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RegioneEmilia-Romagna

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA

Criteria for appropriate use of FDG-PET in esophageal cancer

ORIentamenti 4

Osservatorio regionale per l'innovazione

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List of abbreviations

AIOM	Associazione italiana oncologia medica
ASSR	Agenzia sanitaria e sociale regionale
CDSR	Cochrane database of systematic reviews
CCT	controlled clinical trial
CENTRAL	Central register of controlled trials - the Cochrane Library
CRD	Centre for Reviews and Dissemination
CT	computed tomography
CTV	clinical target volume
DARE	database of abstracts of reviews of effects
ESMO	European Society of Medical Oncology
EUS	endoscopic ultrasonography
FDG	fluoro-deoxyglucose
FN	false negatives
FP	false positives
GVT	gross target volume
LR	likelihood ratio
MA	meta-analysis
MRI	magnetic resonance imaging
NICE	National Institute of Clinical Excellence
PET	positron emission tomography
PVT	planned target volume
RCT	randomized controlled trial
RER	Regione Emilia-Romagna
RT	radiotherapy
SIGN	Scottish Intercollegiate Guidelines Network
SR	systematic review
TN	true negatives
TP	true positives
US	ultrasonography

Sintesi dei risultati

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

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

- stadiazione N di pazienti con tumore primitivo dell'esofago - Incerto (livello di evidenza: molto basso)
- stadiazione M di pazienti con tumore primitivo dell'esofago - Appropriato (livello di evidenza: moderato)
- definizione del *target volume* nel trattamento radiante con intento curativo - Inappropriato (livello di evidenza: molto basso)
- valutazione della risposta precoce alla terapia neoadiuvante - Inappropriato (livello di evidenza: basso)
- valutazione della risposta alla terapia neoadiuvante al termine del trattamento - Incerto (livello di evidenza: molto basso)
- *follow up* di pazienti con nessun sospetto di recidiva - Inappropriato (livello di evidenza: molto basso)
- diagnosi e stadiazione di sospetta recidiva a distanza - Incerto (livello di evidenza: molto basso)

STADIAZIONE N DI PAZIENTI CON TUMORE PRIMITIVO DELL'ESOFAGO - INCERTO

Il panel ha raggiunto l'accordo nel giudicare incerto l'uso della FDG-PET, in sostituzione dell'ecografia endoscopica (*endoscopic ultrasonography* - EUS), nella stadiazione dei linfonodi regionali in pazienti con tumore dell'esofago.

Il livello di evidenza dell'accuratezza diagnostica della FDG-PET è risultato molto basso, a causa dell'eterogeneità delle stime di sensibilità e specificità.

Tutti gli esiti, correlati a una corretta selezione dei pazienti rispetto alla chemio-radioterapia neoadiuvante, sono stati considerati importanti (mediana del punteggio 6). Data l'alta probabilità pre-test di avere linfonodi positivi nei pazienti con tumore primitivo dell'esofago, il panel ha ritenuto auspicabile l'applicazione di un test meno invasivo rispetto all'EUS. Tuttavia, l'incertezza sull'accuratezza diagnostica della FDG-PET ha indotto il panel a emettere un giudizio molto prudente riguardo il ruolo della FDG-PET nell'indirizzare le opzioni terapeutiche successive.

STADIAZIONE M DI PAZIENTI CON TUMORE PRIMITIVO LOCALMENTE AVANZATO DELL'ESOFAGO - APPROPRIATO

Il panel ha raggiunto l'accordo alla prima votazione nel giudicare appropriato l'uso della FDG-PET per la stadiazione delle metastasi a distanza nei pazienti con tumore dell'esofago localmente avanzato, con lo scopo di indirizzare le successive scelte terapeutiche.

Il livello di evidenza dell'accuratezza diagnostica della FDG-PET è risultato moderato, e la prestazione della FDG-PET è migliore rispetto a quella della TC. Tuttavia il panel non suggerisce una sostituzione della TC da parte della FDG-PET ma ribadisce che debba essere tenuta in considerazione la migliore accuratezza diagnostica di quest'ultima. Il panel ha invece fortemente suggerito che, nel caso di utilizzo di una FDG-PET/TC, venga pianificata una TC diagnostica con contrasto e che venga organizzata una lettura congiunta dei risultati tra radiologo e medico nucleare.

Le conseguenze per i veri positivi - correttamente stadiati a un livello superiore e indirizzati in maniera appropriata al trattamento palliativo - e per i falsi positivi - la incorretta stadiazione a un livello superiore e la rinuncia a un trattamento chirurgico con intento curativo - hanno ottenuto un punteggio mediano di 8. Gli esiti per i veri e falsi negativi hanno ottenuto un punteggio mediano di 7. Di conseguenza tutti e quattro gli esiti sono stati considerati "critici" da parte del panel.

DEFINIZIONE DEL *TARGET VOLUME* NEL TRATTAMENTO RADIANTE CON INTENTO CURATIVO - INAPPROPRIATO

Dopo un forte disaccordo iniziale - con i singoli punteggi distribuiti in tutte le categorie di appropriato, incerto e inappropriato - il panel ha raggiunto l'accordo nel giudicare inappropriato l'uso della FDG-PET per la definizione del *target volume* nel trattamento radiante con intento curativo.

Sul ruolo della FDG-PET nella definizione del campo da irradiare sono stati trovati dati insufficienti (*sparse*). Dato lo scopo e la quantità di dose radiante generalmente erogata, il panel non ha ritenuto necessaria una più accurata definizione del campo rispetto a quella ottenuta con la diagnostica per immagini attualmente disponibile.

Il panel ha evidenziato il fatto che, dato l'uso appropriato della FDG-PET per la stadiazione M dei pazienti con tumore dell'esofago, l'immagine ottenuta a tale scopo può essere utilizzata anche per supportare la stadiazione N o la definizione del campo da irradiare. Tuttavia questi dati vanno interpretati con molta cautela e le decisioni non possono essere basate solo su di essi.

VALUTAZIONE DELLA RISPOSTA PRECOCE ALLA TERAPIA NEOADIUVANTE - INAPPROPRIATO

Dopo un forte disaccordo iniziale - con i singoli punteggi distribuiti in tutte le categorie di appropriato, incerto e inappropriato - il panel ha raggiunto l'accordo nel giudicare inappropriato l'uso della FDG-PET per la valutazione della risposta precoce alla terapia neoadiuvante.

Il livello di evidenza dell'accuratezza diagnostica della FDG-PET è risultato basso a causa della eterogeneità delle stime di sensibilità (comprese tra 44 e 100%).

Dato che la percentuale di pazienti che rispondono alla chemio-radioterapia neoadiuvante è attorno al 43%, il panel ha giudicato "critici" gli esiti correlati alla possibile corretta o scorretta sospensione del trattamento, con un punteggio maggiore per i pazienti falsi *non responder* (mediana del punteggio 8, *range* 2-9). Le conseguenze per i falsi *responder* - che completano un trattamento inefficace - sono state considerate meno importanti (mediana del punteggio 5, *range* 2-9).

Nonostante sia sentita la necessità di un test che distingua correttamente i pazienti *responder* da quelli *non responder*, il panel ha giudicato l'accuratezza della FDG-PET e il possibile danno derivato da una scorretta sospensione di un trattamento efficace maggiore rispetto ai possibili benefici ottenuti dall'interruzione di un trattamento inefficace.

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

In entrambe le votazioni è stato registrato disaccordo tra i membri del panel, con i singoli punteggi distribuiti in tutte le categorie alla prima votazione e compresi tra incerto e inappropriato alla seconda votazione. Pertanto l'uso della FDG-PET in aggiunta alla TC nella valutazione della risposta alla terapia neoadiuvante al termine del trattamento, allo scopo di decidere tra trattamento curativo o palliativo, è risultato incerto per disaccordo.

Il livello di evidenza dell'accuratezza diagnostica della FDG-PET è risultato molto basso, a causa della eterogeneità sia della sensibilità che della specificità.

Gli esiti per i pazienti che risultano *responder* alla terapia - veri e falsi *responder* - e per i falsi *non responder* sono stati giudicati "critici" (mediana del punteggio pari a 7), mentre gli esiti per i veri *non responder* sono stati considerati "importanti".

FOLLOW UP DI PAZIENTI CON NESSUN SOSPETTO DI RECIDIVA - INAPPROPRIATO

Dopo un iniziale leggero disaccordo tra giudizio inappropriato e incerto, il panel ha raggiunto l'accordo nel giudicare inappropriato l'uso della FDG-PET nel *follow up* dei pazienti con nessun sospetto di recidiva.

Il livello di evidenza dell'accuratezza diagnostica della FDG-PET è risultato molto basso, in quanto basato su tre soli studi di bassa qualità metodologica.

Gli esiti per i pazienti con recidiva - veri positivi e falsi negativi - così come gli esiti per i pazienti correttamente diagnosticati come negativi sono stati giudicati "importanti" (mediana del punteggio pari a 4). Un punteggio lievemente superiore (mediana 6, *range* 1-9) è stato assegnato all'esito dei pazienti incorrettamente giudicati positivi per metastasi a distanza, a causa del successivo inutile carico di ansia e di stress provocati da una diagnosi errata.

DIAGNOSI E STADIAZIONE DI SOSPETTA RECIDIVA A DISTANZA - INCERTO

È stato registrato un disaccordo tra i membri del panel in entrambe le votazioni, con i singoli punteggi compresi tra le categorie di incerto e appropriato. L'uso della FDG-PET come test aggiuntivo per la diagnosi e lo *staging* della recidiva a distanza nei pazienti con sospetto di recidiva o con risultato incerto alla diagnostica per immagini convenzionale è quindi risultato incerto per disaccordo.

Il livello di evidenza dell'accuratezza diagnostica della FDG-PET è risultato molto basso, in quanto basato su un solo studio con pochi pazienti.

Gli esiti per i veri e falsi positivi, così come per i falsi negativi, sono stati considerati "critici" (mediana del punteggio pari a 7). Per i pazienti correttamente risultati negativi gli esiti sono stati giudicati importanti (mediana del punteggio pari a 6).

Summary of results

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

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

- N staging of primary esophageal cancer - Uncertain (level of evidence: very low)
- M staging of primary esophageal cancer - Appropriate (level of evidence: moderate)
- target volume definition of curative radiation treatment - Inappropriate (level of evidence: very low)
- evaluation of early response to neoadjuvant therapy - Inappropriate (level of evidence: low)
- evaluation of response to neoadjuvant therapy at the end of treatment - Uncertain (level of evidence: very low)
- follow up in patients with no suspicion of recurrence - Inappropriate (level of evidence: very low)
- diagnosis and staging of suspect distant recurrence - Uncertain (level of evidence: very low)

N STAGING OF PRIMARY ESOPHAGEAL CANCER - UNCERTAIN

The panel agreed to judge as uncertain the use of FDG-PET in staging patients with esophageal cancer for regional lymph nodes, in replacement of endoscopic ultrasonography (EUS).

The level of evidence for diagnostic accuracy of FDG-PET was very low, with heterogeneous estimates for both sensitivity and specificity.

All outcomes, related to the correct selection of patients eligible for neoadjuvant chemoradiation therapy were considered "important" (median score 6). A less invasive test was also deemed highly desirable, given the high pre-test probability of patients diagnosed for primary esophageal cancer having positive lymph node. However the uncertainty on the diagnostic accuracy of FDG-PET made the panel very cautious in suggesting the use of FDG-PET results to direct therapeutic options.

M STAGING OF PRIMARY ESOPHAGEAL CANCER - APPROPRIATE

The panel agreed at the first round in rating as appropriate the use of FDG-PET in staging patients with esophageal cancer for distant metastasis, in order to decide on subsequent appropriate therapeutic approach.

The level of evidence for diagnostic accuracy of FDG-PET was moderate, with FDG-PET performing better than CT.

However the panel did not suggest that FDG-PET should replace CT, but that its higher accuracy in detecting distant metastases should be taken into account. Rather, it was strongly suggested that when using FDG-PET/CT scanners, a diagnostic CT with contrast should be planned and joint results readings between radiologists and nuclear physicians arranged.

The consequences for true positives - correct upstage and appropriate palliative treatment - and for false positives - incorrect upstage and denial of surgical curative treatment - received a median score of 8. Outcomes for true and false negatives obtained a median score of 7, meaning that all four outcomes were considered "critical" by the panel.

TARGET VOLUME DEFINITION OF CURATIVE RADIATION TREATMENT - INAPPROPRIATE

After an initial strong disagreement, with ratings falling in all regions of appropriateness, uncertainty and inappropriateness, the panel reached an agreement in judging the use of FDG-PET for the field definition of radiation treatment as inappropriate.

Only sparse data evaluating diagnostic accuracy of FDG-PET in the target volume definition were found, and given the scope and dose delivery of the radiation treatment, the panel expressed no particular need for more accurate field definition than that conveyed by available imaging.

It was highlighted by the panel that having judged as appropriate the use of FDG-PET for M staging of patients diagnosed with esophageal cancer, available FDG-PET images can be examined, alongside other test results, in support of N staging or of radiation field definition. However, great caution should be placed in interpreting these data and decisions should not rely solely on them.

EVALUATION OF EARLY RESPONSE TO NEOADJUVANT THERAPY - INAPPROPRIATE

After an initial strong disagreement, with ratings falling in all regions of appropriateness, uncertainty and inappropriateness, the panel reached an agreement in judging the use of FDG-PET for the evaluation of early response to neoadjuvant therapy as inappropriate.

The level of evidence for diagnostic accuracy of FDG-PET was low, due also to the heterogeneity of estimates for sensitivity (ranging from 44 to 100%).

Given that the proportion of patients responding to neoadjuvant chemoradiation is around 43%, the panel voted "critical" the outcomes related to the possibility of correctly or incorrectly suspending the treatment, with a higher score of importance for the patients resulting false non responders (median score 8; range 2-9). Consequences for

false responders - completing ineffective therapy - were considered less important (median score 5; range 2-9). Though expressing the need for a test that could correctly discriminate responders from non responders, given the low accuracy of FDG-PET, the panel judged the accuracy of FDG-PET as insufficient and the risk of incorrectly suspending an effective treatment higher than the possible benefits of interrupting an ineffective one.

EVALUATION OF RESPONSE TO NEOADJUVANT THERAPY AT THE END OF TREATMENT - UNCERTAIN

A disagreement among panelists was registered in both rounds of voting, with ratings falling in all three regions in the first round, and ratings falling within the uncertain and inappropriate regions in the second round. The use of FDG-PET, in addition to CT, in the evaluation of response to neoadjuvant therapy at the end of treatment, in order to decide between curative or palliative therapeutic course of action, resulted as uncertain due to disagreement.

The level of evidence for diagnostic accuracy was very low, with heterogeneity for both sensitivity and specificity. Outcomes for patients testing as responders - true and false responders - and for false non responders were voted "critical" (median score 7), while outcomes for true non responders were considered "important".

FOLLOW UP IN PATIENTS WITH NO SUSPICION OF RECURRENCE - INAPPROPRIATE

After an initial slight disagreement between inappropriate and uncertain, the panel agreed to judge as inappropriate the use of FDG-PET for patients in follow up with no suspicion of recurrence.

Level of evidence for diagnostic accuracy of FDG-PET in follow up was very low and coming from three primary studies of low methodological quality. Outcomes for patients with recurrence - true positives and false negatives, as well as outcomes for patients correctly diagnosed as negatives were voted "important" (median score 4). A slightly higher score (median 6; range 1-9) was assigned to the outcomes of patients incorrectly testing positive for distant metastases and experiencing unnecessary stress and anxiety.

DIAGNOSIS AND STAGING OF SUSPECT DISTANT RECURRENCE - UNCERTAIN

A disagreement among panelists was registered in both round of voting, with ratings falling in both the uncertain and appropriate region. The use of FDG-PET as an add on test for the diagnosis and staging of distant recurrence in patients with clinical suspicion of recurrence or unclear conventional imaging results resulted as uncertain due to disagreement.

Level of evidence for diagnostic accuracy of FDG-PET was very low, coming from only one study with very few patients. Outcomes were considered "critical" (median score 7) for true and false positives, as well as for false negatives, and "important" (median score 6) for patients correctly found negatives.

Foreword

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

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

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

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

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

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

This Dossier is published in 2011 and will be considered for review in five years. Any update in the interim period will be noted on the ASSR website
http://asr.regione.emilia-romagna.it

1. Introduction and objectives

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

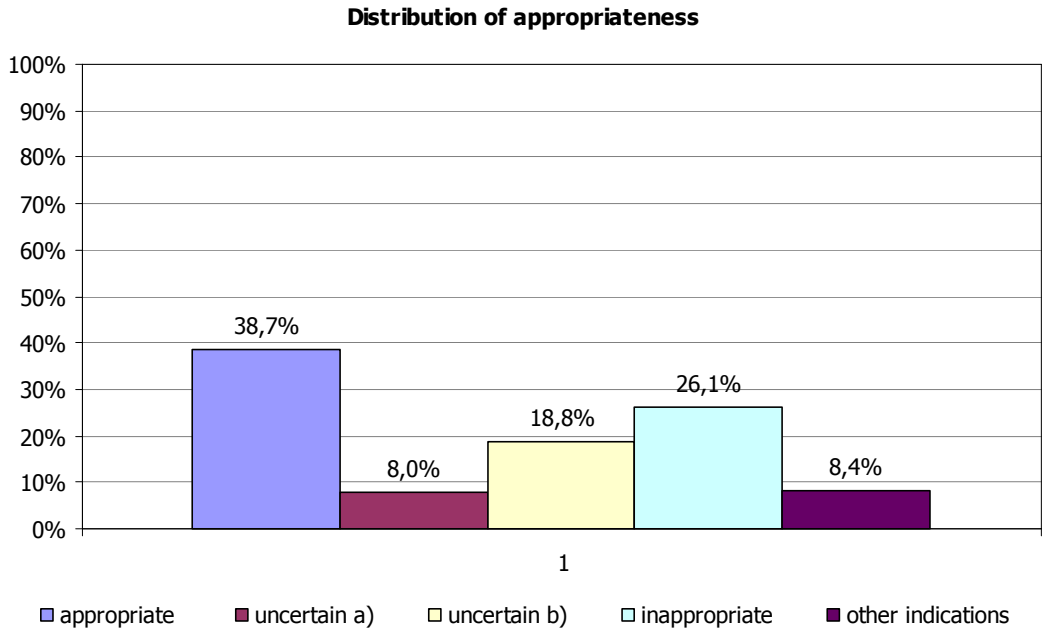
Since its introduction in the Emilia-Romagna Regional Health Service the Agenzia sanitaria e sociale regionale (ASSR) has been committed to promote and support regional research programs aimed at assessing clinical indications for FDG-PET and supporting programming policies.

