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RegioneEmilia-Romagna

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA

Criteria for appropriate use of FDG-PET in colorectal cancer

ORIentamenti 5

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 ultrasound
FDG	fluoro-deoxyglucose
FN	false negatives
FP	false positives
LR	likelihood ratio
MA	meta-analysis
MRI	magnetic resonance imaging
NICE	National Institute of Clinical Excellence
PET	positron emission tomography
RCT	randomized controlled trial
RER	Regione Emilia-Romagna
RT	radiotherapy
SIGN	Scottish Intercollegiate Guidelines Network
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 del colon-retto

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

- diagnosi di tumore maligno primitivo del colon-retto -
  Inappropriato per mancanza di ruolo diagnostico della FDG-PET
- stadiazione N di tumore maligno primitivo del colon-retto -
  Inappropriato per mancanza di ruolo diagnostico della FDG-PET
- stadiazione M di tumore localmente avanzato del colon-retto -
  Appropriato (livello di evidenza: moderato)
- definizione del *target volume* nel trattamento radioterapico curativo in pazienti con tumore del retto -
  Inappropriato per mancanza di ruolo diagnostico della FDG-PET
- valutazione, durante il trattamento, della risposta precoce alla terapia per metastasi epatiche nel tumore del colon-retto -
  Indeterminato per mancanza di studi
- valutazione della risposta alla fine della radioterapia neoadiuvante per il tumore del retto -
  Inappropriato per mancanza di ruolo diagnostico della FDG-PET
- valutazione della malattia residua dopo trattamento ablativo delle metastasi epatiche -
  Incerto (livello di evidenza: molto basso)
- *follow up* in pazienti senza sospetto di recidiva -
  Inappropriato (livello di evidenza: molto basso)
- stadiazione di recidiva in pazienti trattati per tumore del colon-retto -
  Appropriato (livello di evidenza: moderato)

DIAGNOSI DI TUMORE MALIGNO PRIMITIVO DEL COLON-RETTO - INAPPROPRIATO

Pochi studi hanno valutato l'accuratezza della PET nella diagnosi di tumore maligno primitivo del colon-retto. Tuttavia il *panel* ha stabilito che non vi è un ruolo diagnostico della FDG-PET in questa indicazione clinica e ha concordato in modo unanime nel giudicare questo utilizzo inappropriato.

STADIAZIONE N DI TUMORE PRIMITIVO DEL COLON-RETTO - INAPPROPRIATO

Sono stati individuati una revisione sistematica e sei studi primari che hanno valutato l'accuratezza della FDG-PET nella stadiazione N del tumore primitivo del colon-retto. Tuttavia il *panel* ha stabilito che non vi è un ruolo diagnostico della FDG-PET in questa indicazione clinica e ha concordato in modo unanime nel giudicare questo utilizzo inappropriato.

STADIAZIONE M DI TUMORE LOCALMENTE AVANZATO DEL COLON-RETTO - APPROPRIATO

Dopo un iniziale forte disaccordo, durante la seconda riunione il *panel* ha concordato di considerare appropriato l'impiego della FDG-PET come esame di secondo livello nella stadiazione di pazienti con tumore del colon-retto localmente avanzato. Il disaccordo è stato risolto principalmente mediante una chiara definizione del ruolo diagnostico della FDG-PET, ovvero la selezione dei pazienti che possono maggiormente beneficiare di un trattamento chirurgico radicale.

L'impatto sulla sopravvivenza che si ottiene con una resezione chirurgica appropriata della lesione localizzata e delle metastasi resecabili è stato l'unico *outcome* considerato critico (punteggio mediano: 8, *range*: 2-9) mentre gli altri *outcome* (veri e falsi positivi e falsi negativi) sono stati considerati importanti.

Il livello delle evidenze che forniscono le stime dell'accuratezza diagnostica della FDG-PET è stato considerato moderato.

DEFINIZIONE DEL *TARGET VOLUME* NEL TRATTAMENTO RADIOTERAPICO CURATIVO IN PAZIENTI CON TUMORE DEL RETTO - INAPPROPRIATO

Il ruolo diagnostico della FDG-PET nella definizione del *target volume* del trattamento radioterapico a intento curativo è stato valutato in una revisione sistematica e in cinque studi primari. Tuttavia il *panel* ha ritenuto che non vi fosse un ruolo diagnostico della FDG-PET in questo ambito e pertanto ha unanimemente giudicato il suo utilizzo inappropriato.

VALUTAZIONE, DURANTE IL TRATTAMENTO, DELLA RISPOSTA PRECOCE ALLA TERAPIA PER METASTASI EPATICHE NEL TUMORE DEL COLON-RETTO - INDETERMINATO

Il *panel* ha discusso a lungo la problematica relativa alla risposta precoce al trattamento del tumore maligno del colon-retto, distinguendo tra pazienti con malattia plurimetastatica e pazienti trattati per metastasi epatiche potenzialmente resecabili. I voti espressi durante la prima votazione sono risultati molto disomogenei a causa di una differente interpretazione del ruolo diagnostico della FDG-PET. Durante il secondo incontro, il *panel* ha deciso di restringere il quesito clinico alla valutazione della risposta precoce al trattamento solo nei pazienti trattati per metastasi epatiche potenzialmente resecabili. Tutti gli esiti sono stati giudicati critici con un punteggio mediano di 7 tranne nel caso dei falsi *responder* (punteggio mediano: 6) che continuerebbero un trattamento di fatto non efficace.

Nonostante si sia concordato che sarebbe utile disporre di uno strumento diagnostico che possa discriminare tra pazienti *responder* e *non responder* alla terapia, l'assenza di evidenze per l'accuratezza diagnostica della FDG-PET in questa indicazione clinica ha portato il *panel* a concordare unanimemente nel giudicarne l'uso indeterminato.

VALUTAZIONE DELLA RISPOSTA ALLA FINE DELLA RADIOTERAPIA NEOADIUVANTE PER IL TUMORE DEL RETTO - INAPPROPRIATO

L'accuratezza della FDG-PET nella valutazione della risposta alla fine del trattamento radioterapico neoadiuvante in pazienti con tumore del retto è stata valutata in due revisioni sistematiche e in due studi primari. Tuttavia il *panel* ha concordato che non vi fosse un ruolo diagnostico della FDG-PET in questa indicazione clinica e ha giudicato in modo unanime il suo utilizzo come inappropriato. Il *panel* ha inoltre suggerito che la ricerca clinica potrebbe stabilire se la FDG-PET possa essere utilizzata al posto dell'indagine bioptica per identificare i pazienti con risposta completa al trattamento neoadiuvante al fine di decidere se optare per una chirurgia conservativa o demolitiva.

VALUTAZIONE DELLA RISPOSTA ALLA FINE DEL TRATTAMENTO ABLATIVO DELLE METASTASI EPATICHE - INCERTO

Il *panel* ha giudicato gli esiti importanti per il paziente correlati alla corretta individuazione di metastasi epatiche residue o ricorrenti per lo più critici (fatta eccezione per gli esiti per i veri negativi giudicati importanti). Il livello di evidenza a supporto dell'accuratezza diagnostica della FDG-PET è stato giudicato molto basso e il *panel* ha discusso a lungo il suo impatto sugli esiti clinici, poiché alcuni componenti del gruppo di lavoro hanno espresso dubbi sulla reale efficacia del trattamento ablativo delle metastasi epatiche. Questo si è manifestato nel disaccordo che si è registrato in entrambe le votazioni, con punteggi che vanno dall'inappropriato all'incerto. L'utilizzo della FDG-PET per la valutazione della malattia residua dopo trattamento ablativo delle metastasi epatiche è pertanto risultato incerto per disaccordo.

FOLLOW UP IN PAZIENTI SENZA SOSPETTO DI RECIDIVA - INAPPROPRIATO

Durante la discussione il *panel* ha preso in considerazione il ruolo della FDG-PET nei pazienti trattati per tumore maligno del colon-retto senza sospetto di recidiva per via dei risultati promettenti in favore di un *follow up* intensivo. Gli esiti clinici dei pazienti per i quali l'introduzione di un nuovo test avrebbe un impatto grazie a una diagnosi precoce e un trattamento tempestivo di eventuali ricadute sono stati considerati critici mentre l'esito relativo a un eventuale ritardo nell'individuazione e nel trattamento delle ricadute, che rappresenta la situazione attuale, è stato considerato importante.

Tuttavia, dati il livello molto basso delle evidenze relative all'accuratezza diagnostica della FDG-PET e la prevalenza della malattia, il *panel* ha ritenuto che fosse impraticabile proporre un'indagine FDG-PET a tutti i pazienti in *follow up* e quindi, dopo un lieve disaccordo iniziale tra incerto e inappropriato, durante la seconda votazione ha concordato nel giudicare l'utilizzo della FDG-PET in questo ambito inappropriato.

STADIAZIONE DI RECIDIVA IN PAZIENTI TRATTATI PER TUMORE DEL COLON-RETTO - APPROPRIATO

Dopo un iniziale lieve disaccordo, durante la seconda votazione il *panel* ha concordato nel giudicare appropriato l'utilizzo della FDG-PET nella diagnosi e stadiazione di sospetta recidiva in pazienti trattati per tumore del colon-retto. Il livello di evidenza per l'accuratezza diagnostica della FDG-PET è stato giudicato moderato e i membri del *panel* hanno considerato critici gli esiti clinici per i pazienti con metastasi resecabili o potenzialmente resecabili, sostenendo che una corretta identificazione dei pazienti che potrebbero beneficiare di una resezione chirurgica è da considerare l'obiettivo più importante.

Summary of results

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

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

- diagnosis of primary colorectal cancer -
  Inappropriate due to lack of diagnostic role of FDG-PET
- N staging of primary colorectal cancer -
  Inappropriate due to lack of diagnostic role of FDG-PET
- M staging of locally advanced colorectal cancer -
  Appropriate (level of evidence: moderate)
- target volume definition of curative radiation treatment in patients with rectal cancer -
  Inappropriate due to lack of diagnostic role of FDG-PET
- during treatment evaluation of early response to therapy of liver metastases in colorectal cancer -
  Indeterminate due to lack of studies
- end of treatment evaluation of response to neoadjuvant radiotherapy for rectal cancer -
  Inappropriate due to lack of diagnostic role of FDG-PET
- evaluation of residual disease following ablative treatment of liver metastases -
  Uncertain (level of evidence: very low)
- follow up in patients with no suspicion of recurrence -
  Inappropriate (level of evidence: very low)
- staging of recurrence in patients treated for colorectal cancer -
  Appropriate (level of evidence: moderate)

DIAGNOSIS OF PRIMARY COLORECTAL CANCER - INAPPROPRIATE

Few studies evaluating FDG-PET's accuracy in the diagnosis of primary colorectal cancer have been published. However the panel established that there is no diagnostic role of FDG-PET in this clinical indication and unanimously agreed to judge its use as inappropriate.

N STAGING OF PRIMARY COLORECTAL CANCER - INAPPROPRIATE

One systematic review and six primary studies evaluating FDG-PET's accuracy in N staging of primary colorectal cancer have been retrieved. However the panel established that there is no diagnostic role of FDG-PET in this clinical indication and unanimously agreed to judge its use as inappropriate.

M STAGING OF LOCALLY ADVANCED COLORECTAL CANCER - APPROPRIATE

After an initial strong disagreement, the panel agreed during the second meeting in rating the use of FDG-PET in staging patients with locally advanced primary colorectal cancer as appropriate.

The disagreement was resolved through a clearer definition of the diagnostic role of FDG-PET for the selection of patients who would most benefit from radical surgery.

The impact on survival obtained with appropriate surgical resection of localized disease and resectable metastases was in fact the only outcome considered critical (median score of 8; range 2-9), while remaining outcomes for true and false positives and for false negatives were judged important.

The level of evidence for estimates of FDG-PET's diagnostic accuracy was moderate.

TARGET VOLUME DEFINITION OF CURATIVE RADIATION TREATMENT IN PATIENTS WITH RECTAL CANCER - INAPPROPRIATE

One systematic review and five studies have assessed the role of FDG-PET in the target volume definition of radiation treatment in patients with rectal cancer. However the panel established that there is no diagnostic role of PET in this clinical indication and unanimously agreed to judge its use as inappropriate.

DURING TREATMENT EVALUATION OF EARLY RESPONSE TO THERAPY OF LIVER METASTASES IN COLORECTAL CANCER - INDETERMINATE

The panel discussed at length the issue of early response to treatment of metastatic colorectal cancer, differentiating patients treated for plurimetastatic disease from patients treated for potentially resectable liver metastases. Votes of the first round resulted highly heterogeneous due to the different interpretation of the diagnostic role of FDG-PET. During the second meeting the panel agreed to restrict the rationale in favour of evaluation of early response to treatment only for patients treated for potentially resectable liver metastases. Outcomes were voted critical with a median score of 7 in all cases except for false responders (median score of 6), who would continue a potentially ineffective treatment. Although it was agreed that a diagnostic tool differentiating responders from non responders would be useful, the absence of evidence for the diagnostic accuracy of FDG-PET in this clinical indication led the panel to unanimously agree to judge it as indeterminate due to lack of studies

END OF TREATMENT EVALUATION OF RESPONSE TO NEOADJUVANT RADIOTHERAPY FOR RECTAL CANCER - INAPPROPRIATE

Two systematic reviews and two primary studies have assessed the role of FDG-PET in the evaluation of end-of-treatment response to neoadjuvant therapy of rectal cancer. Nevertheless the panel agreed that there is no diagnostic role of PET in this clinical indication and unanimously agreed to judge its use as inappropriate.

The panel suggested that clinical research could be conducted investigating whether FDG-PET could replace biopsy in identifying patients with a complete response to neoadjuvant therapy at the end of treatment, in order to decide whether to opt for a conservative or more aggressive surgical approach.

EVALUATION OF RESIDUAL DISEASE FOLLOWING ABLATIVE TREATMENT OF LIVER METASTASES - UNCERTAIN

The panel judged the patient-important outcomes related to the correct identification of residual or recurrent liver metastatic lesion as mostly critical (except for outcomes of true negatives judged important). Level of evidence for FDG-PET diagnostic accuracy was graded as very low and the panel discussed at length the impact on clinical outcomes as some members express perplexities on the clinical effectiveness of ablative treatment. This is reflected in the unresolved disagreement between inappropriate and uncertain ratings registered in both rounds of voting. The use of PET for the evaluation of residual disease following ablative treatment of liver metastases resulted as uncertain due to disagreement.

FOLLOW UP IN PATIENTS WITH NO SUSPICION OF RECURRENCE - INAPPROPRIATE

During the discussion the panel envisaged a role of PET in the follow up of patients treated for colorectal cancer with no suspicion of recurrence, because of the promising results emerging in favor of an intensive follow up. The outcomes of patients for whom the introduction of a new test would impact upon, such as early detection and treatment of recurrence were in fact judged as critical, while possible delay in recurrence detection and treatment, which represent current situation, was rated as important. However, given the very low level of evidence and the prevalence of the disease, the panels considered impractical to offer a FDG-PET scan to all patients in follow up. The level of evidence for FDG-PET's diagnostic accuracy was judged very low and, after an initial light disagreement between uncertain and inappropriate, the panel agreed during the second voting round to judge the use of PET as inappropriate.

STAGING OF RECURRENCE IN PATIENTS TREATED FOR COLORECTAL CANCER - APPROPRIATE

After an initial light disagreement, the panel agreed during the second meeting in rating as appropriate the use of PET in diagnosis and staging of suspect recurrence in patients treated for colorectal cancer. Level of evidence for PET's diagnostic accuracy was graded moderate and panelists considered most critical the outcomes for patients with resectable/potentially resectable metastases, viewing most important the correct identification of patients who could benefit from surgical resection.

Foreword

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

The Dossiers are developed 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 colorectal cancer has been carried out between December 2010 and February 2011.

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

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

This Dossier is published in 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.

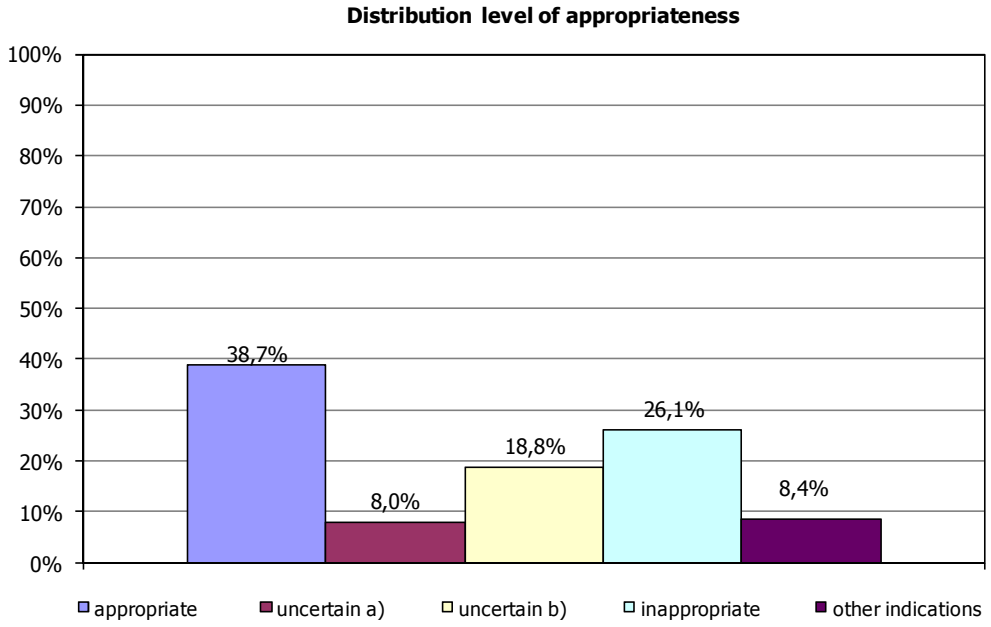
Since its introduction in the Emilia-Romagna Regional Health Service, the ASSR has been committed to promote and support regional research programmes aimed at assessing clinical indications for PET and supporting programming policies.

