) and an increment in passive mobility (from 6% to 9%; Table 1) was observed; further analysis are necessary to investigate these phenomena in details.

Table 18. Umbria Region exam based active and passive mobility 2008-2010

	Active mobility		Passive mobility	
Year	**N° of exams**	**%**	**N° of exams**	**%**
2008	1035	24	197	6
2009	989	24	238	7
2010	886	21	335	9

Synthesis- Volumes and regional mobility of PET/CT scans by region

In table 19 are reported the volumes of PET/CT scans and the regional mobility by region. Emilia-romagna is the region with the higher volumes of PET/CT (17 119 scans).

The range of the active mobility is between 2.5% of the Sicilia region to 24% of Emilia-Romagna region.

The range of the passive mobility is between 7% of Emilia-Romagna region to 30% of Puglia region.

Table 19 Volumes and regional mobility of PET/CT scans by region -2010 year (administrative data)

Region	Volumes	Regional mobility	
	Number of PET/CT scan	active (%)	passive (%)
Emilia-Romagna	17,119	24.0	7.0
Sicilia	9,413	2,5	8,5
Provincia Autonoma di Trento	1,896		
Lazio	15,327	13.0	23.0
Puglia	10,311	3.0	30.0
Umbria	4,063	21.0	9.0

5.2.2 Patients submitted to PET/CT scan for oncologic disease

Objective

The aim of this section is to quantify the proportion of patients with an oncologic disease submitted to a PET/CT scan.

Materials and Methods

The quantification of patients resident in the six regions considered in the report and submitted to PET/CT scan for oncologic disease in 2010 was obtained through 3 steps:

1. selection of patients resident in Emilia-Romagna region submitted to PET/CT scan in 2010;
2. Identification of resident patients in Emilia-Romagna region with first or subsequent hospitalization for oncologic disease through Hospital Discharge Database in the period 2004-2011;
3. Deterministic record linkage between the patients with PET/CT scan (ASA) and the patients with an hospitalization (SDO).

In the next session only patients resident in the six regions are taken into consideration.

Selection of patients submitted to PET/CT scan in 2010

Administrative data of Regional Outpatient Database (ASA - Assistenza Specialistica Ambulatoriale) and Hospital Discharge Database (SDO - Schede Dimissione Ospedaliera) were used to select patients submitted to PET/CT scan in 2010; ICD9-CM codes used for patients' selection are reported in Table 2.

Identification of patients with first and subsequent hospitalization for oncologic disease through Hospital Discharge Records Database.

The identification of patients with first or subsequent hospitalizations for oncologic disease in 2004-2011 was carried out by selecting from Hospital Discharge Database the patients who had both a discharge date in the study year (2004-2011) and an ICD-9-CM diagnosis of cancer. Codes used to select the data are reported in Table 20.

Table 20. Selected ICD-9-CM codes

Data source	ICD9-CM diagnoses Codes
Hospital Discharge Database (SDO) codes	140-208
	230-239
	V58.0
	V58.1, V58.11
	V10.X

Results

Emilia-Romagna region (RER)

Selection of patients submitted to PET/CT scan in 2010

The PET/CT scans performed for Emilia-Romagna patients in 2010 are 14,008 (Table 21, 13,017 performed in RER and 991 in other Region) corresponding to 11,415 patients of which 9,337 with one PET/CT scan performed and 2,078 (18%) with more than one exam.

Table 21. PET/CT scans performed for RER patients by region provider-2010

Provider	Number of PET/CT scans	Number of patients
Total	**14,008**	**11,415**
Emilia-Romagna	**13,017**	**10,661***
Other Region	**991**	**818***

*The sum of 10,661 and 818 on the second column in the Table 21 is different from the total 11,415 due to the fact that 64 patients had a PET/CT scan both in RER and in other regions.

Identification of patients with first and subsequent hospitalization for oncologic disease through Hospital Discharge Records Database.

The number of Emilia-Romagna patients identified with the selected codes (Table 20) with a first or subsequent hospitalizations for oncologic disease in the period 2004-2011 and still alive at January 2010 is 307,866. These

represent the oncologic patients for which the PET/CT may have a role for cancer staging, evaluation of response to treatment, or recurrence.

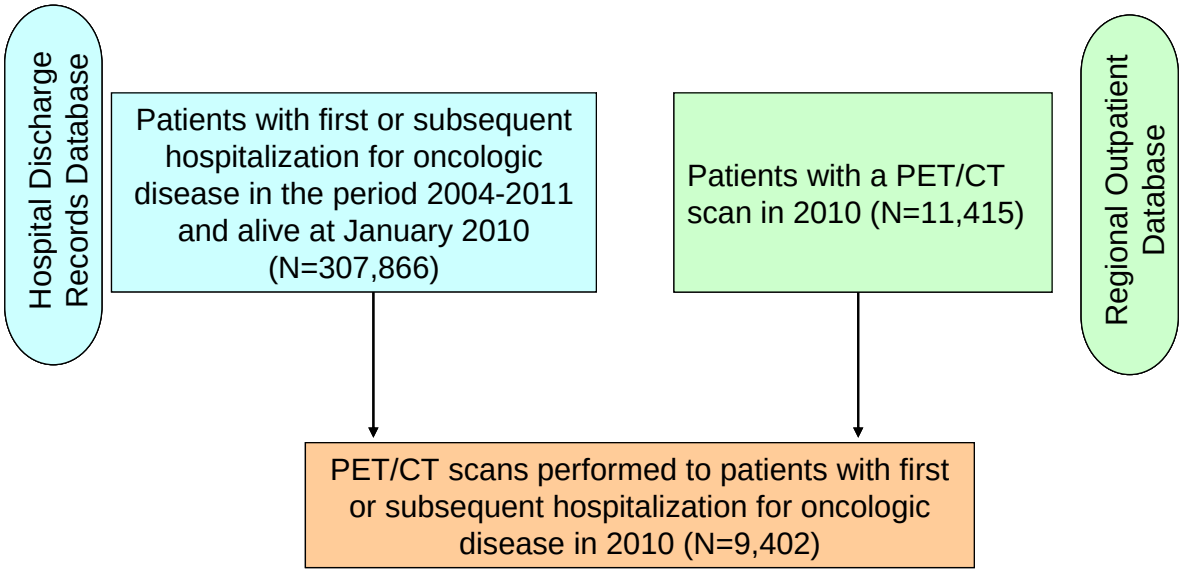
Record linkage

Record linkage between the dataset of patients with "first or subsequent" hospitalizations for oncologic disease in the period 2004-2011 and the patients with at least one PET/CT exam in 2010 (11,415) shows that 9,402 patients have done a PET/CT scan for oncologic disease that represents 82% of all patients with PET/CT scans (11,415). This result is coherent with literature information that around 85-90% (England Department of Health 2005) of PET/CT scans is done for oncologic disease. Among the 2013 (18%) patients with a PET/CT not performed for cancer disease, 1,455 (13%) patients had an hospitalization for other diseases and 558 (5%) were not linked with the Hospital Discharge Database (SDO).

As already reported, the administrative data underestimates the "real" volumes of PET/CT exams and about 24% (5,499 scans) undetected exams may have been done for any disease. For this reason the "real" proportion of PET/CT performed for oncologic disease (82%) could be higher.

Figure 17 shows the result of the record linkage between the two data sources (SDO 2004-2011 and ASA-2010).

Figure 17. RER patients submitted to PET/CT for oncologic disease-2010



Sicilia region (SR)

Selection of patients submitted to PET/CT scan in 2010

The PET/CT scans performed for Sicilian patients in 2010 were 10,027 (Table 22 – 9,173 performed in Sicilia and 854 in an other Region) corresponding to 8,728 patients of which 8,334 with one PET/CT scan performed and 694 (8%) with more than one exam.

Table 22. PET/CT scans performed for Sicilia patients by region provider-2010

Provider	Number of PET/CT scans	Number of patients
Total	**10,027**	**8,728**
Sicilia	**9,173**	
Other Region	**854**	

Identification of patients with first and subsequent hospitalization for oncologic disease through Hospital Discharge Records Database.

The number of Sicilia patients identified with the selected codes (Table 20) with a first or subsequent hospitalizations for oncologic disease in the period 2004-2011 is 170,493. These represent the oncologic patients for which the PET/CT may have a role for cancer staging, evaluation of response to treatment, or recurrence.

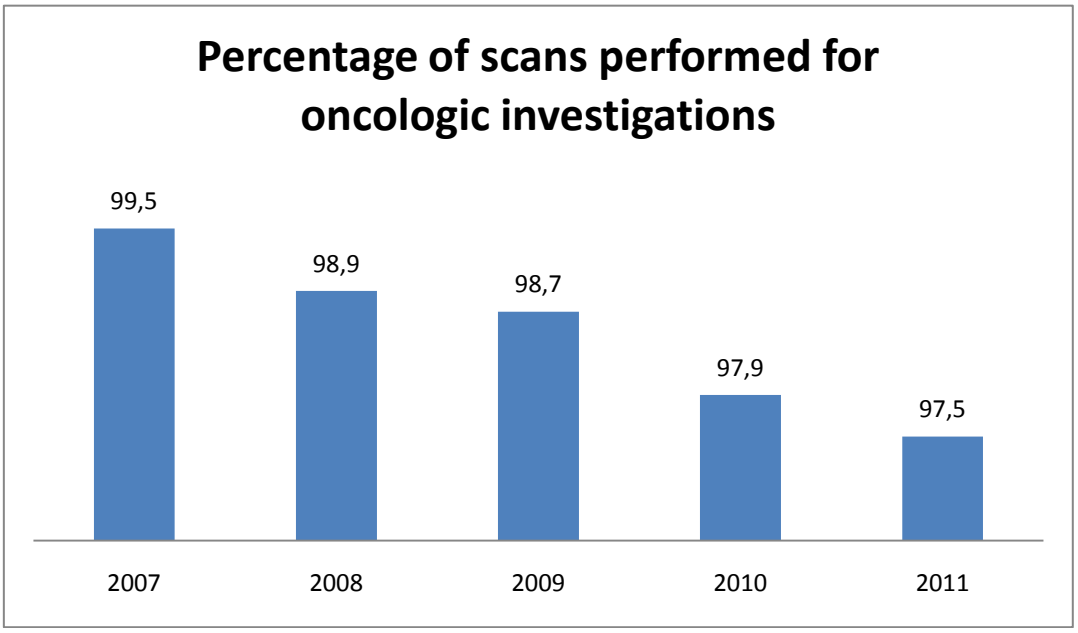
Provincia Autonoma di Trento (PAT)

Selection of patients submitted to PET/CT scan in 2007-2011

The quantification of patients resident in Provincia Autonoma di Trento submitted to PET/CT scan for oncologic disease between 2007 and 2011 was obtained searching the PET/CT register.

The percentage of PET/CT scans performed each year between 2007 and 2011 for oncologic patients is illustrated in figure 18. Cancer investigation is by far the main source of PET/CT investigation request in Trentino, ranging from 99.5% of the examinations in 2007 to 97.5% of the examinations in 2011. Such slightly downward trend can be justified by taking into account the recent adoption at the Santa Chiara Hospital in Trento of new radiopharmaceuticals for different diagnostic purposes. The main limitation for the employment of PET/CT for other purposes might be the lack of a local cyclotron devoted to the production of short half-life radionuclides.

Figure 18. Percentages of PET/CT scans in PAT-2007-2011 for oncologic diagnostics



Lazio region (LR)

Selection of patients submitted to PET/CT scan in 2010

The PET/CT scans performed for Lazio patients in 2010 are 17,151 (Table 23, 13,119 performed in Lazio and 4,032 in other Region) corresponding to 13,878 patients of which 11,205 with one PET/CT scan performed and 2,673 (24%) with more than one exam.