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

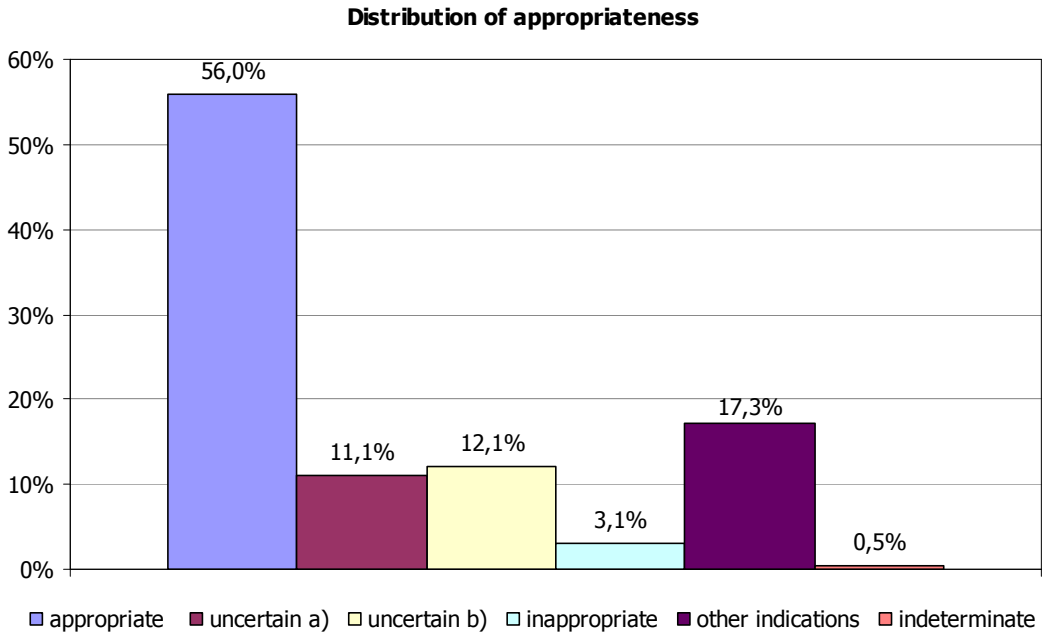
Following the increase in number of PET scanners (from 1 to 6) an update of the 2003 report was commissioned to a second regional panel and published in 2007. The second report addressed the role of FDG-PET in 18 types of cancer for a total of 65 clinical indications, and a second clinical audit was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

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

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



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



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

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

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

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

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

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

1.2. Context

Incidence of esophageal cancer

Crude incidence rate of esophageal cancer in Emilia-Romagna Region in 2004 (RER 2009): 5.2 per 100 000 male inhabitants per year and 1.9 per 100 000 female inhabitants per year.

Prevalence of esophageal cancer

Cumulative 10 years prevalence estimate of esophageal cancer in Emilia-Romagna Region at 1/1/2005 (RER 2009): 8.9 per 100 000 male inhabitants, corresponding to 180 cases in Emilia-Romagna region, and 3.3 per 100 000 female inhabitants, corresponding to 70 cases.

2. Methods

A panel of 26 experts, comprising nuclear physicians, radiologists, radiotherapists, surgeons, oncologists, ENT specialists, hematologists and health directors working in Health Trusts and Teaching Hospitals of Emilia-Romagna was convened to discuss and agree on the methodology for a research program aimed at defining the criteria for appropriate use of PET in oncology.

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

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

2.1. Clinical questions to be addressed

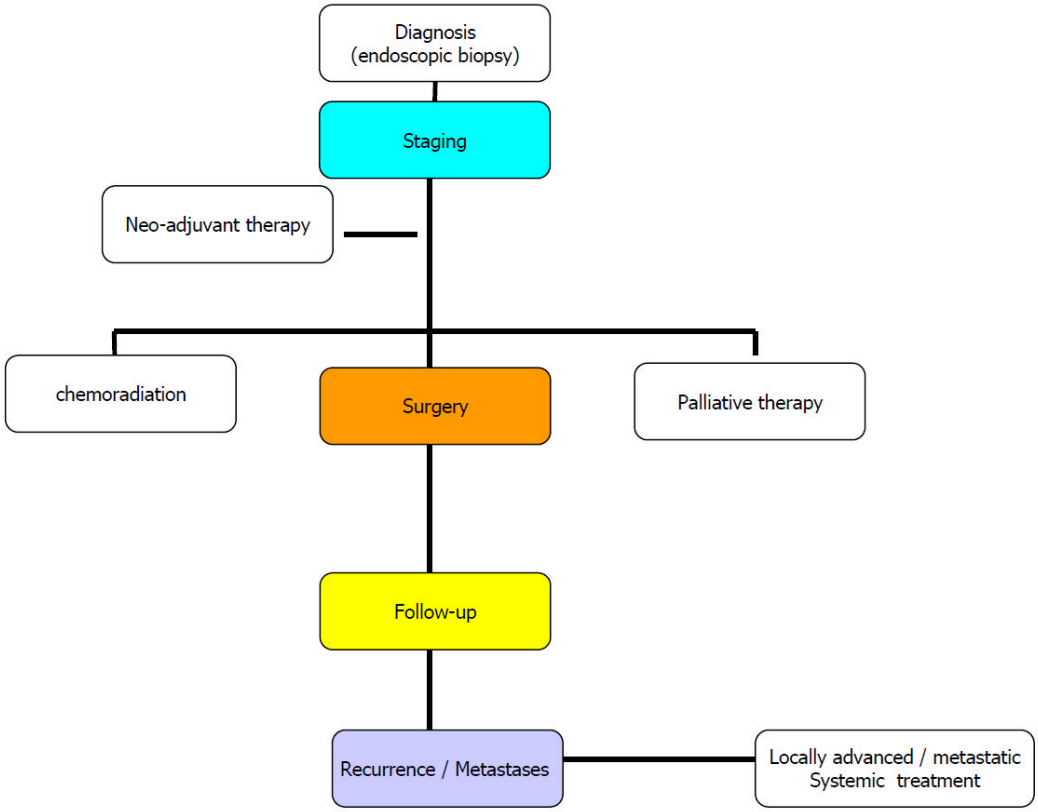
On the basis of the clinical pathway of patients with esophageal cancer (*Figure 2.1*), shared by most international clinical practice guidelines, the panel examined and assessed the role of FDG-PET for seven clinical indications (*Table 2.1*).

As the diagnosis of esophageal cancer is placed by endoscopic biopsy with histology (ESMO 2010), the use of FDG-PET in the diagnosis has not been considered by the panel.

Table 2.1. Clinical indications selected by the panel

• N staging of primary esophageal cancer
• M staging of primary esophageal cancer
• Target volume definition of curative radiation treatment
• Evaluation of early response to neoadjuvant therapy
• Evaluation of response to neoadjuvant therapy at the end of treatment
• Follow up in patients with no suspicion of recurrence
• Diagnosis and staging of suspect distant recurrence

Figure 2.1. Clinical pathway for esophageal cancer

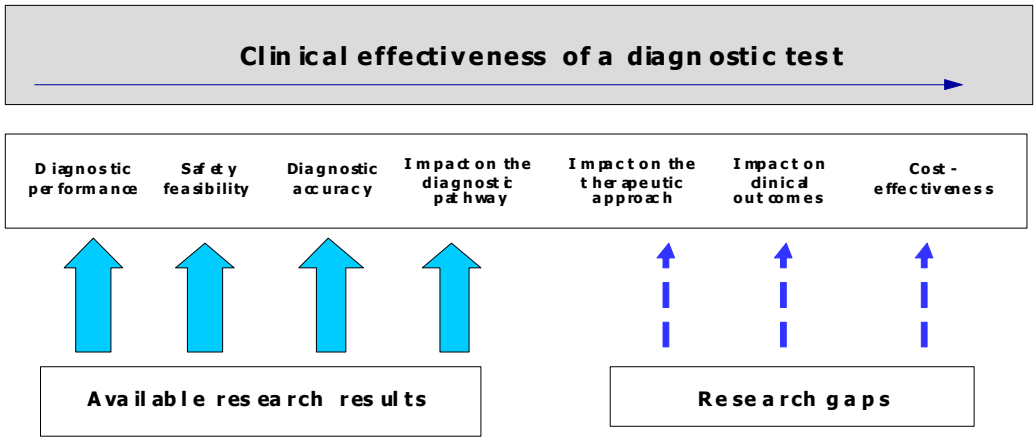


The starting point for the development of answerable "research questions", based on the PICO structure (Patient Intervention Comparator Outcome), has been the broad definition of appropriateness of a diagnostic test, which implies:

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

As for the previously published report, the evidence profile necessary to comprehensively assess and evaluate the role of a diagnostic test was defined and is represented in Figure 2.2.

Figure 2.2. Evidence profile for a diagnostic test



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

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

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

The intervention was either FDG-PET or CT/PET with a specific role within the diagnostic pathway and with a pre-defined position in relation to the comparator (replacement, triage, add on) as defined by Bossuyt *et al*. (Bossuyt 2006).

The comparator was identified as the currently used or existing test for the diagnostic role under consideration.

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

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

balance or trade off between the presumed benefits and the presumed harms, together with the quality of evidence on diagnostic accuracy, are used by panel members to judge the level of appropriateness of a test.

2.2. Systematic review of literature

Search methods for the identification of the studies

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

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

Language restrictions: English, Italian, French and Spanish.

Reference lists of identified articles were checked for additional references.

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

Selection criteria

Type of studies	systematic reviews, RCTs, CCTs, cross sectional diagnostic studies, prospective or retrospective cohort studies, case series of at least 10 patients
Participants	patients with esophageal cancer
Intervention	FDG-PET or CT/PET
Reference standard	histology or clinical follow up (for diagnostic accuracy studies)
Comparator	any other imaging technique
Outcomes	sensitivity, specificity, LR, accuracy in clinical target volume (CTV) definition, metabolic/tumor response, time to recurrence, local, locoregional and distant recurrence, disease free survival, disease survival, overall survival

Assessment of methodological quality of studies

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

Systematic reviews	criteria drawn from the AMSTAR checklist (Shea 2007)
Diagnostic cross sectional studies	criteria drawn from the QUADAS checklist (Whiting 2003)
Randomized controlled trials	criteria suggested by the Cochrane Handbook (Higgins 2009)
Case control studies and cohort studies	criteria drawn from the New Castle-Ottawa checklist
Case series	no standardized checklists have been published for the assessment of methodological quality of case series; the following two criteria have been used: prospective vs retrospective recruitment; consecutive recruitment

Data collection and analysis

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

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

Data synthesis

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

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

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

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

With SRs/MA and primary studies available, if patients included in primary studies published after systematic reviews or meta-analyses added up to a number smaller than the patients included in the SRs/MA, results from primary studies were analyzed only for consistency. With SRs/MA and primary studies available, if patients included in primary studies published after SRs/MA added up to a number greater than the patients included in the SRs/MA, estimates of all studies have been pooled and re-calculated and heterogeneity of diagnostic estimates of FDG-PET has been tested.

2.3. Level of evidence

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

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

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

high	no risk of bias or important study limitations, consistent results from several studies and a large number of patients
moderate	some study limitations, possible risk of bias, consistent results from several studies and a large number of patients
low	presence of bias, inconsistency and heterogeneity of results for one estimate of diagnostic accuracy (either sensitivity or specificity), results coming from several studies and a large number of patients
very low	presence of bias, sparse data or inconsistency and heterogeneity of results for both estimates of diagnostic accuracy (sensitivity and specificity)

2.4. Voting process

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

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

Voting forms

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

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

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

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

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

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

Voting procedure

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

Two rounds of voting were requested for the judgment of appropriateness and results were analyzed using the RAND/UCLA Appropriateness Method,[1] which allows to measure both the rating on appropriateness and the level of agreement or disagreement among the panelists' rating.

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

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

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

2.5. Definition of criteria of appropriateness

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

APPROPRIATE

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

[1] http://www.rand.org/pubs/monograph_reports/MR1269.html
(last access May 25, 2011)

UNCERTAIN

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

INAPPROPRIATE

- Clinical indications for which there is NO rationale for change in management related to a patient-important clinical outcome
- Clinical indications for which there is a rationale for change in management related to a patient-important clinical outcome, there is a high or moderate level of evidence on diagnostic accuracy of FDG-PET and the presumed harm - resulting from the test results - is greater than the presumed benefit.

INDETERMINATE

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

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

3. Systematic review of literature

3.1. Overall results

Methods and results of the systematic review of literature are reported in full in Appendix 2. The initial search identified 634 records; 128 were excluded because duplicates and a further 400 did not meet the inclusion criteria. Full text was acquired for the remaining potentially eligible 106 records, from which 50 studies were excluded on the basis of inclusion criteria while another 22 resulted already included in systematic reviews. Thirty-four studies were finally included.

Table 3.1 reports number and type of studies for each clinical question and endpoint as well as conclusions from the previous 2007 report (Liberati 2007 - *Dossier 157*).

Only three studies evaluating impact on clinical outcomes were found and included, and the remaining 31 included studies evaluated only diagnostic accuracy of FDG-PET.

Table 3.1. Number of included studies for questions and endpoints

Clinical question / Endpoint	Staging	Target Volume definition for radical RT	Early response to therapy (during treatment)	Response to therapy (end of treatment)	Follow up	Detection and staging of suspected recurrence
Diagnostic accuracy	Systematic reviews: 1 N staging primary studies: 12 M staging primary studies: 4	Systematic reviews: 1 Primary studies: 1	Systematic reviews: 2 Primary studies: 1	Systematic reviews: 3 Primary studies: 7	Systematic reviews: 0 Primary studies: 3	Systematic reviews: 0 Primary studies: 1
Impact on clinical outcomes	Systematic reviews: 0 Primary studies: 2	Systematic reviews: 0 Primary studies: 0	Systematic reviews: 0 Primary studies: 1	Systematic reviews: 0 Primary studies: 0	Systematic reviews: 0 Primary studies: 0	Systematic reviews: 0 Primary studies: 0
Dossier 157	N staging not considered M staging appropriate	Not considered	Not considered	Not considered	Not considered	Potentially useful (uncertain A)

4. N staging of patients with primary esophageal cancer

Rationale

Surgical treatment is the therapy of choice for all patients with potentially curable esophageal cancer and who are fit for major surgery (AIOM 2009; ESMO 2010; NCCN 2010; SIGN 2006).

Accurate pre-operative staging is necessary to correctly direct patients to curative surgery, non curative surgery or non surgical therapy (combined chemoradiation).

N staging is used to decide on need for neoadjuvant treatment.

Diagnostic role of FDG-PET

It is suggested that FDG-PET could represent a less invasive diagnostic test for the correct identification and selection of patients candidate to neoadjuvant treatment.

Treatment effectiveness

The expected 2-year survival after curative surgical treatment (without neoadjuvant chemoradiotherapy) ranges between 20 and 50%. In case of regional lymph node involvement long-term survival does not exceed 25%. In patients with locally advanced cancer pre-operative chemoradiotherapy improves the 2-year survival by 13% (absolute difference) compared to surgical treatment only (Gebski 2007).

Pre-test probability and change in management

The median pre-test probability of cancer involvement of regional nodes is 59.9% (range 6.9-95.2%; data from studies on FDG-PET in van Vliet 2008), which could be considered to be the hypothetical maximum extent of change in management, achievable through accurate N staging.

Research question: FDG-PET as replacement

Is FDG-PET better (i.e. has higher diagnostic accuracy) than the available comparators (CT and EUS) in staging regional lymph nodes of patients with esophageal cancer?

4.1. Systematic review of literature: results

Results from update of systematic review of literature from Jan 2006

Only studies evaluating diagnostic accuracy were found and results are reported below.

Systematic reviews

One systematic review (van Vliet 2008), comparing the diagnostic accuracy of endoscopy ultrasonography (EUS), computed tomography (CT) and FDG-PET in staging regional lymph node, has been included (*Table 4.1*). The characteristics of recruited patients were not reported. Methodological quality of this systematic review is judged as intermediate. According to the authors virtually all studies included in the review are prone to verification bias, and some of them are not blind.

Table 4.1. Main results of the van Vliet's 2008 systematic review on N staging

Reference	van Vliet 2008
Update to	January 2006
Number of studies	10
Number of patients	424 (median 43, range 21-81)
FDG-PET / PET-CT	sensitivity: pooled 57% (95% CI 43-70) specificity: pooled 85% (95% CI 76-95)
Comparator	EUS (31 studies, 1 841 patients) sensitivity: pooled 80% (95% CI 75-84) specificity: pooled 70% (95% CI 65-75) CT (17 studies, 943 patients) sensitivity: pooled 50% (95% CI 41-60) specificity: pooled 83% (95% CI 77-89)
Reference standard	resection fine needle aspiration autopsy/follow up

Primary studies

Twelve studies evaluating diagnostic accuracy of FDG-PET in the staging of patients with esophageal cancer published after the above reported systematic review were included (*Table 4.2*; Buchmann 2006; Choi 2010; Hsu 2009; Hu 2009; Kato 2008; Katsoulis 2007; Little 2007; Okada 2009; Roedl 2009a; Sandha 2008; Schreurs 2008; Yuan 2006). Eight studies applied FDG-PET and 4 FDG-PET/CT. Studies included patients with squamous cell carcinoma (6) or adenocarcinoma (2) or both (4).

As number of patients of primary studies not included in the van Vliet's 2008 systematic review added up to a number greater than those included in van Vliet 2008, all studies have been pooled and heterogeneity of diagnostic estimates of FDG-PET tested (*Table 4.3*).

Table 4.2. Main results of primary studies on N staging published after van Vliet's 2008 systematic review

Reference	Buchmann 2006; Choi 2010; Hsu 2009; Hu 2009; Kato 2008; Katsoulis 2007; Little 2007; Okada 2009; Roedl 2009a; Sandha 2008; Schreurs 2008; Yuan 2006
Number of studies	12
Number of patients	622 (median 47.5, range 18-173)
FDG-PET/PET-CT	sensitivity: median 68% (0-100%) specificity: median 92% (67-100%)
Comparator	EUS (3 studies, 261 patients) sensitivity: range 41.8-91.7% specificity: range 60-97.6% CT (5 studies, 429 patients) sensitivity: median 48.3% (range 33.3-75%) specificity: median 92.6% (range 66.7-100%)
Reference standard	resection fine needle aspiration autopsy/follow up

Table 4.3. Main results on diagnostic accuracy of studies on N staging

Diagnostic accuracy	
Number of studies	22
Number of patients	957 (median 45, range 12-173)
Pre-test probability	median 59.9% (6.9-95.2%)
FDG-PET/PET-CT	sensitivity: median 62% (range 0-100%) *heterogeneity chi-squared = 106.50 (d.f. = 19) p = 0.000* *inconsistency (I-square) = 82.2%* specificity: median 89% (range 60-100%) *heterogeneity chi-squared = 58.11 (d.f. = 19) p = 0.000* *inconsistency (I-square) = 67.3%*
Reference standard	resection fine needle aspiration autopsy/follow up
References	primary studies from van Vliet 2008; Buchmann 2006; Choi 2010; Hsu 2009; Hu 2009; Kato 2008; Katsoulis 2007; Little 2007; Okada 2009; Roedl 2009a; Sandha 2008; Schreurs 2008; Yuan 2006

Comments of ASSR reviewer

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

Diagnostic accuracy estimates

FDG-PET sensitivity: (heterogeneous) range 0-100%
FDG-PET specificity: (heterogeneous) range 60-100%

EUS sensitivity:* (pooled) 80%
EUS specificity:* (pooled) 70%

* data from studies evaluating FDG-PET included in van Vliet 2008.

LEVEL OF EVIDENCE: VERY LOW

4.2. Clinical outcomes

To evaluate the balance between benefits and risks, the panel agreed to consider the presumed patient-important outcomes reported below (*Table 4.4*), and voted on the level of importance for each outcome. Median scores and ranges are reported for each outcome.