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

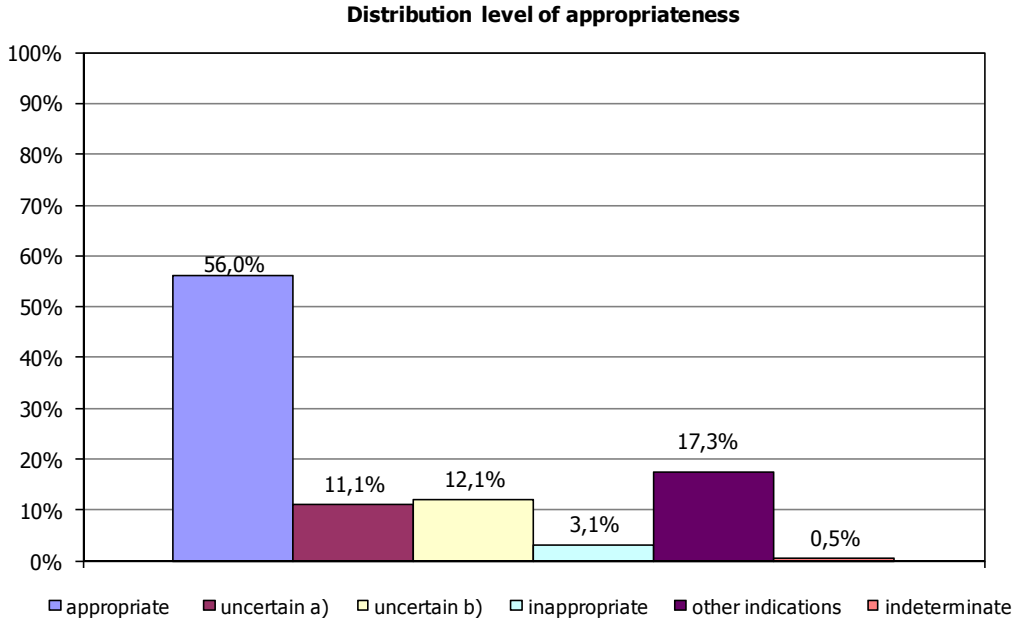
Following the increase in number of PET scanners (from 1 to 6) an update of the 2003 report was commissioned to a second regional panel and published in 2007. The second report addressed the role of PET in 18 types of cancer for a total of 65 clinical indications, and a second clinical audit was carried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

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

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



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



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

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

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

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

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

1.2. Context

Incidence of colorectal cancer

Crude incidence rate of colorectal cancer in Emilia-Romagna Region in 2004 (RER 2009): was 107.1 per 100 000 male inhabitants per year and 85.1 per 100 000 female inhabitants per year.

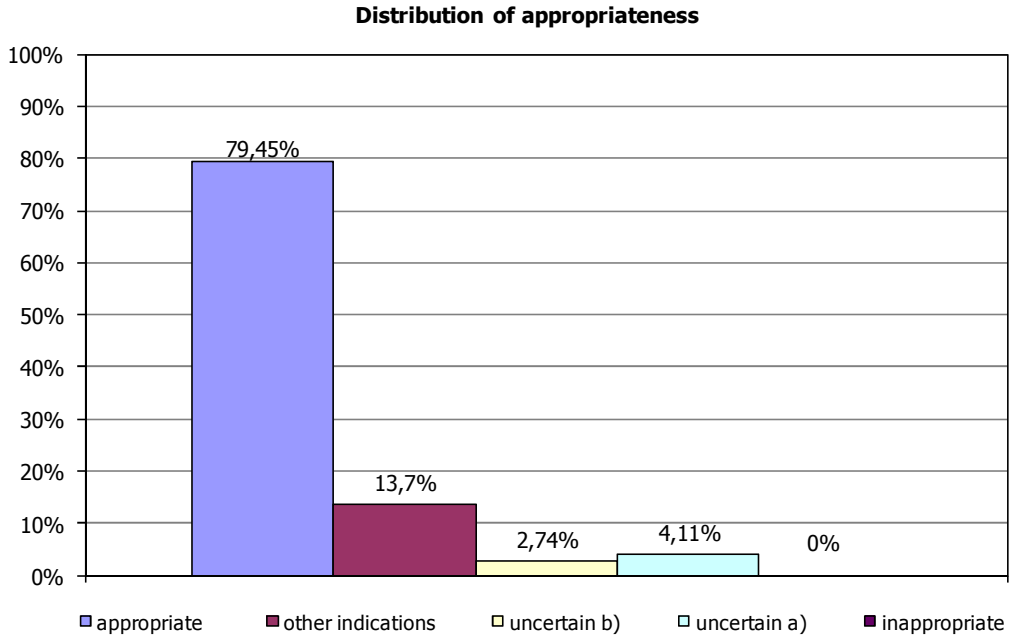
Prevalence of colorectal cancer

Cumulative 10 years prevalence estimate of colorectal cancer in Emilia-Romagna Region at 1/1/2005 (RER 2009) was 485.7 per 100 000 male inhabitants, corresponding to 9 800 cases in Emilia-Romagna region, and 396.1 per 100 000 female inhabitants, corresponding to 8 451 cases.

In the regional audit carried out in 2002, FDG-PET scans requested for patients with colorectal cancer represented 11% of the total sample included, and only 8% of requests were considered inappropriate, while the remaining 92% fell in the appropriate category.

In the 2007 audit, following the criteria update in 2006, PET scans for colorectal cancer represented 12.4% of the total sample and 86.3% fell in the appropriate and uncertain category, with no inappropriate requests (*Graph 3*). The remaining 13.7% of requests fell into the "other indications" category.

Graph 3. Clinical audit 2006 - appropriate use of FDG-PET in colorectal cancer (73 FDG-PET scans)



2. Methods

A panel of 24 experts, comprising nuclear physicians, radiologists, radiotherapists, surgeons, oncologists, ENT specialists, haematologists, methodologists and health directors working in Health Trusts and Teaching Hospitals of Emilia-Romagna was convened to discuss and agree on the methodology for a research programme aimed at defining the criteria for appropriate use of FDG-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.

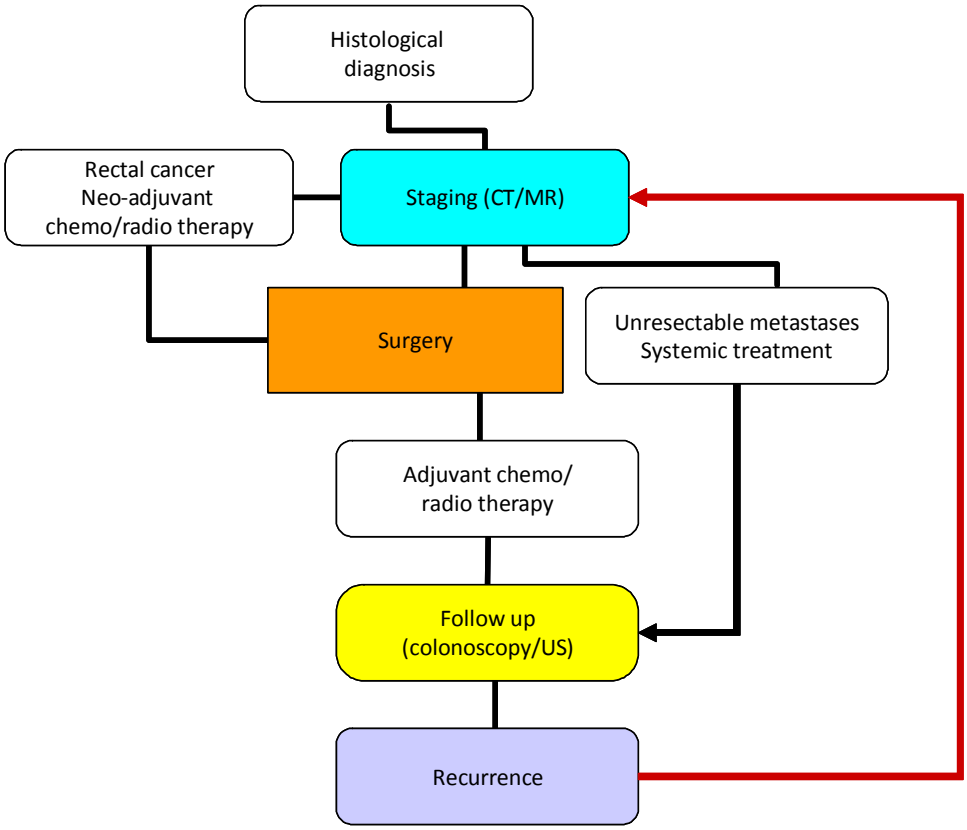
2.1. Clinical questions to be addressed

On the basis of the clinical pathway of patients with colorectal cancer (*Figure 2.1*), shared by most international clinical practice guidelines, the panel examined and assessed the role of FDG-PET for 9 clinical indications (*Table 2.1*).

Table 2.1. Clinical indications selected by the panel

• Diagnosis of primary colorectal cancer
• N staging of primary colorectal cancer
• M staging of locally advanced colorectal cancer
• Target Volume definition of curative radiation treatment in patients with rectal cancer
• During treatment evaluation of early response to therapy of liver metastases in colorectal cancer
• End of treatment evaluation of response to neoadjuvant therapy for rectal cancer
• Evaluation of residual disease following ablative treatment of liver metastases
• Follow up in patients with no suspicion of recurrence
• Staging of suspect distant recurrence in patients treated for colorectal cancer

Figure 2.1. Clinical pathway for colorectal cancer

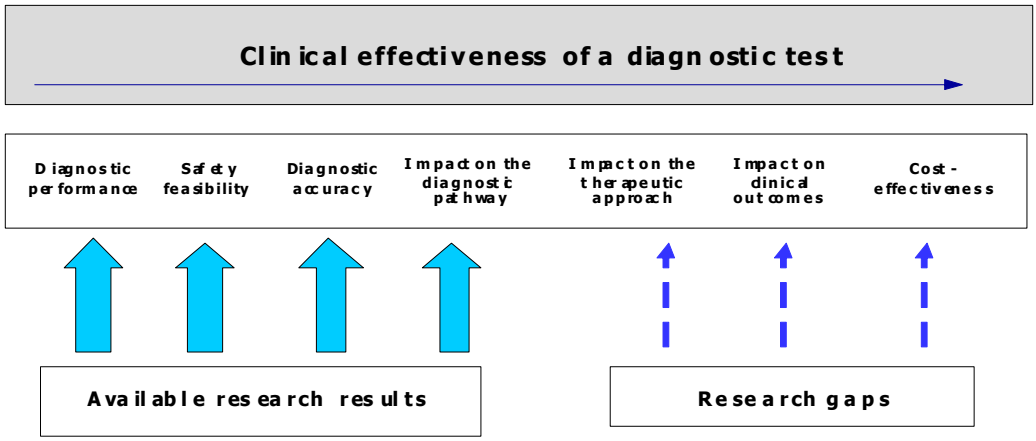


The starting point for the development of answerable "research questions", based on the PICO structure (patient intervention comparator outcome), has been the broad definition of appropriateness of a diagnostic test, which implies:

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

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

Figure 2.2. Evidence profile for a diagnostic test



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

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

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

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

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

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

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

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

2.2. Systematic review of literature

Search methods for the identification of the studies

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

- Cochrane Database of Systematic Reviews (CDSR - The Cochrane Library);
- Database of Abstracts of Reviews of Effects (DARE - Centre for Reviews and Dissemination);
- Health Technology Assessment Database (HTA Database - Centre for Reviews and Dissemination 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 colorectal cancer
Intervention	FDG-PET or FDG-PET/CT
Reference standard	histology or clinical follow up (for diagnostic accuracy studies)
Comparator	any other imaging technique
Outcomes	sensitivity, specificity, LR, accuracy in Clinical Target Volume (CTV) definition, metabolic/tumor response, quality of life, adverse events, time to recurrence, local, 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, analysed all articles acquired in full text and assessed methodological quality for risk of bias addressing selection bias and blind interpretation of results of index and verification tests.

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

Data synthesis

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

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

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

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

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

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

2.3. Level of evidence

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

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

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

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

2.4. Voting process

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

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

Voting forms

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

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

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

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

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

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

Voting procedure

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

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

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

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

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

2.5. Definition of criteria of appropriateness

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

APPROPRIATE

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

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

UNCERTAIN

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

INAPPROPRIATE

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

INDETERMINATE

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

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

3. Systematic review of literature

3.1. Overall results

Full methods and results of the systematic review of literature are reported in full in Appendix 2. The initial search identified 620 records; 487 were excluded as they did not meet the inclusion criteria or were duplicates. Full text was acquired for the remaining potentially eligible 133 records, from which 90 studies were excluded on the basis of inclusion criteria. Forty-three studies were finally included. Table 3.1 reports number and type of studies for each clinical question and end-point as well as conclusions from the previous 2007 report (Liberati 2007 - *Dossier 157*).

Thirty-nine studies evaluated diagnostic accuracy of FDG-PET and five studies evaluated the impact of FDG-PET on clinical outcomes.

Table 3.1. Number of included studies for questions and endpoints

Clinical question / Endpoint	Diagnosis	Staging	Curative intent RT field definition	Response to therapy during treatment	Response to therapy (end of treatment)	Follow up	Detection and re-staging of suspected recurrence
Diagnostic accuracy	System reviews: 1 Primary studies: 3	Systematic reviews: N staging: 1 M staging: 1 Primary studies: N staging: 6 M staging: 3	System reviews: 1 Primary studies: 5	System reviews: 2 Primary studies: 1	System reviews: 2 Primary studies: 2	System reviews: 0 Primary studies: 2	System reviews: 3 Primary studies: 15
Impact on clinical outcomes	System reviews: 0 Primary studies: 0	System reviews: 0 Primary studies: 0	System reviews: 0 Primary studies: 0	System reviews: 0 Primary studies: 0	System reviews: 0 Primary studies: 0	System reviews: 0 Primary studies: 1	System reviews: 0 Primary studies: 4
Results of ASSR Dossier 157/2007 (Liberati 2007)	Not considered	Appropriate: staging of potentially resectable metastatic lesion Uncertain A: pre-surgery staging of rectal cancer Uncertain B: pre-surgery staging of colon cancer	Not considered		Not considered	Not considered	Appropriate

4. Diagnosis of primary colorectal cancer

Rationale

Diagnosis of colorectal cancer is made by colonoscopy, followed by possible biopsy and polypectomy (AIOM 2009; ESMO 2010a; SIGN 2003). Double contrast barium enema is an alternative when colonoscopy is difficult for anatomical reasons.

Diagnosis of rectal cancer is based on a digital rectal examination including sigmoidoscopy with biopsy for histopatological examination (ESMO 2010b).

Diagnostic role of PET

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

Systematic reviews

One systematic review has been retrieved (Facey 2007) assessing the accuracy of FDG-PET for the diagnosis of primary colorectal cancer (*Table 4.1*). The methodological quality is low.

Three studies were included. In two studies patients were not described while patients recruited in the third study had known adenoma. In all cases the reference standard was the colonoscopy with histological examination of specimens. The metanalysis of data was not planned and results are provided only in narrative form.

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

Reference	Facey 2007
Update to	August 2005
Number of studies	3
Number of patients	85 (range 16-45)
FDG-PET	pooled sensitivity and specificity not calculated: only descriptive results complete data reported only for 1 study (45 patients): sensitivity: 62% specificity: 100%
Comparator	none
Reference standard	histopathology by colonoscopy or surgery

Primary studies

Three studies (*Table 4.2*), not included in or published after the above systematic review and evaluating accuracy of FDG-PET in the primary diagnosis of colorectal cancer were found (Drenth 2001; Ravizza 2010; Weston 2010). All studies have an opportunistic retrospective design, i.e. they include a retrospective sample of patients that performed both FDG-PET (1 study) or FDG-PET/CT (2 studies) and colonoscopy for any reason, with the aim of looking for any kind of colorectal neoplasm (cancer, adenomas, other malignancies). Two studies performed a lesion-based analysis. All studies are burdened by probable spectrum bias, by uncertainty of blind comparison between index test and reference standard and by low directness.

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

Reference	Drenth 2001; Ravizza 2010; Weston 2010
Number of studies	3
Number of patients	461 (range 39-330)
FDG-PET/PET-CT	(2 studies lesion-based analysis) sensitivity: median 53% (range 29.8-77.0%) specificity: median 81.1% (range 80.7-93.0%)
Comparator	none
Reference standard	histopathology by colonoscopy or surgery

A summary table for diagnostic accuracy of FDG-PET is not provided as lack of raw data from more than one primary study does not allow to test for heterogeneity of estimates and no pooled estimates were provided by the systematic review (Facey 2007).