Table 23. PET/CT scans performed for Lazio patients by region provider-2010

Provider	Number of PET/CT scans	Number of patients
Total	**17,151**	**13,878**
Lazio	**13,119**	**10,855**
Other Region	**4,032**	**3,203**

Identification of patients with first and subsequent hospitalization for oncologic disease through Hospital Discharge Records Database

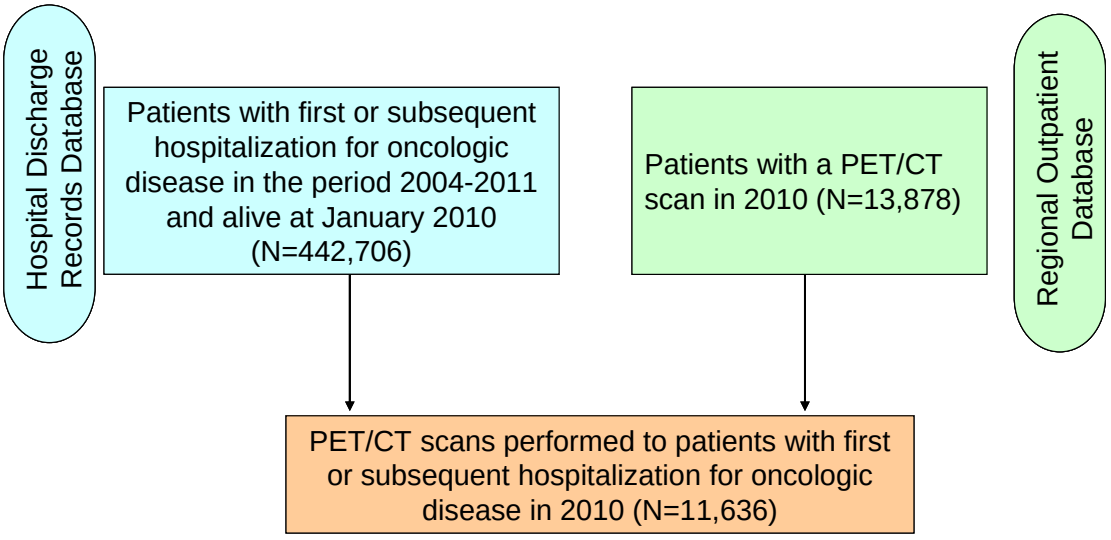
The number of Lazio patients identified with the selected codes (Table 20) with a first or subsequent hospitalizations for oncologic disease in the period 2004-2011 (passive mobility not available for 2011) is

442,706. These represent the oncologic patients for which the PET/CT may have a role for cancer staging, evaluation of response to treatment, or recurrence.

Record linkage

From the record linkage between the dataset of patients with "first or subsequent" hospitalizations for oncologic disease in the period 2004-2011 and the patients with at least one PET/CT exam in 2010 (13,878) it results that 11,636 patients have done a PET/CT scan for oncologic disease that represents 84% of all patients with PET/CT scans (13,878). This result is coherent with literature information that around 85-90% (England Department of Health 2005) of PET/CT scans is done for oncologic disease. Among the 2,242 (16%) patients with a PET/CT not performed for cancer disease, 445 (3%) patients had an hospitalization for other diseases and 1,797 (13%) were not linked with the Hospital Discharge Database (SDO).
Figure 19 shows the result of the record linkage between the two data sources (SDO 2004-2011 and SIAS-2010).

Figure 19. Lazio patients submitted to PET/CT for oncologic disease-2010



*Passive mobility not available in 2011.

Puglia region (PR)

Selection of patients submitted to PET/CT scan in 2010

The PET/CT scans performed for Puglia patients in 2010 are 14,094 (Table 24: 9,907 performed in PR and 4,187 in other Regions) corresponding to 9,253 patients.

Table 24. PET/CT scans performed for Puglia patients by region provider-2010

Provider	Number of PET/CT scans	Number of patients
Total	**14,094**	**9,337**
Puglia	**9,907**	**6,112**
Other Regions	**4,187**	**3,225**

Identification of patients with first and subsequent hospitalization for oncologic disease through Hospital Discharge Records Database.

The number of Puglia patients identified with the selected codes (Table 20) with a first and subsequent hospitalizations for oncologic disease in the period 2004-2011 and still alive at January 2010 is 222,211. These represent the oncologic patients for which the PET/CT may have a role for cancer staging, evaluation of response to treatment, or recurrence.

Record linkage

From the record linkage between the dataset of patients with "first or subsequent" hospitalizations for oncologic disease in the period 2004-2011 and the patients with at least one PET/CT exam in 2010 (9,337) it results that (7,778) patients have done a PET/CT scan for oncologic disease that represents 83.3% of all patients with PET/CT scans (9,337). This result is coherent with literature information that around 85-90% (England Department of Health 2005) of PET/CT scans is done for oncologic disease.
As already reported, the administrative data underestimates the "real" volumes of PET/CT exams and about 17% (2,118 scans) undetected exams may have been done for any disease. For this reason the "real" proportion of PET/CT performed for oncologic disease (83,3%) could be higher.

Umbria region (UR)

Selection of patients submitted to PET/CT scan in 2010

The PET/CT scans performed for Umbria patients in 2010 are 3,679 (Table 25) 3,344 performed in UR and 335 in other Regions) corresponding to 2,672 patients.

Table 25. PET/CT scans performed forUmbria patients by region provider-2010

Provider	Number of PET/CT scans	Number of patients
Total	**3,679**	**2,672***
Umbria	**3,344**	**2,406**
Other Regions	**335**	**283**

*The patients that have undergone a PET/CT both in Umbria and in Other Regions (in 2010) are counted only once.

Identification of patients with first or subsequent hospitalization for oncologic disease through Hospital Discharge Records Database.

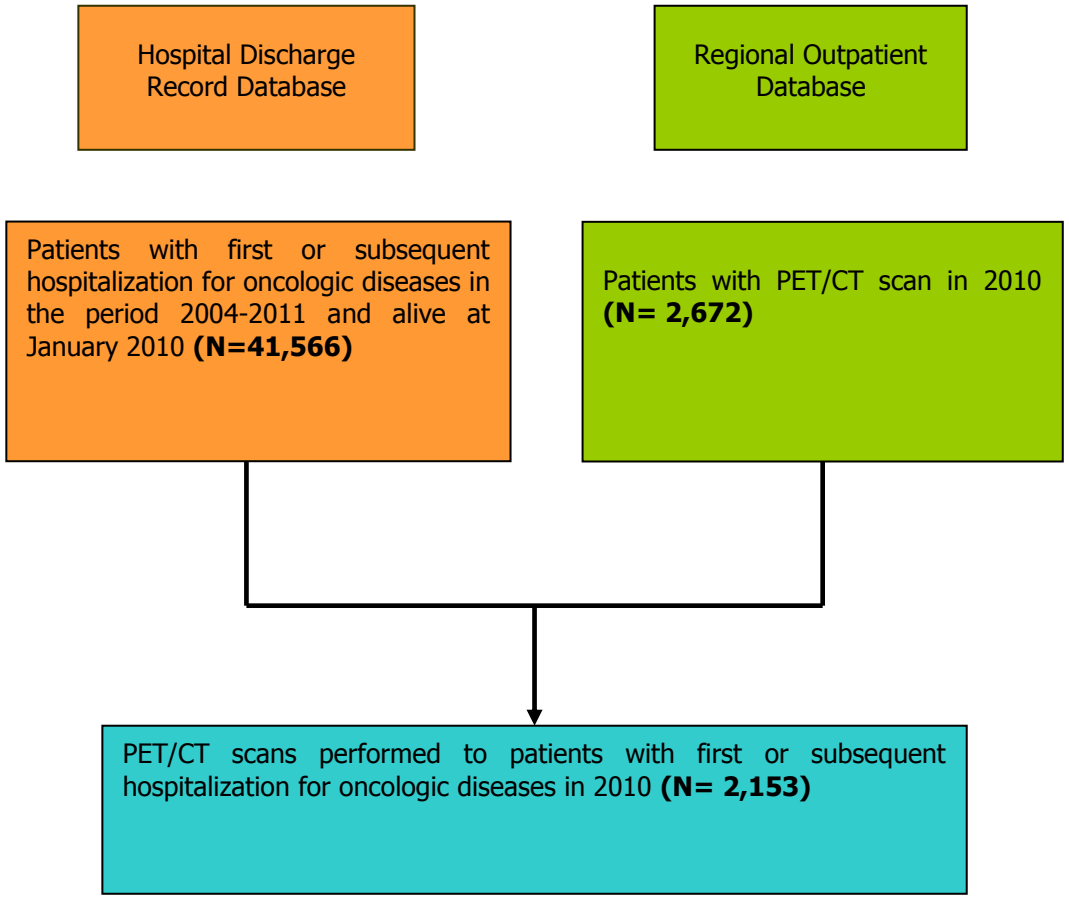
The number of Umbria patients identified with the selected codes (Table 20) with a first or subsequent hospitalizations for oncologic disease in the period 2004-2011 and still alive at 4th January 2010 is 41,566. These represent the oncologic patients for which the PET/CT may have a role for cancer staging, evaluation of response to treatment, or recurrence.

Record linkage

From the record linkage between the dataset of patients with "first or subsequent" hospitalizations for oncologic disease in the period 2004-2011 and the patients with at least one PET/CT exam in 2010 (2,672) it results that 2,153 patients have done a PET/CT scan for oncologic diseases that represents 80.5% of all patients with PET/CT scans (2,672). This result is coherent with literature information that around 85-90% (England Department of Health 2005) of PET/CT scans is done for oncologic diseases.
As already reported, the administrative data underestimates the "real" volumes of PET/CT exams and about 7.5% (340 scans) undetected exams may have been done for any disease. For this reason the "real" proportion of PET/CT performed for oncologic disease (80.5%) could be higher.

Figure 20 shows the result of the record linkage between the two data sources (SDO 2004-2011 and ASA-2010).

Figure 20. UR patients submitted to PET/CT for oncologic diseases



Synthesis-Oncologic patients submitted to PET/CT scan by region

Table 26 shows the number of patients submitted to PET/CT scan and the percentage of the cases with an oncologic disease.

Provincia Autonoma di Trento has the higher proportion of patients submitted to PET/Ct for oncologic disease while the other regions have similar percentages. Probably the difference is due to the datasources; in fact Provincia Autonoma di Trento derived the data from a PET/CT register and this type of information system is probably more accurate than administrative data.

Table 26. Patients submitted to PET /CT scans by region -2010 year

Region	Patients with a PET/CT scan	Patients with a PET/CT scan for oncologic disease (%)	Data sources
Emilia-Romagna	11,415	82.0	Administrative database
Sicilia	8,728		
Provincia Autonoma di Trento		97.5	PET/CT Register
Lazio	13,878	84.0	Administrative database
Puglia	9,337	83.3	Administrative database
Umbria	2,672	80.5	Administrative database

Discussion

The analysis of the infrastructures of PET/CT (scanners and cyclotrons), the pattern of use of PET/CT and the healthcare mobility in the six Italian regions highlighted a variable situation.

The range of number of inhabitants per PET/CT is between 297,035 of Sicilia region to 1,136,374 of Lazio region.

The range of number of inhabitants per cyclotron is between 906,486 of Umbria region to 4,084,035 of Puglia region.