All outcomes were voted "important".

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

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

Table 4.4. Patient-important clinical outcomes and median scores of importance

Patient-important outcomes	**Median score (range)**
Consequences of test for patients with involvement of regional nodes	
• True positives - patients are correctly upstaged and undergo neodjuvant therapy, which could improve survival	6 (4-9)
• False negatives - patients are incorrectly downstaged and do not receive necessary neoadjuvant therapy, which could have improved survival	6 (4-9)
Consequences of test for patients without involvement of regional nodes	
• True negatives - patients proceed directly to curative resection of primary tumor, aimed at improving survival	6 (3-9)
• False positives - patients are incorrectly upstaged and have to undergo unnecessary neodjuvant therapy, with no improvement on survival and possible unnecessary peri/post-operative adverse effects.	6 (3-9)

4.3. Voting results

After an initial slight disagreement, with ratings falling in the uncertain and appropriate regions (median score 6; range 4-8), the second voting round registered an agreement on uncertain with a median score of 5 and range from 4 to 6.

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

UNCERTAIN

4.4. Conclusions

The panel agreed to judge as uncertain the use of FDG-PET in staging patients with esophageal cancer for regional lymph nodes, in replacement of endoscopic ultrasonography (EUS).

The level of evidence for diagnostic accuracy of FDG-PET was very low, with heterogeneous estimates for both sensitivity and specificity.

All outcomes, related to the correct selection of patients eligible for neoadjuvant chemoradiation therapy were considered "important" (median score 6). A less invasive test was also deemed highly desirable, given the high pre-test probability of patients diagnosed for primary esophageal cancer having positive lymph node. However the uncertainty on the diagnostic accuracy of FDG-PET made the panel very cautious in suggesting use of FDG-PET results to direct therapeutic options.

5. M staging of patients with primary esophageal cancer

Rationale

Tumor stage at diagnosis and comorbidity are strong predictors of outcome and determinants of survival. M staging has a role in identifying and selecting patients candidate to curative surgery.

Diagnostic role of FDG-PET

It is suggested that FDG-PET could be more accurate in discriminating patients eligible for curative surgery from patients eligible for treatment of distant metastases.

Treatment effectiveness

Only palliative treatment is available for metastatic esophageal cancer, aimed at improving quality of life.

Pre-test probability and change in management

The median pre-test probability of occurrence of distant metastases is 35.7% (range 8.6-54.2%; data from studies on FDG-PET in van Vliet 2008).

Evidence from 18 studies on change in management following FDG-PET exams shows a median estimate of 20%, with almost all patients upstaged, with a change from curative to palliative intent treatment (Berrisford 2008; Buchmann 2006; Chatterton 2009; Duong 2006a; Gananadha 2008; Katsoulis 2007; Malik 2006; McDonough 2008; Meyers 2007; Noble 2009; Pfau 2007; Pifarré-Montaner 2009; Salahudeen 2008; Smith 2009; van Westreenen 2007; Walker 2011; Williams 2009).

Research question: FDG-PET as replacement

Is FDG-PET better (i.e. has higher diagnostic accuracy) than the available comparator (CT) in staging patients with primary esophageal cancer for distant metastasis?

5.1. Systematic review of literature: results

Results from update of systematic review of literature from Jan 2006

One systematic review and four primary studies evaluating diagnostic accuracy were found, as well as two studies evaluating impact of FDG-PET on clinical outcomes. Results are reported below.

DIAGNOSTIC ACCURACY

Systematic reviews

One systematic review (van Vliet 2008) comparing the diagnostic accuracy of computed tomography (CT) and FDG-PET in staging distant metastases, has been included (*Table 5.1*). The characteristics of recruited patients were not reported. Methodological quality of this systematic review is judged as intermediate. According to the authors, virtually all studies included in the review are prone to verification bias, and some of them are not blind.

Table 5.1. Results of systematic review on M staging (distant metastases)

Reference	van Vliet 2008
Update to	January 2006
Number of studies	9
Number of patients	475 (median 48, range 35-81)
FDG-PET/PET-CT	sensitivity: pooled 71% (95% CI 62-79) specificity: pooled 93% (95% CI 89-97)
Comparator	CT sensitivity: pooled 52% (95% CI 33-71) specificity: pooled 91% (95% CI 86-96)
Reference standard	resection fine needle aspiration autopsy/follow up

Primary studies

Four studies evaluating diagnostic accuracy of FDG-PET in the staging of patients with esophageal cancer published after the above reported systematic review were included (Buchmann 2006; Katsoulis 2007; Little 2007; Noble 2009). All studies applied FDG-PET. Studies included patients with adenocarcinoma (1) or squamous cell carcinoma and adenocarcinoma (3). The studies have been retrieved and assessed only for overall consistency with results on diagnostic accuracy of the above reported systematic review (*Table 5.2*).

As results of primary studies are consistent with those of the systematic reviews, the latter's pooled estimates were chosen.

Table 5.2. Results of primary studies on M staging

Reference	Buchmann 2006; Katsoulis 2007; Little 2007; Noble 2009
Number of studies	4
Number of patients	291 (median 40, range 20-191)
FDG-PET/PET-CT	sensitivity: median 88% (range 60-91%) specificity: median 94.5% (range 86-100%)
Reference standard	resection fine needle aspiration autopsy/follow up

Comments of ASSR reviewer

Results from the systematic review (SR) for detection of distant metastases show a higher performance for FDG-PET compared to CT. Specificity is higher than sensitivity. Due to possible verification bias all results could overestimate diagnostic accuracy.

As results from primary studies published since 2006 confirm the diagnostic accuracy estimates of van Vliet's SR (2008) - i.e. a better performance of FDG-PET in M staging than N staging and higher values of specificity than sensitivity - estimates of diagnostic accuracy were based on the SR's pooled estimates.

Diagnostic accuracy estimates

FDG-PET sensitivity: (pooled) 71%
FDG-PET specificity: (pooled) 93%

CT* specificity: (pooled) 52%,
CT* specificity: (pooled) 91%

* data from studies evaluating FDG-PET

LEVEL OF EVIDENCE: MODERATE

IMPACT ON CLINICAL OUTCOMES

Primary studies

Two studies evaluating secondary clinical outcomes (burden of diagnostic test) were found (Meyers 2007; Westerterp 2008). The first study (Meyers 2007) included 189 patients eligible for curative surgery and found that 2 patients (1%) suffered the adverse consequences of the change in management due to a false positive FDG-PET result. The first patient underwent adrenalectomy with subsequent therapy for adrenal insufficiency, the second patient had a wound complication following confirmatory procedure. The second study (Westerterp 2008) included 82 patients eligible for curative surgery, who carried out a subjective comparative evaluation of the burden, in terms of discomfort, embarrassment and anxiety, of diagnostic tests performed for the staging, such as FDG-PET, CT, US (with or without fine needle aspiration) and EUS (with or without fine needle aspiration). The perceived burden of FDG-PET was lower than that of EUS, and higher than that of CT, although the large majority of subjects reported "none" or "little" burden for all tests and all dimensions.

Comments of ASSR reviewer

No studies investigating the main aspects of impact on clinical outcomes of FDG-PET were found, but two studies investigating two ancillary aspects were retrieved (one study reporting the adverse consequences of the change in management due to a false positive FDG-PET result and another study investigating the patient burden for the different imaging tests during staging). Due to the paucity of data no firm conclusion could be drawn.

LEVEL OF EVIDENCE: VERY LOW

5.2. Clinical outcomes

To evaluate the balance between benefits and risks, the panel agreed to consider the presumed patient-important outcomes reported below (*Table 5.3*), and voted on the level of importance for each outcome. Median scores and ranges are reported for each outcome.

All outcomes were considered "critical" by the panel with consequences for true and false positives receiving a median score of 8, and outcomes for true and false negatives a median score of 7.

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

A matrix of "natural frequencies" was provided (*Table 5.4*).

Table 5.3. Patient-important clinical outcomes and median scores of importance

Patient-important outcomes	Median score (range)
Consequences of test for patients with distant metastases	
• True positives - patients are correctly upstaged and proceed to palliative treatment, aimed at improving quality of life	8 (2-9)
• False negatives - patients are incorrectly downstaged and undergo unnecessary curative surgical treatment, which might not improve survival	7 (3-9)
Consequences of test for patients without distant metastases	
• True negatives - patients correctly proceed to curative surgical treatment, which could improve survival	7 (2-9)
• False positives - patients are incorrectly upstaged and denied necessary curative surgical treatment, which could have improved survival, and proceed to palliative treatment.	8 (3-9)

Table 5.4. "Natural frequencies" of patients staged for distant metastasis

		N of patients out of 100 submitted to the exam	
		According to FDG-PET	**According to CT**
Patients with distant metastasis	True positives	26	19
	False negatives	10	17
Patients without distant metastasis	True negatives	60	58
	False positives	4	6
		100	100

5.3. Voting results

The first voting round registered an agreement (median score 8; range 7-9) on appropriate rating.

FINAL RATING FOR THE USE OF FDG-PET FOR M STAGING OF PRIMARY ESOPHAGEAL CANCER:

APPROPRIATE

5.4. Conclusions

The panel agreed at the first round in rating as appropriate the use of FDG-PET in staging patients with esophageal cancer for distant metastasis, in order to decide on subsequent appropriate therapeutic approach.

The level of evidence for diagnostic accuracy of FDG-PET was moderate, with FDG-PET performing better than CT.

However the panel did not suggest that FDG-PET should replace CT, but that its higher accuracy in detecting distant metastases should be taken into account. Rather, it was strongly suggested that when using FDG-PET/CT scanners, a diagnostic CT with contrast should be planned and joint results readings between radiologists and nuclear physicians arranged.

The consequences for true positives - correct upstage and appropriate palliative treatment - and for false positives - incorrect upstage and denial of surgical curative treatment - received a median score of 8. Outcomes for true and false negatives obtained a median score of 7, meaning that all four outcomes were considered "critical" by the panel.

6. Target volume definition of curative radiation treatment

Rationale

Radiotherapy (with chemotherapy) is recommended as neoadjuvant treatment for locally advanced esophageal cancer by the majority of guidelines (AIOM 2009; ESMO 2010; NCCN 2010). All examined guidelines (AIOM 2009; ESMO 2010; NCCN 2010; SIGN 2006) propose radiotherapy (with or without chemotherapy) with curative intent for patients unfit for or unwilling to undergo surgery.

Diagnostic role of FDG-PET

A more precise diagnostic tool allowing a better definition of target volume could reduce adverse effects of radiation treatment.

Treatment effectiveness

For patients with locally advanced disease or operable esophageal cancer who decline surgery or who are unfit for surgery, chemoradiation may be an appropriate alternative (SIGN 2006).

Change in management

No available data.

Research question: FDG-PET in addition to CT

Does adding FDG-PET imaging lead to a better target volume definition of curative radiotherapy in patients with esophageal cancer?

6.1. Systematic review of literature: results

Results from update of systematic review of literature from Jan 2006

One systematic review on volume definition and one study evaluating diagnostic accuracy were found. Results are reported below.

Systematic reviews

Only one systematic review assessing the role of FDG-PET in tumor volume definition in radiotherapy treatment planning in esophageal cancer was included (Muijs 2010), that incorporated also the studies included and assessed by a previous systematic review (van Baardwijk 2006). Methodological quality was judged as low (*Table 6.1*).

Table 6.1. Results of systematic review on diagnostic accuracy of FDG-PET in the field definition of curative radiotherapy

Reference	Muijs 2010
Update to	2009
Number of studies	10
Number of patients	231
Results	changes in the delineation of target volumes (GTV/CTV/PTV*) in a proportion of patients ranging from 20 to 94% compared to CT (data from 6 studies, 142 patients); TV increases in a proportion of 10-31% of patients; TV decreases in a proportion of 10-62.5% of patients 3 out of 4 studies (89 patients) reported a significant positive correlation (r raging from 0.74 to 0.89) between FDG-PET tumor length and pathologic findings
Reference standard	histopathology (4 studies) autopsy/follow up

* GTV = gross target volume
CTV = clinical target volume
PTV = planned target volume

Primary studies

One study (Shimizu 2009), not included in the SR by Muijs 2010, was found. Twenty patients with squamous cell carcinoma of the esophagus who underwent surgical esophagectomy were examined by CT and FDG-PET/CT in order to evaluate the diagnostic accuracy in the definition of the CTV of metastatic lymph nodes compared to histopathological verification after surgery. It was found that CTV did not cover the hystopatologically detected positive lymph nodes in 8 out of 20 patients undergoing CT and in 7 out of 20 patients undergoing FDG-PET/CT. The study was limited by a possible bias in the selection of patients; however the imaging reading lecture was blinded.

Comments of ASSR reviewer

From the systematic review the use of FDG-PET/CT resulted in changes of target volumes in comparison with CT alone planning. Nevertheless there are no data providing evidence, in term of diagnostic accuracy estimates, that FDG-PET-based changes in target volume represent better pathological tumor coverage than CT-based volume delineation.

Data from one small study suggest that there is no difference in accuracy of CTV delineation of metastatic lymph nodes between FDG-PET/CT and CT alone.

LEVEL OF EVIDENCE: VERY LOW

6.2. Clinical outcomes

After a lengthy discussion the panel agreed that, given the scope and dose delivery of radiation treatment, conventional imaging is more than adequate for field definition and no patient-important outcomes have been proposed and voted.

6.3. Voting results

The first voting round registered a strong disagreement, with ratings falling in the inappropriate, uncertain and appropriate regions (median score 4; range 2-9). The second voting round registered an agreement on inappropriate (median score 2; range 1-3).

FINAL RATING FOR THE USE OF FDG-PET FOR TARGET VOLUME DEFINITION OF CURATIVE RADIATION TREATMENT:

INAPPROPRIATE

6.4. Conclusions

After an initial strong disagreement, with ratings falling in all regions of appropriateness, uncertainty and inappropriateness, the panel reached an agreement in judging the use of FDG-PET for the field definition of radiation treatment as inappropriate.

Only sparse data evaluating diagnostic accuracy of FDG-PET in the definition of the radiation field were found, and given the scope and dose delivery of the radiation treatment, the panel expressed no particular need for more accurate field definition than that conveyed by available imaging.

7. Evaluation of early response to neoadjuvant therapy

Rationale

As pre-operative chemotherapy/chemoradiotherapy could increase the risk of post-operative mortality (ESMO 2010), a selection of responders to chemotherapy/ chemoradiotherapy after the first cycles could spare non responders the risks of a futile full-length chemotherapy/chemoradiotherapy, hypothetically improving survival of these patients.

Diagnostic role of FDG-PET

To identify non responders who could interrupt ineffective treatment and proceed to curative surgery, sparing them the risks associated with primary systemic therapy.

Treatment effectiveness

There is evidence that in patients with locally advanced cancer, pre-operative chemoradiation improves the 2-year survival by 13% (absolute difference) compared to surgical treatment only (Gebski 2007). Pre-operative chemotherapy could increase the risk of post-operative mortality (ESMO 2010).

Pre-test probability and change in management

The median pre-test probability of histopathologic response after pre-operative chemotherapy/chemoradiotherapy is 43% (range 10-57%; data from studies on FDG-PET in Ngamruengphong 2010 and Lorenzen 2007), which could be considered to be the hypothetical maximum extent of change in management, achievable with an accurate evaluation of early response to pre-operative therapy.

Research question: FDG-PET as replacement

Is FDG-PET accurate in evaluating the early response to pre-operative chemoradiation of patients treated for locally advanced esophageal cancer?

7.1. Systematic review of literature: results

Results from update of systematic review of literature from Jan 2006

Two systematic reviews and one primary study evaluating diagnostic accuracy were found, as well as one non randomized controlled study evaluating impact of FDG-PET on clinical outcomes. Results are reported below.

DIAGNOSTIC ACCURACY

Systematic reviews

Two systematic reviews (Ngamruengphong 2010; Rebollo Aguirre 2009) have been included, assessing the diagnostic accuracy of FDG-PET in evaluating response to therapy in patients with esophageal cancer during neoadjuvant therapy prior to surgical treatment (*Table 7.1*). The recruited patients have a stage II or III cancer of different histological type. Neoadjuvant therapy consisted in varied cytotoxic drugs, mostly including platinum-based agents, associated with radiotherapy. Methodological quality was judged high for both reviews. According to the review authors' QUADAS quality assessment (Ngamruengphong 2010) several studies included in the review are prone to verification bias.

Table 7.1. Results of systematic reviews

Reference	Ngamruengphong 2009	Rebollo Aguirre 2009
Update to	February 2008	August 2006
Number of studies	6	3
Number of patients	293 (median 35, range 13-119)	84
FDG-PET/ PET-CT	all studies both during and after therapy sensitivity: range 42-100% specificity: range 27-100% AUC: 0.80 (95% CI 0.72-0.89) FDG-PET during therapy AUC: 0.78 (95% CI 0.62-0.93) no significant differences between accuracy during and after therapy	sensitivity: range 75-93% specificity: range 75-87%
Reference standard	pathologic confirmation	histopathology other imaging techniques clinical follow up of at least 1 year

Primary studies

One study (Lorenzen 2007), not included in the above reported SRs, was found (*Table 7.2*). Eleven patients with adenocarcinoma or squamous cell carcinoma underwent a neoadjuvant therapy regimen (capecitabine and docetaxel) and performed a FDG-PET evaluation at baseline and after two weeks of treatment. Metabolic response according to FDG-PET was compared with clinical response according to RECIST guidelines (including CT) at the end of treatment (reference standard). The study was limited by the low number of patients and the uncertainty on blinding of index test (FDG-PET) when evaluating the reference test (RECIST guidelines criteria).

As a metanalysis of studies was not performed in the above cited systematic reviews (Ngamruengphong 2010; Rebollo Aguirre 2009), the whole number of studies was pooled and heterogeneity of diagnostic estimates of FDG-PET tested (*Table 7.3*).

Table 7.2. Results of primary studies

References	Lorenzen 2007
Number of patients	11
Pre-test probability (prevalence of responders)	45%
FDG-PET/PET-CT	sensitivity: 100% specificity: 60%
Reference standard	clinical response according to RECIST guidelines

Table 7.3. Overall results for diagnostic accuracy

Diagnostic accuracy	
Number of studies	7
Number of patients	269 (median 32, range 11-104)
Pre-test probability	median 42% (range 10-57%)
FDG-PET/PET-CT	sensitivity: range 44-100% heterogeneity chi-squared = 21.30 (d.f. = 6) p = 0.0016 inconsistency (I-square) = 71.8% specificity: median 74% (range 52-88%) heterogeneity chi-squared = 8.00 (d.f. = 6) p = 0.238 inconsistency (I-square) = 25%
Reference standard	resection, fine needle aspiration, autopsy/follow up
References	primary studies from Ngamruengphong 2009 and Rebollo Aguirre 2009; Lorenzen 2007

Comments of ASSR reviewer

Estimates of sensitivity of FDG-PET in evaluating the response to therapy during neoadjuvant treatment are heterogeneous and range from 44 to 100%. Estimates of specificity on the other hand do not show heterogeneity, resulting in a median value of 74%.