Comments of ASSR reviewers

As patients included in studies were recruited on an opportunistic base (retrospective samples that performed FDG-PET and colonoscopy for any reason), the evidence available is prone to probable spectrum bias and low directness.

Diagnostic accuracy estimates

It is not possible to provide estimates of diagnostic accuracy of FDG-PET for the diagnosis of primary colorectal cancer.

LEVEL OF EVIDENCE: VERY LOW

4.2. Clinical outcomes

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

4.3. Voting results

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

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

INAPPROPRIATE

4.4. Conclusions

Few studies evaluating FDG-PET's accuracy in the diagnosis of primary colorectal cancer have been published. However the panel established that there is no diagnostic role of FDG-PET in this clinical indication and unanimously agreed to judge its use as inappropriate.

5. N staging of patients with primary colorectal cancer

Rationale

Pre-operative N staging usually does not affect the initial treatment choice (AIOM 2009). Postsurgical histopathological lymph node status is a predictor of long-term prognosis in colorectal cancer (ESMOa 2010).

Diagnostic role of FDG-PET

Although one systematic review and six primary studies were retrieved, the panel unanimously agreed that there is no diagnostic role of FDG-PET for N staging of patients with primary colorectal cancer.

5.1. Systematic review of literature: results

Results from update of systematic review of literature from Jan 2006

Only studies evaluating diagnostic accuracy were found and included.

Systematic reviews

One systematic review, including one study, has been retrieved (Facey 2007) assessing the accuracy of FDG-PET for N staging of primary colorectal cancer (*Table 5.1*). The methodological quality is low. The reference standard was histopathology following surgery or clinical follow up. The metanalysis of data was not planned.

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

Reference	Facey 2007
Update to	August 2005
Number of studies	1
Number of patients	34
FDG-PET/PET-CT	sensitivity: 29% specificity: 88%
Comparator	none
Reference standard	following surgery detailed histopathology or clinical follow up

Primary studies

Six studies (*Table 5.2*) evaluating diagnostic accuracy of FDG-PET in N staging of patients with colorectal cancer published after the systematic review by Facey 2007 were included (Akiyoshi 2009; Furukawa 2006; Kosugi 2008; Llamas-Elvira 2007; Ono 2009; Tsunoda 2008). Five of them applied FDG-PET and 1 FDG-PET/CT. Four studies included patients eligible for curative surgery of primary colorectal cancer, two studies included patients with locally advanced cancer or with known metastasis.

Table 5.2. Results of primary studies on FDG-PET for N staging

Reference	Akiyoshi 2009; Furukawa 2006; Kosugi 2008; Llamas-Elvira 2007; Ono 2009; Tsunoda 2008
Number of studies	6
Number of patients	347 (median 55, range 23-90)
FDG-PET/PET-CT	sensitivity: median 39.8% (range 20.8-66.7%) specificity: median 94.4% (range 83.3-100%)
Comparator	macroscopic diagnosis during surgery (1 study) sensitivity: 68.4% specificity: 72.2% CT (2 studies) sensitivity: 25-92.8% specificity: 50.6-100% multidetector row CT (2 studies) sensitivity: 57.9-88.6% specificity: 52.4-66.7% diffusion-weighted MRI (1 study) sensitivity: 80% specificity: 76.9%
Reference standard	following surgery histopathology 2 studies also clinical follow up 1 study also biopsy of extra-abdominal lesions and autopsy

As the patients included in studies published after Facey's 2007 update add up to a number greater than those included in the systematic review, estimates of diagnostic accuracy of FDG-PET were pooled and heterogeneity assessed (*Table 5.3*).

Table 5.3. Results from all studies on N staging with FDG-PET

Diagnostic accuracy	
Number of studies	7
Number of patients	379 (median 53, range 23-90)
Pre-test probability	median 50.1% (range 21.9-62.5%)
FDG-PET/PET-CT	sensitivity: median 36.8% (range 20.8-66.7%) heterogeneity chi-squared = 4,99 (d.f. = 4) p = 0,288 inconsistency (I-square) = 19,8% no. studies = 5 specificity: median 93.5% (range 83.3-100%) heterogeneity chi-squared = 5,09 (d.f. = 4) p = 0,278 inconsistency (I-square) = 21,4% no. studies = 5
Comparator	macroscopic diagnosis during surgery (1 study) sensitivity: 68.4% specificity: 72.2% CT (2 studies) sensitivity: 25-92.8% specificity: 50.6-100% multidetect or row CT (2 studies) sensitivity: 57.9-88.6% specificity: 52.4-66.7% diffusion-weighted MRI (1 study) sensitivity: 80% specificity: 76.9%
Reference standard	studies from Facey 2007 and Furukawa 2006; Llamas-Elvira 2007; Kosugi 2008; Tsunoda 2008; Akiyoshi 2009; Ono 2009

Comments of ASSR reviewers

For N staging, a low sensitivity and a high specificity of FDG-PET is reported.

Diagnostic accuracy estimates

FDG-PET sensitivity: (median) 36.8%
FDG-PET specificity: (median) 93.5%

LEVEL OF EVIDENCE: MODERATE

5.2. Clinical outcomes

As the panel agreed on absence of diagnostic role of FDG-PET in N staging of primary colorectal cancer no patient-important outcomes have been proposed and voted.

5.3. Voting results

Due to the lack of diagnostic role for FDG-PET the panel agreed not to follow the full voting procedure, but expressed an unanimous judgement of inappropriateness.

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

INAPPROPRIATE

5.4. Conclusions

One systematic review and six primary studies evaluating FDG-PET's accuracy in N staging of primary colorectal cancer have been retrieved. However the panel established that there is no diagnostic role of FDG-PET in this clinical indication and unanimously agreed to judge its use as inappropriate.

6. M staging of patients with locally advanced colorectal cancer

Rationale

Pre-operative M staging is important to differentiate localized from disseminated disease (AIOM 2009; SIGN 2003).

About 15-25% of patients with primary colorectal cancer have synchronous liver metastases (NCCN 2011a) and 2% have synchronous lung metastases (of these about 2/3 have additional extra pulmonary metastases; Mitry 2010). In the cancer of the rectal ampulla the risk of synchronous lung metastases is about two-fold that of colon cancer (Mitry 2010). Thus pre-operative imaging of the liver and chest is required to detect possible metastases and to decide the general therapeutic strategy (AIOM 2009; ESMO 2010; SIGN 2003).

Localized disease is treated with radical curative surgery; surgery of liver and lung metastases is reserved for selected patients with resectable lesions (10-20% of synchronous liver metastases and 2-4% of lung metastases; Mitry 2010; Penna 2002), while palliative surgery is indicated for patients with unresectable metastatic lesions. In locally advanced rectal cancer (T4) pre-operative chemoradiotherapy is recommended (ESMO 2010).

Diagnostic role of FDG-PET

Characterization of liver or solitary lung distant metastases with FDG-PET can direct to surgical resection if metastases appear resectable or to systemic therapy if disease is disseminated. In selected patients unresectable liver metastasis can also be considered for in situ ablation.

Treatment effectiveness

Patients undergoing surgical resection of resectable liver metastatic disease have a 5-year survival rates of 40% compared with no survival at 5 years for untreated patients (Geoghegan 1999). Unresectale liver metastases can be treated with ablation, although benefit is unclear (SIGN 2003). Survival can also be improved by resection of lung mestastasis (SIGN 2003).

Pre-test probability and change in management

The median pre-test probability of occurrence of pre-operative liver metastasis is 22.1% (range 17.3-33.8%; data from Facey 2007, Llamas-Elvira 2007, Akiyoshi 2009, Mainenti 2010), which could be considered to be the hypothetical maximum extent of change in management, achievable through accurate M staging.

One study (Llamas-Elvira 2007) on change in management in patients with colorectal cancer showed that FDG-PET revealed pathological - liver, abdominal or lung - deposits undetected by conventional diagnostic methods in 19.2% of patients, changed the staging of the disease in 13.5% of patients and modified the intent of surgery in 11.5% of patients. One study (Dossier 157/2007) on change in management in patients with locally advanced rectal cancer modified the management in 17% of patients.

Research question: FDG-PET as add on

Is FDG-PET accurate in detecting liver metastases in patients with locally advanced primary colorectal cancer and unclear CT results?

6.1. Systematic review of literature: results

Results from update of systematic review of literature from Jan 2006

Only studies evaluating diagnostic accuracy for liver metastases have been found and included. No studies on lung metastasis were found.

Systematic reviews

One systematic review has been retrieved (Facey 2007) assessing the accuracy of FDG-PET for the M staging of primary colorectal cancer (*Table 6.1*). The methodological quality is low.

One study was included considering patients with primary colorectal cancer staged for liver metastasis. The reference standard was histopathology following surgery or clinical follow up.

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

Reference	Facey 2007
Update to	August 2005
Number of studies	1
Number of patients	34
FDG-PET	sensitivity: 78% specificity: 96%
Comparator	CT sensitivity: 67% specificity: 100% US sensitivity: 25% specificity: 100%
Reference standard	histopathology following surgery or clinical follow up

Primary studies

Three studies (*Table 6.2*) evaluating diagnostic accuracy of FDG-PET in the M staging of patients with colorectal cancer published after the systematic review by Facey 2007 were included (Akiyoshi 2009; Llamas-Elvira 2007; Mainenti 2010). Two of them applied FDG-PET and one FDG-PET/CT. Two studies focused on liver metastasis and one study both on liver and other distant metastases. Patients included were those eligible for curative surgery of primary colorectal cancer, with locally advanced cancer and suspected liver metastasis in one study.

As the patients included in studies published after Facey's 2007 update add up to a number greater than those included in the systematic review, estimates of diagnostic accuracy of FDG-PET were pooled and heterogeneity assessed (*Table 6.3*).

Table 6.2. Results from primary studies on M staging for liver metastasis with FDG-PET

References	Akiyoshi 2009; Llamas-Elvira 2007*; Mainenti 2010
Number of studies	3
Number of patients	203 (median 65, range 34-104)
FDG-PET/PET-CT*	sensitivity: median 90.9% (range 89.9-100%) specificity: median 96.4% (range 93-100%)
Comparator	CT (1 study) sensitivity 44% specificity 95.3% multidetector row CT (2 studies) sensitivity 83.3-100% specificity 96.4-97.7% gadolinium enhanced MRI (1 study) sensitivity 83.3% specificity 100% superparamagnetic-iron-oxide enhanced MRI (1 study) sensitivity 83.3% specificity 96.4% contrast enhanced US (1 study) sensitivity 83.3% specificity 85.7%
Reference standard	surgery and histopathology 2 studies also clinical follow up 1 study also biopsy of extra-abdominal lesions and autopsy 1 study also intraoperative US

* In the study by Llamas-Elvira 2007, diagnostic accuracy estimates are inclusive of both liver metastasis and any kind of metastasis

Table 6.3. Overall results from studies on M staging for liver metastasis with FDG-PET

Diagnostic accuracy	
Number of studies	4
Number of patients	237 (median 50, range 34-104)
Pre-test probability	median 22.1% (range 17.3-33.8%)
FDG-PET/PET-CT	sensitivity: median 89.9% (range 77.8-100%) heterogeneity chi-squared = 2,41 (d.f. = 3) p = 0,492 inconsistency (I-square) = 0% specificity: median 96.2% (range 93-100%) heterogeneity chi-squared = 5,09 (d.f. = 3) p = 0,165 inconsistency (I-square) = 41%
Comparator	CT (2 studies) sensitivity: 44-66.7% specificity: 95.3-100% multidetector row CT (2 studies) sensitivity: 83.3-100% specificity: 96.4-97.7% gadolinium enhanced MRI (1 study) sensitivity: 83.3% specificity: 100% superparamagnetic-iron-oxide enhanced MRI (1 study) sensitivity: 83.3% specificity: 96.4% contrast enhanced US (1 study) sensitivity: 83.3% specificity: 85.7% US (1 study) sensitivity: 25% specificity: 100%
References	Facey 2007; Llamas-Elvira 2007; Akiyoshi 2009; Mainenti 2010

Comments of ASSR reviewers

Four studies investigated the diagnostic accuracy of FDG-PET in detecting liver mestastases in patients with primary colorectal cancer before radical surgical treatment (1 study including only patients with locally advanced cancer and suspected liver metastasis). Consistently high sensitivity and high specificity of FDG-PET are reported, however other diagnostic tools (multidetector row CT, gadolinium enhanced MRI, contrast enhanced US) seem to have similar diagnostic performance.

Diagnostic accuracy estimates

FDG-PET sensitivity: (median) 89.9%
FDG-PET specificity: (median) 96.2%

multidetector row CT* sensitivity: (range) 83.3-100%
multidetector row CT* specificity: (range) 96.4-97.7%

* data from studies evaluating FDG-PET

LEVEL OF EVIDENCE: MODERATE

6.2. Clinical outcomes

To evaluate the balance between benefits and risks, the panel agreed to consider the presumed patient-important outcomes reported below (*Table 6.4*), and voted on the level of importance.

Outcomes for true negatives were judged critical, receiving a median score of 8, while all remaining outcomes were judged important with a mean score of 6.

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

The following matrix of "natural frequencies" was provided (*Table 6.5*).

Table 6.4. Patient-important clinical outcomes and median scores of importance

Patient-important outcomes	Median score (range)
Consequences of test for patients with disseminated disease / unresecatble metastases	
• True positives - patients correctly upstaged to disseminated disease undergo systemic therapy	6 (2-9)
• False negatives - patients incorrectly downstaged to localized disease proceed to futile radical surgery	6 (2-9)
Consequences of test for patients with localized disease / resectable metastases	
• True negatives - patients correctly staged for localized disease / resectable metastases proceed to radical surgery, which impacts on survival	8 (2-9)
• False positives - patients incorrectly upstaged to disseminated disease undergo systemic therapy instead of radical surgery, which could have improved survival.	6 (2-9)

Table 6.5. "Natural frequencies" of patients assessed for distant metastases

		N of patients out of 100 submitted to the exam	
		According to FDG-PET	**According to multirow CT**
Patients with disseminated disease/ unresecatble metastases	True positives	20	18 - 22
	False negatives	2	4 - 0
Patients with localized disease / resectable metastases	True negatives	75	75 - 76
	False positive	3	3 - 2
		100	100

6.3. Voting results

The first voting round registered a strong disagreement with ratings falling in all three regions (inappropriate, uncertain and appropriate) with a median score of 5 (range 3-7). The second voting round registered an agreement on appropriate with a median score of 7 and a range of 7-8.

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

APPROPRIATE

6.4. Conclusions

After an initial strong disagreement, during the second meeting the panel agreed in rating the use of FDG-PET in staging patients with locally advanced primary colorectal cancer as appropriate. The disagreement was resolved mainly through a clearer definition of the diagnostic role of FDG-PET for the selection of patients who would most benefit from radical surgery.

The level of evidence for estimates of FDG-PET's diagnostic accuracy was moderate.

The impact on survival obtained with appropriate surgical resection of localized disease and resectable metastases was considered a critical outcome (median score of 8; range 2-9), while remaining outcomes for true and false positives and for false negatives were judged important.

7. Target volume definition of curative radiation treatment in patients with rectal cancer

Rationale

In patients with locally advanced resectable rectal cancer pre-operative or neoadjuvant radiotherapy (with or without chemotherapy), followed by total mesorectal excision, reduce local recurrence rates (AIOM 2009; ESMO 2010b; NCCN 2011b; SIGN 2003). In locally advanced unresectable rectal cancer pre-operative or neoadjuvant radiotherapy (with chemotherapy) can obtain the downsizing necessary to allow radical surgical treatment (ESMO 2010b; NCCN 2011b).

Diagnostic role of FDG-PET

Although one systematic review and five primary studies were retrieved, the panel unanimously agreed that there is no diagnostic role of FDG-PET in the target volume definition of curative radiation treatment in patients with rectal cancer.

7.1. Systematic review of literature: results

Results from update of systematic review of literature from Jan 2006

Only studies comparing target volumes were found and included.

Systematic reviews

One systematic review has been retrieved (Facey 2007) assessing the role of FDG-PET in field definition of radiation treatment with curative intent in patients with primary rectal cancer. The methodological quality is low.

One study (11 patients) comparing CT and FDG-PET estimated treatment volumes was included. No verification test was applied. The resulting regions (in term of GTV) were closely correlated (r2 = 0.84), but the study presented no outcome data.

Primary studies

We retrieved five studies (Anderson 2007; Bassi 2008; Paskeviciute 2009; Roels 2009; Yavuz 2010), including patients with rectal cancer candidate to pre-operative radiotherapy, where target volumes assessed by FDG-PET (2 studies) or FDG-PET/CT (3 studies) were compared to target volumes assessed by CT (four studies) or MRI (two studies) results. In all but one study no verification test was applied (*Table 7.1*).