Passive healthcare mobility highlights the differences in the accessibility to technology: Puglia and Lazio are the regions with the higher value of passive mobility (30% and 23%) and Emilia-Romagna, Sicilia and Umbria are the regions with the lower value (7%, 8.5% and 9%).

The region with the higher value of active mobility are the Emilia-romagna and Umbria regions (24% and 21%) while the regions with the lower value are Sicilia (2.5%) and Puglia (3%).

The use of PET/CT scan for oncologic disease has similar pattern in 5 regions (Umbria, Emilia-Romagna, Sicilia, Puglia, Lazio) with values ranging between 80.5% to 84.0% while Provincia Autonoma di Trento has the highest proportion of oncologic PET/CT (97.7%). Probably the difference is due to the datasources; Provincia Autonoma di Trento derived the data from a PET/CT register while the other regions from administrative database.

5.2.3 Definition of target population and estimate of expected volumes of FDG-PET/CT *scans in cancer staging*

Epidemiological background

Every year in Italy, an estimated 250,000 new cancer cases are diagnosed and according to the latest national data available from ISTAT (National Institute of Statistics) there were 168,664 deaths due to cancer-related diseases (AIRTUM 2009).

In the period 2003-2005 there were 7 new cases per 1,000 inhabitants among men and 5 new cases per 1,000 inhabitants among women, in the same period an yearly average of 346 deaths due to cancer every 100,000 men and 250 every 100,000 women was reported.

Although overall crude cancer incidence rate (males and females together) has increased over time, the standardized incidence rate shows that this increase is mainly due to ageing of the population.

An increase in incidence is also due to anticipation of diagnosis as a consequence of the implementation of screening programs (e.g., pap smear, mammography, fecal occult blood test) for some tumors, like cervical cancer, breast and colorectal cancer.

The crude mortality rates do not show any decrease due to population ageing but standardized mortality rates show a marked decrease due to mortality reduction for several relevant cancer sites, e.g. lung among males, female breast, colorectal, stomach, urinary bladder, etc.

Figure 21 shows, by gender, the proportional incidence for main relevant cancers during 2003-2005.

The five most frequent cancers among males were prostate (18.5%), non melanoma skin (15.8%), lung (13.1%), colorectal (12.0%), bladder (5.7%); among women, breast (24.9%), non melanoma skin (15.1%), colorectal (11.9%), lung (5.0%) and stomach (4.1%).

Figure 21. Five most frequently diagnosed cancers in Italy - 2003-2005 – Men and Women (AIRTUM Register)

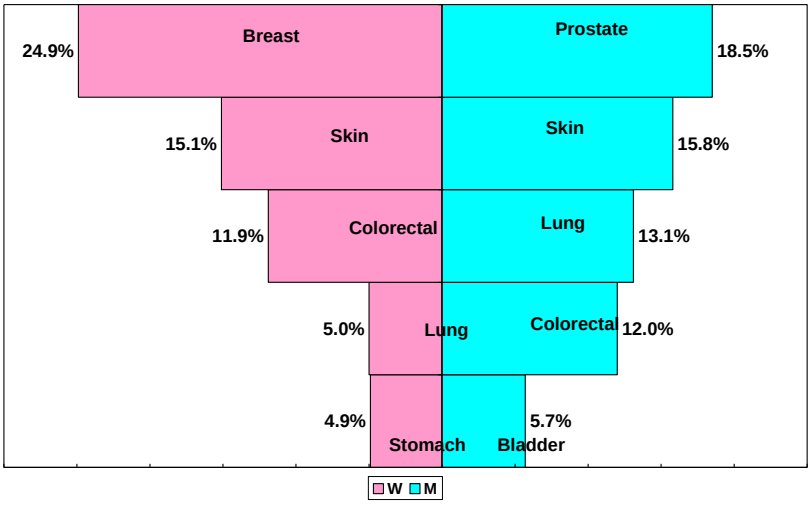
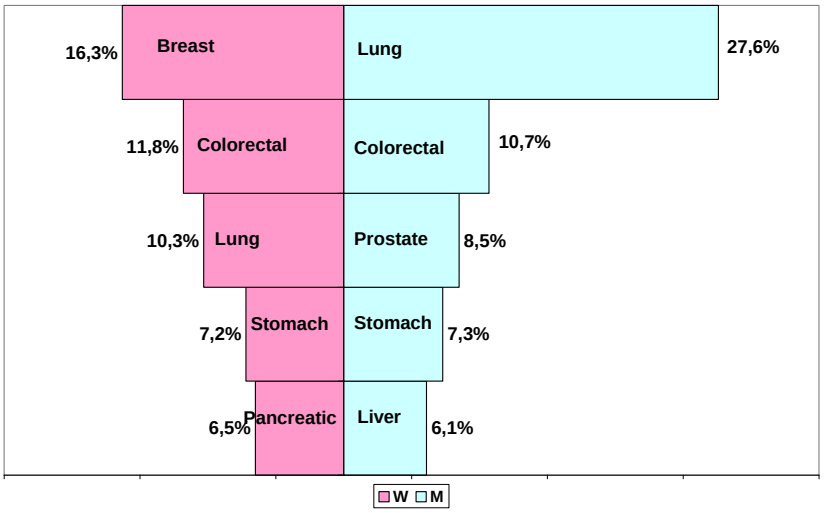


Figure 22 shows, for males and females, the five most important causes of cancer deaths that emerged from the Italian Network of Cancer registries (AIRTUM 2009) during 2003-2005:

- lung cancer (27.6%), colorectal cancer (10.6%), prostate cancer (8.5%), stomach cancer (7.3%) and liver cancer (6.1%) for men
- breast cancer (16.3%) followed by colorectal cancer (11.8%), lung cancer (10.3%), stomach cancer (7.2%) and pancreas cancer (6.5%) for women.

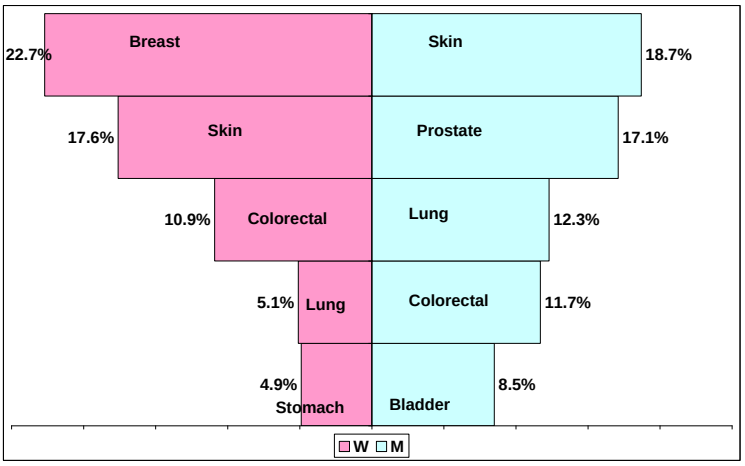
Figure 22. Five most important causes of cancer deaths in Italy - 2003-2005 – Men and Women (AIRTUM Register)



In 2007, in Emilia-Romagna, 35,739 new cases of cancer (19,577 males and 16,162 females) and about 13,600 deaths due to cancer-related diseases were detected. Considering the population, 9 new cases per 1,000 men and 7 per 1,000 women were detected (I tumori in Emilia-Romagna, 2007).

The proportional incidence, reported in Figure 23, shows regional data in line with the national data, except for skin cancer in males for which the proportion appears to be higher.

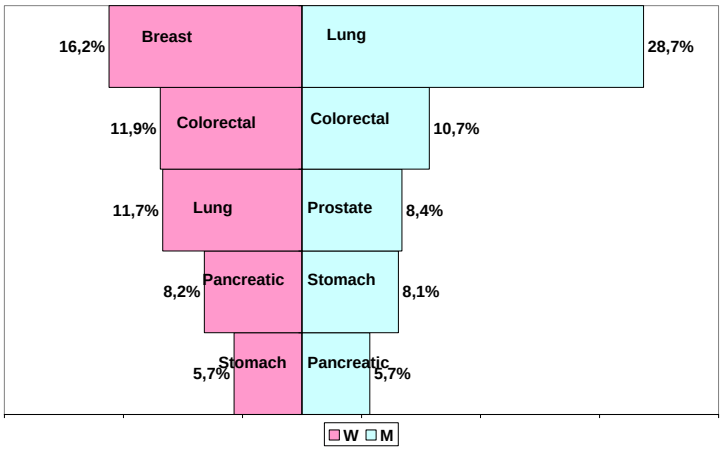
Figure 23. Five most frequently diagnosed cancer in Emilia-Romagna – 2007 – Men and Women (Emilia-Romagna Tumour Register)



The proportional mortality reported in Figure 24, shows regional data in line with the national data, except for:

- the pancreatic cancer for men that is the fifth most important cause of death in regional data while in the national data is not among the top five main cancer causes of death
- the pancreatic cancer and stomach cancer for women in regional data have a reversal in the ranking (4th e 5th most frequent cause of death) when compared to the national data.

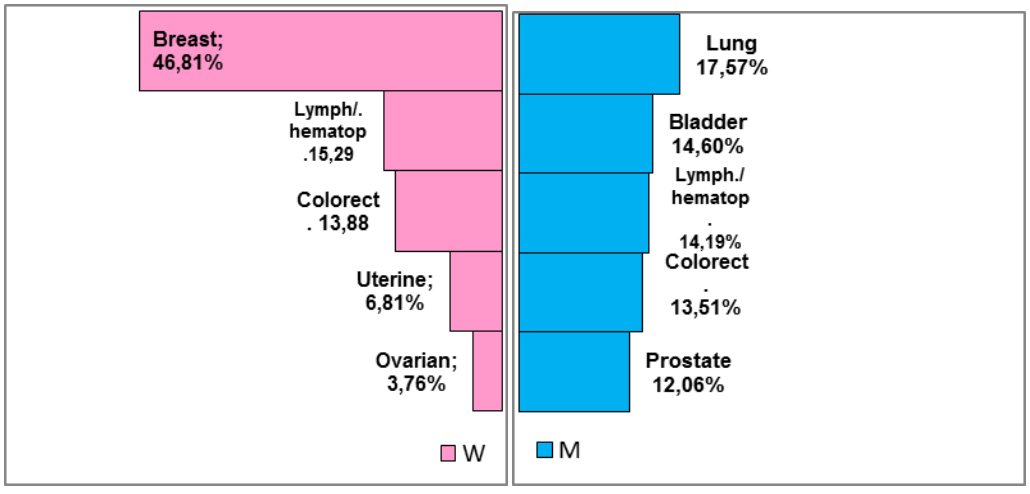
Figure 24. Five most important causes of cancer deaths Emilia-Romagna – 2007 – Men and Women (Emilia-Romagna Tumour Register)



In 2000, in Sicilia, 19,559 new cases of cancer (10,668 males and 10,668 females) and 9,051 deaths due to cancer-related diseases were detected. Considering the population, 4.5 new cases per 1,000 men and 3.5 per 1,000 women were detected (Sicilia Tumour Register 2000).

Figure 25 shows, by gender, the proportional incidence for main relevant cancers during 2000.