Diagnostic accuracy estimates

FDG-PET sensitivity: (heterogeneous) range 44-100%
FDG-PET specificity: (median) 74%

Comparator current practice: all patients complete pre-operative treatment

LEVEL OF EVIDENCE: LOW

IMPACT ON CLINICAL OUTCOMES

Primary studies

One non randomized controlled study (Lordick 2007) assessed the impact on clinical outcome following FDG-PET-response guided neoadjuvant chemotherapy to patients with locally advanced (cT3 or cT4) adenocarcinoma of the esophageal junction (*Table 7.4*).

A cohort of 110 patients was assigned to 2 weeks of platinum and fluorouracil-based induction chemotherapy. Those showing a decrease in tumor glucose standard uptake values (SUVs) (predefined decreases of 35% or more at the end of the evaluation period) were defined as metabolic responders. Responders continued to receive neoadjuvant chemotherapy for 12 weeks and then proceeded to surgery. Metabolic non responders discontinued chemotherapy after the 2-week evaluation period and proceeded to surgery. The overall survival and event-free (death or relapse) survival were compared between the two groups after a median follow up of 2.3 years (IQR 1.7-3.0); the diagnostic predictive value of metabolic response of FDG-PET was verified with the histopathological tumor response evaluated on the surgical specimens. The results are reported in the table below. According to the Newcastle-Ottawa Quality Assessment Scale the study has the limitation of a narrow representativeness of the studied cohort, an uncertain blinding in assessing the outcomes and a partial control of confounding factors.

Table 7.4. Results of primary studies

Reference	Lordick 2007
Number of patients	110 (104 underwent surgical resection)
Metabolic response	54/110 (49%)
Histopathological response (6 patients lost)	29/104 (28%) (all metabolic responders)
Metabolic non responders	56/110 (51%)
Histopathological non responders (6 patients lost)	75/104 (72%) (includes all metabolic non responders)
Metabolic responders vs metabolic non responders	
Overall survival	HR 2.13 (95% CI 1.14-3.99), p = 0.015
Event-free survival	HR 2.18 (95% CI 1.32-3.62), p = 0.002
3 or 4 grade adverse events	
diarrhoea	9 pts vs 0
emesis	5 pts vs 2
nausea	4 pts vs 2
fatigue	5 pts vs 1
death	2 pts vs 0
Metabolic and histopathological responders vs metabolic responders and histopathological non responders	
Overall survival	HR 4.55 (95% CI 1.37-15.04), p = 0.004
Event-free survival	HR 3.03 (95% CI 1.28-7.16), p = 0.006
Metabolic responders and histopathological non responders vs metabolic non responders (all histopathological non responders)	
Overall survival	HR 1.21 (95% CI 0.56-2.63), p = 0.549
Event-free survival	HR 1.29 (95% CI 0.69-2.45), p = 0.430
Reference standard	clinical response according to RECIST guidelines

Comments of ASSR reviewer

Limited to the group of adenocarcinoma of the junctional esophagus, FDG-PET evaluation of metabolic response after two weeks of neoadjuvant chemotherapy for locally advanced cancer seems to have a good negative predictive value of the histopathological response, with correct classification of all histopathological responders and of a consistent number of non responders. A better overall and event-free survival was observed for the metabolic responder group, which suffered a higher incidence of chemotherapy related adverse events than the non responders group.

LEVEL OF EVIDENCE: VERY LOW

7.2. Clinical outcomes

To evaluate the balance between benefits and risks, the panel agreed to consider the presumed patient-important outcomes reported below (*Table 7.5*), and voted on the level of importance for each outcome. Median scores and ranges are reported for each outcome.

All consequences were voted "critical", except for false responders who would continue therapy as at present.

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

The following matrix of "natural frequencies" was provided (*Table 7.6*).

Table 7.5. Patient-important clinical outcomes and median scores of importance

Patient-important outcomes	**Median score (range)**
Consequences of test for responders	
• True responders - responders complete clinically effective pre-operative treatment, which could improve survival but might carries some risk of post-operative mortality	7 (3-9)
• False non responders - responders interrupt clinically effective treatment, which could have improved survival, and proceed directly to surgery	8 (2-9)
Consequences of test for non responders	
• True non responders - non responders interrupt ineffective treatment, which would not have improved survival, and proceed directly to surgery, with lower risks of post-operative mortality	7 (3-9)
• False responders - non responders complete ineffective pre-operative treatment, with no possible gain in survival but with some risk of post-operative mortality	5 (2-9)

Table 7.6. "Natural frequencies" of patients assessed for response to therapy

		N of patients out of 100 submitted to the exam	
		According to FDG-PET	**According to current practice**
Patients responders	True responders	19 - 43	43
	False non responders	24 - 0	0
Patients non responders	True non responders	42	0
	False responders	15	57
		100	100

7.3. Voting results

The first voting round registered a strong disagreement with ratings falling in the inappropriate, uncertain and inappropriate regions (medians score 4; range 2-9), while in the second voting round agreed on the inappropriate rating (median score 2; range 1-3).

FINAL RATING FOR THE USE OF FDG-PET FOR THE EVALUATION OF EARLY RESPONSE TO NEOADJUVANT THERAPY:

INAPPROPRIATE

7.4. Conclusions

After an initial strong disagreement, with ratings falling in all regions of appropriateness, uncertainty and inappropriateness, the panel reached an agreement in judging the use of FDG-PET for the evaluation of early response to neoadjuvant therapy as inappropriate.

The level of evidence for diagnostic accuracy of FDG-PET was low, due also to the heterogeneity of estimates for sensitivity (ranging from 44% to 100%).

Given that the proportion of patients responding to neoadjuvant chemoradiation is around 43%, the panel voted "critical" the outcomes related to the possibility of correctly or incorrectly suspending the treatment, with a higher score of importance for the patients resulting false non responders (median score 8; range 2-9). Consequences for false responders - completing ineffective therapy - were considered less important (median score 5; range 2-9). Though expressing the need for a test that could correctly discriminate responders from non responders, given the low accuracy of FDG-PET, the panel judged the accuracy of FDG-PET as insufficient and the risk of incorrectly suspending an effective treatment higher than the possible benefits of interrupting an ineffective one.

8. Evaluation of response to neoadjuvant therapy at the end of treatment

Rationale

In patients with locally advanced disease treated with neoadjuvant chemotherapy/ chemoradiotherapy, their response to treatment should be evaluated in order to decide for subsequent type and aim of treatment - surgical, curative, palliative (SIGN 2006). At least 10% of patients with locally advanced disease could proceed to potentially curative resection following a good response to chemotherapy (data from a trial of patients with locally advanced or metastatic esophageal or gastric cancer; Ross 1996).

Diagnostic role of FDG-PET

FDG-PET could be a non invasive test useful to evaluate response to neoadjuvant treatment in order to discriminate patients candidate to curative therapy from those eligible for palliative treatment.

Treatment effectiveness

Surgical treatment is the therapy of choice for all patients with potentially curable esophageal cancer and who are fit for major surgery (AIOM 2009; ESMO 2010; NCCN 2010; SIGN 2006).

Pre-test probability and change in management

The median pre-test probability of histopathologic response after pre-operative chemotherapy/chemoradiotherapy is 42% (range 16-84%; Ngamruengphong 2009; Kwee 2010), which could be considered the hypothetical maximum degree of change in management achievable with an accurate evaluation of response to treatment.

The only one study (53 patients; Duong 2006b) found dealing with change in management disclosed a 9.4% of change (5.6% from curative to palliative intent and 3.8% from palliative to curative intent).

Research question: FDG-PET in add on

Does adding FDG-PET to CT lead to a more accurate evaluation of response to neoadjuvant therapy at the end of treatment?

8.1. Systematic review of literature: results

Results from update of systematic review of literature from Jan 2006

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

Systematic reviews

Three systematic reviews (Kwee 2010; Ngamruengphong 2009; Rebollo Aguirre 2009) have been included, assessing the diagnostic accuracy of FDG-PET in evaluating response at the end of treatment for patients with esophageal cancer receiving neoadjuvant therapy prior to surgical treatment (*Table 8.1*). The recruited patients have a stage II or III cancer of different histological types. Neoadjuvant therapy consisted in different cytotoxic drugs, mostly including platinum-based agents, associated with radiotherapy.

Methodological quality was judged as high for all reviews.

Table 8.1. Results of systematic reviews

Reference	Kwee 2010	Ngamruengphong 2009	Rebollo Aguirre 2009
Update to	June 2009	February 2008	August 2006
Number of studies	20	11	4
Number of patients	849 (median 32, range 11-104)	555 (median 38, range 13-103)	164
FDG-PET/ PET-CT	sensitivity: range 33-100% specificity: range 30-100% significant heterogeneity for both AUC: 0.7815	all studies (both during and after therapy) sensitivity: range 42-100% specificity: range 27-100% AUC: 0.80 (95% CI 0.72-0.89) all studies after therapy AUC: 0.80 (95% CI 0.71-0.89) FDG CT/PET studies after therapy AUC: 0.77 (95% CI 0.39-1.00) no significant differences between PET and CT/PET no significant differences between accuracy during and after therapy	primary tumor response sensitivity: range 27-93% specificity: range 42-95% N restaging sensitivity: range 16-67.5% specificity: range 86-100% meta-analysis not performed because of significant heterogeneity
Comparator		EUS sensitivity: range 20-100% specificity: range 36-100% AUC: 0.86 (95% CI 0.77-0.96)	from the SR of Westerterp 2005 indirect comparisons with EUS sensitivity: range 50-100% specificity: range 36-100% CT sensitivity: range 33-55% specificity: range 50-71%
Reference standard	histopathology	pathologic confirmation	histopathology other imaging techniques clinical follow up of at least 1 year

Primary studies

Seven studies were found (Erasmus 2006; Higuchi 2008; Kim 2007; Klaeser 2009; Roedl 2008; Roedl 2009b; Wieder 2007), published after the above reported SRs, on diagnostic accuracy of FDG-PET in the evaluation of patients' response to neoadjuvant therapy (*Table 8.2*). Four studies applied FDG-PET and 3 FDG-PET/CT. The overall number of patients studied was 329. Studies included patients with squamous cell carcinoma (3) or adenocarcinoma (1) or both (3). The studies have been retrieved and assessed only for overall consistency with results on diagnostic accuracy of systematic reviews.

Table 8.2. Synthesis of main results of primary studies

References	Erasmus 2006; Higuchi 2008; Kim 2007; Klaeser 2009; Roedl 2008; Roedl 2009b; Wieder 2007
Number of studies	7
Number of patients	329 (median 49, range 24-62)
FDG-PET/PET-CT	sensitivity: range 47-91% specificity: range 52-93%

Comments of ASSR reviewer

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

For the evaluation of metabolic response, sensitivity and specificity of FDG-PET resulted highly heterogeneous. A similar heterogeneity was documented for EUS. Heterogeneity of estimates is confirmed by the primary studies published since 2006.

Diagnostic accuracy estimates

FDG-PET sensitivity: (heterogeneous) range 27-100%
FDG-PET specificity: (heterogeneous) range 30-100%

EUS* sensitivity: (heterogeneous) range 20-100%
EUS* specificity: (heterogeneous) range 36-100%

CT* sensitivity: range 33-55%
CT* specificity: range 50-71%

* data from studies evaluating FDG-PET

LEVEL OF EVIDENCE: VERY LOW

8.2. Clinical outcomes

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

The panel voted "critical" the consequences for responders - true and false responders - and for false non responders, while outcomes for true non responders were considered "important".

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

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

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

Patient-important outcomes	**Median score (range)**
Consequences of test for responders	
• True responders - responders proceed to curative, radical treatment, which could improve survival	7 (1-9)
• False non responders - responders do not receive curative, radical treatment, which could have improved survival, and proceed to less radical, palliative treatment	7 (3-9)
Consequences of test for non responders	
• True non responders - non responders proceed to less radical, palliative treatment	6 (1-9)
• False responders - non responders proceed to curative, radical treatment, with no possible gain in survival	7 (3-9)

8.3. Voting results

The first voting round registered a strong disagreement between panelists, with ratings falling in the inappropriate, uncertain and appropriate regions (median score 5; range 3-8). The disagreement decreased in the second voting round, with ratings between inappropriate and uncertain and a median score of 3 (range 1-6).

FINAL RATING FOR THE USE OF FDG-PET FOR EVALUATION OF RESPONSE TO THERAPY AT THE END OF TREATMENT:

UNCERTAIN

8.4. Conclusions

A disagreement among panelists was registered in both round of voting, with ratings falling in all three regions in the first round, and ratings falling within the uncertain and inappropriate regions in the second round. The use of FDG-PET, in addition to CT, in the evaluation of response to neoadjuvant therapy at the end of treatment, in order to decide between curative or palliative therapeutic course of action, resulted as uncertain due to disagreement.

The level of evidence for diagnostic accuracy was very low, with heterogeneity for both sensitivity and specificity. Outcomes for patients testing as responders - true and false responders - and for false non responders were voted "critical" (median score 7), while outcomes for true non responders were considered "important".

9. Follow up in patients with no suspicion of recurrence

Rationale

Follow up of patients with esophageal or gastric cancer should monitor symptoms, signs and nutritional status in order to detect disorders of function either related to recurrent disease or affecting quality of life (SIGN 2006).

No guideline recommends any kind of active follow up (AIOM 2009; ESMO 2010; NCCN 2010; SIGN 2006).

Anticipating the diagnosis of recurrence could lead to a curative resection of a solitary metastasis or an early start of chemotherapy/chemoradiotherapy.

Diagnostic role of FDG-PET

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

Treatment effectiveness

There is no evidence that regular follow up after initial therapy may influence the outcome (ESMO 2010) and no evidence has been identified to support regular imaging or measurement of serum tumor markers in the follow up of patients with esophageal cancer (SIGN 2006). Aim of treatment is purely palliative.

Pre-test probability and change in management

The median pre-test probability of cancer recurrence is 56% (range 55-57%; data from three studies: Roedl 2008; Sun 2009; Teyton 2009), which could be considered the hypothetical maximum degree of change in management achievable with a correct detection of recurrence in asymptomatic patients treated for esophageal cancer.

Evidence from 1 study (Sun 2009) on change in management following the application of FDG-PET shows an estimate of 60% (no details about the kind of change are reported).

Research question

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

9.1. Systematic review of literature: results

Results from update of systematic review of literature from Jan 2006

Only three primary studies on diagnostic accuracy and no systematic reviews were found. Results are reported below.

Primary studies

Three studies (Roedl 2008; Sun 2009; Teyton 2009) were included, 1 study applying FDG-PET/CT, 1 applying FDG-PET and 1 applying both (*Table 9.1*). The overall number of patients studied was 108 (range 20-47). Studies included patients that, after curative surgery, with or without previous neoadjuvant chemoradiotherapy, underwent FDG-PET evaluation during follow up every 6 months for at least 24 months. All studies used biopsy of the suspected recurrence and clinical follow up as reference standard. The studies were all limited by the low number of patients, possible verification bias, and possible unblinding of the index test when evaluating the reference standard.

Table 9.1. Results of primary studies

References	Roedl 2008; Sun 2009; Teyton 2009
Number of studies	3
Number of patients	108 (range 20-47)
Pre-test probability (frequency of recurrence)	range 55-57%
FDG-PET/PET-CT	FDG-PET sensitivity: range 89-100% specificity: range 55-85.3% FDG-PET/CT sensitivity: range 89-100% specificity: range 67-75%
Comparator	CT sensitivity: 65% specificity: 91.2%
Reference standard	biopsy of the suspected lesion or clinical follow up

Comments of ASSR reviewers

The evidence about the validity of the FDG-PET in detecting recurrence of esophageal cancer in patients with no suspicion of recurrence after definitive treatment (follow up) comes from only three studies on a limited number of patients.

Diagnostic accuracy estimates

Estimates of diagnostic accuracy are not robust and show an heterogeneity for specificity.

LEVEL OF EVIDENCE: VERY LOW

9.2. Clinical outcomes

To evaluate the balance between benefits and risks, the panel agreed to consider the presumed patient-important outcomes reported below (*Table 9.2*), and voted on the level of importance for each outcome. Median scores and ranges are reported for each outcome.

All outcomes were voted "important".

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

No matrix of "natural frequencies" was provided because of sparse data.

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

Patient-important outcomes	Median score (range)
Consequences of test for patients relapsing	
• True positives - patients undergo further test to confirm positive results and proceed to palliative treatment	4 (1-79)
• False negatives - patients remain in follow up until symptoms occur	4 (1-9)
Consequences of test for patients not relapsing	
• True negatives - patients remain in follow up and are reassured, after certain amount of stress	4 (1-9)
• False positives - patients undergo unnecessary further tests to prove negative and are exposed to unnecessary anxiety	6 (1-9)

9.3. Voting results

The first voting round registered a light disagreement of ratings between inappropriate and uncertain (median score 2.5; range 1-4), while the second voting round registered an agreement on inappropriate (median score 2; range 1-3).

FINAL RATING FOR THE USE OF FDG-PET IN FOLLOW UP OF PATIENTS WITH NO SUSPICION OF RECURRENCE:

INAPPROPRIATE

9.4. Conclusions

After an initial slight disagreement between inappropriate and uncertain, the panel agreed to judge as inappropriate the use of FDG-PET for patients in follow up with non suspicion of recurrence.

Level of evidence for diagnostic accuracy of FDG-PET in follow up was very low and coming from three primary studies of low methodological quality.

Outcomes for patients with recurrence - true positives and false negatives, as well as outcomes for patients correctly diagnosed as negatives were voted "important" (median score 4). A slightly higher score (median 6; range 1-9) was assigned to the outcomes of patients incorrectly testing positive for distant metastases and experiencing unnecessary stress and anxiety.

10. Diagnosis and staging of suspect distant recurrence

Rationale

After curative surgery it could be difficult to interpret occurring symptoms and signs and correctly differentiate local recurrence from scar.

Diagnostic role of FDG-PET

As more specific test, to resolve ambiguities resulting from conventional imaging and correctly identify relapsing patients needing treatment.

Treatment effectiveness

Recurrences of patients treated with radiation therapy with curative intent could be treated with surgery (NCCN 2010), while patients relapsing after surgery should be treated with palliative intent (AIOM 2009).

Pre-test probability and change in management

80.4% of patients with suspected recurrence have metastases (Guo 2007).

Research question: FDG-PET in add on

Has FDG-PET sufficient specificity to be used as an add on test to diagnose recurrence in patients with unclear results from conventional imaging?

10.1. Systematic review of literature: results

Results from update of systematic review of literature from Jan 2006

Only one study evaluating diagnostic accuracy of FDG-PET in suspected recurrence and no systematic reviews were found. Results are reported below.

Primary studies

One study (Guo 2007) was found (*Table 10.1*). Fifty-six patients with suspected recurrence of esophageal squamous cell carcinoma after definitive treatment performed a FDG-PET. FDG-PET validity in diagnosing recurrence was assessed comparing results with histopathology or clinical follow up (reference standard). The study was limited by the low number of patients belonging to a subgroup of esophageal cancer, by a possible verification bias and absence of blinding about the index test (FDG-PET) when evaluating the reference standard.