Table 7.1. Results from studies on diagnostic accuracy of FDG-PET in target volume definition

References	Anderson 2007; Bassi 2008; Paskeviciute 2009; Roels 2009; Yavuz 2010
Number of studies	5
Number of patients	122 (median 23, range 15-36)
Results	In 3 studies FDG-PET volumes were smaller than CT volumes (a mean difference of about 9 cm^3 in 1 study). In 2 studies FDG-PET volumes were larger (difference of 14-20 cm^3 greater for the GTV FDG-PET-CT than the GTV CT - due to "geographic" missing). 3 studies: 8-26% of change of the radiation treatment plan or change of management (due to upstaging of patients for detection of N or distant metastases)
Reference standard	histopathology (1 study) or none

* GTV = gross target volume

Comments of ASSR reviewers

According to few studies, the use of FDG-PET/CT resulted in changes of target volumes in comparison with CT or MRI planning. Both a reduction and an increase in target volumes resulting from FDG-PET imaging were observed. An increase of target volume (with change of staging of 8-26% of patients) are seen when "geographic" misses at CT of lymph nodes or distant metastases are considered. However there is no data providing evidence that FDG-PET-based changes in target volume represent better pathological tumor coverage than CT/MRI-based volume delineation.

Diagnostic accuracy estimates

Not available.

LEVEL OF EVIDENCE: VERY LOW

7.2. Clinical outcomes

As the panel agreed on absence of diagnostic role of FDG-PET in target volume definition of curative radiation treatment in patients with rectal cancer, no patient-important outcomes have been proposed and voted.

7.3. Voting results

Due to the lack of diagnostic role of FDG-PET the panel agreed not to follow the full voting procedure, but expressed a unanimous judgement of inappropriateness.

FINAL RATING FOR THE USE OF FDG-PET FOR TARGET VOLUME DEFINITION IN RECTAL CANCER:

INAPPROPRIATE

7.4. Conclusions

One systematic review and five studies have assessed the role of FDG-PET in the target volume definition of radiation treatment in patients with rectal cancer. Nevertheless the panel agreed that there is no diagnostic role of FDG-PET in this clinical indication and unanimously agreed to judge its use as inappropriate.

8. During treatment evaluation of early response to therapy for liver metastases in colorectal cancer

Rationale

Initially unresectable liver metastases can become resectable after downsizing with chemotherapy. For patients with initially unresectable liver metastases, a strong correlation between response rate to neoadjuvant treatment of metastatic colorectal cancer and resection rate has been demonstrated.

The therapeutic strategy is aimed at achieving a very good response in patients with initially unresectable disease in order to convert unresectable metastases into resectable metastases (ESMO 2010). Pathologic response seems to be predictive of clinical outcomes.

Diagnostic role of FDG-PET

During treatment evaluation (after 2 or 3 cycles/months) of response to treatment could allow avoidance of unnecessary toxicity and costs for non responding patients.

Treatment effectiveness

Neoadiuvant chemotherapy (oxaliplatin and fluorouracil and folinic acid) can allow surgical resection in 13.5% of patients treated for liver metastases; subsequent survival was similar to a comparable series of operable patients treated by surgical resection (SIGN 2003; Adam 2001).

Surgical resection of resectable liver metastatic disease can lead to a 5-year survival rates of 40% compared with no survival at 5 years of untreated patients (Geoghegan 1999). Unresectale liver metastases can be treated with ablation, although benefit is unclear (SIGN 2003).

Pre-test probability and change in management

Standard combination chemotherapy regimens comprising 5-FU/LV in combination with either irinotecan, typically FOLFIRI, or oxaliplatin (FOLFOX) have been reported to facilitate the resection of 7-40% of patients with initially unresectable metastases depending upon the initial selection of patients (ESMO 2010).

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

Is FDG-PET accurate in evaluating during treatment response to systemic therapy of liver metastases?

8.1. Systematic review of literature: results

Results from update of systematic review of literature from Jan 2006

Only studies on diagnostic accuracy of FDG-PET in evaluating response to treatment for metastatic colorectal cancer were retrieved.

Systematic reviews

Two systematic reviews (Facey 2007; Geus-Oei 2009) have been included, assessing the diagnostic accuracy of FDG-PET in evaluating response to therapy in patients with metastatic colorectal cancer (*Table 8.1*). Therapy of metastatic disease consisted in different types of chemoradiotherapy in almost all studies (only radiotherapy in 1 study and added hyperthermia in 2 studies).

Methodological quality was judged as low for both reviews; in particular no review performed a quality assessment of primary studies.

Table 8.1. Synthesis of results of the systematic reviews (Facey 2007; Geus-Oei 2009)

Reference	Facey 2007	Geus-Oei 2009
Update to	August 2005	December 2008
Number of studies	1 (in common with Geus-Oei 2009)	5 (1 in common with Facey 2007)
Number of patients	28	127 (median 25, range 6-50)
FDG-PET	only descriptive results of the study	only descriptive results of single studies
Comparator	none	none
Reference standard	not reported	not reported

Of the studies included in the above systematic reviews, only one study resulted eligible for the clinical question (Findlay 1996), which included only 18 patients with liver metastasis receiving adjuvant therapy with a now obsolete treatment (5-fluorouracil) evaluated for response with FDG-PET after 4-5 weeks of treatment. Reference test was CT or MRI. Sensitivity was 100% and specificity 75%.

Primary studies

One study (Bystrom 2009), not included in the above reported systematic reviews, was found (*Table 8.2*). Fifty-one patients with metastastic colorectal cancer receiving first-line combination adjuvant chemotherapy (irinotecan and fluorouracil) performed a FDG-PET/CT evaluation before start of treatment and after two cycles. Metabolic response according to FDG-PET/CT was compared with clinical tumor response with CT at chest and abdomen evaluated according to RECIST after every four cycles. This study was finally not included because the clinical question was different from that chosen by the panel.

Comments of ASSR reviewers

Estimates for diagnostic accuracy on during treatment response of liver metastases are not available.

Diagnostic accuracy estimate

Not available.

LEVEL OF EVIDENCE: NONE

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.

All outcomes but one (false responders) were voted "critical"; outcome for false responders were judged important.

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

As it was not possible to provide estimates for diagnostic accuracy, the matrix of "natural frequencies" was not provided.

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

Patient-important outcomes	Median score (range)
Patients not responding to treatment	
• True non responders - patients interrupt ineffective treatment, avoiding unnecessary toxicity, and could change to different line of therapy, which might impact on survival	7 (4-9)
• False responders - patients continue ineffective treatment, which will non impact on survival, suffer unnecessary toxicity and do not change to other, perhaps more effective, line of treatment	6 (4-9)
Consequences of test for patients responding to treatment	
• True responders - patients continue effective treatment, which could lead to downsizing with benefits on survival	7 (5-9)
• False non responders - patients interrupt effective treatment, which could have led to downsizing, and unnecessarily change therapeutic	7 (3-9)

8.3. Voting results

During the first voting round, seven out of twenty panelists voted the clinical question as indeterminate for lack of studies. The remaining members showed a light disagreement with ratings falling in the inappropriate and uncertain regions (median score 5; range 2-5). In the second voting round the panel unanimously agreed in judging the use of FDG-PET for evaluation of early response to treatment as indeterminate for lack of studies.

FINAL RATING FOR THE USE OF FDG-PET FOR DURING TREATMENT EVALUATION OF EARLY RESPONSE TO THERAPY FOR LIVER METASTASES: INDETERMINATE

8.4. Conclusions

The panel discussed at length the issue of early response to treatment of metastatic colorectal cancer, differentiating patients treated for plurimetastatic disease from patients treated for potentially resectable liver metastases. Votes of the first round resulted highly dishomogeneous due to the different interpretation of the diagnostic role of FDG-PET. During the second meeting the panel agreed to restrict the rationale for evaluation of early response to treatment only for patients treated for potentially resectable liver metastases. Outcomes were voted critical with a median score of 7 in all cases except for false responders (median score 6), who would continue a potentially ineffective treatment. Although it was agreed that a diagnostic tool differentiating responders from non responders would be useful, the absence of evidence for the diagnostic accuracy of FDG-PET in this clinical indication led the panel to unanimously agree to judge it as indeterminate.

9. End of treatment evaluation of response to neoadjuvant radiotherapy in patients with rectal cancer

Rationale

In patients with locally advanced resectable rectal cancer pre-operative or neoadjuvant radiotherapy (with or without chemotherapy), followed by curative surgery, reduce local recurrence rates (AIOM 2009; ESMO 2010b; NCCN 2011b; SIGN 2003). The response to pre-operative therapy may influence prognosis and subsequent therapy in terms of extent (local excision or total mesorectal excision) of surgery (ESMO 2010b).

In selected cases, after neoadjuvant therapy patients can undergo a histopathologic restaging - with multiple biopsies or excision biopsy - and, if a pathologic complete response is achieved, no further therapy is provided and the rectum is preserved (ESMO 2010b).

Finally, in patients with locally advanced unresectable rectal cancer neoadjuvant chemoradiotherapy can achieve the necessary downsizing to allow the radical surgical treatment (ESMO 2010b; NCCN 2011b).

Diagnostic role of FDG-PET

Although two systematic reviews and two primary studies were retrieved, the panel unanimously agreed that there is no diagnostic role of FDG-PET in evaluating end-of-treatment response to neoadjuvant radiotherapy for rectal cancer, due to lack of therapeutic options.

9.1. Systematic review of literature: results

Results from update of systematic review of literature from Jan 2006

Two systematic reviews and two primary studies evaluating diagnostic accuracy were retrieved.

Systematic reviews

Two systematic reviews (Facey 2007, Geus-Oei 2009) have been included, assessing the diagnostic accuracy of FDG-PET in evaluating response to therapy in patients with resectable locally advanced rectal cancer at the end of neoadjuvant therapy prior to surgical treatment (*Table 9.1*). The recruited patients had a stage II or III cancer. Neoadjuvant therapy consisted in varied chemoradiotherapy in almost all studies (only radiotherapy in 1 study and added hyperthermia in 2 studies). Methodological quality was judged low for both reviews; in particular no review performed a quality assessment of primary studies.

Table 9.1. Synthesis of main results of the systematic reviews (Facey 2007; Geus-Oei 2009)

Reference	Facey 2007	Geus-Oei 2009
Update to	August 2005	December 2008
Number of studies	5 (4 in common with Geus-Oei 2009)	18 (4 in common with Facey 2007)
Number of patients	164 (median 23, range 15-81)	588 (median 27.5, range 9-88)
FDG-PET	only descriptive results of single studies. "changes in SUV between pre-therapy and post-therapy scans may predict response in the majority of patients. One small study reported changes in patient management."	"In primary rectal cancer, 18F-FDG PET is applicable after neoadjuvant treatment in a pre-operative setting (important for the pre-operative selection for an individually tailored surgical approach) and correlates better with pathology than morphologic imaging modalities. Interestingly, when 18F-FDG PET is able to predict the final outcome, it may be used to guide adjuvant chemotherapy for rectal cancer after optimal neoadjuvant and local treatments."
Comparator	none	none
Reference standard	pathologic confirmation	pathologic confirmation

Primary studies

Two studies (Capirci 2009; Martoni 2011), not included in the above reported systematic reviews, were found (*Table 9.2*). Patients with locally advanced rectal cancer, suitable for receiving neoadjuvant radiochemotherapy performed a FDG-PET/CT evaluation at baseline and before curative surgery. Maximum standardized uptake value (SUVmax) at baseline and metabolic response according to FDG-PET/CT was compared with pathologic response at the end of neoadjuvant treatment and delta SUV was computed (cut off 66.1% in Martoni 2011 and 63.4% in Capirci 2009). The studies were limited by the uncertainty on blinding of index test (FDG-PET) when evaluating the reference test (pathologic response).

Table 9.2. Synthesis of results of the primary studies

References	Capirci 2009; Martoni 2011
Number of patients	80-81
FDG-PET/CT	sensitivity 1 study 93.7% (CI 95% 69.8-99.8%) 1 study 84.5% specificity 1 study 31.2% (CI 95% 20.2-44.1%) 1 study 80%
Comparator	none
Reference standard	pathological analysis of surgical specimens: 1 study criteria from Dworak 1997, 1 study criteria from Mandard 1994

As a metanalysis of studies' results was not performed in the above cited systematic reviews (Facey 2007; Geus-Oei 2009), estimates from the nine studies were pooled and heterogeneity of diagnostic estimates of FDG-PET tested (*Table 9.3*). The studies performed FDG-PET (4) or FDG-PET/CT (5) after a period of radiochemotherapy ranging from 2-4 weeks to 8-9 weeks. Heterogeneity can be noticed in the applied criteria of metabolic response for FDG-PET (visual evaluation or delta SUV ranging from 36% to 75%) and of pathologic response (complete response only or complete response plus partial response, according to three different scales).

Table 9.3. Results of primary studies on diagnostic accuracy of FGD-PET in evaluating response to neoadjuvant therapy of patients with advanced rectal cancer

Diagnostic accuracy	
Number of studies	9
Number of patients	398 (median 30, range 17-81)
Pre-test probability	median 49% (range 20-65%)
FDG-PET/PET-CT	sensitivity: range 35.7-100% heterogeneity chi-squared = 31.07 (d.f. = 8) p = 0,000 inconsistency (I-square) = 74.2% specificity: range 28.6-85.7% heterogeneity chi-squared = 44.38 (d.f. = 8) p = 0,000 inconsistency (I-square) = 82%
Comparator	EUS (1 study) sensitivity: 33% specificity: 80% CT (1 study) sensitivity: 54% specificity: 80% MRI (1 study) sensitivity: 71% specificity: 67%
Reference standard	pathologic confirmation
Reference	primary studies from Facey 2007 and Geus-Oei 2009; Capirci 2009; Martoni 2011

Comments of ASSR reviewers

Both diagnostic accuracy estimates are heterogeneous. This could be due to the different populations studied (i.e. in baseline T staging), different time-intervals in performing FDG-PET, different criteria in evaluating metabolic and/or pathologic response.

Diagnostic accuracy estimates

FDG-PET sensitivity: (heterogeneous) range 37.5-100%
FDG-PET specificity: (heterogeneous) range 28.6-85.7%

comparator EUS* sensitivity: 33%
comparator EUS* specificity: 80%

comparator CT* sensitivity: 54%
comparator CT* specificity: 80%

comparator MRI* sensitivity: 71%
comparator MRI* specificity: 67%

* data from studies evaluating FDG-PET

LEVEL OF EVIDENCE: VERY LOW

9.2. Clinical outcomes

As the panel agreed on absence of a diagnostic role for FDG-PET in evaluation of response to neoadjuvant radiotherapy at the end of treatment in patients with rectal cancer no patient-important outcomes have been proposed and voted.

9.3. Voting results

Due to the lack of diagnostic role of FDG-PET the panel agreed not to follow the full voting procedure, but expressed an unanimous judgement of inappropriateness.

FINAL RATING FOR THE USE OF FDG-PET
FOR EVALUATION OF RESPONSE TO NEOADJUVANT RADIOTHERAPY
AT THE END OF TREATMENT IN RECTAL CANCER PATIENTS:

INAPPROPRIATE

9.4. Conclusions

Two systematic reviews and two primary studies have assessed the role of FDG-PET in the evaluation of end-of-treatment response to neoadjuvant therapy of rectal cancer. However the panel agreed that there is no diagnostic role of FDG-PET in this clinical indication and unanimously agreed to judge its use as inappropriate.

The panel suggested that clinical research could be conducted investigating whether FDG-PET could replace biopsy in identifying patients with a complete response to neoadjuvant therapy at the end of treatment, in order to decide whether to opt for a conservative or more aggressive type of surgical approach.

10. Evaluation of residual disease following ablative treatment of liver metastases

Rationale

In patients with colorectal unresectable liver metastases local ablative techniques that result in intrahepatic tumor removal have emerged as alternative treatment options (Geus-Oei 2009). Different morphologic imaging techniques have been used to facilitate intraoperative localization. However, success of local ablation cannot easily be ascertained with intraoperative ultrasonography because of the hyperechogenicity that is induced within the treated area. Furthermore, evaluation with CT or MRI of residual tumor after the ablation procedure is hampered by a rimlike increase in contrast enhancement that occurs immediately after radio frequency ablation and that resembles peripheral hyperperfusion. This area of contrast enhancement may interfere with the adequate detection of, or not clear differentiation between, incomplete local ablative treatment and the occurrence of new metastases in regions adjacent to the treatment site.

Diagnostic role of FDG-PET

To evaluate success of ablation and assess presence of residual or recurrent metastases in order to repeat ablation procedure.

Treatment effectiveness

Intrahepatic tumor destruction through ablation has emerged as a viable treatment option for unresectable liver metastases, although positive effects on patients' survival remain to be established (Geus-Oei 2009).

Pre-test probability and change in management

The median pre-test probability of residual disease or local recurrence after ablation of liver metastases in patients with colorectal cancer is 23.5% (range 16.3%-53.8%; Geus-Oei 2009), which could be considered to be the hypothetical maximum extent of change in management, achievable through accurate residual disease or local recurrence assessment.

Research question: FDG-PET as replacement

Has FDG-PET higher diagnostic accuracy than the available comparators (conventional imaging) in detecting residual disease or local recurrence after ablation of liver metastasis in patients with colorectal cancer?

10.1. Systematic review of literature: results

Results from update of systematic review of literature from Jan 2006

Only one systematic review on diagnostic accuracy was retrieved.