Figure 25. Five most frequently diagnosed cancer in Sicilia – 2000 – Men and Women (Sicilia Tumour Register - 2000)



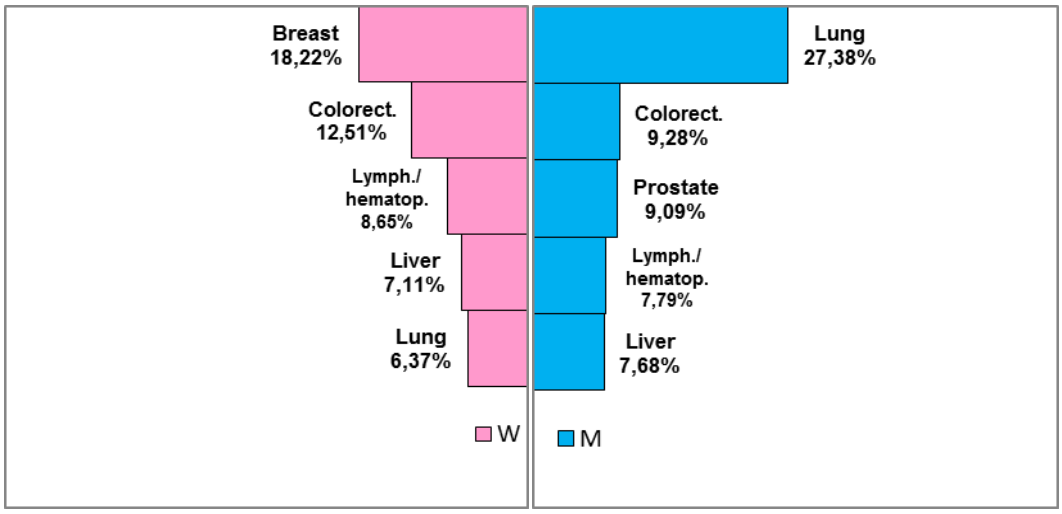
The proportional incidence, reported in Figure 25, shows several difference between the regional and the national data. Skin cancer in males and females, for instance, did not appear among the five most frequent cancer, while lymphatic and hematopoietic tumours in males and in females did appear.

Among men the proportional incidence of lung and bladder cancers were higher than national one, while the proportional incidence of prostate cancer is lower.

In women the proportional incidence of uterine and ovarian cancer were higher than national one, while the proportional incidence of lung and stomach cancer is lower.

Figure 26 shows, for males and females, the five most important causes of cancer deaths that emerged from the Sicilia Tumour Register (2000):

Figure 26. Five most important causes of cancer deaths in Sicilia – 2000 – Men and Women (Sicilia Tumour Register)

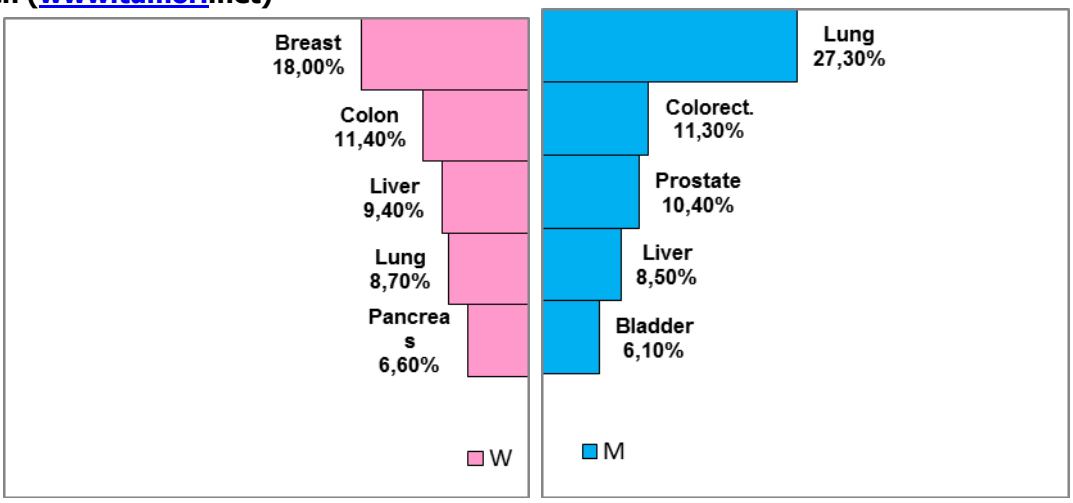


The proportional mortality reported in Figure 26, shows regional data in line with the national data, except for:

- the lymphatic and hematopoietic cancer is among the most important cause of death in regional data, while in the national data is not among the top five main cancer causes of death
- the stomach cancer, that in national data is the fourth important cause of death, did not appear in the top five cause death in Sicilia
- the skin cancer for women, that is the second most important cause of death in national data, is not among the top five main cancer causes of death in Sicilia

Figure 27 shows, for males and females, the five most important causes of cancer deaths in the years 2004 – 2011 (www.tumori.net) that emerged from the sito Tumori.net.

Figure 27. Five most important causes of cancer deaths in Sicilia – 2004-2011 – Men and Women (www.tumori.net)



In 2003-2006, in Provincia Autonoma di Trento (PAT), 12,555 new cases of cancer (6,701 males and 5,854 females, i.e. approx 1,675 and 1,463 cases per year, respectively, figure 28, 29) and about 5,710 (approx 1,428 per year) deaths due to cancer-related diseases were detected (figure 30,31). Considering the population (248,108 males and 258,922 females in 2006), approx. 7 new cases per 1,000 men and 6 per 1,000 women were detected (L'incidenza dei tumori maligni in provincia di Trento: anni 2003-2006).

Figure 28. Five most frequently diagnosed cancer in PAT – 2003 - 2006 – Males

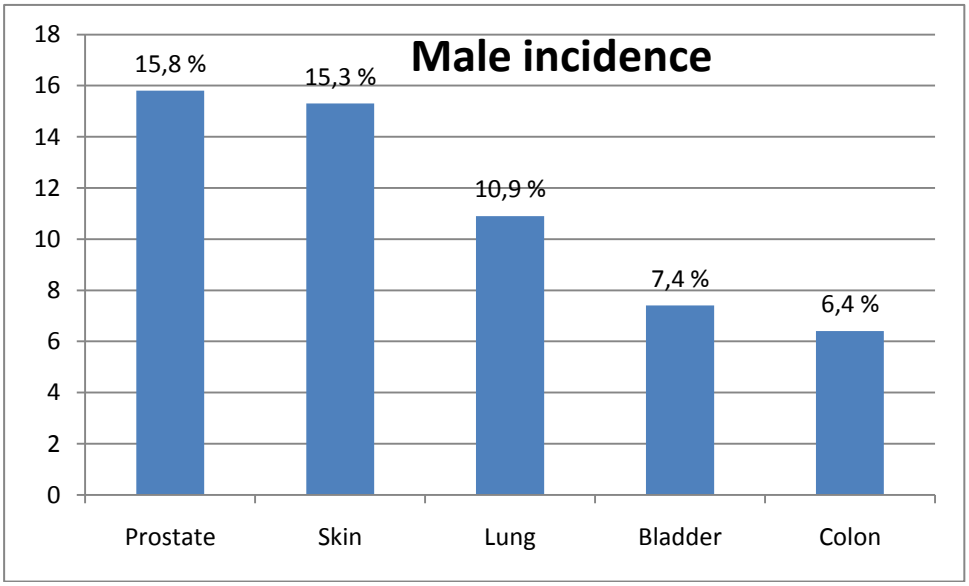


Figure 29. Five most frequently diagnosed cancer in PAT – 2003 - 2006 – Females

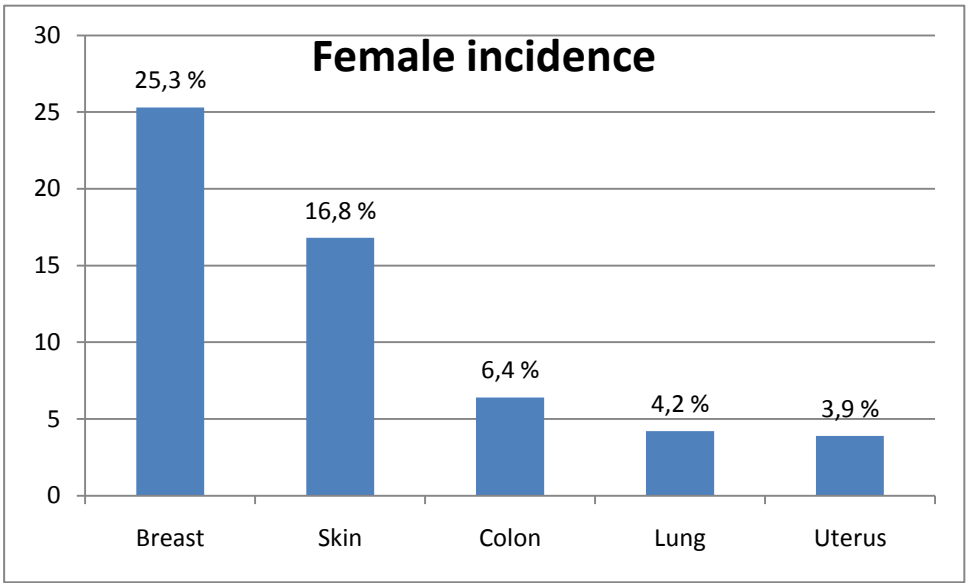


Figure 30. Five most important causes of cancer deaths PAT – 2003 - 2006 – Males

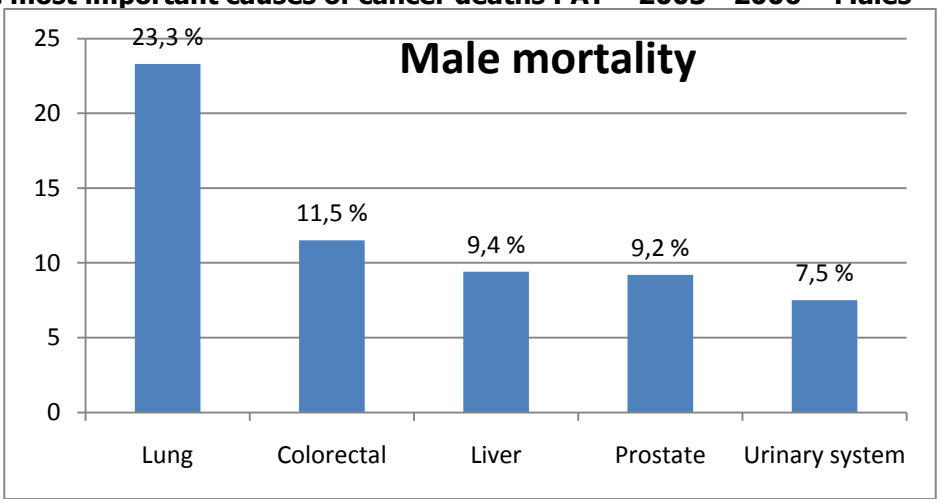
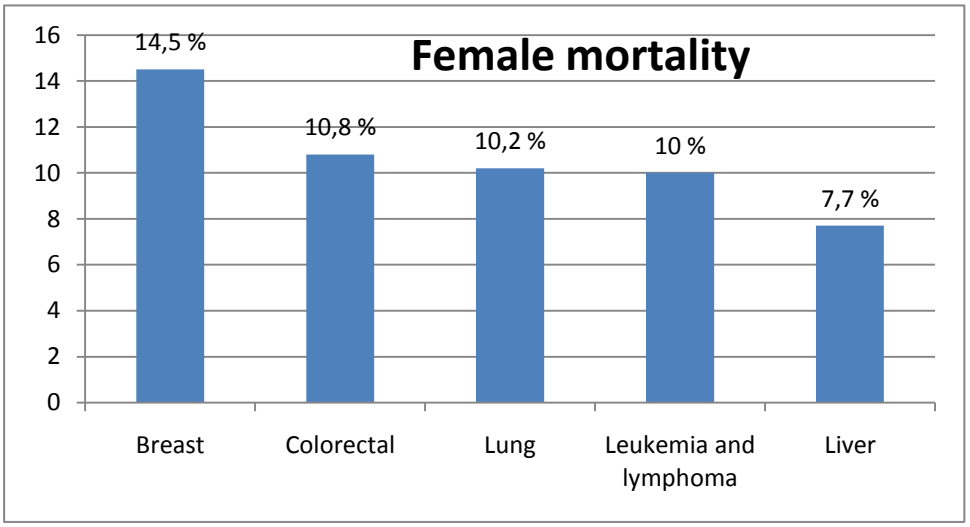


Figure 31. Five most important causes of cancer deaths PAT – 2003 - 2006 – Females



In Lazio, a Regional Cancer Register does not exist; however, a Register at provincial level is available for Latina and data for Lazio are estimated by the National Institute for Health in Italy.