Table 10.1. Results of primary studies

Reference	Guo 2007
Number of patients	56
Pre-test probability (frequency of recurrence)	80.4%
FDG-PET/PET-CT	sensitivity: 95.6% specificity: 54.5%
Reference standard	histopatology or follow up

Comments of ASSR reviewer

The only evidence about the validity of the FDG-PET in diagnosing recurrence of esophageal cancer after definitive treatment comes from just one study on very few patients.

Diagnostic accuracy estimates

Not available as data on the validity of FDG-PET in diagnosing recurrence of esophageal cancer after definitive treatment comes from only one study on very few patients.

LEVEL OF EVIDENCE: VERY LOW

10.2. Clinical outcomes

To evaluate the balance between benefits and risks, the panel agreed to consider the presumed patient-important outcomes reported below (*Table 10.2*), and voted on the level of importance for each outcome. Median scores and ranges are reported for each outcome.

Outcomes were considered by the panel "critical" for all patients, except for true negative patients, whose consequences were voted "important".

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

No matrix of "natural frequencies" was provided because of sparse data.

Table 10.2. Patient-important clinical outcomes and median scores of importance

Patient-important outcomes	**Median score (range)**
Consequences of test for patients with recurrence	
• True positives - patients proceed to treatment for recurrence	7 (5-9)
• False negatives - patients delay start of treatment until symptoms occur, with a possible negative impact on quality of life	7 (2-9)
Consequences of test for patients without recurrence	
• True negatives - patients remain in follow up, after a considerable amount of stress	6 (2-7)
• False positives - patients undergo unnecessary treatment, with a possible negative impact on quality of life and suffer unnecessary distress	7 (4-9)

10.3. Voting results

Both voting rounds registered a slight disagreement with ratings fallings between uncertain and appropriate with a median score of 6 (range 4-7) in the first round and a median score of 7 (range 6-7) in the second round.

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

UNCERTAIN

10.4. Conclusions

A disagreement among panelists was registered in both round of votes, with ratings falling in both the uncertain and appropriate region. The use of FDG-PET as an add on test for the diagnosis and staging of distant recurrence in patients with clinical suspicion of recurrence or unclear conventional imaging results resulted as uncertain due to disagreement.

Level of evidence for diagnostic accuracy of FDG-PET was very low, coming from only one study with very few patients. Outcomes were considered "critical" (median score 7) for true and false positives, as well as for false negatives, and "important" (median score 6) for patients correctly found negatives.

Conclusions

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

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

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Peer review reports

Reviewers 1 & 2

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

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

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

Thank you for sharing this valuable work.

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April 27th 2011

Reviewer 3

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

With regard to the esophageal cancer review:

- interim PET does reliably predict outcome of neoadjuvant therapy, but to date this has not been translated into response-adapted clinical strategies. One hopes this recommendation won't keep that from happening;
- the review of response assessment at the end of neoadjuvant therapy should also have addressed the frequency of upstaging to M1 disease, thus precluding surgery, in these patients.

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May 2nd 2011

Appendices

Appendix 1.
Voting forms

ORI
Osservatorio Regionale per l'Innovazione

CRITERIA FOR APPROPRIATE USE OF POSITRON EMISSION TOMOGRAPHY IN ONCOLOGY

2010-2011

ESOPHAGEAL CANCER

VOTING FORMS

NAME

_____

Agenzia sanitaria e sociale regionale

RegioneEmilia-Romagna

CLINICAL QUESTION

Staging patients with primary esophageal cancer

a - N staging of patients with primary esophageal cancer

Rationale

Surgical treatment is the therapy of choice for all patients with potentially curable esophageal cancer and who are fit for major surgery.

Accurate pre-operative staging is necessary to correctly direct patients to curative surgery, non curative surgery or nonsurgical therapy (combined chemoradiation).

N staging is used to decide on need for neoadjuvant treatment.

Treatment effectiveness

The expected 2-year survival after curative surgical treatment (without neoadjuvant chemoradiotherapy) ranges between 20 and 50%. In case of regional lymph node involvement long-term survival does not exceed 25%. In patients with locally advanced cancer pre-operative chemoradiotherapy improves the 2-year survival by 13% (absolute difference) compared to surgical treatment only (Gebski Lancet Oncology 2007)

Research question: FDG-PET as replacement
Is FDG-PET better (i.e. has higher diagnostic accuracy) than the available comparator (EUS) for N staging of regional lymph nodes in patients with esophageal cancer?

Pre-test probability

61.3% of patients diagnosed with primary esophageal cancer have positive lymph node (van Vliet 2008).

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

FDG-PET	sensitivity: (heterogeneous) range 0-100% specificity: (heterogeneous) range 60-100%
Comparator EUS*	sensitivity: (pooled) 80% specificity: (pooled) 70%

* data from studies evaluating FDG-PET included in van Vliet 2008

Consequences of TEST for		Level of importance* (1-9)
Patients with involvement of regional nodes	True positives: patients are correctly upstaged and undergo neoadjuvant therapy, which could improve survival False negatives: patients are incorrectly downstaged and do not receive necessary neoadjuvant therapy, which could have improved survival	
Patients without involvement of regional nodes	True negatives: patients proceed directly to curative resection of primary tumor, aimed at improving survival False positives: patients are incorrectly upstaged and have to undergo unnecessary neoadjuvant therapy, with no improvement on survival and possible unnecessary peri/post-operative adverse effects	

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

CLINICAL QUESTION

Role of FDG-PET in N staging of patients with primary esophageal cancer

APPROPRIATENESS of FDG-PET 1-2-3 inappropriate 4-5-6 uncertain 7-8-9 appropriate	1	2	3	4	5	6	7	8	9
INDETERMINATE									

b - M staging of patients with primary esophageal cancer

Rationale

Tumor stage at diagnosis and comorbidity are strong predictors of outcome and determinants of survival. M staging is used to identify and select patients eligible for curative surgery.

Treatment effectiveness

Only palliative treatment is available for metastatic esophageal cancer, aimed at improving quality of life.

Research question: FDG-PET as replacement
Is FDG-PET better (i.e. has higher diagnostic accuracy) than the available comparator (CT) in staging patients with primary esophageal cancer for distant metastasis?

Pre-test probability

35.7% of patients diagnosed for primary esophageal cancer has distant metastases (van Vliet 2008).

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

FDG-PET	sensitivity: (pooled) 71% specificity: (pooled) 93%
Comparator CT*	sensitivity: (pooled) 52% specificity: (pooled) 91%

* data from studies evaluating FDG-PET

Consequences of TEST for		Level of importance* (1-9)
Patients with distant metastases	True positives: patients are correctly upstaged and proceed to palliative treatment, aimed at improving quality of life	
	False negatives: patients are incorrectly downstaged and undergo unnecessary curative surgical treatment, which might not improve survival	
Patients without distant metastases	True negatives: patients correctly proceed to curative surgical treatment, which could improve survival	
	False positives: patients are incorrectly upstaged and denied necessary curative surgical treatment, which could have improved survival, and proceed to palliative treatment	

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

		M staging	
		N of patients out of 100 submitted to the exam	
		According to FDG-PET	According to CT
Patients with distant metastases	True positives	26	19
	False negatives	10	17
Patients without distant metastases	True negatives	60	58
	False positives	4	6
		100	100

CLINICAL QUESTION

Role of FDG-PET in M staging of patients with primary esophageal cancer

APPROPRIATENESS of FDG-PET 1-2-3 inappropriate 4-5-6 uncertain 7-8-9 appropriate	1	2	3	4	5	6	7	8	9
INDETERMINATE									

CLINICAL QUESTION

Target volume definition of radiation treatment with curative intent in patients with esophageal cancer

Rationale

Radiotherapy (with chemotherapy) is recommended as neoadjuvant treatment for locally advanced esophageal cancer by the majority of guidelines (AIOM 2009; ESMO 2010; NCCN 2010). Moreover consistently all the guidelines considered (AIOM 2009; ESMO 2010; NCCN 2010; SIGN 2006) propose (chemo)RT with curative intent for patients unfit for or unwilling surgery.

Research question: FDG-PET as add on
Does adding FDG-PET imaging lead to a better field definition of curative RT in patients with esophageal cancer?

Treatment effectiveness

For patients with locally advanced disease or operable esophageal cancer who decline surgery or who are unfit for surgery, chemoradiation may be an appropriate alternative (SIGN 2006).

Level of evidence: none

Diagnostic accuracy estimates

No data on diagnostic accuracy available.

CLINICAL QUESTION

Role of FDG-PET in the target volume definition of radiation treatment with curative intent in patients with esophageal cancer

APPROPRIATENESS of FDG-PET 1-2-3 inappropriate 4-5-6 uncertain 7-8-9 appropriate									
	1	2	3	4	5	6	7	8	9
INDETERMINATE									

CLINICAL QUESTION

Role of FDG-PET in early response to pre-operative chemoradiation of patients treated for locally advanced esophageal cancer

Rationale

As pre-operative chemotherapy/chemoradiotherapy could increase the risk of post-operative mortality (ESMO 2010), a selection of respondents to chemotherapy/ chemoradiotherapy after the first cycles could spare non respondents the risks of a futile full-length chemotherapy/chemoradiotherapy, hypothetically improving survival of these patients.

Treatment effectiveness

There are evidence that in patients with locally advanced cancer, pre-operative chemoradiation improves the 2-year survival by 13% (absolute difference) compared to surgical treatment only (Gebski Lancet Oncology 2007). On the other hand pre-operative chemotherapy could increase the risk of post-operative mortality (ESMO 2010).

Research question: FDG-PET as replacement
Is FDG-PET accurate in evaluating the early response to pre-operative chemoradiation of patients treated for locally advanced esophageal cancer?

Pre-test probability

43% of patients show an histopathological response to neoadjuvant chemotherapy (Lorenz 2007; Ngamruengphong 2010).

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

FDG-PET sensitivity: (heterogeneous) range 44-100%
specificity: (median) 74%

Comparator current practice
all patients complete pre-operative treatment

Consequences of TEST for		Level of importance* (1-9)
Patients responders	True responders: responders complete clinically effective pre-operative treatment, which could improve survival but might carries some risk of post-operative mortality	
	False non responders: responders interrupt clinically effective treatment, which could have improved survival, and proceed directly to surgery	
Patients non responders	True non responders: non responders interrupt ineffective treatment, which would not have improved survival, and proceed directly to surgery, with lower risks of post-operative mortality	
	False responders: non responders complete ineffective pre-operative treatment, with no possible gain in survival but with some risk of post-operative mortality	

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

		N of patients out of 100 submitted to the exam	
		According to FDG-PET	According to current practice
Patients responders	True responders	19 - 43	43
	False non responders	24 - 0	0
Patients non responders	True non responders	42	0
	False responders	15	57
		100	100

CLINICAL QUESTION

Role of FDG-PET in early response to pre-operative chemoradiation of patients treated for locally advanced esophageal cancer

APPROPRIATENESS of FDG-PET 1-2-3 inappropriate 4-5-6 uncertain 7-8-9 appropriate	1	2	3	4	5	6	7	8	9
INDETERMINATE									

CLINICAL QUESTION

Role of FDG-PET in evaluating response to neoadjuvant therapy at the end of treatment

Rationale

In patients with locally advanced disease treated with neoadjuvant chemotherapy/ chemoradiotherapy, their response to treatment should be evaluated in order to decide for subsequent type and aim of treatment (surgical, curative, palliative).

Treatment effectiveness

Surgical treatment is the therapy of choice for all patients with potentially curable esophageal cancer and who are fit for major surgery (AIOM 2009; ESMO 2010; NCCN 2010; SIGN 2006).

Research question: FDG-PET as add on

Does adding FDG-PET to CT lead to a more accurate evaluation of response to neoadjuvant therapy at the end of treatment?

Pre-test probability

42% of patients show an histopathological response to neoadjuvant chemotherapy (Kwee 2010; Ngamruengphong 2010).

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

High heterogeneity in both estimates of diagnostic accuracy are reported

FDG-PET	sensitivity: range 27-100
	specificity: range 30-100
EUS*	sensitivity: range 20-100
	specificity: range 36-100
CT*	sensitivity: range 33-55
	specificity: range 50-71

* data from studies evaluating FDG-PET

Consequences of TEST for		Level of importance* (1-9)
Patients responders	True responders: responders proceed to curative, radical treatment, which could improve survival False non responders: responders do not receive curative, radical treatment, which could have improved survival, and proceed to less radical, palliative treatment	
Patients non responders	True non responders: non responders proceed to less radical, palliative treatment False responders: non responders proceed to curative, radical treatment, with no possible gain in survival	

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

CLINICAL QUESTION

Role of FDG-PET in evaluating response to neoadjuvant therapy at the end of treatment

APPROPRIATENESS of FDG-PET 1-2-3 inappropriate 4-5-6 uncertain 7-8-9 appropriate	1	2	3	4	5	6	7	8	9
INDETERMINATE									

CLINICAL QUESTION

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

Rationale

Follow up of patients with esophageal or gastric cancer should monitor symptoms, signs and nutritional status in order to detect disorders of function either related to recurrent disease or affecting quality of life (SIGN 2006).

Treatment effectiveness

There is no evidence that regular follow up after initial therapy may influence the outcome (ESMO 2010) and no evidence has been identified to support regular imaging or measurement of serum tumor markers in the follow up of patients with esophageal cancer (SIGN 2006). Aim of treatment is purely palliative.

Research question: FDG-PET introduced as new test

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

Pre-test probability

55-57% of patients have distant recurrence (Roedl 2008; Sun 2009; Teyton 2009).

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

The evidence about the validity of the FDG-PET in detecting recurrence of esophageal cancer in patients with no suspicion of recurrence after definitive treatment (follow up) comes from three low quality study providing heterogeneous estimates for both sensitivity and specificity.

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

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

CLINICAL QUESTION

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

APPROPRIATENESS of FDG-PET 1-2-3 inappropriate 4-5-6 uncertain 7-8-9 appropriate	1	2	3	4	5	6	7	8	9
INDETERMINATE									

CLINICAL QUESTION

Role of FDG-PET in the diagnosis and staging of suspected recurrence in patients treated for esophageal cancer with clinical suspicion of recurrence or unclear conventional imaging results

Rationale

After curative surgery it could be difficult to interpret occurring symptoms and signs and correctly differentiate local recurrence from scar. In case of a local recurrence a new resection of the tumor could be planned.

Treatment effectiveness

Recurrences of patients treated with radiation therapy with curative intent could be treated with surgery (NCCN 2010), while patients relapsing after surgery should be treated with palliative intent (AIOM 2009).

Research question: FDG-PET as add on

Has FDG-PET sufficient specificity to be used as an add on test to diagnose recurrence in patients with unclear results from conventional imaging?

Pre-test probability

80.4% of patients with suspected recurrence have metastases (Guo 2007).

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

The evidence about the validity of FDG-PET in diagnosing recurrence of esophageal cancer after definitive treatment comes from only one study on very few patients.

Consequences of TEST for		Level of importance* (1-9)
Patients with recurrence	True positives: patients proceed to treatment for recurrence False negative: patients delay start of treatment until symptoms occur, with a possible negative impact on quality of life	
Patients without recurrence	True negatives: patients remain in follow up, after a considerable amount of stress False positives: patients undergo unnecessary treatment, with a possible negative impact on quality of life and suffer unnecessary distress	

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

CLINICAL QUESTION

Role of FDG-PET in the diagnosis and staging of suspected recurrence in patients treated for esophageal cancer with clinical suspicion of recurrence or unclear conventional imaging results

APPROPRIATENESS of FDG-PET 1-2-3 inappropriate 4-5-6 uncertain 7-8-9 appropriate									
	1	2	3	4	5	6	7	8	9
INDETERMINATE									

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

ORI
Osservatorio Regionale per l'Innovazione

CRITERIA FOR APPROPRIATE USE OF POSITRON EMISSION TOMOGRAPHY IN ONCOLOGY

ESOPHAGEAL CANCER

SEARCH STRATEGY AND TABLES OF EVIDENCE

Agenzia sanitaria e sociale regionale

RegioneEmilia-Romagna

SEARCH STRATEGY

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

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

Reference lists of identified articles were checked for additional references.

CDSR, DARE, HTA database, CENTRAL search strategy

1. "Positron-Emission Tomography" *[MeSH descriptor explode all trees]*
2. "Fluorodeoxyglucose F18" [MeSH descriptor explode all trees]
3. "positron emission tomography": *ti,ab,kw*
4. pet*: *ti,ab,k*w
5. pet scan*: *ti,ab,kw*
6. "Fluorodeoxyglucose F18": *ti,ab,kw or*
7. fdg NEAR/2 18: *ti,ab,kw*
8. **1/7 OR**
9. "Esophageal Neoplasms" *MeSH descriptor explode all trees*
10. "esophageal cancer": *ti,ab,kw*
11. "Esophageal Neoplasm": *ti,ab,kw*
12. "Esophagus Cancer": *ti,ab,kw*
13. "Esophagus Neoplasm": *ti,ab,kw*
14. "esophageal cancer": *ti,ab,kw*
15. "esophagus cancer": *ti,ab,kw*
16. **10/15 OR**
17. **8 AND 16**

Publication date: 2006-2010

MEDLINE search strategy

1. "Fluorodeoxyglucose F18"[Mesh]
2. "2-Fluoro-2-deoxyglucose" [All Fields]
3. "18F Fluorodeoxyglucose" [All Fields]
4. "F 18 Fluorodeoxyglucose" [All Fields]
5. Fludeoxyglucose* [All Fields]
6. "2 fluoro 2 deoxy d glucose"[All Fields]
7. 18fluorodesoxyglucose*[All Fields]
8. fluorodeoxyglucose*[All Fields]
9. "fluorine 18 fluorodeoxyglucose" [All Fields]
10. 18fdg*[All Fields])
11. 18fluorodeoxyglucose*[All Fields]
12. 18fdg [All Fields]
13. 18 fdg* [All Fields]
14. fdg 18* [All Fields]
15. fdg/* [All Fields]
16. "fdg pet"[All Fields]
17. "Positron-Emission Tomography"[Mesh]
18. "positron emission tomography" [title/abstract]
19. pet [title/abstract]
20. "pet scan" [All Fields]
21. "pet scans" [All Fields]
22. "pet scanner" [All Fields]
23. petscan [All Fields]
24. **1/24 OR**
25. "esophageal cancer"[All Fields]
26. "esophagus cancer"[All Fields]
27. "Esophageal Neoplasms"[Mesh]
28. "Esophageal Neoplasm"
29. "Esophageal Cancer"
30. "Esophagus Neoplasm"
31. "Esophagus Cancer"
32. **25/31 OR**
33. **24 AND 32**
34. "editorial"[Publication Type]
35. "comment"[Publication Type]

36. "letter"[Publication Type]
37. "review"[Publication Type]
38. "case reports"[Publication Type]
39. 34/38 OR
40. **33 NOT 39**