Systematic reviews

One systematic review (Geus-Oei 2009) has been included, assessing the diagnostic accuracy of FDG-PET in evaluating residual disease or recurrence after local ablative therapy of patients with liver metastasis of colorectal cancer (*Table 10.1*). Studies included patient submitted to cryosurgery ablation (CSA - applied in 2 studies), radiofrequency ablation (RFA - applied in 4 studies) or laser-induced thermotherapy (LITT - applied in 1 study) of liver metastasis when complete resection could not be achieved with surgical procedures. The studies performed FDG-PET within 1-4 weeks. Methodological quality of the systematic review was judged as low; in particular quality assessment of primary studies was not performed.

Table 10.1. Synthesis of results of the systematic review

Reference	Geus-Oei 2009
Update to	December 2008
Number of studies	5
Number of patients	114 (median 21, range 11-43)
FDG-PET	only descriptive results of single studies "18F-FDG PET could play a central role in optimizing the use of local ablative treatment of liver metastases because it recognizes, at early times, incomplete tumor ablation that is not detectable by CT. 18F-FDG PET could play a pivotal role in determining the need for further investigations and in guiding the reading of CT scans; the interpretation of the latter alone at early times after local ablative therapy appears to be difficult."
Comparator	CT or none
Reference standard	not reported

Primary studies

None retrieved.

As a metanalysis was not performed by the above systematic review (Geus-Oei 2009), results of the four out of five studies included in the review and providing data for diagnostic accuracy were pooled (*Table 10.2*).

Table 10.2. Results of primary studies on diagnostic accuracy of FGD-PET in evaluating residual disease or recurrence after local ablative therapy of liver metastasis

Diagnostic accuracy	
Number of studies	4
Number of patients	92 (median 19, range 11-43)
FDG-PET/PET-CT	sensitivity: range 65-100% heterogeneity not assessable as only 2 studies with raw data available specificity: range 97-100% heterogeneity not assessable as only 2 studies with raw data available
Reference standard	clinical follow up
Reference	primary studies from Geus-Oei 2009

Comments of ASSR reviewers

Only studies with few patients were found. It is not possible to draw any conclusion about the accuracy of FDG-PET in evaluating residual disease or recurrence after local ablative therapy of patients with liver metastasis of colorectal cancer.

Diagnostic accuracy estimates

It is not possible to provide estimates.

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 10.3*), and voted on the level of importance.

Outcomes for true positives, false negatives and false positives were voted critical, while outcomes for true negatives were judged important.

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

As it was not possible to provide estimates for diagnostic accuracy, the matrix of "natural frequencies" was not provided.

Table 10.3. Patient-important clinical outcomes and median scores of importance

Patient-important outcomes	**Median score (range)**
Patients not responding to treatment	
• True positives - patients undergo further ablative procedure, which has uncertain impact on their survival	7 (1-9)
• False positives - patients considered clear of local lesions, and do not receive further ablative procedures, which has uncertain impact on their survival	7 (1-9)
Consequences of test for patients responding to treatment	
• True negatives - patients correctly considered clear of local lesions and in no need of further interventions	6 (1-9)
• False negatives - patients undergo further futile ablative procedures	7 (1-9)

10.3. Voting results

Both voting rounds registered a light disagreement with ratings falling in both the inappropriate and uncertain regions, with a median score of 4 (range 1-6) for the first round and a median score of 3 (range 3-4) for the second round. Final rating resulted uncertain due to disagreement.

FINAL RATING FOR THE USE OF FDG-PET
FOR EVALUATION OF RESIDUAL DISEASE
FOLLOWING ABLATIVE TREATMENT OF LIVER METASTASES:
UNCERTAIN

10.4. Conclusions

The panel judged the patient-important outcomes related to the correct identification of residual or recurrent liver metastatic lesion as mostly critical (except for outcomes of true negatives judged important). Level of evidence for FDG-PET diagnostic accuracy was graded as very low and the panel discussed at length the impact on clinical outcomes as some members express perplexities on the clinical effectiveness of ablative treatment. This is reflected in the unresolved disagreement between inappropriate and uncertain ratings registered in both rounds of voting. The use of FDG-PET for the evaluation of residual disease following ablative treatment of liver metastases resulted as uncertain due to disagreement.

11. Follow up in patients treated for colorectal cancer with no suspicion of recurrence

Rationale

About 30-50% of patients with colorectal cancer will relapse and die after curative surgical resection, with or without adjuvant chemotherapy (ESMO 2010a). Detecting relapse in advance is the main goal of surveillance after primary treatment. Recently consistent evidence has demonstrated an improved survival for patients undergoing more intensive surveillance compared to those receiving non-intensive follow up (AIOM 2009; ESMO 2010a). However optimal strategy for an intensive follow up is not yet clearly defined, in particular in terms of diagnostic tests to be used, surveillance intervals and duration of follow up.

Diagnostic role of FDG-PET

Early detection of recurrence for timely surgical treatment of resectable metastases, which could improve survival.

Treatment effectiveness

The estimated overall survival gain due to an intensive follow up is between 7% and 13% and the improvement has been attributed to earlier detection of recurrent disease and in particular to a higher rate of detection, and treatment, of isolated metastasis (AIOM 2009; ESMO 2010a).

Pre-test probability and change in management

Recurrence rate in patients previously treated for primary colorectal cancer ranges between 35% (only in liver) and 75% (any recurrence) after a follow up of about 2 years (Kuehl 2008; Sobhani 2008). This rate could be considered the hypothetical 2-year cumulative maximum extent of change in management in this clinical scenario.

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

Does introducing FDG-PET in current follow up strategy for patients with no suspicion of recurrence allow an earlier detection of relapses?

11.1. Systematic review of literature: results

Results from update of systematic review of literature from Jan 2006

Two primary studies evaluating diagnostic accuracy and one study evaluating impact of PET on clinical outcomes were found and included

DIAGNOSTIC ACCURACY OF FDG-PET

Systematic reviews

None retrieved.

Primary studies

Two studies (Kuehl 2008; Sobhani 2008) were retrieved on the diagnostic accuracy of FDG-PET/CT in follow up of patients with no suspicion of recurrence after curative treatment (*Table 11.1*). The first is a prospective study (Kuehl 2008) in which a scheduled follow up every three/six months up to 22 months (mean) with FDG-PET - and MRI - was applied to colorectal patients treated with ablative therapy for liver metastasis.

The second study is a randomized controlled trial comparing two modalities of active follow up (conventional work up versus FDG-PET plus conventional work up) of patients after curative surgery for colorectal cancer (see below). The objective of the study was to compare the diagnostic accuracy of the two modalities of follow up.

Table 11.1. Results from studies on diagnostic accuracy of FDG-PET in the follow up of asymptomatic patients after curative treatment

Reference	Kuehl 2008 *	Sobhani 2008 **
Number of patients	15	130
FDG-PET / PET-CT	FDG-PET sensitivity: 61% specificity: 98% FDG-PET/CT sensitivity: 84% specificity: 100%	FDG-PET sensitivity: 96% specificity: 93%
Comparator	MRI sensitivity: 73% specificity: 100%	conventional work up sensitivity: 91% specificity: 92.1%
Reference standard	follow up and histology	follow up and histology
Notes	* lesion based analysis of liver recurrence	** any recurrence

Comments of ASSR reviewers

Only two studies in two different clinical context were retrieved. One study with very few patients evaluated the diagnostic accuracy of FDG-PET/CT in detecting liver recurrence during the follow up of asymptomatic patients after ablative treatment of liver metastasis and did not disclose major differences between FDG-PET and MRI. The second study, including patients submitted to active follow up program after curative surgery, did not show major differences in diagnostic accuracy for recurrence detection between FDG-PET and conventional work up.

Diagnostic accuracy estimates

It is not possible to provide estimates.

LEVEL OF EVIDENCE: VERY LOW

IMPACT OF FDG-PET ON CLINICAL OUTCOMES

Systematic reviews

None retrieved.

Primary studies

One randomized controlled trial (Sobhani 2008) was retrieved exploring the impact of follow up with FDG-PET/CT in asymptomatic patients after curative surgery. One hundred and thirty participants were allocated to active conventional work up (physical examination, biomarker essays and US every three months, chest X ray every 6 months, abdominal CT scan after 9 and 15 months of follow up) or to the same work up plus FDG-PET (after 9 and 15 months from curative surgery). The primary outcome was the recurrence rate; other outcomes considered were time to recurrence, curative surgical tumor resection, time to curative surgical tumor resection, death (*Table 11.2*).

Table 11.2. Results from studies on impact on clinical outcomes of FDG-PET in the follow up of patients with no suspect of recurrence

Reference	Sobhani 2008
Number of studies	1
Number of patients	130
Follow up	24 months
Recurrence	FDG-PET group 38.5% control group 32.3% p = 0.55
Time to recurrence (month) ± s.d.	FDG-PET group 12.1 ± 3.6 control group 15.4 ± 4.9 p = 0.01
Time to therapy (month) ± s.d.	FDG-PET group 15.5 ± 5 control group 17.5 ± 6 p = 0.09
R0 curative, N (% over recurrences)	FDG-PET group 10 (40) control group 2 (9.5) p < 0.01
Death, N (% over recurrences)	FDG-PET group 3 (13) control group 6 (28.5) p = 0.33

Comments of ASSR reviewers

One randomized controlled trial explored the impact of active follow up with FDG-PET/CT in asymptomatic patients after curative surgery. FDG-PET application compared to active conventional diagnostic work up shortened the time to recurrence detection and increased the number of curative surgical tumor resection. No difference in mortality was disclosed. Due to the scarcity of data no conclusion can be drawn.

LEVEL OF EVIDENCE: VERY LOW

11.2. Clinical outcomes

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

The panel judged as most critical (median score 7) the outcomes of patients for whom the introduction of a new test would impact upon (true and false positives and true negatives), while possible delay of recurrence detection and treatment, which represent current situation, was rated as important.

The only randomised study on 130 patients showed a statistically significant shorter time to recurrence detection, but no significant difference in mortality.

As estimates for diagnostic accuracy were not available, the matrix of "natural frequencies" was not provided.

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

Patient-important outcomes	**Median score (range)**
Patients relapsing	
• True positives - patients with recurrence start treatment for recurrence earlier, which might impact on survival	7 (6-9)
• False positives - patients delay treatment for recurrence, with a possible negative impact on survival	6 (4-9)
Patients not relapsing	
• True negatives - patients remain in follow up	7 (2-9)
• False negatives - patients start unnecessary treatment, which will bring toxicity and morbidity, with no gain on survival	7 (5-9)

11.3. Voting results

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

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

INAPPROPRIATE

11.4. Conclusions

During the discussion the panel envisaged a role of FDG-PET in the follow up of patients treated for colorectal cancer with no suspicion of recurrence, because of the promising results emerging in favor of an intensive follow up. The outcomes of patients for whom the introduction of a new test would impact upon, such as early detection and treatment of recurrence, were in fact judged as critical, while possible delay in recurrence detection and treatment, which represent current situation, was rated as important. However, given the very low level of evidence and prevalence of the disease, the panel considered it impracticable to offer a FDG-PET scan to all patients in follow up. The level of evidence for FDG-PET's diagnostic accuracy was judged very low and, after an initial light disagreement between uncertain and inappropriate, the panel agreed during the second voting round to judge the use of FDG-PET as inappropriate.

12. Staging of recurrence in patients treated for colorectal cancer

Rationale

Approximately 30-50% of patients with colorectal cancer will relapse and die after curative surgical resection, with or without adjuvant chemotherapy (ESMO 2010a). Although most metastatic diseases are not suitable for resection, it is important to select patients with resectable metastases and those with initially unresectable metastases, that could become resectable following response to a combined chemotherapy (ESMO 2010c).

Diagnostic role of FDG-PET

To characterize the extent of metastatic disease and assess whether metastases are resectable (ESMO 2010c) in order to direct patients to either surgical treatment or palliative systemic treatment.

Treatment effectiveness

Patients with resected liver disease have a 5-year survival rates of 40% compared with no survival at 5 years of untreated patients (Geoghegan 1999). Resection of resectable lung metastases offers also 25-35% 5-year survival rates in carefully selected patients (ESMO 2010c). Initially unresectable liver metastases can become resectable after downsizing with chemotherapy (ESMO 2010c). However, in the patient with recurrent disease, even if surgical removal offers the only chance of cure, quality of life may be adversely affected and represent an unnecessary burden in futile resection (SIGN 2003).

Pre-test probability and change in management

The median pre-test probability of liver metastasis in patients with suspected recurrence of colorectal cancer is 36.2% (range 15-63.4%; data from primary studies included in Floriani 2010). This variability is probably due to the differences in patient populations, depending on whether metastasis is known or suspected.

The median pre-test probability of whole body metastasis in patients with suspected recurrence of colorectal cancer is 67.3% (range 41.3-90%; data from Chen 2007; Kitajima 2009; Kyoto 2010; Lee 2010; Metser 2010; Potter 2009; Sarikaya 2007; Shamim 2010; Shen 2006).

The change in management due to FDG-PET on recurrent colorectal cancer ranges from 19% to 47% of patients (Watson 2006; data from 914 patients studied in 15 studies). FDG-PET's greatest impact was in detecting unresectable disease and thereby averting inappropriate surgery.

Research question: FDG-PET in add on

Is FDG-PET sufficiently accurate to characterize the extent of metastatic disease in patients with potentially resectable metastases?

12.1. Systematic review of literature: results

Results from update of systematic review of literature from Jan 2006

Three systematic reviews and 14 primary studies evaluating diagnostic accuracy were found and included.

Four studies evaluating impact of FDG-PET on clinical outcomes were also included.

DIAGNOSTIC ACCURACY OF FDG-PET

Systematic reviews

Three systematic reviews (Facey 2007; Floriani 2010; Zhang 2009) which assessed the diagnostic accuracy of FDG-PET in detecting suspected recurrence and/or metastases were included (*Tables 12.1, 12.2, 12.3*). Facey 2007 reported descriptive results of 1 systematic reviews and 7 primary studies considering any kind of recurrence of colorectal cancer. Zhang 2009 included and performed the metanalysis for patients with whole body recurrence, liver metastasis, pelvic and local regional recurrence. Floriani 2010 included and performed the metanalysis for patients with liver metastasis and compared results between four different imaging tests (FDG-PET itself, ultrasonography, CT, MRI). The methodological quality was judged as low for Facey 2007 and intermediate for Zhang 2009 and Floriani 2010. The systematic review by Floriani pointed out that major sources of bias could include verification bias and unblinding of interpretation of results.

Table 12.1. Systematic reviews on diagnostic accuracy of FDG-PET in patients with suspected whole body metastasis of colorectal cancer after treatment

Reference	Facey 2007	Zhang 2009
Update to	August 2005	January 2008
Number of studies	7 primary studies 1 systematic review of 13 primary studies	19 primary studies
Number of patients	510 (from 7 primary studies)	1 206 patients
FDG-PET	only descriptive results from single studies	sensitivity: pooled 91% (95% CI 88-92%) specificity: pooled 83% (95% CI 79-87%) heterogeneity for sensitivity and specificity (p <0.0000 and 0.0001). A clear influence by 3 studies was noted as they have contributed most toward heterogeneity; values were seen to be outside Galbraith's plot confidence bands. The calculated area under SROC curves and Q* value were 0.9309 and 0.8662
Comparator	not considered	not considered
Reference standard	not reported	pathology (histology or biopsy) and/or clinical follow up

Table 12.2. Systematic reviews on diagnostic accuracy of FDG-PET in patients with suspected liver metastasis of colorectal cancer after treatment

Reference	Zhang 2009	Floriani 2010
Update to	January 2008	August 2008
Number of studies	16 primary studies	25 primary studies (24 CT, 14 FDG-PET, 11 MRI, 6 US)
Number of patients	910 (median 52; range 24-134)	1 816 (median 55.5; range 8-365) FDG-PET 699 (median 50; range 19-100)

(to be continued)

Reference	Zhang 2009	Floriani 2010
Update to	January 2008	August 2008
FDG-PET	sensitivity: pooled 97% (95% CI 95-98%) specificity: pooled 98% (95% CI 97-99%) heterogeneity for specificity (p<0.0004) not for sensitivity (p<0.4505) The calculated area under SROC curves and Q* value were 0.9904 and 0.9594	sensitivity: pooled 93.8% (95%CI 90-97.7%) specificity: pooled 98.7% (95% CI 97.2-100%) LR+: pooled 51.53 (95% CI 31.99-82.99) LR-: pooled 0.008 (95% CI 0.005-0.013)
Comparator	none	CT sensitivity: pooled 74.8% (95% CI 71.2-78.3%) specificity: pooled 95.6% (95% CI 93.4-97.8%) LR+: pooled 11.66 (95% CI 7.74-17.55) LR-: pooled 0.38 (95% CI 0.25-0.58) MRI sensitivity: pooled 81.1% (95% CI 76-86.1%) specificity: pooled 97.2% (95% CI 94.5-99.9%) LR+: pooled 29.16 (95% CI 15.04-56.56) LR-: pooled 0.35 (95% CI 0.18-0.69) US sensitivity: pooled 63% (95% CI 56-70%) specificity: pooled 97.6% (95% CI 95.6-99.5%) LR+: pooled 16.88 (95% CI 9.85-28.92) LR-: pooled 0.34 (95% CI 0.20-0.58)
Reference standard	pathology (histology or biopsy) and/or clinical follow up	pathology (histology or biopsy), intraoperative US and/or clinical follow up

Table 12.3. Systematic reviews on diagnostic accuracy of FDG-PET in patients with suspected pelvic metastasis or local recurrence of colorectal cancer after treatment

Reference	Zhang 2009
Update to	January 2008
Number of studies	14 primary studies
Number of patients	884
FDG-PET	sensitivity: pooled 94% (95% CI 91-97%) specificity: pooled 94% (95% CI 92-96%) no heterogeneity for sensitivity and specificity (p<0.2716 and 0.090) the calculated area under SROC curves and Q* value were 0.9776 and 0.9328
Comparator	none
Reference standard	pathology (histology or biopsy) and/or clinical follow up

Primary studies

Nine studies (Chen 2007; Kitajima 2009; Kyoto 2010; Lee 2010; Metser 2010; Potter 2009; Sarikaya 2007; Shamim 2010; Shen 2006) not included in the above reported systematic reviews and assessing the accuracy of FDG-PET in the diagnosis of whole body metastasis have been retrieved (*Tables 12.4*). They included patients with suspected distant metastasis, with or without elevated CEA. As the whole number of participants does not exceed that included in the systematic review by Zhang 2009, the results are checked only for consistency with the systematic review estimates.