In 2010, in Lazio Region, 26,011 new cases of cancer (13,561 males and 12,450 females) (excluding multiple tumours) and about 11,400 deaths due to cancer-related diseases were detected. Considering the population, 50 new cases per 10,000 men and 44 per 10,000 women were detected (Micheli A, Francisci S, Baili P, De Angelis R. Current cancer profiles of the Italian Regions. Tumori 93(4), 2007).

Figure 32 shows the proportional incidence for the most important causes of cancer in Lazio.

Figure 32. Five most important diagnosed cancer in Lazio – 2010 (2005 for prostate tumour) – Men and Women (estimates provided by the National Institute for Health)

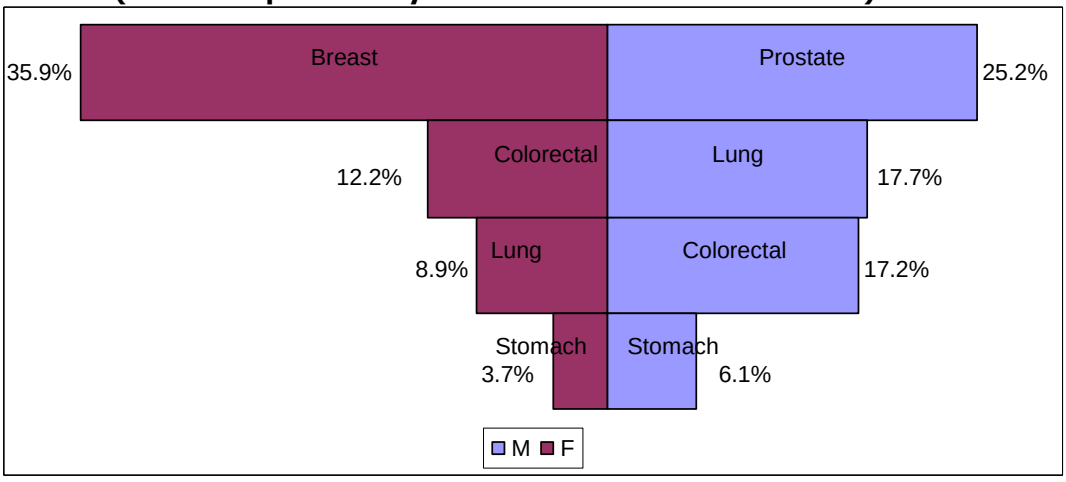
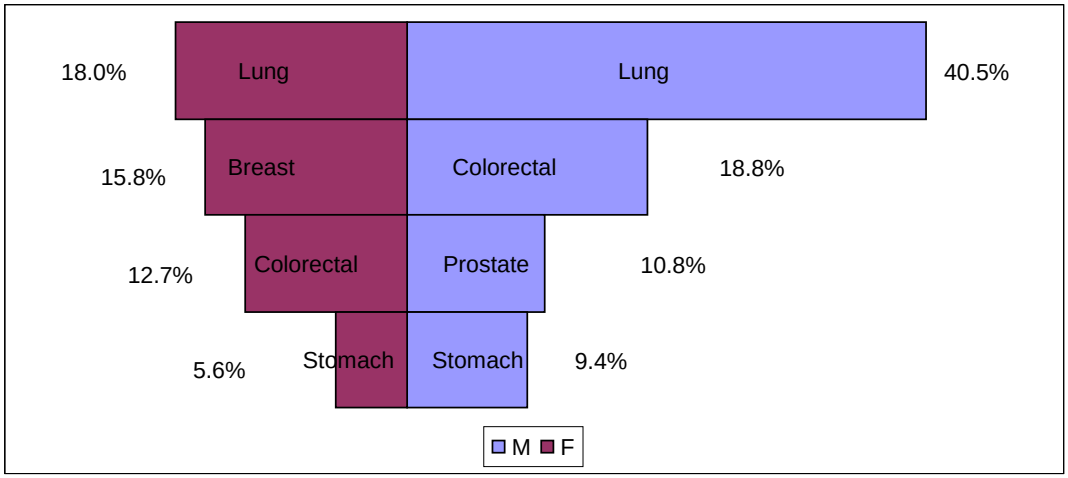


Figure 33 shows the proportional mortality for the most important causes of cancer deaths in Lazio.

Regional data are not completely comparable with those at national level because the source and the methodology applied to estimate incidences are different.

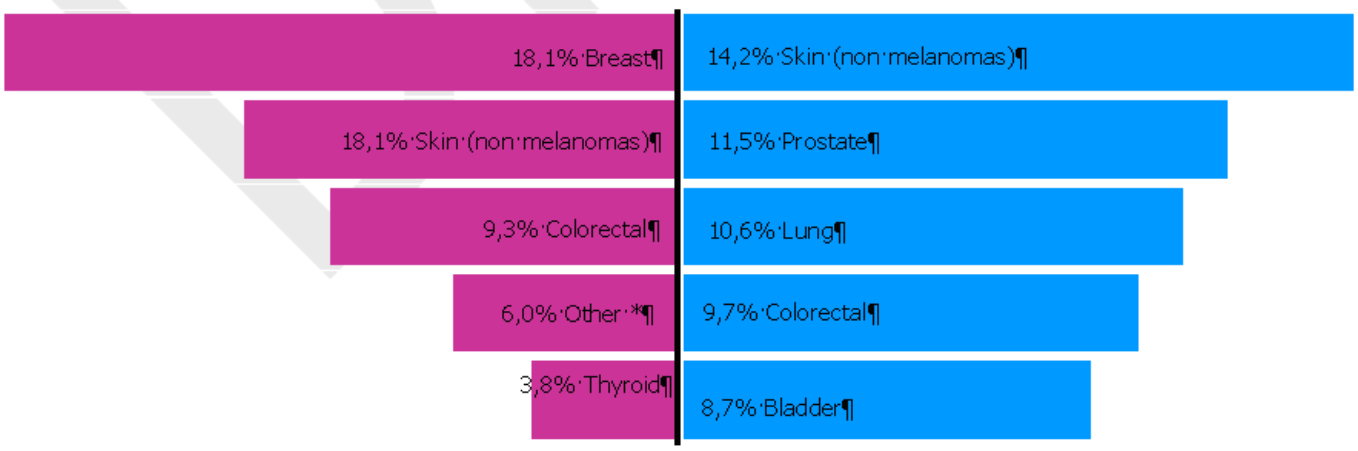
Figure 33. Five most important causes of cancer deaths Lazio – 2010 (2005 for prostate tumour) – Men and Women (estimates provided by the National Institute for Health)



The proportional incidence in Puglia region , as reported in Figure 34, when compared with national data, shows that:

- among women, thyroid cancers and other malignant tumours without indication of the site are more frequently diagnosed and breast, skin and colorectal cancers are less diagnosed;
- among men, even being skin cancer the most common diagnosis of cancer, it is recognised less frequently then at national level; prostate, lung and colorectal cancers are less frequent, and bladder tumours are more frequently diagnosed.

Figure 34. Five most frequently diagnosed cancer in Puglia – 2007 – Men and Women (Puglia Tumours Register)

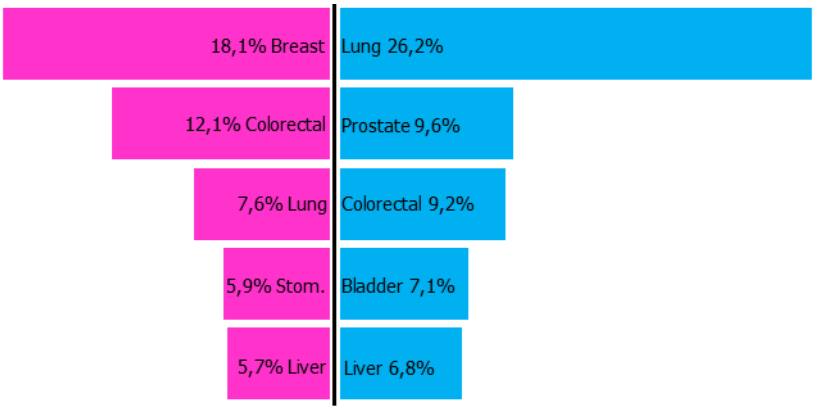


*other malignant tumours without indication of the site

The proportional mortality in Puglia region (Figure 35), when compared with national data, shows that:

- among women, lung and stomach cancers are less frequent causes of death while breast cancer is a more frequent cause of death;
- among men, lung and colorectal cancers are less frequent causes of death while prostate and liver cancers are more frequent causes of death;
- the liver cancer for women that is the fifth most important cause of death in regional data while in the national data is not among the top five main cancer causes of death;
- the bladder cancer for men that is the fourth most important cause of death in regional data while in the national data is not among the top five main cancer causes of death;
- the prostate and colorectal cancers for men in regional data have a reversal in the ranking (2nd and 3rd most frequent cause of death) when compared to the national data.

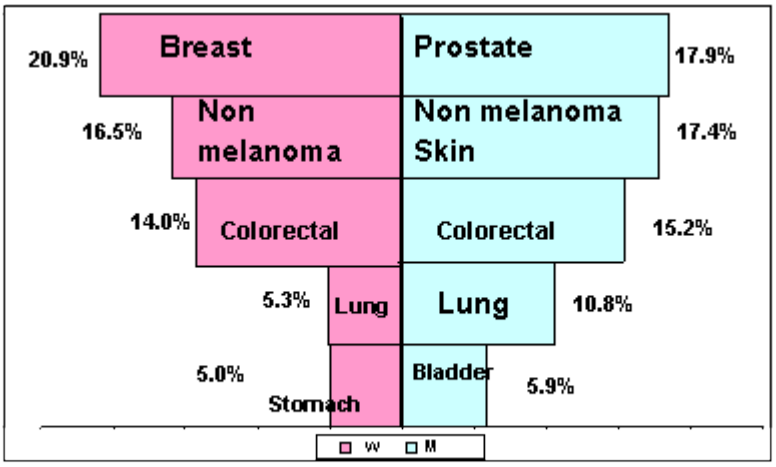
Figure 35. Five most important causes of cancer deaths Puglia – 2007 – Men and Women (Puglia Tumours Register)



In 2007, in Umbria, 6,715 new cases of cancer (3,874 males and 2,841 females) and about 2,719 deaths due to cancer-related diseases were detected. Considering the population (on 1 January 2008: 884,450, 427,042 males, 457,408 females), 9.1 new cases per 1,000 men and 6.2 per 1,000 women were detected (Umbrian Population Cancer Registry, 2007- http://www.rtup.unipg.it/).