Limits: humans

Publication date: 2006-2010

Languages: English, French, Italian, Spanish

EMBASE search strategy

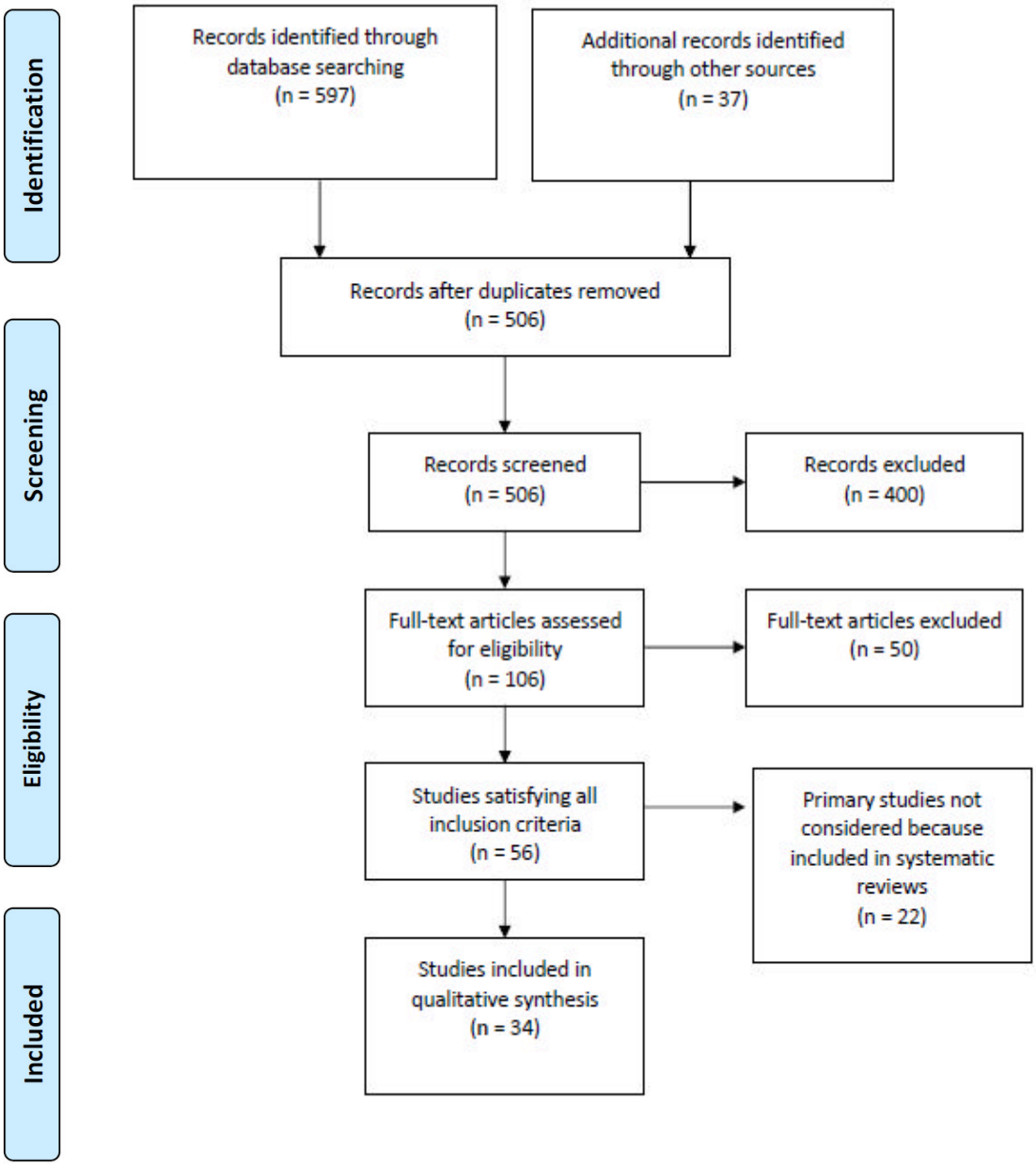
1. 'esophagus cancer'/exp
2. 'esophagus cancer'
3. 'esophagus cancer'/syn
4. 'esophageal NEXT (cancer OR neoplasm OR tumor)
5. **1/4 OR**
6. 'positron emission tomography'/syn
7. 'fluorodeoxyglucose f 18'/exp
8. ('fluorodeoxyglucose f 18'/syn
9. 'computer assisted emission tomography'/exp
10. 'computer assisted emission tomography' OR
11. pet
12. 'pet scans'
13. 'pet scanner'
14. 'pet scan'
15. 'pet/ct scan'
16. 'pet/ct scans'
17. 'pet/ct'
18. 'positron emission tomography/computed tomography'
19. pet NEAR/4 scan*
20. pet NEAR/4 ct
21. **6/20 OR**
22. **5 AND 21**

Limits: humans

Publication date: 2006-2010

Languages: English, French, Italian, Spanish

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



TABLES OF EVIDENCE

Chapter 4
N staging of patients with primary esophageal cancer

Diagnostic accuracy

Systematic reviews

Author, year	**van Vliet 2008**
Technology	FDG-PET
Disease	esophageal cancer
Objective	to assess: ▪ staging
Inclusion criteria	P patients with newly diagnosed esophageal cancer who did not received previous radiation or chemotherapy I FDG-PET C endoscopic ultrasonography (EUS), CT R histopathology following resection or FNA, clinical follow up with or without radiological examination O diagnostic accuracy for N staging, M staging S diagnostic accuracy studies with prospective or retrospective recruitment
Years covered by the search	up to January 2006
Study selection data abstraction, quality assessment performed by two authors independently	yes
Comprehensive bibliographic search: at least two databases searched	no Medline
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	yes (only reference lists)
Searched also unpublished studies	no
Language restriction	not specified
Overall number of references retrieved and n. of included studies reported	yes

N. and references of excluded studies reported, reason given	no
Characteristics of included studies clearly reported in tables	yes
Methodological quality of primary studies assessed; criteria reported	no; but two methodological criteria used in the regression model (consecutive or not recruitment, blinded or not interpretation of results)
Results of quality assessment used to formulate results and conclusions	yes; two methodological criteria used in the regression model (consecutive or not recruitment, blinded or not interpretation of results)
Meta-analysis performed with appropriate statistic methods	yes
Publication bias assessed	yes
N. of included studies Study design	EUS 31 for N staging CT 17 for N staging, 7 for M staging FDG-PET 10 for N staging, 9 for M staging
Patients of included studies	not reported data on patients characteristics
Pre-test probability when given	
N. of included patients	EUS 1 841 CT N staging 943, M staging 437 FDG-PET N staging 424, M staging 475
Reference standard	histopathology following resection or FNA clinical follow up with or without radiological examination
Comparator	EUS, CT
Performance results	N staging EUS sensitivity: 80% (95% CI 75-84) specificity: 70% (95% CI 65-75) CT sensitivity: 50% (95% CI 41-60) specificity: 83% (95% CI 77-89) FDG-PET sensitivity: 57% (95% CI 43-70) specificity: 85% (95% CI 76-95)
Impact on management	not assessed
Impact on clinical outcome	not assessed

Authors' recommendations and conclusions	EUS was significantly more sensitive but less specific than CT and PET for the detection of regional lymph nodes. The overall diagnostic performance of the three tests was similar. PET is more sensitive and specific in the detection of distant metastases compared with CT. The presence of malignant regional lymph nodes can be determined by EUS, CT or FDG-PET. To exclude the presence of positive lymph nodes, EUS should be used, whereas detected lesions should be confirmed with FNA or, alternatively, with CT or PET. Both CT and PET can be used to detect distant metastases, however the results suggest that PET has higher diagnostic performance.
Comments of ASSR reviewers	indirect comparisons

Synoptic table of primary studies on N staging

Author, year	Technology	Patient number	Population	Staging	Sensitivity (%)	Specificity (%)
Yuan 2006	FDG-PET	45	SCC	N staging	81,71	87,3
	FDG-PET/CT				93,9	92,06
Buchmann 2006	FDG-PET	20	SCC	N staging	20	100
Little 2007	FDG-PET	58	AC	N staging	0	94
Katsoulis 2007	FDG-PET	22	SCC, AC	N staging	71	67
Kato 2008	FDG-PET	117	SCC	N staging	55	86
	FDG-PET/CT	50			75,9	81
Sandha 2008	FDG-PET	29	SCC, AC	N staging	36	100
Schreurs 2008	FDG-PET	125	SCC, AC	N staging	100	98
		55			100	95
	FDG-PET/CT	125			100	99
		55			100	98
Hsu 2009	FDG-PET	45	SCC	regional N staging	57,1	83,3
				not regional N staging	36,4	82,4
Hu 2009	single time point FDG-PET	28	SCC	N staging	76,06	85,16
	dual time point FDG-PET			N staging	88,73	91,87

Author, year	Technology	Patient number	Population	Staging	Sensitivity (%)	Specificity (%)
Okada 2009	FDG-PET	18	SCC	regional N staging	60	99,5
				paratracheal N staging	56	97,3
Roedl 2009	FDG-PET	81	AC	N staging	75	85
	FDG-PET/CT				76	96
Choi 2010	FDG-PET	109	SCC	N staging	49	87
Alberini 2009	FDG-PET/CT	62		95%	100%	33.3%

SCC = squamous cell carcinoma; AC = adenocarcinoma

Chapter 5
M staging of patients with primary esophageal cancer

Diagnostic accuracy

Systematic reviews

Author, year	van Vliet 2008
Technology	FDG-PET
Disease	esophageal cancer
Objective	to assess: ▪ staging
Inclusion criteria	P patients with newly diagnosed esophageal cancer who did not received previous radiation or chemotherapy I FDG-PET C endoscopic ultrasonography (EUS), CT R histopathology following resection or FNA, clinical follow up with or without radiological examination O diagnostic accuracy for N staging, M staging S Diagnostic accuracy studies with prospective or retrospective recruitment
Years covered by the search	up to January 2006
Study selection data abstraction, quality assessment performed by two authors independently	yes
Comprehensive bibliographic search: at least two databases searched	no Medline
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	yes (only reference lists)
Searched also unpublished studies	no
Language restriction	not specified
Overall number of references retrieved and n. of included studies reported	yes
N. and references of excluded studies reported, reason given	no
Characteristics of included studies clearly reported in tables	yes

Methodological quality of primary studies assessed; criteria reported	no; but two methodological criteria used in the regression model (consecutive or not recruitment, blinded or not interpretation of results)
Results of quality assessment used to formulate results and conclusions	yes; two methodological criteria used in the regression model (consecutive or not recruitment, blinded or not interpretation of results)
Meta-analysis performed with appropriate statistic methods	yes
Publication bias assessed	yes
N. of included studies Study design	EUS 31 for N staging CT 17 for N staging, 7 for M staging FDG-PET 10 for N staging, 9 for M staging
Patients of included studies	not reported data on patients characteristics
Pre-test probability when given	
N. of included patients	EUS 1 841 CT N staging 943, M staging 437 FDG-PET N staging 424, M staging 475
Reference standard	histopathology following resection or FNA clinical follow up with or without radiological examination
Comparator	EUS, CT
Performance results	M staging CT sensitivity: 52% (95% CI 33-71) specificity: 91% (95% CI 86-96) FDG-PET sensitivity: 71% (95% CI 62-79) specificity: 93% (95% CI 89-97)
Impact on management	not assessed
Impact on clinical outcome	not assessed
Authors' recommendations and conclusions	EUS was significantly more sensitive but less specific than CT and PET for the detection of regional lymph nodes. The overall diagnostic performance of the three tests was similar. PET is more sensitive and specific in the detection of distant metastases compared with CT. The presence of malignant regional lymph nodes can be determined by EUS, CT or PET. To exclude the presence of positive lymph nodes, EUS should be used, whereas detected lesions should be confirmed with FNA or, alternatively, with CT or PET. Both CT and PET can be used to detect distant metastases, however the results suggest that PET has higher diagnostic performance.
Comments of ASSR reviewers	indirect comparisons

Synoptic table of primary studies on M staging

Author, year	Technology	Patient number	Population	Staging	Sensitivity (%)	Specificity (%)
Buchmann 2006	FDG-PET	20	SCC	M staging	60	86
Little 2007	FDG-PET	58	AC	M staging	n.c.	95
Katsoulis 2007	FDG-PET	22	SCC, AC	M staging	88	100
Noble 2009	FDG-PET	191	SCC, AC	M staging	91	94

SCC = squamous cell carcinoma; AC = adenocarcinoma

Impact on clinical outcomes

Primary studies on adverse events of change in management according to FDG-PET results during staging

Author, year	Technology	Limits	Patient number	Patient characteristics	Standard practice	Verification test	Results
Meyers 2007	FDG-PET	not consecutive sample	189	patients with locally advanced esophageal cancer (T1-3, N0-1, M0)	usual clinical management (CT, MRI, scintigraphy, NOT EUS)	additional studies or biopsies in case of abnormalities by FDG-PET that suggested metastases	2 patients (1%) with false positive FDG-PET result ▪ 1 adrenalectomy with subsequent therapy for adrenal insufficiency ▪ 1 wound complication after a confirmatory procedure

Primary studies on patient burden of FDG-PET during staging

Author, year	Technology	Limits	Patient n.	Patient characteristics	Comparator	Results
Westerterp 2008	FDG-PET	-	82	(67 males, 15 females) Their mean age was 64.3 (SD ± 8.3) years After conventional workup ▪ 5 patients had a T1 tumor ▪ 10 patients a T2 tumor ▪ 63 patients a T3 tumor ▪ 4 patients had a T4 tumor	CT, US with/out fine needle aspiration, EUS with/out fine needle aspiration	For most tests and most dimensions of burden, the large majority of subjects was in categories 1 and 2 Embarrassment/discomfort: 4 (very) or 5 (very much) score: EUS: 7 pts (8.5%) US: 3 pts (3.6%) FDG-PET: 3 pts (3.6%) CT: 1 pt (1.2%) Anxiety 4 (very) or 5 (very much) score: FDG-PET: 6 pts (7.3%) EUS: 5 pts (6.1%) US: 2 pts (2.4%) CT: 2 pt (2.4%)

Chapter 6
Target volume definition of curative radiation treatment

Diagnostic accuracy

Systematic reviews

Author, year	Muijs 2010
Technology	FDG-PET FDG CT/PET
Disease	esophageal cancer
Objective	to assess: ▪ curative intent RT field definition (only solid tumors)
Inclusion criteria	P patients with esophageal cancer eligible for curative treatment I CT/PET C CT R histopathology O diagnostic accuracy in target volume delineation; evaluation of the consequences for radiotherapy treatment planning with regard to either target volumes or organs at risk S cross sectional studies with prospective or retrospective recruitment with at least 10 patients
Years covered by the search	up to 2009
Study selection data abstraction, quality assessment performed by two authors independently	no
Comprehensive bibliographic search: at least two databases searched	yes Medline, Cochrane Library
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	yes (only reference lists)
Searched also unpublished studies	no
Language restriction	yes (English)
Overall number of references retrieved and n of included studies reported	yes
N. and references of excluded studies reported, reason given	no
Characteristics of included studies clearly reported in tables	yes

Methodological quality of primary studies assessed; criteria reported	no
Results of quality assessment used to formulate results and conclusions	no
Meta-analysis performed with appropriate statistic methods	not applicable
Publication bias assessed	no
N. of included studies Study design	CT/PET: 12 studies (considering the questions of interest) prospective or retrospective cross sectional studies
Patients of included studies	not reported data on patients characteristics
Pre-test probability when given	
Patients of included studies	not reported
n. of included patients	247 (considering the questions of interest)
Reference standard	histopathology (4 studies)
Comparator	CT
Performance results	▪ changes in the delineation of target volumes (CTV/GTV/PTV) in a proportion of patients ranging from 20 to 94% with respect to CT (data from 6 studies: 142 patients); TV increase in a proportion of 10-31% of patients; TV decrease in a proportion of 10-62.5% of patients ▪ 3 out of 4 studies (89 patients) reported a significant positive correlation (r raging from 0.74 to 0.89) between FDG-PET tumor length and pathologic findings
Impact on management	▪ 1 study (16 patients): inadequate dose coverage in 38% of patients with treatment plan based on CT alone with respect to FDG-PET/CT-based PTV; no difference in radiation doses to the near organs ▪ 1 study (34 patients): changes in dose distribution to normal tissues in "virtually all patients" ▪ 1 study (21 patients): significant changes in dose distribution to heart and lungs
Impact on clinical outcome	no studies retrieved
Recommendations and conclusions	The use of FDG-PET/CT resulted in changes of target volumes, and consequently in changes in treatment planning. However, evidence supporting the validity of the use of FDG-PET/CT in the tumor delineation process is very limited. Tumor length comparison as pathological validation has important shortcomings and seems therefore unreliable. Furthermore, there are no studies demonstrating the use of PET/CT in terms of improved locoregional control or survival. Standard implementation of FDG-PET/CT into the tumor delineation process for radiation treatment seems therefore unjustified at this moment and needs further clinical validation first.

Primary studies

Author, year	Shimizu 2009
Country	Japan
Technology	PET/CT
Disease	esophageal cancer
Objective	to assess: ▪ curative intent RT field definition
Patients characteristics	20 (1 764 lymph nodes), 15 males and 5 females; median age 61 years (range 47-75 years), with squamous cell carcinoma of the esophagus, who consented to receive surgical esophagectomy. There were: 3 stage I patients, 8 stage II patients, 9 stage III patients.
Index test	FDG-PET/CT
Comparator	CT, PET/CT with EUS, CT with EUS
Verification test	histopathology after surgery
Outcomes considered	diagnostic accuracy: clinical target volume (CTV) of lymph node metastases
Results	53 (3.0%) of 1 764 nodes in the 20 patients were histopathologically positive for cancer cells. CTV not adequate to cover histopathologically detected positive lymph nodes ▪ 7/20 (35%) PET/CT ▪ 8/20 (40%) on CT ▪ 5/20 (25%) on PET/CT+EUS ▪ 5/20 (25%) on CT+EUS
Study design	prospective cohort
Consecutive recruitment	not known
independent and blind interpretation of index test and verification test results	yes
Authors' recommendations and conclusions	The detection rate of subclinical lymph node metastasis did not improve with the use of PET-CT, for either the cervical and supraclavicular, mediastinal, or abdominal regions. It is not recommended to use FDG-PET or PET-CT alone as a diagnostic tool to determine CTV if pathologically involved lymphatic regions are to be included in the CTV in the treatment protocol. The accuracy of PET/CT must be further improved in order to better detect positive nodes and improve the definition of the CTV.