Table 12.4. Results of primary studies on diagnostic accuracy of FDG-PET in patients with suspected whole body metastasis of colorectal cancer after treatment

Reference	Chen 2007; Kitajima 2009; Kyoto 2010; Lee 2010; Metser 2010; Potter 2009; Sarikaya 2007; Shamim 2010; Shen 2006
Number of studies	9
Number of patients	837 (median 63, range 39-269)
FDG-PET	sensitivity: median 92.6% (range 81.5-97.3%) specificity: median 86.1% (range 60-96.3%)
Comparator	none
Reference standard	pathology or clinical follow up

Five studies (Chua 2007; Glazer 2010; Kong 2008; Orlacchio 2009; Wiering 2007b) not included in the above reported systematic reviews and assessing the accuracy of FDG-PET in the diagnosis of liver metastasis have been retrieved. They included patients with suspected or known liver metastasis (in 2 studies patients were selected for metastasis surgical resection).

As the patients included in studies published after the update performed by Floriani 2010 add up to a number smaller than those included in the systematic review, estimates of diagnostic accuracy of FDG-PET from primary studies were only checked for consistency with estimates given by the systematic review (*Table 12.5*).

Table 12.5. Primary studies on diagnostic accuracy of FDG-PET in patients with suspected liver metastasis of colorectal cancer after treatment

Reference	Chua 2007; Glazer 2010; Kong 2008; Orlacchio 2009; Wiering 2007b
Number of studies	5
Number of patients	876 (median 131; range 65-467)
FDG-PET	sensitivity: median 95.5% (range 89.9-98.4%) specificity: median 91.6% (range 22.2-100%)
Comparator	none
Reference standard	pathology, clinical follow up, intraoperative US, laparotomy

One study (Shyn 2010) not included in the above reported systematic reviews and assessing the accuracy of FDG-PET in the diagnosis of local recurrence has been retrieved. As the patients included in this study published after the update performed by Zhang 2010 add up to a number smaller than those included in the systematic review, estimates of diagnostic accuracy of FDG-PET from this primary study were only checked for consistency with estimates given by the systematic review (*Table 12.6*).

Table 12.6. Primary studies on diagnostic accuracy of FDG-PET in patients with suspected local recurrence of colorectal cancer after treatment

Reference	Shyn 2010
Number of studies	1
Number of patients	79
FDG-PET	sensitivity: 100% specificity: 97.1%
Comparator	none
Reference standard	histology or follow up

To summarise diagnostic accuracy results (*Table 12.7*) we chose the estimates available from the systematic review by Zhang 2009 for the diagnosis of whole body and pelvic metastasis or local recurrence. For the diagnosis of liver metastasis, as the results between the systematic reviews by Zhang 2009 and Floriani 2010 are consistent, we chose the diagnostic estimates from the systematic review that considered also comparator tests (Floriani 2010).

Table 12.7. Results on diagnostic accuracy of FGD-PET in assessing metastasis in patients with suspected recurrence of colorectal cancer

Diagnostic accuracy	Whole body metastasis	Liver metastasis	Pelvic metastasis or local recurrence
Number of studies	19	25 (24 CT; 14 FDG-PET; 11 MRI; 6 US)	14
Number of patients	1 206	1 816 (699 FDG-PET)	884
FDG-PET	sensitivity: pooled 91% (95% CI 88-92%) specificity: pooled 83% (95% CI 79-87%)	sensitivity: pooled 93.8% (95% CI 90-97.7%) specificity: pooled 98.7% (95% CI 97.2-100%)	sensitivity: pooled 94% (95% CI 91-97%) specificity: pooled 94% (95% CI 92-96%)
Comparator	none	CT sensitivity: pooled 74.8% (95% CI 71.2-78.3%) specificity: pooled 95.6% (95% CI 93.4-97.8%) MRI sensitivity: pooled 81.1% (95% CI 76-86.1%) specificity: pooled 97.2% (95% CI 94.5-99.9%) US sensitivity: pooled 63% (95% CI 56-70%) specificity: pooled 97.6% (95% CI 95.6-99.5%)	none
Reference standard	pathology (histology or biopsy) and/or clinical follow up	pathology (histology or biopsy), intraoperative US and/or clinical follow up	pathology (histology or biopsy) and/or clinical follow up
Reference	Zhang 2009	Floriani 2010	Zhang 2009

Comments of ASSR reviewers

The systematic reviews, of intermediate methodological quality, include a large number of studies. Primary studies published after the systematic reviews show consistent result.

FDG-PET seems to have a good sensitivity for the diagnosis of whole body metastasis, liver metastasis and pelvic or local recurrence of colorectal cancer. Specificity is disclosed as good for liver metastasis and pelvic recurrence; specificity for whole body metastasis is slightly lower.

Comprehensive data on comparative tests are available only for the diagnosis of liver metastasis. Ultrasound, CT, MRI and FDG-PET have similar high specificity estimates; whereas FDG-PET seems to have higher sensitivity in comparison with the other tests.

Diagnostic accuracy estimates

Whole body metastasis

FDG-PET sensitivity: (pooled) 91%
FDG-PET specificity: (pooled) 83%

Liver metastasis

FDG-PET sensitivity: (pooled) 93.8%
FDG-PET specificity: (pooled) 98.7%

CT sensitivity: (pooled) 74.8%
CT specificity: (pooled) 95.6%

MRI sensitivity: (pooled) 81.1%
MRI specificity: (pooled) 97.2%

US sensitivity: (pooled) 63%
US specificity: (pooled) 97.6%

Pelvic metastasis or local recurrence

FDG-PET sensitivity: (pooled) 94%
FDG-PET specificity: (pooled) 94%

LEVEL OF EVIDENCE: MODERATE

IMPACT OF FDG-PET ON CLINICAL OUTCOMES FOR PATIENTS WITH LIVER METASTASES

Systematic reviews

None retrieved.

Primary studies

Two historical series with control group (Pawlik 2009; Wiering 2007a) and one randomized controlled trial (Ruers 2009) were retrieved evaluating outcomes of patients selected for resection/ablation of suspected liver metastasis of colorectal cancer on the basis of FDG-PET results (*Table 12.8*).

The historical series included patients submitted to laparotomy for intended resection of colorectal liver metastases and evaluated the impact of FDG-PET on the reduction of the rate of non therapeutic laparotomy compared with a control group of patients not submitted to FDG-PET. One study (Wiering 2007a) evaluated also the impact on 3-year overall survival and disease-free survival. Both studies are limited by an inadequate control of confounders.

The open randomized controlled trial (Ruers 2009) included 150 patients selected through conventional diagnostic imaging to laparotomy with curative intent of suspected liver metastasis. Seventy-five of them were allocated through randomization directly to laparotomy and 75 to FDG-PET for a new evaluation and, if results were confirmed, to laparotomy. The primary outcome was the rate of futile laparotomy; other outcomes considered were the 3-year overall survival and disease-free survival. This study is limited by a too extensive definition of futile laparotomy (see below).

Table 12.8. Results from studies on impact on clinical outcomes of FDG-PET for patients with suspected liver metastasis of colorectal cancer

References	Pawlik 2009; Ruers 2009; Wiering 2007a		
Number of studies	3		
Number of patients	664 (historical series) 150 (RCT)		
Follow up	36 months (2 studies)		
Futile/non therapeutic laparotomy rate	FDG-PET group 5.6% (historical series) 19.4% (historical series) 28% (RCT)	Conventional group 12.4% (historical series) 28% (historical series) 45% (RCT)	 p<0.05 p>0.05 p<0.05 *
3-year overall survival	FDG-PET group 60.1% (historical series) 61.3% (RCT)	Conventional group 57.1% (historical series) 65.8% (RCT)	 p>0.05 p>0.05
3-year disease-free survival	FDG-PET group 31.4% (historical series) 35.5% (RCT)	Conventional group 23% (historical series) 29.8% (RCT)	 p>0.05 p>0.05
Perioperative mortality	FDG-PET group 3% (historical series)	Conventional group 3% (historical series)	
Notes	* too extensive definition of futile laparotomy: actually only 5 out 75 participants avoided laparotomy in the FDG-PET group		

Comments of ASSR reviewers

Two historical series and one randomized controlled trial explored the impact of FDG-PET-based selection of patients for resection/ablation of suspected liver metastasis of colorectal cancer. FDG-PET application compared with conventional diagnostic work up could reduce the rate of non therapeutic laparotomy, but it seems that FDG-PET has no impact on overall and disease-free survival.

LEVEL OF EVIDENCE: VERY LOW

IMPACT ON CLINICAL OUTCOMES OF FDG-PET FOR PATIENTS WITH LUNG METASTASES

Systematic reviews

None retrieved.

Primary studies

One historical series with control group (Munoz Llarena 2007) was retrieved evaluating overall survival of patients selected for resection of suspected pulmonary metastasis of colorectal cancer on the basis of FDG-PET results compared with a control group of patients not submitted to FDG-PET (*Table 12.9*). The study is limited by a not adequate control of confounders.

Table 12.9. Results from studies on impact on clinical outcomes of FDG-PET for patients with suspected pulmonary metastasis of colorectal cancer

Reference	Munoz Llarena 2007		
Number of studies	1		
Number of patients	55		
Follow up	5 years		
Median overall survival	FDG-PET group 41,4 months (95% CI 8.7-74.1)	Conventional group 31,5 months (95% CI 22.9-40.1)	p = 0.14

Comments of ASSR reviewers

One historical series explored the impact of FDG-PET for patients with suspected pulmonary metastasis of colorectal cancer. FDG-PET application compared with conventional diagnostic work up seems not to have any impact on overall survival. However, due to the scarcity of data no conclusion can be drawn.

LEVEL OF EVIDENCE: VERY LOW

12.2. Clinical outcomes

To evaluate the balance between benefits and risks, the panel agreed to consider the presumed patient-important outcomes reported below (*Table 12.10*), and voted on the level of importance.

All patient-important outcomes were voted critical, with outcomes for patients with resectable/potentially resectable metastases scoring a higher median of 8, showing that a correct identification of patients who could benefit from surgical resection is considered most important.

The two studies evaluating impact on clinical outcomes reported a reduction in surgical resection but no difference on overall and disease-free survival.

The following matrix of "natural frequencies" was provided (*Table 12.11*).

Table 12.10. Patient-important clinical outcomes and median scores of importance

Patient-important outcomes	**Median score (range)**
Patients with diffuse metastatic disease	
• True positives - patients correctly upstaged to diffuse metastatic disease receive palliative systemic treatment	7 (4-9)
• False positives - patients incorrectly downstaged proceed to unnecessary surgery	7 (5-9)
Patients with resectable / potentially resectable metastases	
• True negatives - patients with resectable/potentially resectable metastases receive surgery with radical intent or combined chemotherapy aimed at downsizing, which could improve their survival	8 (6-9)
• False negatives - patients incorrectly upstaged do not receive surgical treatment, which could have improved their survival, but receive palliative systemic treatment	8 (6-9)

Table 12.11. "Natural frequencies" of patients assessed for diagnosis of suspected recurrence and staging of recurrence

		N of patients out of 100 submitted to the exam	
		According to FDG-PET	**According to MRI**
Patients with disseminated disease/ unresecatble metastases	True positives	34	29
	False negatives	2	7
Patients with localized disease / resectable metastases	True negatives	63	62
	False positives	1	2
		100	100

12.3. Voting results

The first voting round registered a light disagreement with ratings falling in the regions of uncertainty and appropriateness (median score 7, range 4-8), while the second voting round reported an agreement on appropriateness (median score 8; range 7-8).

FINAL RATING FOR THE USE OF FDG-PET IN DIAGNOSIS OF SUSPECTED RECURRENCE AND STAGING OF RECURRENCE IN PATIENTS TREATED FOR COLORECTAL CANCER:

APPROPRIATE

12.4. Conclusions

After an initial light disagreement, the panel agreed during the second meeting in rating the use of FDG-PET in diagnosis and staging of suspect recurrence in patients treated for colorectal cancer as appropriate. Level of evidence for FDG-PET's diagnostic accuracy was graded as moderate and panelists considered most critical the outcomes for patients with resectable/potentially resectable metastases, viewing most important the correct identification of patients who could benefit from surgical resection.

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 Emilia-Romagna's need for PET and for setting up priorities for future research programs on the clinical use of FDG-PET in oncology.

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Appendices

Appendix 1.
Voting forms

ORI
Osservatorio Regionale per l'Innovazione

CRITERIA FOR APPROPRIATE USE OF FDG-PET IN COLORECTAL CANCER

2011

VOTING FORMS

NAME

_____

Agenzia sanitaria e sociale regionale

RegioneEmilia-Romagna

CLINICAL QUESTION

Diagnosis of patients with primary colorectal cancer

Rationale

Diagnosis of colorectal cancer is made by colonoscopy, followed by possible biopsy and polypectomy (AIOM 2009; ESMO 2010a; SIGN 2003). Double contrast barium enema is an alternative when colonoscopy is difficult for anatomical reasons. Diagnosis of rectal cancer is based on a digital rectal examination including sigmoidoscopy with biopsy for histopatological examination (ESMO 2010b).

Diagnostic role of FDG-PET

There is no diagnostic role of FDG-PET.

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

N staging of patients with primary colorectal cancer

Rationale

Pre-operative N staging usually does not affect the initial treatment choice (AIOM 2009). Postsurgical histopathological lymph node status is a predictor of long-term prognosis in colorectal cancer (ESMOa 2010).

Diagnostic role of FDG-PET

There is no diagnostic role of FDG-PET.

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

M staging of patients with locally advanced colorectal cancer

Rationale

Pre-operative M staging is important to differentiate a localized disease from a disseminated disease (SIGN 2003, AIOM 2009). Pre-operative imaging of the liver and chest is required to detect possible metastases and to decide on the general therapeutic strategy (SIGN 2003, AIOM 2009, ESMO 2010). Localized disease is treated with radical curative surgery, surgery of liver and lung metastases is reserved/intended for selected patients with resectable lesions while palliative surgery is indicated for patients with unresectable metastatic lesions.

Diagnostic role of FDG-PET

Characterization of liver or solitary lung distant metastases with FDG-PET can direct to surgical resection if metastases appear resectable or to systemic therapy if disease is disseminated. In selected patients unresectable liver metastasis can also be considered for in situ ablation.

Treatment effectiveness

Surgical resection of resectable liver metastatic disease can lead to a 5-year survival rates of 40% compared with no survival at 5 years for untreated patients (Geoghegan 1999). Unresectale liver metastases can be treated with ablation, although benefit is unclear (SIGN 2003). Survival can also be improved by resection of lung mestastasis (SIGN 2003).

Pre-test probability and change in management

The median pre-test probability of occurrence of pre-operative liver metastasis is 22.1% (range 17.3-33.8%; data from Facey 2007, Llamas-Elvira 2007, Akiyoshi 2009, Mainenti 2010).

Research question: FDG-PET in add on

Is FDG-PET accurate in detecting liver metastases in patients with locally advanced primary colorectal cancer and unclear CT results?

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

FDG-PET	sensitivity: median 89.9% specificity: median 96.2%
Comparator multirow CT*	sensitivity: (range) 83.3%-100% specificity: (range) 96.4%-97.7%

* data from studies evaluating FDG-PET

Consequences of TEST for		**Level of importance* (1-9)**
Patients with disseminated disease/ unresecatble metastases	True positives: patients correctly upstaged to disseminated disease undergo systemic therapy False negatives: patients incorrectly downstaged to localized disease proceed to futile radical surgery	
Patients with localized disease / resectable metastases	True negatives: patients correctly staged for localized disease / resectable metastases proceed to radical surgery, which impacts on survival False positives: patients incorrectly upstaged to disseminated disease undergo systemic therapy instead of radical surgery, which could have improved survival	

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

Matrix of natural frequencies

		N of patients out of 100 submitted to the exam	
		According to FDG-PET	**According to multirow CT**
Patients with disseminated disease/ unresecatble metastases	True positives	20	18 - 22
	False negatives	2	4 - 0
Patients with localized disease / resectable metastases	True negatives	75	75 - 76
	False positives	3	3 - 2
		100	100

CLINICAL QUESTION

Role of FDG-PET in M staging of patients with locally advanced primary colorectal 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 rectal cancer

Rationale

In patients with locally advanced resectable rectal cancer pre-operative or neoadjuvant radiotherapy (with or without chemotherapy), followed by total mesorectal excision, reduces local recurrence rates (AIOM 2009; ESMO 2010b; NCCN 2011b; SIGN 2003), while in locally advanced unresectable rectal cancer it can obtain the downsizing necessary to allow radical surgical treatment (ESMO 2010b; NCCN 2011b).