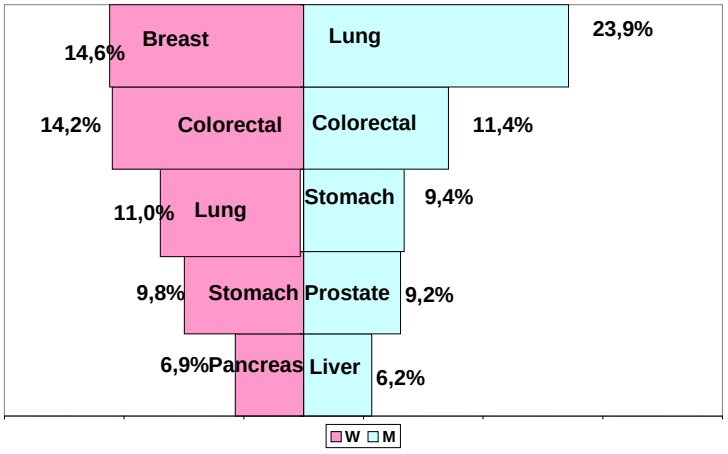
The proportional incidence, reported in Figure 36, shows some differences with the national data. In women, breast cancer has a lower proportion than national one (20.9% VS 24.9%), while colorectal cancer is slightly higher (14% VS 11.9). In men, the third most frequent is colorectal cancer (15.2% VS 12.0%) followed by lung cancer (10.8% VS 13.1%). The remaining proportional incidences are in line with national data.

Figure 36. Five most frequently diagnosed cancer in Umbria – 2007 – Men and Women (RTUP-Umbrian Population Cancer Registry)



The proportional mortality reported in Figure 37, shows regional data in line with the national data, except for: the stomach cancer and prostate cancer for men in regional data have a reversal in the ranking (3rd e 4th most frequent cause of death) when compared to the national data.

Figure 37. Five most important causes of cancer deaths in Umbria – 2007 – Men and Women (Umbrian Population Cancer Registry)



Objective

To estimate expected volumes of FDG-PET/CT scans and expected expenditure, on the basis of literature evidence on diagnostic accuracy of FDG-PET/CT and incidence rates registered for specific tumours.

Methods

Number of incident cases for the year 2010 are calculated on the basis of 2007 incidence rates drawn from the Tumour Register of the six regions. Male and female 2007 incident rates were applied to the 2010 or 2011(Provincia Autonoma di Trento) regional population - thus assuming that while size of population varies, incident rates remain constant..
Estimate incident cases for 2010 are calculated as follows:

2010 incidence : (2007 crude male incidence rate x 2010 male population +2007 crude female incidence rate x 2010 female population)/100 000 inhabitants

The example for colorectal cancer is reported below:

2010 colorectal incidence: (111,3*2,135,966+81,5 x 2,259,640)/100 000 inhabitants=4,219

Results from systematic review of literature on diagnostic accuracy of FDG-PET/CT in initial staging of patients diagnosed with cancer (chapter 4), are used as follows:

- when results from the available literature deem Positron Emission Tomography more accurate than conventional imaging, expected volumes of FDG-PET/CT scans are considered coincident with number of incident cases (e.g. staging of patients diagnosed with Non-Hodgkin Lymphoma).
- if FDG-PET/CT target population reported in the systematic literature represents a sub-population of incident cases, for example patients diagnosed with Non Small Cell Lung Cancer, the expected volumes of FDG-PET/CT scans correspond to the proportion of incident cases estimated to represent the target condition. Proportions are drawn from evidence-based guidelines and references are provided.

Table 27 reports the list of cancers for which FDG-PET/CT could be appropriate in the initial staging, following the results of the systematic review on diagnostic accuracy. Table 28 lists the tumours for which results for FDG-PET/CT's accuracy in staging are uncertain.

Table 27 . List of tumours for which results are in favour of FDG-PET/CT in N or M staging.

Neoplasm	Target population	Target condition
Head and neck cancer	All patients	N and M staging
Non Small Cell Lung Cancer	Patients with resectable cancer	N and M staging
Colorectal cancer	Patients with locally advanced cancer	M staging
Esophageal cancer	All patients	M staging
Hodgkin Lymphoma	All patients	Staging

Neoplasm	Target population	Target condition
Non-Hodgkin Lymphoma	All patients	Staging
Malignant Melanoma	Patients with locally advanced cancer	M staging

Table 28 . List of tumours for which results for FDG-PET/CT in N or M staging are uncertain.

Neoplasm	Target population	Target condition
Small Cell Lung Cancer	Patients with limited disease	Staging
Breast cancer	Patients with locally advanced cancer	M staging

Expected volumes of patients undergoing an FDG-PET/CT scan for initial staging have been calculated on the basis of incident cases , except for the following cancer:

- number of incident cases of Non Small Cell Lung Cancer has been estimated to represent 80%-85% of any lung cancer incident cases (ESMO 2010) and for the analysis the mean value (82,5%) was applied. The number of patients presenting at diagnosis with resectable cancer has been estimated to represent 25-30 % of Non Small Cell Lung Cancer (ACCP-a 2007) and for the analysis the mean value (27,5%) was applied.
- number of patients presenting at diagnosis with a locally advanced colorectal cancer has been estimated to represent 61% of colorectal incident cases (NICE 2004)
- number of patients presenting at diagnosis with a locally advanced melanoma cancer has been estimated to represent 15 % of melanoma cancer incident cases (NCCN 2012).
- number of incident cases of Small Cell Lung Cancer has been estimated to represent 15%-20% of lung incident cases (ESMO 2010) and for the analysis the mean value (17,5%) was applied. The number of patients presenting at diagnosis with a limited disease Small Cell Lung Cancer have been estimated to represent 30 % of Small Cell Lung Cancer incident cases (ACCP-b 2007).
- number of patients presenting at diagnosis with a locally advanced breast cancer has been estimated to represent 33 % of breast cancer incident cases (National Cancer Institute 2005-2009).

Expected expenditure for the Emilia-Romagna Health Service was calculated on the basis of expected FDG-PET/CT scans. Considering that outpatient tariffs related to ICD9-CM procedure codes are similar (1,127€ and 1,286€ for codes 92.11.6 and 92.11.7-92.18.6 respectively) and that more than 96% of outpatient FDG-PET/CT scans provided in Emilia-Romagna Region in 2010 were recorded as ICD9-CM procedure code 92.18.6, the tariff of 1,286€ has been applied. Sicilia region has applied the same tariff.

Expected expenditure for the Lazio Health Service was calculated on the basis of expected FDG-PET/CT scans. Considering that outpatient tariffs related to ICD9-CM procedure codes are similar (in Lazio 939€ and 1,071€ for codes 92.11.6 and 92.11.7-92.18.6 respectively) and that about than 98% of outpatient FDG-PET/CT scans provided in Lazio Region in 2010 were recorded as ICD9-CM procedure code 92.18.6, the tariff of 1,071.65€ has been applied.

Expected expenditure for the Puglia Health Service was calculated on the basis of expected FDG-PET/CT scans. Considering the outpatient tariffs related to ICD9-CM procedure codes (1,127€ and 1,286€ for codes 92.11.6 and 92.11.7-92.18.6 respectively) and that near 70% of outpatient FDG-PET/CT scans provided in Puglia Region in 2010 were recorded as ICD9-CM procedure code 92.18.6 (the other 30% was recorded as 92.11.6), a weighted tariff of 1,237.50€ has been applied.

Results

Table 29 reports the numbers of estimated incident cases in 2010 for each tumour for five of the six participant regions.

For Lazio region only partial data are available.

The table highlights incidence variability between Sicilia region, Emilia-Romagna and Puglia regions for all type of cancer. Sicilia region with a population of about 5 millions of inhabitants has a lower incidence than Emilia-Romagna (about 4 millions of inhabitants).

Puglia region with similar population of Emilia-Romagna has lower incidence. This should be due to a bias of the record system detection.

Table 29. Estimated incidence-2010 year (emilia-Romagna , Lazio, Provincia Autonoma Di Trento, Puglia)

	Incidence (estimate 2010)				
	Emilia-Romagna	Sicilia	Lazio	Provincia Autonoma di Trento	Puglia
Head & Neck cancer	735	712	-		
Oesophageal cancer	123	62	-	39	82
Stomach cancer	1,486	893	1,282	128	491
Colorectal cancer	4,219	2,722	3,851	346	1,747
Liver cancer	816	920	-	140	707
Pancreatic cancer	979	784	-	91	368
Lung cancer	3,351	2,228	3,516	255	1,661
Malignant Melanoma	812	292	-	57	256
Skin non melanoma	6,775	4,744	-	524	2,325
Breast cancer	3,864	2,566	4,470	387	1,858
Cervical cancer	176	235	-	75	120

Uterine cancer	678	569	-		507
Ovarian cancer	398	339	-	40	210
Other female genital cancer	127	104	-		
Prostate cancer	3,475	1,308	-	276	1,216
Testicular cancer	141	78	-	21	108
Kidney and urinary tract cancer	1,138	323	-	255	346
Bladder cancer	2,144	1,809	-		1,222
SNC	461	351	-	39	279
Thyroid cancer	1,103	316	-	54	522
Hodgkin's lymphoma	136	138	-	221	127
Non-Hodgkin's lymphoma	1,112	617	-		560
Myeloma cancer	441	347	-		196
Leukemia	690	2,085	-		33
Bone cancer	46	61	-	5	
Salivary gland cancer	50	75	-		
Laryngeal cancer	360	193	-		40
Kaposi sarcoma	68	44	-		89
Soft tissue cancer	134	95	-		45
Mesothelioma cancer	107	27	-		226
Gallbladder,Biliary cancer	312	383	-		412
Metastases	481	575	-		
Other unspecified cancer	356		-	215	934
All tumours	37,294	19,884	-	3,168	16,690

Emilia-Romagna Region (RER)

Table 30 reports estimated volumes of patients undergoing an FDG-PET/CT scan for initial staging of tumours for which FDG-PET/CT would be considered appropriate, while Table 31 reports estimated volumes for tumours for which results on FDG-PET/CT are still uncertain.

Table 30. Number of RER patients expected to undergo FDG-PET/CT for cancer staging: results in favour of FDG-PET/CT.

	Expected 2010 incidence based on 2007 rate			**Expected scans for neoplasm with evidence supporting FDG-PET/CT**	
	M	F	All	**Freq.**	**%**
Head & Neck cancer	572	177	735	**735**	**13**
Lung cancer - NSCLC	2,060	705	2,765	**760**	**14**
Colorectal cancer	2,377	1,842	4,219	**2,574**	**46**
Esophageal cancer	96	127	123	**123**	**2**
Hodgkin's lymphoma	68	68	136	**136**	**2**
Non-Hodgkin's lymphoma	592	520	1,112	**1,112**	**20**
Malignant Melanoma	376	436	812	**122**	**2**
Total				**5,562**	**100**

Table 31. Number of RER patients expected to undergo FDG-PET/CT for cancer staging: uncertain results on FDG-PET/CT's diagnostic accuracy.

	Expected 2010 incidence based on 2007 rate			**Expected scans for neoplasm with uncertain evidence on FDG-PET/CT**	
	M	F	All	**Freq.**	**%**
Lung Cancer SCLC	437	149	586	**176**	**12**
Breast cancer		3,864	3,864	**1,275**	**88**
Total				**1,451**	**100**

As Table 32 shows, FDG-PET/CT scans expenditure for tumours for which FDG-PET/CT would be considered appropriate amount to over 7 millions of euro each year. Taking into consideration also tumours with FDG-PET/CT results still uncertain, implies a further expenditure of 1.9 millions (Table 33).

Table 32. RER Expenditure on FDG-PET/CT for cancer staging: results in favour of FDG-PET/CT.