Chapter 7
Evaluation of early response to neoadjuvant therapy

Diagnostic accuracy

Systematic reviews

Author, year	Rebollo Aguirre 2009
Technology	FDG-PET PET/CT
Disease	esophageal cancer
Objective	to assess: ▪ early response to therapy (FDG-PET during treatment) only when not adjuvant therapy
Inclusion criteria	P patients with proven esophageal cancer treated with neoadjuvant therapy I FDG-PET, CT/PET C none R histopathology, other imaging techniques, clinical follow up of at least 1 year O diagnostic accuracy evaluating response during treatment S diagnostic accuracy studies with prospective or retrospective recruitment with at least 10 patients
Years covered by the search	from 2004 to August 2006 (updating of the Westerterp 2005 systematic review)
N. of included studies Study design	FDG-PET: 3 assessment of response during treatment (none CT/PET)
Patients of included studies	patients with stage II and III with different histologic types. Neoadjuvant therapy consisted of varied cytotoxic drugs, mostly including platinum-based agents, + RT (except 1 study only chemotherapy)
Pre-test probability when given	not given
N. of included patients	FDG-PET during therapy: 84 CT/PET: 48
Reference standard	histopathology other imaging techniques clinical follow up of at least 1 year
Comparator	
Performance results	primary tumor response sensitivity: range 75-93% specificity: range 75-87% meta-analysis not performed because of significant heterogeneity

Impact on management	not assessed
Impact on clinical outcome	not assessed
Authors' recommendations and conclusions	The systematic review by Westerterp 2005 concluded that CT is inaccurate in evaluating response to neoadjuvant therapy because it does not distinguish between scar tissue and neoplastic tissue; EUS is as accurate as PET but is an invasive method not always feasible with some subjectivity and is operator dependent; so PET is the best method to evaluate induction therapy response. This updating, according to the authors, confirmed these results.
Note ASSR reviewers	both direct and indirect comparisons

Author, year	**Ngamruengphong 2009**
Technology	PET CT/PET
Disease	esophageal cancer
Objective	to assess: ▪ early response to therapy (PET during treatment) only when not adjuvant therapy
Inclusion criteria	P patients with esophageal cancer treated with neoadjuvant therapy I FDG-PET, CT/PET C EUS R histopathology O diagnostic accuracy for restaging after treatment and for assessing response during treatment S diagnostic accuracy studies with prospective or retrospective recruitment with at least 10 patients
Years covered by the search	up to February 2008
N. of included studies Study design	EUS: 7 PET: 6 during treatment (none with CT/PET)
Patients of included studies	patients with stage II and III with different histologic types. Neoadjuvant therapy consisted of varied cytotoxic drugs, mostly including platinum-based agents. Three studies performed interim FDG-PET after 2 weeks of treatment
Pre-test probability when given	median prevalence of responders (i.e. pre-test probability) is 42% (range 18-58%)
N. of included patients	EUS: 352 PET: 293
Reference standard	histopathology
Comparator	EUS
Performance results	EUS sensitivity: range 20-100% specificity: range 36-100% AUC: 0.86 (95% CI 0.77-0.96) FDG-PET and CT/PET all studies (both during and after therapy) sensitivity: range 42-100% specificity: range 27-100% AUC: 0.80 (95% CI 0.72-0.89) FDG-PET during therapy AUC: 0.78 (95% CI 0.62-0.93) no significant differences between accuracy during and after therapy
Impact on management	not assessed

Impact on clinical outcome	not assessed
Recommendations and conclusions	EUS and PET have similar overall diagnostic accuracy for assessment of response to neoadjuvant therapy. Each modality has its unique advantages and limitations and should be considered as complimentary rather than competing technologies. While in the subgroups analysis no significant differences were shown between PET and CT/PET, this technologies has been available only in the last few years and only three studies on CT/PET were included; it is expected that the use of integrated PET/CT scanner will replace PET only machines and that would likely increase the overall diagnostic accuracy of PET studies.
Comments of ASSR reviewers	both direct and indirect comparisons

Primary studies

Author, year	Lorenzen 2007
Country	Germany
Technology	FDG-PET
Disease	esophageal cancer or gastric cancer
Objective	to assess: ▪ early response to therapy (FDG-PET during treatment) only when not adjuvant therapy
Inclusion criteria	P patients with esophageal cancer treated with chemotherapy I FDG-PET after two weeks of chemotherapy C none R clinical response according to RECIST guidelines (including CT) O diagnostic accuracy for restaging after treatment and for assessing response during treatment S diagnostic accuracy studies with prospective or retrospective recruitment with at least 10 patients
Study design	prospective
Spectrum of participants representative of practice	no
Selection criteria described?	yes
Reference standard likely to classify correctly	uncertain
Period between reference standard and index test short	no
Whole sample or a random selection verification using the reference standard	no
Participants receive the same reference standard	yes
Reference standard independent of the index test	yes
Index test described in sufficient detail	yes
Reference standard described in sufficient detail	no
Index test interpreted without knowledge of reference standard	yes
Reference standard interpreted without knowledge index test	uncertain

Same clinical data available when the test results were interpreted as would be available when the test is used in practice	yes
Uninterpretable, indeterminate or intermediate test results reported	yes
Withdrawals explained	yes
N. of included patients	11
Patients of included studies	10 males and 1 female; median age 56 years (range 49-72); 5 adenocarcinoma and 6 squamous cell carcinoma. Neoadjuvant therapy consisted of oral capecitabine (administered at a dose of 1 000 mg m-2 twice daily on days 1-14 every three weeks) and docetaxel administered at a dose of 75 mg m-2 i.v. on day 1 every three weeks. Docetaxel was given 1 h before the first oral dose of capecitabine. Patients were treated until best response or until there was evidence of disease progression
Pre-test probability when given	clinical response rate 45% at the end of treatment
Reference standard	clinical response according to RECIST guidelines (including CT)
Comparator	none
Performance results	FDG-PET during therapy sensitivity: 100% specificity: 60%
Impact on management	not assessed
Impact on clinical outcome	not assessed
Recommendations and conclusions	In this heterogeneous study population, FDG-PET had a limited accuracy in predicting clinical response. However, the metabolic response prediction was particularly good in the subgroup of patients with esophageal squamous cell cancer. Therefore, FDG-PET and assessment of cancer therapy clearly merits further investigation in circumscribed patient populations with metastatic disease.

Impact on clinical outcomes

Primary studies

Author, year	Lordick 2007
Country	Germany
Technology	FDG-PET
Disease	esophageal cancer
Objective	to assess: ▪ early response to therapy (FDG-PET during treatment) only when not adjuvant therapy
Patients characteristics	111 underwent surgical resection. Patients with locally advanced adenocarcinoma of the esophagogastric junction (AEG) type 1 (distal esophageal adenocarcinoma) or type 2 (gastric-cardia-adenocarcinoma) according to Siewert's classification) were eligible. Patients were staged as cT3 or cT4 based on CT and endoscopic ultrasonography. Haematogenous metastases were excluded by FDG-PET. 62 years (IQR 52-67). 77 patients (69%) had AEG type 1 and 34 patients (31%) had AEG type 2. 49 (44%) were treated with cisplatin, folinic acid and fluorouracil; 45 (41%) received additional paclitaxel, and 17 (15%) received oxaliplatin, folinic acid and fluorouracil. Of 110 patients who were evaluable for response (one patient died before assessment), cisplatin, folinic acid, and fluorouracil were given to 26 responders and 22 non responders; oxaliplatin, folinic acid, and fluorouracil were administered to 8 responders and 9 non responders; paclitaxel, cisplatin, folinic acid and fluorouracil were given to 20 responders and 25 non responders.
Intervention	1. FDG-PET WITH metabolic response after two weeks of neoadjuvant chemotherapy (two cycles of cisplatin and folinic acid plus fluorouracil on days 1, 8, 15, 22, 29, and 36, all repeated on day 49. For patients with a glomerular filtration rate of less than 60 mL/Kg/min, oxaliplatin replaced cisplatin. Patients aged 60 years or younger with a good health status were additionally given paclitaxel on days 0, 14, and 28) and continuation until the end of treatment plan. Then patients with AEG type 1 tumors underwent abdominothoracic esophagectomyand those with AEG type 2 tumors had transhiatal extended gastrectomy if the resection margins were tumor-free, or underwent additional abdominothoracic esophagectomy if the resection margins contained tumor tissue 2. FDG-PET WITH metabolic response (the same as above) AND histopathological response

Comparator	1. FDG-PET WITHOUT metabolic response after two weeks of neoadjuvant chemotherapy (two cycles of cisplatin and folinic acid plus fluorouracil on days 1, 8, 15, 22, 29, and 36, all repeated on day 49. For patients with a glomerular filtration rate of less than 60 mL/Kg/min, oxaliplatin replaced cisplatin. Patients aged 60 years or younger with a good health status were additionally given paclitaxel on days 0, 14, and 28) and interruption of chemotherapy then performance of surgical resection. Patients with AEG type 1 tumors underwent abdominothoracic esophagectomyand those with AEG type 2 tumors had transhiatal extended gastrectomy if the resection margins were tumor-free, or underwent additional abdominothoracic esophagectomy if the resection margins contained tumor tissue 2. FDG-PET WITH metabolic response (the same as the Intervention group) WITHOUT histopathological response 3. FDG-PET WITHOUT metabolic response (the same as the Intervention group) WITHOUT histopathological response
Verification test	istopathological tumor regression according to scoring system
Outcomes considered	overall survival event-free survival adverse events diagnostic accuracy (metabolic response vs histopathological response)
Results	Two patients (2%) died during chemotherapy (one non assessable patient and one responder). One of these had a sudden cardiac event, potentially induced by fluorouracil; retrospective analysis showed a skip mutation in exon 14 of the dihydropyrimidine dehydrogenase gene. The other patient had a lethal stroke of unknown relation to chemotherapy. After 2 weeks of chemotherapy, metabolic response was assessable in 110 patients (one patient died before assessment): 54 patients (49% [95% CI 39-59]) were metabolic responders and 56 patients (51% [95% CI 41-61]) were metabolic non responders. No significant differences were noted in the baseline characteristics of responders versus non responders with regard to age, sex, performance status, tumor localisation, T-category tumor size and N-category nodal status, and histological subtype. By contrast, the tumors of metabolically responsive patients tended to be less differentiated, and these patients had significantly higher median baseline SUVs of 8.3 (IQR 6.3-11.0-) versus 6.8 (IQR 5.1-9.0-) in non responders, p = 0.018. The number of patients with metabolic responses were not significantly different between the different chemotherapy regimens (p = 0.245). *(continues)*

	Of the 104 patients who had their tumors resected, 88 patients (85%) had tumor-free resection margins (R0 resection) and 16 patients (15%) had microscopically affected resection margins (R1). R0 resections could be done in 48 of 50 responding patients (96%) versus 40 of 54 non-responding patients (74%, p = 0·002). Post-operative deaths (30-day and in-hospital mortality) occurred in 2 of 104 patients (2%), and post-operative complications were reported in 35 patients (34%), with no statistical difference for metabolic responders versus non responders. In the metabolic responder group, 29 of 50 patients (58% [95% CI 48-67]) achieved a major histopathological response (<10% residual tumor): 8 patients (16%) achieved complete tumor remission; and 21 patients (42%) had subtotal remission. No histological response was noted in metabolic non responders. A higher number of low stage tumors was reported in metabolic responders than in non responders. Median event-free survival of 29·7 months (95% CI 23.6-35.7) for metabolic responders compared with 14.1 months (7.5-20.6) for non responders (HR 2.18 [1.32-3.62], p = 0·002). Median overall survival was not reached in metabolic responders, whereas nonresponders had a median overall survival of 25.8 months (19.4-32.2; HR 2.13 [95% CI 1.14-3.99], p = 0.015). Metabolic responders who also had a major histological response (n = 29) had a significantly better event-free survival (HR 3.03 [1.28-7.16], p=0.006) and overall survival (HR 4.55 [1.37-15.04], p=0.004) than did metabolic responders who did not achieve a histological response (n=21). By contrast, event free survival (HR 1.29 [0.69-2.45], p=0.430) and overall survival (HR 1.21 [0.56-2.63], p=0.549) did not differ significantly when comparing metabolic responders without a histological response (n=21) with metabolic non responders (n=54) Diagnostic accuracy of metabolic response sensitivity: 100% specificity: 72% LR+ = 3.6 LR- = - infinito
Study design	prospective series
Representativeness of the exposed cohort	selected group of users

Selection of the non exposed cohort	from the same community as the exposed cohort

Ascertainment of exposure	secure record
Demonstration that outcome of interest was not present at start of study	yes
Comparability of cohorts on the basis of the design or analysis	study controls for some important factors (select the most important factor) study controls for any additional factor
Assessment of outcome	no description
Was follow up long enough for outcomes to occur	yes
Adequacy of follow up of cohorts	complete follow up - all subjects accounted for subjects lost to follow up unlikely to introduce bias - small number lost X
Authors' recommendations and conclusions	This study confirmed prospectively the usefulness of early metabolic response evaluation, and shows the feasibility of a PET-guided treatment algorithm. These findings might enable tailoring of multimodal treatment in accordance with individual tumor biology in future randomised trials.

Chapter 8

Evaluation of response to neoadjuvant therapy at the end of treatment

Diagnostic accuracy

Systematic reviews

Author, year	Rebollo Aguirre 2009
Technology	FDG-PET PET/CT
Disease	esophageal cancer
Objective	to assess: ▪ response to therapy at the end of treatment
Inclusion criteria	P patients with proven esophageal cancer treated with neoadjuvant therapy I FDG-PET, CT/PET C none R histopathology, other imaging techniques, clinical follow up of at least 1 year O diagnostic accuracy evaluating response during treatment S diagnostic accuracy studies with prospective or retrospective recruitment with at least 10 patients
Years covered by the search	from 2004 to August 2006 (updating of the Westerterp 2005 systematic review)
N. of included studies Study design	FDG-PET: 4 assessment of response after therapy (1 study CT/PET)
Patients of included studies	patients with stage II and III with different histologic types. Neoadjuvant therapy consisted of varied cytotoxic drugs, mostly including platinum-based agents, + RT
Pre-test probability when given	not given
N. of included patients	FDG-PET after therapy: 164 CT/PET: 48
Reference standard	histopathology other imaging techniques clinical follow up of at least 1 year
Comparator	

Performance results	primary tumor response sensitivity: range 27.3-93.3% specificity: range 41.7-95.2% N restaging sensitivity: range 16-67.5% specificity: range 85.7-100% meta-analysis not performed because of significant heterogeneity
Impact on management	not assessed
Impact on clinical outcome	not assessed
Authors' recommendations and conclusions	The systematic review by Westerterp 2005 concluded that CT is inaccurate in evaluating response to neoadjuvant therapy because it does not distinguish between scar tissue and neoplastic tissue; EUS is as accurate as PET but is an invasive method not always feasible with some subjectivity and is operator dependent; so PET is the best method to evaluate induction therapy response. This updating, according to the authors, confirmed these results.
Comments of ASSR reviewers	both direct and indirect comparisons

Author, year	**Ngamruengphong 2009**
Technology	FDG-PET CT/PET
Disease	esophageal cancer
Objective	to assess: ▪ response to therapy at the end of treatment
Inclusion criteria	P patients with esophageal cancer treated with neoadjuvant therapy I FDG-PET, CT/PET C EUS R histopathology O diagnostic accuracy for restaging after treatment and for assessing response during treatment S diagnostic accuracy studies with prospective or retrospective recruitment with at least 10 patients
Years covered by the search	up to February 2008
N. of included studies Study design	EUS: 7 FDG-PET: 11 assessment of response after therapy (3 CT/PET)
Patients of included studies	patients with stage II and III with different histologic types. Neoadjuvant therapy consisted of varied cytotoxic drugs, mostly including platinum-based agents. Three studies performed interim FDG-PET after 2 weeks of treatment
Pre-test probability when given	median prevalence of responders (i.e. pre-test probability) is 42% (range 16-66%)
N. of included patients	EUS: 352 PET: 555 (CT/PET: 180)
Reference standard	histopathology
Comparator	EUS
Performance results	EUS sensitivity: range 20-100% specificity: range 36-100% AUC: 0.86 (95% CI 0.77-0.96) PET and CT/PET all studies (both during and after therapy) sensitivity: range 42-100% specificity: range 27-100% AUC: 0.80 (95% CI 0.72-0.89) PET and CT/PET after therapy AUC: 0.80 (95% CI 0.71-0.89) CT/PET after therapy AUC: 0.77 (95% CI 0.39-1.00) no significant differences between PET and CT/PET no significant differences between accuracy during and after therapy

Impact on management	not assessed
Impact on clinical outcome	not assessed
Recommendations and conclusions	EUS and PET have similar overall diagnostic accuracy for assessment of response to neoadjuvant therapy. Each modality has its unique advantages and limitations and should be considered as complimentary rather than competing technologies. While in the subgroups analysis no significant differences were shown between PET and CT/PET, this technologies has been available only in the last few years and only three studies on CT/PET were included; it is expected that the use of integrated PET/CT scanner will replace PET only machines and that would likely increase the overall diagnostic accuracy of PET studies.
Comments of ASSR reviewers	both direct and indirect comparisons

Author, year	**Kwee 2010**
Technology	PET CT/PET
Disease	esophageal cancer
Objective	to assess: ▪ response to therapy at the end of treatment
Inclusion criteria	P patients with suspected recurrence after definitive treatment of esophageal squamous cell carcinoma I CT/FDG-PET C none R histopathology O diagnostic accuracy evaluating response after treatment S diagnostic accuracy studies with prospective or retrospective recruitment with at least 10 patients
Years covered by the search	up to June 2009
Study selection data abstraction, quality assessment performed by two authors independently	no
Comprehensive bibliographic search: at least two databases searched	yes Medline, Embase, Cochrane Library
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	yes
Searched also unpublished studies	yes
Language restriction	no
Overall number of references retrieved and n of included studies reported	yes
N. and references of excluded studies reported, reason given	yes (only reasons, not references)
Characteristics of included studies clearly reported in tables	yes
Methodological quality of primary studies assessed; criteria reported	yes QUADAS checklist
Results of quality assessment used to formulate results and conclusions	yes
Meta-analysis performed with appropriate statistic methods	yes
Publication bias assessed	no

N. of included studies Study design	FDG-PET: 20 (7 CT/PET) prospective or retrospective cross sectional studies
Patients of included studies	patients with predominantly stage II and III. 7 studies included a single specific histopathology subtype, whereas the rest included different histologic types. Neoadjuvant therapy consisted of varied cytotoxic drugs, mostly including platinum-based agents, and 1 study including hyperthermia. All but 4 studies used concomitant therapeutic regimens of RT. Every study performed at least 2 FDG-PET scans per patient, one before the neoadjuvant treatment and another at the end.
Pre-test probability when given	hstopatologic response prevalence: median 42%, range 16-84%
N. of included patients	849
Reference standard	histopathology
Comparator	none
Performance results	sensitivity: range 33-100%; pooled estimate 67% (95% CI 62-72%) specificity: range 30-100%; pooled estimate 68% (95% CI 64-73%) area under the sROC curve was 0.7815 significant heterogeneity in both the sensitivity and specificity of the included studies ($p < 0.0001$) Spearman r between the logit of sensitivity and the logit of 1 - specificity was 0.086 ($p = 0.719$), which suggested that there was no threshold effect studies performed outside of the United States and studies of higher methodologic quality yielded significantly higher overall accuracy
Impact on management	not assessed
Impact on clinical outcome	not assessed
Recommendations and conclusions	on the basis of current evidence, 18F-FDG PET should not yet be used in routine clinical practice to guide neoadjuvant therapy decisions in patients with esophageal cancer

Synoptic table of primary studies evaluating response to neoadjuvant therapy at the end of treatment

Author, year	Technology	Patient number	Population	Staging	Sensitivity (%)	Specificity (%)
Erasmus 2006	FDG-PET/CT	52	SCC, AC, chemo and/or RT	T staging	47	58
Wieder 2007	FDG-PET	24	AC, chemoT	T staging	75	87
Kim 2007	FDG-PET	62	SCC, chemoT and RT	T staging	51,2	66,7
Higuchi 2008	FDG-PET	50	SCC, chemoT and/or RT	T staging	85,7	93,1
Klaeser 2009	FDG-PET or FDG-PET/CT	45	SCC, AC, chemoT	T staging	68	52
Roedl 2009	FDG-PET or FDG-PET/CT	49	SCC, chemoT and RT	T staging	86,5	91
Roedl 2008	FDG-PET or FDG-PET/CT	47	SCC, AC, chemoT and RT	T staging	91	92