Diagnostic role of FDG-PET

There is no diagnostic role of FDG-PET.

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

During treatment evaluation of early response to systemic therapy of liver metastases in patients with colorectal cancer

Rationale

Initially unresectable liver metastases can become resectable after downsizing with chemotherapy. For patients with initially unresectable liver metastases, a strong correlation between response rate to neoadjuvant treatment of metastatic CRC and resection rate has been demonstrated.Pathological response seems to be a surrogate for predicting the outcome. Thus, the therapeutic strategy is aimed at achieving a very good response in patients with initially unresectable disease in order to convert unresectable metastases into resectable metastases (ESMO 2010).

Diagnostic role of FDG-PET

During treatment evaluation (after two or three cycles/months) of response to treatment could allow avoidance of unnecessary toxicity and costs for non responding patients.

Treatment effectiveness

Surgical resection of resectable liver metastatic disease can lead to a 5-year survival rates of 40% compared with no survival at 5 years of untreated patients (Geoghegan 1999). Unresectale liver metastases can be treated with ablation, although benefit is unclear (SIGN 2003).

Pre-test probability and change in management

Standard combination chemotherapy regimens comprising 5-FU/LV in combination with either irinotecan, typically FOLFIRI, or oxaliplatin (FOLFOX) have been reported to facilitate the resection of 7-40% of patients with initially unresectable metastases depending upon the initial selection of patients (ESMO 2010).

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

Is FDG-PET accurate in evaluating during treatment response to systemic therapy of liver metastases?

Diagnostic accuracy estimates for liver metastases **Level of evidence: none**

Not available

Consequences of TEST for		Level of importance* (1-9)
Patients not responding to treatment	True non responders: patients interrupt ineffective treatment, avoiding unnecessary toxicity, and could change to different line of therapy, which might impact on survival False responders: patients continue ineffective treatment, which will non impact on survival, suffer unnecessary toxicity and do not change to other, perhaps more effective, line of treatment	
Patients responding to treatment	True responders: patients continue effective treatment, which could lead to downsizing with benefits on survival False non responders: patients interrupt effective treatment, which could have led to downsizing, and unnecessarily change therapy	

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

CLINICAL QUESTION

Role of FDG-PET during treatment evaluation of early response to systemic therapy of liver metastases in patients treated for colorectal 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

End of treatment evaluation of response to neoadjuvant radiotherapy for rectal cancer

Rationale

In patients with locally advanced resectable rectal cancer pre-operative or neoadjuvant radiotherapy (with or without chemotherapy), followed by curative surgery, reduces local recurrence rates (AIOM 2009, ESMO 2010b, NCCN 2011b, SIGN 2003). The response to pre-operative therapy may influence prognosis and subsequent therapy in terms of extent (local excision or total mesorectal excision) of surgery (ESMO 2010b). In selected cases, after neoadjuvant therapy patients can undergo a pathological restage - with multiple biopsies or excision biopsy - and, if a pathologic complete response is achieved, no further therapy is provided and the rectum is preserved (ESMO 2010b). Moreover in patients with locally advanced unresectable rectal cancer neoadjuvant chemoradiotherapy can achieve the necessary downsizing to allow the radical surgical treatment (ESMO 2010b, NCCN 2011b).

Diagnostic role of FDG-PET

As there are no alternative therapeutic options there is no diagnostic role for FDG-PET.

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 evaluation of residual disease following ablative treatment of liver metastases

Rationale

In patients with colorectal unresectable liver metastases local ablative techniques that result in intrahepatic tumor removal have emerged as alternative treatment options (Geus-Oei 2009).

Success of local ablation cannot easily be ascertained with intraoperative ultrasonography and residual tumor cannot be accurately detected with CT or MRI. This can lead to either a delayed diagnosis of treatment failure or lack of differentiation between incomplete local ablative treatment and occurrence of new metastases.

Diagnostic role of FDG-PET

To evaluate success of ablation and assess presence of residual or recurrent metastases in order to repeat ablation procedure.

Treatment effectiveness

Intrahepatic tumor removal through ablation has emerged as a viable treatment option for unresectable liver metastases, although positive effects on patients' survival remain to be established (Geus-Oei 2009).

Pre-test probability and change in management

The median pre-test probability of residual disease or local recurrence after ablation of liver metastasis in patients with colorectal cancer is 23.5% (range 16.3%-53.8%; Geus-Oei 2009).

Research question: FDG-PET as replacement

Is FDG-PET better (i.e has higher diagnostic accuracy) than the available comparators (conventional imaging) in detecting residual disease or local recurrence after ablation of liver metastasis in patients with colorectal cancer?

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

It is not possible to provide estimates

Consequences of TEST for		Level of importance* (1-9)
Patients with residual or recurrent metastatic lesions	True positives: patients undergo further ablative procedure, which has uncertain impact on their survival False negatives: patients considered clear of local lesions, and do not receive further ablative procedures, which has uncertain impact on their survival	
Patients without residual or recurrent metastatic lesions	True negatives: patients correctly considered clear of local lesions and in no need of further interventions False positives: patients undergo further futile ablative procedures	

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

CLINICAL QUESTION

Role of FDG-PET in evaluation of residual disease following ablative treatment of liver metastases

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

CLINICAL QUESTION

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

Rationale

About 30-50% of patients with colorectal cancer will relapse and die after curative surgical resection, with or without adjuvant chemotherapy (ESMO 2010a). Detecting relapse in advance is the main goal of surveillance after primary treatment. Recently a consistent evidence has demonstrated an improved survival for patients undergoing more intensive surveillance compared to those receiving non-intensive follow up (AIOM 2009, ESMO 2010a). However optimal strategy for an intensive follow up is not yet clearly defined, in particular in terms of diagnostic tests to be used, surveillance intervals and duration of follow up.

Diagnostic role of FDG-PET

Early detection of recurrence for timely surgical treatment of resectable metastases, which could improve survival

Treatment effectiveness

The estimated overall survival gain due to an intensive follow up is between 7% and 13% and the improvement has been attributed to earlier detection of recurrent disease and in particular to a higher rate of detection, and treatment, of isolated metastasis (AIOM 2009, ESMO 2010a).

Pre-test probability and change in management

Recurrence rate in patients previously treated for a primary colorectal cancer ranges between 35% (only in liver) and 75% (any recurrence) after a follow up of about 2 years (Kuehl 2008, Sobhani 2008).

Research question: replacement (new test)

Does introducing FDG-PET in current follow up strategy for patients with no suspicion of recurrence allow an earlier detection of relapses?

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

Not available

Consequences of TEST for		Level of importance* (1-9)
Patients relapsing	True positives: patients with recurrence start treatment for recurrence earlier, which might impact on survival	
	False negatives: patients delay treatment for recurrence, with a possible negative impact on survival	
Patients not relapsing	True negatives: patients remain in follow up	
	False positives: start unnecessary treatment, which will bring toxicity and morbidity, with no gain on survival	

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

Impact on clinical outcomes estimates **Level of evidence: very low**

1 RCT: conventional follow up versus conventional follow up with FDG-PET (Sobhani 2008).

recurrence: no statistically significant difference

time to surgical resection:
no statistically significant difference

mortality: no statistically significant difference

time to recurrence: absolute difference -3 months p 0.01 (in favor of FDG-PET group)

% of surgical resection:
absolute difference -12% p 0.01 (in favor of FDG-PET group)

CLINICAL QUESTION

Role of FDG-PET in follow up of patients treated for colorectal 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

Staging of recurrence in patients treated for colorectal cancer

Rationale

Approximately 30-50% of patients with colorectal cancer will relapse and die after curative surgical resection, with or without adjuvant chemotherapy (ESMO 2010a). Although most metastatic diseases are not suitable for resection, it is important to select patients with resectable metastases and those with initially unresectable metastases, that could become resectable following response to a combined chemotherapy (ESMO 2010c).

Diagnostic role of FDG-PET

To characterize the extent of metastatic disease and assess whether metastases are resectable (ESMO 2010c) in order to direct patients to either surgical treatment or palliative systemic treatment.

Treatment effectiveness

Patients with resected liver disease have a 5-year survival rates of 40% compared with no survival at 5 years of untreated patients (Geoghegan 1999). Resection of resectable lung metastases offers also 25-35% 5-year survival rates in carefully selected patients (ESMO 2010c). Initially unresectable liver metastases can become resectable after downsizing with chemotherapy. For patients with initially unresectable liver metastases, a strong correlation between response rate to neoadjuvant metastatic treatment and resection rate has been demonstrated (ESMO 2010c).

Pre-test probability and change in management

Median pre-test probability of liver metastasis in patients with suspected recurrence of colorectal cancer: 36.2% (range 15-63.4%; data from primary studies included in Floriani 2010).

Median pre-test probability of whole body metastasis: 67.3% (range 41-90%; Chen 2007; Kitajima 2009; Kyoto 2010; Lee 2010; Metser 2010; Potter 2009; Sarikaya 2007; Shamim 2010; Shen 2006).

Change in management due to PET on recurrent colorectal cancer ranges from 19% to 47% of patients (Watson 2006) mainly through upstaging and avoidance of futile surgery.

Research question: FDG-PET in add on

Is FDG-PET sufficiently accurate to characterize the extent of metastatic disease in patients with potentially resectable metastases?

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

Whole body metastasis

FDG-PET	sensitivity: (pooled) 91% specificity: (pooled) 83%

Liver metastasis

FDG-PET	sensitivity: (pooled) 93.8% specificity: (pooled) 98.7%
Comparator CT	sensitivity: (pooled) 74.8% specificity: (pooled) 95.6%
Comparator MRI	sensitivity: (pooled) 81.1% specificity: (pooled) 97.2%

Consequences of TEST for		**Level of importance* (1-9)**
Patients with diffuse metastatic disease	True positives: patients correctly upstaged to diffuse metastatic disease receive palliative systemic treatment False negatives: patients incorrectly downstaged proceed to unnecessary surgery	
Patients with resectable / potentially resectable metastases	True negatives: patients with resectable/potentially resectable metastases receive surgery with radical intent or combined chemotherapy aimed at downsizing, which could improve their survival False positives: patients incorrectly upstaged do not receive surgical treatment, which could have improved their survival, but receive palliative systemic treatment	

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

Matrix of natural frequencies

		N of patients out of 100 submitted to the exam	
		According to FDG-PET	**According to MRI**
Patients with diffuse metastatic disease	True positives	34	29
	False negatives	2	7
Patients with resectable liver metastases	True negatives	63	62
	False positives	1	2
		100	100

Impact on clinical outcomes estimates: **Level of evidence: very low**

Two historical series with control group (Pawlik 2009, Wiering 2007a) and 1 RCT trial (Ruers 2009) patients treated according to FDG-PET results versus patients treated according to other imaging results.

3 years overall survival: no statistically significant difference

3 years disease free survival: no statistically significant difference

% of futile laparotomy: absolute difference (RCT) -19% p <0.05 (in favour of PET group)

CLINICAL QUESTION

Role of FDG-PET in staging of recurrence in patients treated for colorectal cancer

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

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

ORI
Osservatorio Regionale per l'Innovazione

CRITERIA FOR APPROPRIATE USE OF POSITRON EMISSION TOMOGRAPHY (PET) IN COLORECTAL CANCER

SEARCH STRATEGY

AND

TABLES OF EVIDENCE

March 2011

Agenzia sanitaria e sociale regionale

RegioneEmilia-Romagna

SEARCH STRATEGY

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

- Cochrane Database of Systematic Reviews (CDSR - The Cochrane Library);
- Database of Abstracts of Reviews of Effects (DARE - Centre for Reviews and Dissemination);
- Health Technology Assessment Database (HTA Database - Centre for Reviews and Dissemination 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.

CDSR, DARE, HTA database, CENTRAL search strategy

1. "Positron-Emission Tomography" [MeSH descriptor explode all trees]
2. "Fluorodeoxyglucose F18" [MeSH descriptor explode all trees]
3. "positron emission tomography":ti,ab,kw
4. pet*: ti,ab,kw
5. pet scan*: ti,ab,kw
6. "Fluorodeoxyglucose F18": ti,ab,kw or
7. fdg NEAR/2 18: ti,ab,kw
8. **1/7 OR**
9. "Colorectal Neoplasms" [Mesh descriptor NoExp]
10. "Colonic Neoplasms" [Mesh descriptor NoExp]
11. "Rectal Neoplasms" [Mesh descriptor explode all trees]
12. **9/12 OR**
13. **8 AND 11**

Publication date: 2006-2010

MEDLINE search strategy

1. "Fluorodeoxyglucose F18"[Mesh]
2. "2-Fluoro-2-deoxyglucose" [All Fields]
3. "18F Fluorodeoxyglucose" [All Fields]
4. "F 18 Fluorodeoxyglucose" [All Fields]
5. Fludeoxyglucose* [All Fields]
6. "2 fluoro 2 deoxy d glucose"[All Fields]
7. 18fluorodesoxyglucose*[All Fields]
8. fluorodeoxyglucose*[All Fields]
9. "fluorine 18 fluorodeoxyglucose" [All Fields]
10. 18f dg*[All Fields])
11. 18fluorodeoxyglucose*[All Fields]
12. 18fdg [All Fields]
13. 18 fdg* [All Fields]
14. fdg 18* [All Fields]
15. fdg/* [All Fields]
16. "fdg pet"[All Fields]
17. "Positron-Emission Tomography"[Mesh]
18. "positron emission tomography" [title/abstract]
19. pet [title/abstract]
20. "pet scan" [All Fields]
21. "pet scans" [All Fields]
22. "pet scanner" [All Fields]
23. petscan [All Fields]
24. **1/23 OR**
25. "colorectal carcinoma"[Title/Abstract]
26. "colorectal neoplasm"[Title/Abstract]
27. "colorectal neoplasms"[Title/Abstract]
28. "colorectal cancer"[Title/Abstract]
29. "colorectal cancers"[Title/Abstract]
30. "colonic neoplasm"[Title/Abstract]
31. "colonic neoplasms"[Title/Abstract]
32. "cancer of colon"[Title/Abstract]
33. "colon cancers"[Title/Abstract]
34. "colon cancer"[Title/Abstract]
35. "sigmoid neoplasm"[Title/Abstract]

36. "sigmoid neoplasms"[Title/Abstract]
37. "sigmoid cancer"[Title/Abstract]
38. "sigmoid cancers"[Title/Abstract]
39. "sigmoidal cancer"[Title/Abstract]
40. "cancer of sigmoid"[Title/Abstract]
41. "rectal neoplasm"[Title/Abstract]
42 "rectal neoplasms"[Title/Abstract]
43. "rectal cancer"[Title/Abstract]
44. "rectal cancers"[Title/Abstract]
45. "rectum cancer"[Title/Abstract]
46. "rectum cancers"[Title/Abstract]
47. "cancer of rectum"[Title/Abstract]
48. "Sigmoid Neoplasms"[Mesh:noexp]
49. "Colorectal Neoplasms"[Mesh:noexp]
50. "Colonic Neoplasms"[Mesh:noexp]
51. "Rectal Neoplasms"[Mesh]
52. **25/51 OR**
53. **24 AND 25**
54. "editorial"[Publication Type]
55. "comment"[Publication Type]
56. "letter"[Publication Type]
57. **54/56 OR**
58. **53 NOT 57**

Limits: humans

Publication date: 2006-2010

Languages: English, French, Italian, Spanish

EMBASE search strategy

1. "positron emission tomography"/syn
2. "fluorodeoxyglucose f 18"/exp
3. "fluorodeoxyglucose f 18"/syn
4. "computer assisted emission tomography"/exp
5. "computer assisted emission tomography" OR
6. pet
7. "pet scans"
8. "pet scanner"
9. "pet scan"
10. "pet/ct scan"
11. "pet/ct scans"
12. "pet/ct"
13. "positron emission tomography/computed tomography"
14. pet NEAR/4 scan*
15. pet NEAR/4 ct
16. **1/15 OR**
17. "colon cancer"/de, not exp
18. "colon adenocarcinoma"/de, not exp
19. "colon carcinogenesis"/de, not exp
20. "colon carcinoma"/de, not exp
21. "colorectal cancer"/de, not exp
22. "colorectal carcinoma"/de, not exp
23. "sigmoid carcinoma"/de, not exp
24. "cecum cancer"/de, exp
25. "rectum carcinoma"/de, exp
26. "anus cancer"/ de, exp
27. "colon cancer":ab,ti
28. "colon adenocarcinoma":ab,ti
29. "colon carcinogenesis":ab,ti
30. "colon carcinoma":ab,ti
31. "colorectal cancer":ab,ti
32. "colorectal carcinoma":ab,ti
33. "sigmoid carcinoma":ab,ti
34. "cecum cancer":ab,ti
35. "rectum carcinoma":ab,ti