	Expected scans		**Expenditure** (Tariff: 1,286€)
	Freq.	**%**	**€**
Head & Neck cancer	735	13	**945,210**
Lung cancer - NSCLC	760	14	**977,360**
Colorectal cancer	2,574	46	**3,310,164**
Esophageal cancer	123	2	**158,178**
Hodgkin's lymphoma	136	2	**174,896**
Non-Hodgkin's lymphoma	1,112	20	**1,430,032**
Malignant Melanoma	122	2	**156,892**
Total	5,562	100	**7,152,732**

Table 33. RER Expenditure on FDG-PET/CT for cancer staging: uncertain results on FDG-PET/CT's diagnostic accuracy.

	Expected scans		**Expenditure** (Tariff: 1,286€)
	Freq.	**%**	**€**
Lung Cancer SCLC	176	12	**226,336**
Breast cancer	1,275	88	**1,639,650**
Total	1,451	100	**1,865,986**

Sicilia region (SR)

Table 34 reports estimated volumes of patients undergoing an FDG-PET/CT scan for initial staging of tumours for which FDG-PET/CT would be considered appropriate, while Table 35 reports estimated volumes for tumours for which results on FDG-PET/CT are still uncertain.

Table 34. Number of SR patients expected to undergo FDG-PET/CT for cancer staging: results in favour of FDG-PET/CT.

	Expected 2010 incidence based on 2000 rate	**Expected scans for neoplasm with evidence supporting FDG-PET/CT**	
	Male and Female	**Freq.**	**%**
Head & Neck cancer	712	712	19
Oesophageal cancer	62	62	2
Colorectal cancer	2,722	1,660	44
Lung cancer- NSCLC	1,838	505	14
Hodgkin's lymphoma	138	138	4
Non-Hodgkin's lymphoma	617	617	17
Malignant Melanoma	292	44	1
Total		3,738	100

Table 35. Number of SR patients expected to undergo FDG-PET/CT for cancer staging: uncertain results on FDG-PET/CT's diagnostic accuracy.

	Expected 2010 incidence based on 2000 rate	**Expected scans for neoplasm with uncertain evidence on FDG-PET/CT**	
	Male and Female	**Freq.**	**%**
Lung cancer - SCLC	390	117	12
Breast cancer	2,566	847	88
Total		964	100

As Table 36 shows, FDG-PET/CT scans expenditure for tumours for which FDG-PET/CT would be considered appropriate amount to over 4 millions of euro each year. Taking into consideration also tumours with FDG-PET/CT results still uncertain, implies a further expenditure of 1.2 millions (Table 37).

Table 36. SR Expenditure on FDG-PET/CT for cancer staging: results in favour of FDG-PET/CT.

	Expected scans		Expenditure (Tariff: 1,286€)
	Freq.	**%**	**€**
Head & Neck cancer	712	19	915,632
Oesophageal cancer	62	2	79,732
Colorectal cancer	1,660	44	2,134,760
Lung cancer- NSCLC	505	14	649,430
Hodgkin's lymphoma	138	4	177,468
Non-Hodgkin's lymphoma	617	17	793,462
Malignant Melanoma	44	1	56,584
Total	3,738	100	4,807,068

Table 37. SR Expenditure on FDG-PET/CT for cancer staging: uncertain results on FDG-PET/CT's diagnostic accuracy.

	Expected scans		Expenditure (Tariff: 1,286€)
	Freq.	**%**	**€**
Lung cancer - SCLC	117	12	150,462
Breast cancer	847	88	1,089,242
Total	964	100	1,239,704

Lazio region (LR)

Table 38 reports estimated volumes of patients undergoing an FDG-PET/CT scan for initial staging for Lung cancer – NSCLC and Colorectal cancer (other tumour specific incidence estimates not available) for which FDG-PET/CT would be considered appropriate, while Table 39 reports estimated volumes for tumours for which results on FDG-PET/CT are still uncertain.

Table 38. Number of LR patients expected to undergo FDG-PET/CT for cancer staging: results in favour of FDG-PET/CT.

	Estimated 2010 incidence rate			Expected scans for neoplasm with evidence supporting FDG-PET/CT	
	M	F	All	**Freq.**	**%**
Head & Neck cancer	-	-	-	-	-
Lung cancer - NSCLC	1,984	917	2,901	**798**	-
Colorectal cancer	2,327	1,524	3,851	**2,349**	-
Esophageal cancer	-	-	-	-	-
Hodgkin's lymphoma	-	-	-	-	-
Non-Hodgkin's lymphoma	-	-	-	-	-
Malignant Melanoma	-	-	-	-	-
Total	-	-	-	3,147	-

Table 39. Number of LR patients expected to undergo FDG-PET/CT for cancer staging: uncertain results on FDG-PET/CT's diagnostic accuracy.

	Estimated 2010 incidence rate			Expected scans for neoplasm with uncertain evidence on FDG-PET/CT	
	M	F	All	**Freq.**	**%**
Lung Cancer SCLC	421	194	615	**185**	**11.1**
Breast cancer	-	4,470	4,470	**1,475**	**88.9**
Total	421	4,664	5,085	**1,660**	**100**

As Table 40 shows, FDG-PET/CT scans expenditure for Lung cancer – NSCLC and Colorectal cancer (other tumour specific incidence estimates not available) for which FDG-PET/CT would be considered appropriate amount to over 3.3 millions of euro each year. In addition, the expenditure for those tumours without available incidence estimates should be considered. Taking into consideration also tumours with FDG-PET/CT results still uncertain, implies a further expenditure of almost 1.8 millions (Table 41).

Table 40. LR Expenditure on FDG-PET/CT for cancer staging: results only for Lung cancer – NSCLC and Colorectal cancer in favour of FDG-PET/CT.

	Expected scans		Expenditure (Tariff: 1,071.65€)
	Freq.	**%**	**€**
Head & Neck cancer	-	-	**-**
Lung cancer - NSCLC	798	-	**854,847**
Colorectal cancer	2,349	-	**2,517,424**
Esophageal cancer	-	-	**-**
Hodgkin's lymphoma	-	-	**-**
Non-Hodgkin's lymphoma	-	-	**-**
Malignant Melanoma	-	-	**-**
Total	3,147	-	**3,372,271**

Table 41. LR Expenditure on FDG-PET/CT for cancer staging: uncertain results on FDG-PET/CT's diagnostic accuracy.

	Expected scans		Expenditure (Tariff: 1,071.65€)
	Freq.	**%**	**€**
Lung Cancer SCLC	185	11.1	**197,816**
Breast cancer	1,475	88.9	**1,580,791**
Total	1,660	100	**1,778,607**

Puglia region (PR)

Table 42 reports estimated volumes of patients undergoing an FDG-PET/CT scan for initial staging of tumours for which FDG-PET/CT would be considered appropriate, while Table 43 reports estimated volumes for tumours for which results on FDG-PET/CT are still uncertain.

Table 42. Number of patients expected to undergo FDG-PET/CT for cancer staging: results in favour of FDG-PET/CT.

	Expected 2010 incidence based on 2007 rate			**Expected scans for neoplasm with evidence supporting FDG-PET/CT**	
	M	F	All	**Freq.**	**%**
Lung cancer - NSCLC	1,397	264	1,661	**377**	**17**
Colorectal cancer	1,029	718	1,747	**1,066**	**47**
Oesophageal cancer	70	12	82	**82**	**4**
Hodgkin's lymphoma	61	66	127	**127**	**6**
Non-Hodgkin's lymphoma	314	246	560	**560**	**25**
Malignant Melanoma	128	129	256	**38**	**2**
Total				**2,250**	**100**

Table 43. Number of patients expected to undergo FDG-PET/CT for cancer staging: uncertain results on FDG-PET/CT's diagnostic accuracy.

	Expected 2010 incidence based on 2007 rate			**Expected scans for neoplasm with uncertain evidence on FDG-PET/CT**	
	M	F	All	**Freq.**	**%**
Lung Cancer - SCLC	1,397	264	1,661	**87**	**13**
Breast cancer		1,833	1,833	**605**	**87**
Total				**692**	**100**

As Table 44 shows, FDG-PET/CT scans expenditure for tumours for which FDG-PET/CT would be considered appropriate amount to near 2.8 millions of euro each year. Taking into consideration also tumours with FDG-PET/CT results still uncertain, implies a further expenditure of near 0.9 millions (Table 45). Furthermore, the expenditure for those tumours without available incidence estimates (Head & Neck cancer) should be considered.

Table 44. Expenditure on FDG-PET/CT for cancer staging: results in favour of FDG-PET/CT.

	Expected scans		**Expenditure** (Tariff: 1,237.50€)
	Freq.	**%**	**€**
Lung cancer - NSCLC	377	17	**466,537.50**
Colorectal cancer	1,066	47	**1,319,175.00**
Esophageal cancer	82	4	**101,475.00**
Hodgkin's lymphoma	127	6	**157,162.50**
Non-Hodgkin's lymphoma	560	25	**693,000.00**
Malignant Melanoma	38	2	**47,025.00**
Total	2,250	100	**2,784,375.00**

Table 45. Expenditure on FDG-PET/CT for cancer staging: uncertain results on FDG-PET/CT's diagnostic accuracy.

	Expected scans		**Expenditure** (Tariff: 1,237.50€)
	Freq.	**%**	**€**
Lung Cancer - SCLC	87	13	**107,662.50**
Breast cancer	605	87	**748,687.50**
Total	692	100	**856,350.00**

Synthesis- Expected FDG-PET/CTscans and expenditure for cancer staging by region

Table 46 shows the expected PET/CT scans for cancer staging for 4 of the six participant regions. The comparison between the region is not possible because for 2 regions the data are not available and for Lazio region only partial data on cancer incident cases are available.

Table 46. Expected FDG-PET/CTscans and expenditure for cancer staging

Region	Expected scans for neoplasm with evidence supporting FDG-PET/CT	Expenditure for neoplasm with evidence supporting FDG-PET/CT (€)	Expected scans for neoplasm with uncertain evidence on FDG-PET/CT	Expenditure for neoplasm with uncertain evidence on FDG-PET/CT (€)
Emilia-Romagna	5,562	7,152,732	1,451	1,865,986
Sicilia	3,738	4,807,068	964	1,239,704
Provincia Autonoma di Trento				
Lazio	2,349*	3,372,271*	1,660	1,778,607
Puglia	2,250	2,784,375	692	856,350
Umbria				

* Only for lung cancer and colorectal cancer the data are available. This number underestimates the expected value.

Discussion

Assuming the use of FDG-PET/CT only in the clinical indications for which there is evidence in support of its diagnostic accuracy the expected volumes of FDG-PET/CT scans for patients undergoing initial staging for cancer is estimated to be for:

- Emilia-Romagna region: 5,562 scans corresponding to an expected expenditure of 7,152,732€. Should the use of FDG-PET/CT be extended to the clinical indications for which results on diagnostic accuracy are uncertain, expected volumes of scans would increase by 1,451, giving a total of 7,013 for Emilia-Romagna region. From the point of view of expenditure, adding uncertain clinical indications implies a growth in expenses of 1,865,986€, leading to a total of 9,018,718€;.
- Sicilia region: 3,738 scans corresponding to an expected expenditure of 4,807,068€. Should the use of FDG-PET/CT be extended to the clinical indications for which results on diagnostic accuracy are uncertain, expected volumes of scans would increase by 964, giving a total of 4,702 for Sicilia region. From the point of view of expenditure, adding uncertain clinical indications implies a growth in expenses of 1,239,704€ , leading to a total of 6,046,772€.
- Puglia region: 2,250 scans corresponding to an expected expenditure of 2,784,375€. Should the use of FDG-PET/CT be extended to the clinical indications for which results on diagnostic accuracy are uncertain, expected volumes of scans would increase by 692, giving a total of 2,942 for Puglia region. From the point of view of expenditure, adding uncertain clinical indications implies a growth in expenses of 1 856,350€ , leading to a total of 2,870,010€.