SCC = squamous cell carcinoma; AC = adenocarcinoma
chemoT = chemotherapy
RT = radiotherapy

Chapter 9

Follow up in patients with no suspicion of recurrence

Diagnostic accuracy

Synoptic table of primary studies on follow up of patients with no suspicion of recurrence

Author, year	Technology	Limits	Patient number	Cancer characteristics	Treatment	Comparator	Reference standard	Recurrence rate	Results
Roedl 2008	FDG-PET, FDG-PET/CT	small study, B	47	squamous, adenoCa	surgical resection with neoadjuvant chemoradiotherapy	none	biopsy of the suspected lesion or clinical follow up	57%	FDG-PET sensitivity 89% specificity 55% FDG-PET/CT sensitivity 89% specificity 75%
Sun 2009	FDG-PET/CT	small study, S, R, B	20	not specified	surgical resection followed by radiotherapy	none	biopsy of the suspected lesion or clinical follow up	55%	FDG-PET/CT sensitivity 100% specificity 67%
Teyton 2009	FDG-PET	small study, B	41	squamous, adenoCa	surgical resection with/without neoadjuvant chemoradiotherapy	CT	biopsy of the suspected lesion or clinical follow up	56%	FDG-PET sensitivity 100% specificity 85.3% CT sensitivity 65% specificity 91.2%

Primary studies

Author, year	**Roedl 2008**
Country	USA
Technology	FDG-PET and FDG-PET/CT
Disease	esophageal cancer
Objective	to assess: ▪ follow up in asymptomatic patients
Inclusion criteria	P patients with squamous cell carcinoma and adenocarcinoma of the esophagus who underwent neoadjuvant chemoradiotherapy followed by surgery were included in the study. The clinical stage of all patients before neoadjuvant therapy was stage II or stage III I FDG-PET/CT e FDG-PET every 3 or 6 months till 24th month C none R biopsy of the suspected lesion or follow up with EUS O diagnostic accuracy during follow up
Study design	prospective consecutive
Spectrum of participants representative of practice	yes
Selection criteria described?	yes
Reference standard likely to classify correctly	yes (short follow up)
Period between reference standard and index test short	no
Whole sample or a random selection verification using the reference standard	yes
Participants receive the same reference standard	no
Reference standard independent of the index test	yes
Index test described in sufficient detail	yes
Reference standard described in sufficient detail	yes
Index test interpreted without knowledge of reference standard	yes
Reference standard interpreted without knowledge index test	uncertain

Same clinical data available when the test results were interpreted as would be available when the test is used in practice	yes
Uninterpretable, indeterminate or intermediate test results reported	uncertain
Withdrawals explained	not pertinent
N. of included patients	47
Patients characteristics	patients with squamous cell carcinoma and adenocarcinoma of the esophagus who underwent neoadjuvant chemoradiotherapy followed by surgery were included in the study. The clinical stage of all patients before neoadjuvant therapy was stage II or stage III
Outcomes considered	diagnostic validity: sensitivity/specificity
Pre-test probability	recurrence rate 57,4% (27/47)
Performance results	FDG-PET locoregional recurrence: sensitivity 83%, specificity 56% lymph nodes: sensitivity 68%, specificity 67% distant metastasis: sensitivity 84%, specificity 75% patient based: sensitivity 89%, specificity 55% FDG-PET/CT locoregional recurrence: sensitivity 92%, specificity 81% lymph nodes: sensitivity 82%, specificity 89% distant metastasis: sensitivity 89%, specificity 85% patient based: sensitivity 89%, specificity 75%
Authors' recommendations and conclusions	The present study demonstrates that the decrease of tumor length between the initial and post treatment PET-CT scan more accurately predicts treatment response and disease-free survival than does the decrease of SUV. In the evaluation of tumor recurrence, PET-CT was more accurate than PET both in a patient and in a lesion-based analysis; and PET-CT should be used routinely between 12 and 24 months after surgery to screen for recurrent sites.

Author, year	**Sun 2009**
Country	China
Technology	FDG-PET/CT
Disease	esophageal cancer
Objective	to assess: ▪ follow up in asymptomatic patients
Inclusion criteria	P patients after treatment of esophageal cancer treated with combined surgical treatment and radiotherapy management with or without clinically and/or radiologically suspicious findings for restaging I FDG-PET/CT C none R the standard reference for tumor recurrence consisted of histopathological confirmation or clinical follow up for at least ten months after 18F-FDG PET/CT O diagnostic accuracy after treatment or of suspected recurrence
Study design	retrospective
Spectrum of participants representative of practice	uncertain
Selection criteria described?	yes
Reference standard likely to classify correctly	uncertain (short follow up?)
Period between reference standard and index test short	no
Whole sample or a random selection verification using the reference standard	yes
Participants receive the same reference standard	no
Reference standard independent of the index test	yes
Index test described in sufficient detail	yes
Reference standard described in sufficient detail	no
Index test interpreted without knowledge of reference standard	yes
Reference standard interpreted without knowledge index test	uncertain

Same clinical data available when the test results were interpreted as would be available when the test is used in practice	yes
Uninterpretable, indeterminate or intermediate test results reported	uncertain
Withdrawals explained	no
n. of included patients	20
Patients characteristics	patients with esophageal cancer after surgical resection and following radiotherapy (15 males and 5 females; age range 39-68 years; mean age 55.1 years)
Outcomes considered	diagnostic validity: sensitivity/specificity
Pre-test probability	recurrence rate: 55% (11/20)
Performance results	recurrence sensitivity: 100% specificity: 67% accuracy: 85% negative predictive value (NPV): 100% positive predictive value (PPV): 78.6% the 3 false positive FDG-PET/CT findings were chronic inflammation of mediastinal lymph nodes (2) and anastomosis inflammation (1) clinical decisions of treatment were changed in 12 (60%) patients after introducing 18F-FDG PET/CT into their conventional post-treatment follow up program
Authors' recommendations and conclusions	Whole body 18F-FDG PET/CT is effective in detecting relapse of esophageal cancer after surgical resection and radiotherapy. It could also have important clinical impact on the management of esophageal cancer, influencing both clinical restaging and salvage treatment of patients.

Author, year	**Teyton 2009**
Country	France
Technology	FDG-PET
Disease	esophageal cancer
Objective	to assess: ▪ follow up in asymptomatic patients
Inclusion criteria	P patients with esophageal cancer after initial radical esophagectomy I FDG-PET about every 6 months C CT R biopsy of the suspected lesion or clinical follow up (median 48 months) O diagnostic accuracy during follow up
Study design	prospective consecutive
Spectrum of participants representative of practice	yes (of the lower stages)
Selection criteria described?	yes
Reference standard likely to classify correctly	yes
Period between reference standard and index test short	no
Whole sample or a random selection verification using the reference standard	yes
Participants receive the same reference standard	no
Reference standard independent of the index test	yes
Index test described in sufficient detail	yes
Reference standard described in sufficient detail	yes
Index test interpreted without knowledge of reference standard	yes
Reference standard interpreted without knowledge index test	uncertain
Same clinical data available when the test results were interpreted as would be available when the test is used in practice	yes
Uninterpretable, indeterminate or intermediate test results reported	uncertain

Withdrawals explained	not pertinent		
N. of included patients	41		
Patients characteristics	Thirty-eight were male (93%) and the mean age at the time of diagnosis was 60.7 ± 9.4 years. Most of the tumors were squamous cell carcinoma (76%) and most of the patients had a well differentiated or moderately differentiated tumor (90%). The majority of the tumors originated from the middle and lower esophagus (93%). In the population included in this study, 51% of the patients had an early stage disease (stage I or IIa), while 58% of the patients had a T3 primary lesion. Twenty patients (48%) had lymph node metastases (N1) at presentation		
Outcomes considered	diagnostic validity: sensitivity/specificity/accuracy		
Pre-test probability	recurrence rate: 56.1% (23/41)		
Performance results	FDG-PET		
	locoregional recurrence	sensitivity	93.3%
		specificity	97.4%
		accuracy	96.2%
	distant metastasis	sensitivity	100%
		specificity	89.4%
		accuracy	92.5%
	patient based	sensitivity	100%
		specificity	85.3%
		accuracy	90.7%
	CT		
	locoregional recurrence	sensitivity	60%
		specificity	100%
		accuracy	88.9%
	distant metastasis	sensitivity	66.6%
		specificity	92.1%
		accuracy	84.9%
	patient based	sensitivity	65%
		specificity	91.2%
		accuracy	81.5%

Authors' recommendations and conclusions	Surgery remains a major option in the management of esophageal neoplasms. Early diagnosis of recurrence in asymptomatic patients could be a good way to improve the management of those patients. The present study is the first prospective study systematically using FDG-PET in the follow up of surgically resected patients and it has shown that FDG-PET is accurate for the detection of early recurrence of esophageal cancer after initial surgery. Based on the presented results, FDG-PET could be included in the routine protocol for the evaluation of asymptomatic patients after surgery, as early as 6 months after the initial operative procedure. The use of FDG-PET in comparison with the use of endoscopy, CT scan, and/or echography remains to be demonstrated in terms of cost-effectiveness.

Chapter 10

Diagnosis and staging of suspect distant recurrence

Diagnostic accuracy

Primary studies

Author, year	Guo 2007
Technology	PET/CT
Disease	esophageal cancer
Objective	to assess: ▪ diagnosis of suspected recurrence and staging of recurrence
Inclusion criteria	P patients with suspected recurrence (indication of possible recurrence, such as questionable symptoms or signs, equivocal diagnosis by CT, EUS, MRI, or barium swallow) after definitive treatment of esophageal squamous cell carcinoma I FDG-PET/CT after suspected recurrence C none R histopatology or follow up O diagnostic accuracy of suspected recurrence
Study design	prospective non consecutive
Spectrum of participants representative of practice	no
Selection criteria described?	yes
Reference standard likely to classify correctly	yes
Period between reference standard and index test short	no
Whole sample or a random selection verification using the reference standard	yes
Participants receive the same reference standard	no
Reference standard independent of the index test	yes
Index test described in sufficient detail	yes
Reference standard described in sufficient detail	yes
Index test interpreted without knowledge of reference standard	yes

Reference standard interpreted without knowledge index test	no
Same clinical data available when the test results were interpreted as would be available when the test is used in practice	yes
Uninterpretable, indeterminate or intermediate test results reported	uncertain
Withdrawals explained	yes
N. of included patients	56
Patients characteristics	patients with suspected recurrence (indication of possible recurrence, such as questionable symptoms or signs, equivocal diagnosis by CT, EUS, MRI, or barium swallow) after definitive treatment of esophageal squamous cell carcinoma. 47 males and 9 females; age range 38-77 years. There were 5 stage IIb patients, 38 stage III patients, and 13 stage IV patients. The dominant treatment modalities preceding FDG-PET/CT were primarily surgery (surgery alone 4 patients; surgery plus radiation 11 patients; surgery plus chemoradiation 8 patients; surgery plus chemotherapy 3 patients) or radiotherapy (radiotherapy alone 3 patients; radiotherapy plus chemotherapy 27 patients).
Outcomes considered	diagnostic validity: sensitivity/specificity/accuracy
Pre-test probability	recurrence rate: 80.4% (45/56)
Performance results	Local recurrence sensitivity 96.9% specificity 50% accuracy 84.1% Regional recurrence sensitivity 89.5% specificity 81.8% accuracy 86.7% Distant metastasis sensitivity 90.5% specificity 92.9% accuracy 91.4% Patient based sensitivity 95.6% specificity 54.5% accuracy 87.5% *(continues)*

	Among the 9 false positive (FP) interpretations rendered on FDG-PET/CT, 5 lesions exhibited distinctly increased 18F-FDG uptake at the esophagogastric anastomosis but revealed no biopsy-proven recurrence by repeated endoscopy. The remaining 4 FP interpretations - including 1 focus near the back wall of gastric pull-up, 2 at hilar nodes, and 1 in the left lower lung - had also been excluded from recurrence after close follow up. FDG-PET/CT also had 5 false-negative (FN) interpretations. The first one occurred in a patient who had no positive FDG-PET/CT findings after radical radiotherapy. Five months later, he had dysphagia, and endoscopy validated malignancy at the location of primary tumor. The second patient had a subcarina lymph node measuring 1.2 cm in short-axis diameter on FDG-PET/CT (maximum SUV: 2.3) at 2 months after the completion of radiation therapy. Three months after the FDG-PET/CT scan, the shortest diameter of this node in the transverse axis increased to approximately 3 cm on followup CT. The third patient had a persistent dry cough starting at 2 months after surgery, but both subsequent CT and FDG-PET/CT showed no trace of a cancer-related focus. However, a paratracheal lymph node measuring 2.3 cm in diameter was detected on CT at 6-months follow up after surgery. The fourth FN interpretation involved a supraclavicular lymph node in a patient with upper-segment esophageal cancer that was treated with radiation at both the primary tumor and the regional nodes. The last FN interpretation was a 0.5-cm lung nodule at the right lower lobe. It was first detected by contrast-enhanced CT after radiation and was not visible on the concurrent FDG-PET/CT image. Serial CT images during follow up confirmed this lesion to be a distant metastasis.
Authors' recommendations and conclusions	PET/CT has displayed a remarkable sensitivity and a high specificity and accuracy at regional and distant sites for recurrent ESCC. 18F-FDG PET/CT can be recommended as a preferred tool for patients who have elusive clinical manifestations or equivocal results from conventional imaging modalities. The SUV and the disease pattern (with or without systemic recurrence) on PET/CT can offer incremental information in the prognostic evaluation. Although the specificity at the local area tends to be lower due to a high rate of FP findings, PET/CT remains valuable because positive PET/CT can encourage clinicians to make efforts to establish a definitive diagnosis through biopsies or close follow up, and the patients confirmed with recurrence would benefit from subsequent salvage therapy.

COLLANA DOSSIER

a cura dell'Agenzia sanitaria e sociale regionale

1990

1. Centrale a carbone "Rete 2": valutazione dei rischi. Bologna. **(*)**
2. Igiene e medicina del lavoro: componente della assistenza sanitaria di base. Servizi di igiene e medicina del lavoro. (Traduzione di rapporti OMS). Bologna. **(*)**
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1991

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7. Radioattività naturale nelle abitazioni. Bologna. **(*)**
8. Educazione alimentare e tutela del consumatore "Seminario regionale Bologna 1-2 marzo 1990". Bologna. **(*)**

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99. La sorveglianza per la sicurezza alimentare in Emilia-Romagna nel 2002. Bologna. **(*)**

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103. Assistenza alle persone affette da disturbi dello spettro autistico. Bologna.

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116. Audit delle misure di controllo delle infezioni post-operatorie in Emilia-Romagna. Bologna. **(*)**

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117. Dalla Pediatria di comunità all'Unità pediatrica di Distretto. Bologna. **(*)**

118. Linee guida per l'accesso alle prestazioni di eco-color doppler: impatto sulle liste di attesa. Bologna. **(*)**

119. Prescrizioni pediatriche di antibiotici sistemici nel 2003. Confronto in base alla tipologia di medico curante e medico prescrittore. Bologna. **(*)**

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121. Tomografia computerizzata multistrato per la diagnostica della patologia coronarica. Revisione sistematica della letteratura. Bologna. **(*)**

122. Tecnologie per la sicurezza nell'uso del sangue. Sussidi per la gestione del rischio 5. Bologna. **(*)**

123. Epidemie di infezioni correlate all'assistenza sanitaria. Sorveglianza e controllo. Bologna.

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137. Il profilo assistenziale del neonato sano. Bologna. **(*)**

138. Sana o salva? Adesione e non adesione ai programmi di screening femminili in Emilia-Romagna. Bologna. **(*)**

139. La cooperazione internazionale negli Enti locali e nelle Aziende sanitarie. Premio Alessandro Martignani - IV edizione. Catalogo. Bologna.

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145. Disuguaglianze in cifre. Potenzialità delle banche dati sanitarie. Bologna. **(*)**

146. Gestione del rischio in Emilia-Romagna 1999-2007. Sussidi per la gestione del rischio 8. Bologna. **(*)**

147. Accesso per priorità in chirurgia ortopedica. Elaborazione e validazione di uno strumento. Bologna. **(*)**

148. I Bilanci di missione 2005 delle Aziende USL dell'Emilia-Romagna. Bologna. **(*)**

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151. "Devo aspettare qui?" Studio etnografico delle traiettorie di accesso ai servizi sanitari a Bologna. Bologna. **(*)**

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153. Faringotonsillite in età pediatrica. Linea guida regionale. Bologna. **(*)**

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158. Mediare i conflitti in sanità. L'approccio dell'Emilia-Romagna. Sussidi per la gestione del rischio 9. Bologna. **(*)**

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166. Assistenza all'ictus. Modelli organizzativi regionali. Bologna. **(*)**

167. La chirurgia robotica: il robot da Vinci. ORIentamenti 1. Bologna. **(*)**

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175. Percorso nascita e qualità percepita. Analisi bibliografica. Bologna. **(*)**

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177. Ricerca e innovazione tecnologica in sanità. Opportunità e problemi delle forme di collaborazione tra Aziende sanitarie e imprenditoria biomedicale. Bologna. **(*)**

178. Profili di assistenza degli ospiti delle strutture residenziali per anziani. La sperimentazione del Sistema RUG III in Emilia-Romagna. Bologna. **(*)**

179. Profili di assistenza e costi del diabete in Emilia-Romagna. Analisi empirica attraverso dati amministrativi (2005 - 2007). Bologna. **(*)**

180. La sperimentazione dell'audit civico in Emilia-Romagna: riflessioni e prospettive. Bologna. **(*)**

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187. Studi per l'integrazione delle medicine non convenzionali. 2006-2008. Bologna. **(*)**

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188. Misure di prevenzione e controllo di infezioni e lesioni da pressione. Risultati di un progetto di miglioramento nelle strutture residenziali per anziani. Bologna. **(*)**

189. "Cure pulite sono cure più sicure" - Rapporto finale della campagna nazionale OMS. Bologna. **(*)**

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191. I contratti di servizio tra Enti locali e ASP in Emilia-Romagna. Linee guida per il governo dei rapporti di committenza. Bologna. **(*)**

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195. Indagine sul dolore negli ospedali e negli *hospice* dell'Emilia-Romagna. Bologna. **(*)**

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197. TB FLAG BAG. La borsa degli strumenti per l'assistenza di base ai pazienti con tubercolosi. Percorso formativo per MMG e PLS. Bologna. **(*)**

198. La ricerca sociale e socio-sanitaria a livello locale in Emilia-Romagna. Primo censimento. Bologna. **(*)**

199. Innovative radiation treatment in cancer: IGRT/IMRT. Health Technology Assessment. ORIentamenti 2. Bologna. **(*)**

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202. Master in Politiche e gestione nella sanità, Europa - America latina. Tracce del percorso didattico in Emilia-Romagna, 2009-2010. Bologna. **(*)**

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206. Contributi per la programmazione e la rendicontazione distrettuale. Bologna. **(*)**

207. Criteria for appropriate use of FDG-PET in breast cancer. ORIentamenti 3. Bologna. **(*)**

208. Il ruolo dei professionisti nell'acquisizione delle tecnologie: il caso della protesi d'anca. Bologna. **(*)**

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