- Lazio region: only the expected volumes of FDG-PET/CT scans for patients for the staging of Lung cancer was quantify – NSCLC and Colorectal cancer in favour of FDG-PET/CT is estimated to be 3,147, corresponding to an expected expenditure of 3,372,271€.Should the use of FDG-PET/CT be extended to the clinical indications for which results on diagnostic accuracy are uncertain, expected volumes of scans would increase by 1 660, giving a total of 4,807 for Lazio region (considering only Lung cancer – NSCLC and Colorectal cancer in favour of FDG-PET/CT, and Lung Cancer SCLC and Breast cancer with uncertain results on FDG-PET/CT's diagnostic accuracy). From the point of view of expenditure, adding uncertain clinical indications implies a growth in expenses of 1,778,607€, leading to a total of 5,150,878€.

Nevertheless, effect on expenses should not be interpreted as budget impact due to the different role of FDG-PET/CT in the diagnostic pathways of the various tumours, sometimes representing a new test some others provided in substitution of conventional imaging or of further more invasive diagnostic procedures. This means that for a structured budget impact analysis a detailed diagnostic pathway for each tumours is needed.
Finally, these estimates should not be considered to represent the overall expected volumes of FDG-PET/CT scans, as there are other clinical indications reported in the literature, such as re-staging or evaluation of response to therapy, which have not been considered in the present report and in this analysis.

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6 Systematic review of economic evaluation and economic aspect of PET-CT for cancer staging

We did not carry out a formal economic evaluation. We updated the systematic review [Paone, 2011] carried out by Agenas in 2011 of the economic evaluation on the use of PET-CT for cancer staging. This systematic review produced disappointing results. The quantity and quality of the evidence presented in the literature was low. We found only two studies [Heinrich, 2005 and Schreyogg, 2010] that satisfied the inclusion criteria and they were of medium/low methodological quality. The studies identified did not indicate a clear methodology for the collection of the cost data in the study. The unit costs were not indicated, nor were the temporal horizon and discounting rates reported. Nor indeed is there explanation of the methods of estimating the QALY and even the sensitivity analyses appears incomplete. Clarity of reporting and good methods are fundamental for an accurate economic evaluation.

This absence applied to a high economic impact technology such as PET-CT cannot be justified, as it prevents decision makers from basing their decision on clear evidence. There appears to be a consolidated practice of translating the results of diagnostic accuracy and efficacy of PET to PET-CT. In the included studies the follow-up was of insufficient length to enable evaluation of the real impact of the technology on patient prognosis. In the study where the cost-benefit was correlated to the surgical procedures avoided thanks to utilisation of PET-CT, the economic evaluation failed to consider the costs related to palliative care. As a result the potential economic savings are not properly highlighted. Finally the choice of comparator does not appear to be fully justified, as it fails to consider all the variables in the oncological diagnostic-therapeutic process (the clinical condition of the patient, the economic aspects or specific health system etc.).

6.1 Methods

We searched on the Italian and international scientific literature to identify and describe the economic evaluations of PET-CT for cancer staging.

Literature search

We carried out a search of the literature on the following databases: MEDLINE, EMBASE, Cochrane Library. Details on the research strategy are provided at Appendix 21.

Inclusion criteria

The inclusion criteria were: economic evaluations based on all types of economic analysis (CEA, CUA, BUA; CCA; CMA) comparing the use of PET-CT with other methods for cancer staging, in Italian and English, from March 2011 to date.

Study selection

We used ProCite programme (version 5 for MS Windows) to manage the studies. The selection of the studies to be included followed these steps:

1. exclusion on the basis of title and abstract;
2. full text retrieving of the potentially iteresting studies;
3. reading of the selected articles and application of the inclusion criteria.

Data extraction

Data extraction from the selected studies was carried out using an extraction sheet. Extraction was performed in double by two independent reviewers (TJ and SP). The results of the extraction were compared and differences discussed. Resolution of the differences in the extraction was achieved by mutual agreement.

Methodological quality assessment

The assessment of the methodological quality was carried out using the checklist for economic evaluations of health programmes [Drummond 1997].

Analysis and synthesis

Studies were analysed and synthetised using a tabulation constructed on the basis of the data extracted sheet. No quantitative analysis was performed as the results of the review did not allow this.

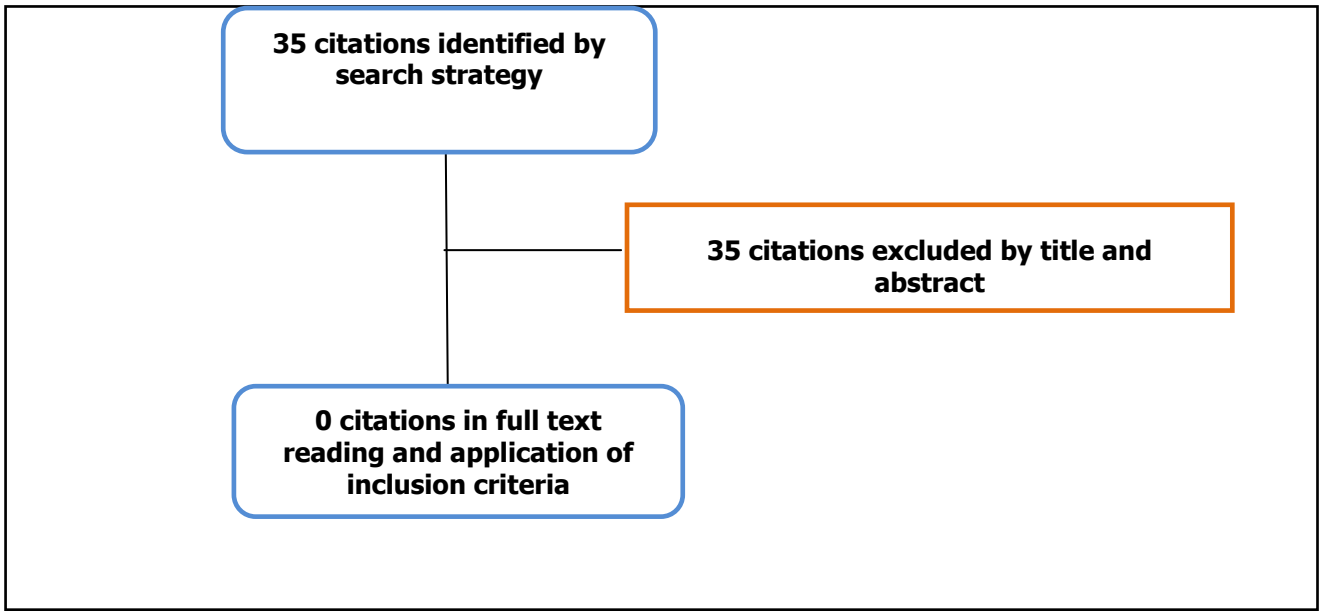
Interpretation of results

Interpretation of the studies' results was carried out in terms of numerosity, quality and consistency.

6.2 Results

The search strategy identified 35 bibliographic items. Using the ProCite bibliography management programme, we read all the titles and abstracts selected and all were excluded. Figure 1 shows the flow diagram of included studies. Appendix 9 provides a list of the included and excluded studies.

Figure 1. Flow diagram of economic evaluation of PET-CT



6.3 Conclusions

We did not carry out a Badget Impact Analysis of PET-CT for cancer staging. This is due to the fact that the systematic review of diagnostic accuracy occupied most of the time of the working group. However in the context analysis (Chapter 5) Italian regions participating in the report estimate expected volumes of FDG-PET/CT scans and expected expenditure. For this reason we considered only the evidence of economic studies from the published literature, updating the systematic review of the literature conducted by Agenas on PET-CT [Paone, 2011]. As we concluded in this review, the methodological aspects of systematic reviews of economic studies are not always clear and explicit. Namely what seems not to be clear is the link between a specific economic evaluation and the use of the clinical data on the efficacy that spread from the systematic review of the clinical studies related to the technology at stake. The rules for production of systematic reviews of clinical efficacy do not necessarily apply to economics. This preliminary impression (subsequently confirmed by our review) led to the need to approach the systematic review of the economics of PET-CT with a preliminary methodological investigative work, to deal with the uncertainty. We attempted to answer two questions: which methods form the basis for the production of a manual on the conduction of systematic reviews of economic studies? How are systematic reviews conducted within HTA reports? To answer the first question, we carried out an analysis on the manuals produced by HTA agencies adhering to INAHTA. Of the 26 manuals available, only 5 contained information about systematic reviews of economic data. In addition to those 5 manuals, we also considered the Cochrane manual for the production of systematic reviews. None of these texts contained information on the methodology utilised for the production of the manual, nor on the reasons underlying the choice of paths recommended. The manuals are substantially limited to indicating a path and providing a procedural guide to the conduction of systematic reviews. As to the second question, the reading of the HTA reports showed a limited use of the results of the systematic reviews of the economic evaluations. This means that when performing their own economic evaluations many HTA researchers ended up by NOT using the data/results of the systematic review of economic evaluations performed. The use of context specific economic data extracted from the selected studies in one's own economic evaluations appears to be highly problematic. Economic evaluations are closely linked to the context in which the data is produced and their results are not easly generalisable. This is probably due to the absence of an agreed methodology for this specific kind of systematic reviews.

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7. Discussion

(See also Chapter 4, paragraph 4).

PET/CT is a potentially important and very expensive imaging procedure. Its importance is reflected in the huge amount of detailed work in the report and in previous high quality reports which we based our update on.

The potential advantages of using PET/CT are clear. Better, timely diagnosis and assessment of nature and spread of the neoplasia should (if treatments effective and tolerable) achieve gains in quality and quantity of life for those unfortunate enough to have one of the basket of tumors in the review.

For some important cancers such as Hodgkin's lymphoma, non-Hodgkin's lymphoma, NSCC and head and neck cancer the evidence is promising enough to allow us to consider its use appropriate.

For some cancers such as brain tumor, PET/CT has clear technical limits which will probably never be overcome.

Our choice of tracer (FDG) virtually excluded other very important tumors such as prostate cancer in which FDG is a very poor second-best tracer to choline.

In other cases of very important pathologies such as cervical cancer breast cancer and mesothelioma the story is slightly different. Lack of interest or attention to the problem coupled sometimes with poor methods and reporting have impeded our capability for appropriateness assessment. This is not a good thing and should be urgently addressed by generation of good quality evidence following carefully designed and ethically approved protocols. Our findings should provide the basis for the preparation recommendation for approapriate clinical use of FDG PET/CT with an emphasis to linking its use to specific therapeutic options and prespecified outcomes. However good quality research is still neeed for the preparation of ethical clinical recommendations for its use.

8. Recommendations

We recommend that

Evidence for the effects of PET/CT be sought following ethical protocols for cancers which have so far not been assessed: breast, cervix, kidney, mesothelioma, pancreas, gastric adenocarcinoma, bladder, uterine, testicular and penile cancers.

Recommendations for the clinical use of FDG PET/CT be linked to its clinical use and predetermined outcomes which the operators want to achieve.

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10. Competing interests declaration

The authors declare that they will not receive either benefits or harms from the publication of this report. None of the authors have or have held shares, consultancies or personal relationships with any of the producers of the devices assessed in this document.