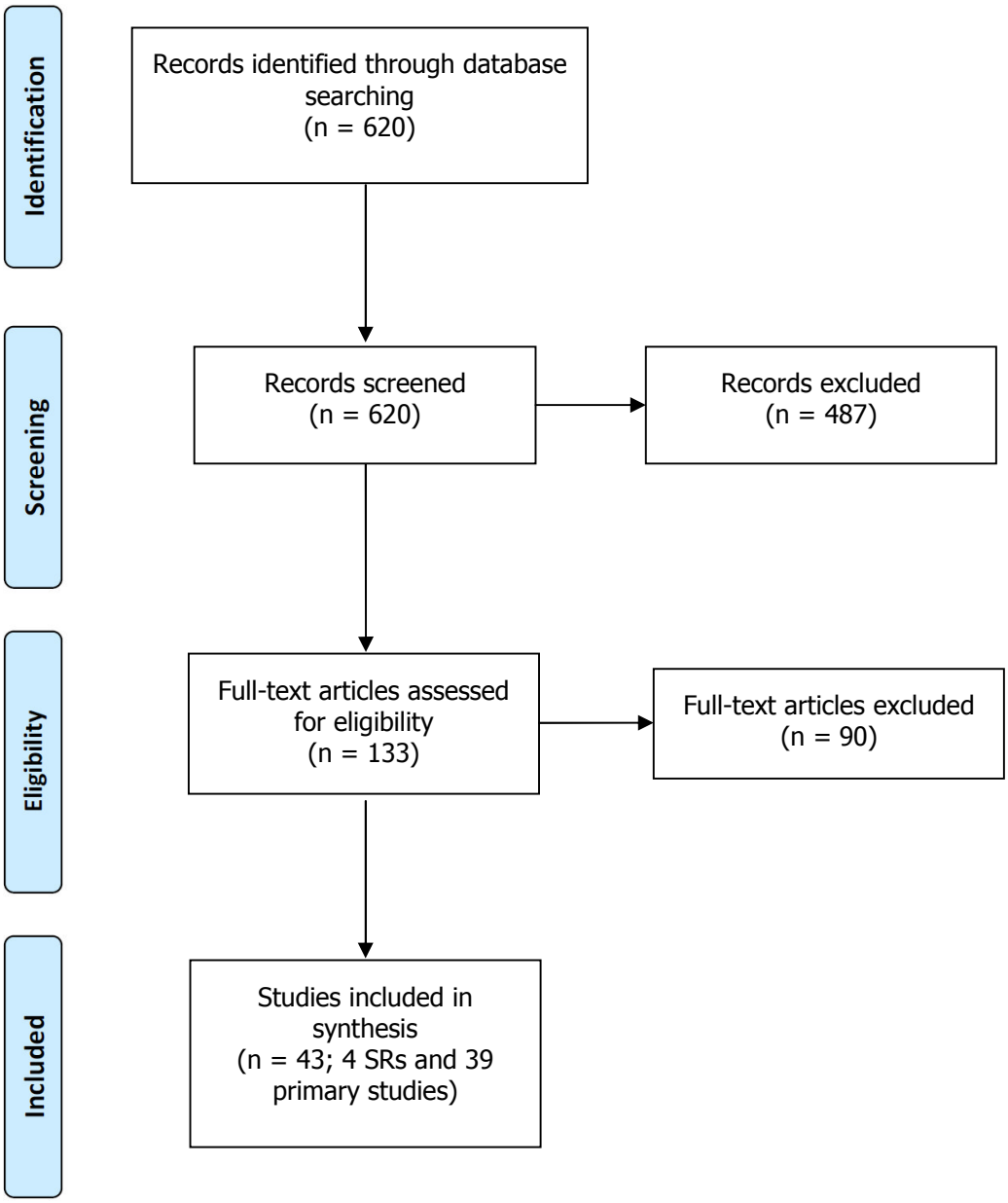
36. "anus cancer":ab,ti
37. "colonic cancer":ab,ti
38. "rectosigmoid adenocarcinoma":ab,ti
39. "carcinoma coli":ab,ti
40. "anal cancer":ab,ti
41. "caecal cancer":ab,ti
42. "caecum cancer":ab,ti
43. "cecum sarcoma":ab,ti
44. **17/43 OR**
45. **16 AND 44**
46. **45 AND ("article" OR "review" OR "short survey" OR "in press article")**

Limits: humans

Publication date: 2006-2010

Languages: English, French, Italian, Spanish

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



TABLES OF EVIDENCE

Chapter 4
Diagnosis of primary colorectal cancer

Diagnostic accuracy

Systematic reviews

Author, year	Facey 2007
Technology	FDG-PET
Disease	colorectal cancer
Objective	to assess: ▪ primary diagnosis ▪ staging ▪ response to therapy (after treatment) ▪ diagnosis of suspected recurrence or restaging
Inclusion criteria	P patients with colorectal cancer I FDG-PET C all available R not specified O diagnostic accuracy for primary diagnosis, staging, re-staging after treatment, recurrence S retrospective and prospective studies
Years covered by the search	up to August 2005
Study selection data abstraction, quality assessment performed by two authors independently	not specified
Comprehensive bibliographic search: at least two databases searched	yes Medline, EMBASE, Cochrane Library, HTA database
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	no
Searched also unpublished studies	no
Language restriction	yes only English literature
Overall number of references retrieved and n. of included studies reported	yes

N. and references of excluded studies reported, reason given	no
Characteristics of included studies clearly reported in tables	yes
Methodological quality of primary studies assessed; criteria reported	yes (QUADAS)
Results of quality assessment used to formulate results and conclusions	yes, qualitative report in the result section
Meta-analysis performed with appropriate statistic methods	not performed
Publication bias assessed	no
N. of included studies Study design	3 studies: primary diagnosis cross sectional diagnostic accuracy studies, with prospective or retrospective recruitment
N. of included patients	85
Reference standard	histopathology by colonoscopy or surgery
Comparator	none
Pre-test probability	median 28.9% (1 study)
Performance results	not calculated: only descriptive results complete data reported only for 1 study: FDG-PET sensitivity 62% specificity 100%
Recommendations and conclusions	In the UK, it is unlikely that PET would be used routinely before biopsy as a tool for diagnosis.
Comments of ASSR reviewers	metanalysis not performed

Synoptic table of primary studies on primary diagnosis of primary colorectal cancer

Author, year	Technology	Patient number	Patient characteristics	Pre-test probability	Sensitivity (%)	Specificity (%)
Drenth 2001	FDG-PET	39	patients that underwent FDG-PET for any reason and sigmoidoscopy or colonoscopy for any reason in the same period	n.c.	77%	80.7%
Ravizza 2010	FDG-PET/CT	92	patients that underwent FDG-PET for any reason and sigmoidoscopy or colonoscopy for any reason in the same period	n.c.	29.8%	81.1%
Weston 2010	FDG-PET/CT	330	patients that underwent FDG-PET for any reason and sigmoidoscopy or colonoscopy for any reason in the same period	n.c.	53%	93%

Primary studies

Author, year	Drenth 2001
Country	The Netherlands
Technology	FDG-PET
Disease	colorectal cancer and adenomas
Objective	to assess diagnostic accuracy in detecting primary tumor
Patients characteristics	39 patients that underwent to FDG-PET for any reason and to sigmoidoscopy or colonoscopy for any reason in the same period; mean age 62.3 years (SD 9.6 years)
Index test	FDG-PET
Comparator	none
Reference standard	histopathology by colonoscopy or surgery
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with opportunistic retrospective recruitment
spectrum of patients representative of the individuals who will receive the test in practice	no
patients selection criteria clearly described	no
verification by reference standard of all subjects	yes
time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	yes
execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
execution of the reference standard described	yes
independent and blind interpretation of index test and reference standard results	not clear
withdrawals from the study explained	no withdrawals
Pre-test probability	not computable (lesion-base analysis)

Results	FDG-PET sensitivity 77.8% specificity 80.7%
Authors' recommendations and conclusions	FDG-PET is able to detect significant endoscopic findings and in most cases accumulation of FDG correlates with carcinomas or large adenomatous polyps. FDG-PET detected all the colorectal carcinomas in our sample but sometimes missed (small) adenomas. Significant pathology was detected in two-thirds of the cases in which FDG-PET generated an endoscopy procedure, resulting in a significant change in the clinical management. Our study suggests that FDG-PET can be regarded as a useful adjunct in the non-invasive follow up of patients with colorectal carcinomas and that unanticipated pathological FDG uptake should be verified by endoscopy.
Comment of ASSR reviewers	very low quality study

Author, year	**Ravizza 2010**
Country	Italy
Technology	FDG-PET/CT
Disease	colorectal cancer and adenomas
Objective	to assess diagnostic accuracy in detecting primary tumor
Patients characteristics	92 patients that underwent to FDG-PET for any reason and to sigmoidoscopy or colonoscopy for any reason in the same period; mean age 63 years, range 32-81
Index test	FDG-PET/CT
Comparator	none
Reference standard	histopathology by colonoscopy or surgery
Outcomes considered	sensitivity, specificity, PPV, NPV
Study design	diagnostic cross sectional study with opportunistic retrospective recruitment
spectrum of patients representative of the individuals who will receive the test in practice	no
patients selection criteria clearly described	no
verification by reference standard of all subjects	yes
time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	yes
execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
execution of the reference standard described	yes
independent and blind interpretation of index test and reference standard results	not clear
withdrawals from the study explained	no withdrawals
Pre-test probability	not computable (lesion-base analysis)

Results	By considering the adenomas together with the malignant lesions (hyperplastic polyps excluded) - lesion-based analysis sensitivity 29.8% specificity 81.1% PPV 84.8% NPV 24.6%
Authors' recommendations and conclusions	18F-FDG PET/CT has a low sensitivity for detecting adenomas. However, because of the specificity and PPV of the technique for neoplastic colorectal lesions, the presence of a focal colorectal FDG uptake justifies the patient undergoing colonoscopy.
Comment of ASSR reviewers	very low quality study

Author, year	**Weston 2010**
Country	USA
Technology	FDG-PET/CT
Disease	sgnificant colonic findings (colorectal cancer and adenomas, other malignancies)
Objective	to assess diagnostic accuracy in detecting primary tumor
Patients characteristics	330 patients that underwent to FDG-PET for any reason and to sigmoidoscopy or colonoscopy for any reason in the same period; mean age 61 years
Index test	FDG-PET/CT
Comparator	none
Reference standard	histopathology by colonoscopy
Outcomes considered	sensitivity, specificity, PPV, NPV
Study design	diagnostic cross sectional study with opportunistic retrospective recruitment
spectrum of patients representative of the individuals who will receive the test in practice	no
patients selection criteria clearly described	no
verification by reference standard of all subjects	yes
time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	yes
execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
execution of the reference standard described	yes
independent and blind interpretation of index test and reference standard results	not clear
withdrawals from the study explained	no withdrawals
Pre-test probability	non computable

Results	sensitivity 53% specificity 93% positive predictive value 65% negative predictive value 89% accuracy 85%
Authors' recommendations and conclusions	Incidental colonic activity detected by PET-CT warrants further evaluation with colonoscopy. However, negative PET-CT does not rule out significant colonic pathology including colon cancer, advanced adenomas, or lymphoma.
Comment of ASSR reviewers	very low quality study

Chapter 5
N staging of patients with primary colorectal cancer

Diagnostic accuracy

Systematic reviews

Author, year	Facey 2007
Technology	FDG-PET
Disease	colorectal cancer
Objective	to assess: ▪ primary diagnosis ▪ staging ▪ response to therapy (after treatment) ▪ diagnosis of suspected recurrence or restaging
Inclusion criteria	P patients with colorectal cancer I FDG-PET C all available R not specified O diagnostic accuracy for primary diagnosis, staging, re-staging after treatment, recurrence S retrospective and prospective studies
Years covered by the search	up to August 2005
Study selection data abstraction, quality assessment performed by two authors independently	not specified
Comprehensive bibliographic search: at least two databases searched	yes Medline, EMBASE, Cochrane Library, HTA database
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	no
Searched also unpublished studies	no
Language restriction	yes, only English literature
Overall number of references retrieved and n. of included studies reported	yes
N. and references of excluded studies reported, reason given	no
Characteristics of included studies clearly reported in tables	yes

Methodological quality of primary studies assessed; criteria reported	yes (QUADAS)
Results of quality assessment used to formulate results and conclusions	yes, qualitative report in the result section
Meta-analysis performed with appropriate statistic methods	not performed
Publication bias assessed	no
N. of included studies Study design	1 cross sectional diagnostic accuracy studies
N. of included patients	34
Reference standard	following surgery detailed histopathology or clinical follow up
Comparator	CT, US
Pre-test probability	N staging: 21.9% (1 study) liver metastasis: 26.5% (1 study)
Performance results	N staging (1 study) FDG-PET sensitivity 29% specificity 88%
Recommendations and conclusions	One diagnostic study of staging showed that PET (like other imaging methods) had poor sensitivity to detect regional lymph-node involvement, but better sensitivity for liver metastases. Specificity was high in all situations.
Comments of ASSR reviewers	metanalysis not performed

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

Author, year	Patient number	Patient characteristics	Technology	Staging	Reference standard	Pre-test probability	Sensitivity (%)	Specificity (%)
Furukawa 2006	44	mean age 61.4 primary tumor from right colon (2), sigmoid colon (4), or rectum (38)	FDG-PET	N staging	following surgery histopathology	51.4%	37	83
			MDCT	N staging			58	67
			macroscopic diagnosis during surgery	N staging			68	72
Llamas-Elvira 2007	90	mean age 66.8 tumors were located in the rectum (56), sigmoid colon (20), ascending colon (2), transverse colon (6), descending colon (4), caecum (10) and splenic flexure (6)	FDG-PET	N staging	surgery, histopathology, biopsy of extra-abdominal metastases, clinical follow up, autopsy examination	53%	21	95
			CT	N staging			25	100

Author, year	Patient number	Patient characteristics	Technology	Staging	Reference standard	Pre-test probability	Sensitivity (%)	Specificity (%)
Kosugi 2008	53	mean age 60.1 locally advanced colorectal adenocarcinoma (20 colon, 33 rectal)	FDG-PET	N staging	following surgery detailed histopathology	not computable	lesion-based analysis reported for N level strata (N1-N2-N3-N4) range 52.2-100	lesion-based analysis reported for N level strata (N1-N2-N3-N4) range 87.5-100
			CT	N staging			lesion-based analysis Reported for N level strata (N1-N2-N3-N4) range 91.3-100	lesion-based analysis reported for N level strata (N1-N2-N3-N4) range 17.6-72.2
Tsunoda 2008	88	mean age 60.6 the location of the primary colorectal cancer was the colon in 37 patients, and the rectum in 51 patients.	FDG-PET/CT	N staging	following surgery histopathology	48.9%	lesion-based analysis reported for 3 analysis methods range 28.6-53.1	lesion-based analysis reported for 3 analysis methods range 90.6-95.3

Author, year	Patient number	Patient characteristics	Technology	Staging	Reference standard	Pre-test probability	Sensitivity (%)	Specificity (%)
Akiyoshi 2009	65	mean age 62 patients with - suspected metastases of lymph nodes or liver on MDCT - pre-operative serum carcinoembryonic antigen ≥5 ng/ml - lower rectal cancer who were planned to pre-operative chemoradiotherapy or laparoscopic resection tumors located in the anal canal (1), rectum (27), rectosigmoid colon (6), sigmoid colon (13), descending colon (2), transverse colon (6), ascending colon (8), caecum (n = 1) and appendix (1)	FDG-PET	N staging	following surgery histopathology	62.5%	43	95
			MDCT	N staging			89	52

Author, year	Patient number	Patient characteristics	Technology	Staging	Reference standard	Pre-test probability	Sensitivity (%)	Specificity (%)
Ono 2009	25	27 surgically proven colorectal cancers ranging from 10 to 70 mm (mean 40.4 mm). They were 9 women and 16 men ranging in age from 51 to 84 years (mean 67.3 years) and were treated between September 2004 and February 2007. All underwent DW-MRI and FDG-PET study within nine days	FDG-PET	N staging	Following surgery histopathology and clinical follow up	43.5%	30	100
			DW-MRI	N staging			80	76.9

Primary studies

Author, year	Furukawa 2006
Country	Japan
Technology	FDG-PET
Disease	colorectal cancer
Objective	to assess diagnostic accuracy in pre-operative N staging
Index test	FDG-PET
Comparator	multidetector row CT (MDCT), macroscopic diagnosis during surgery
Reference standard	following surgery detailed histopathology
Outcomes considered	sensitivity, specificity, PPV, NPV, accuracy
Study design	diagnostic cross sectional study with prospective recruitment
spectrum of patients representative of the individuals who will receive the test in practice	yes
patients selection criteria clearly described	yes
verification by reference standard of all subjects	yes
time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	yes
execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
execution of the reference standard described	yes
independent and blind interpretation of index test and reference standard results	no
withdrawals from the study explained	7 patients without verification
Patients' characteristics	44 patients: 33 men and 11 women with a mean age of 61.4 years (range 38-82) The primary tumor originated from the right colon (n = 2), sigmoid colon (n = 4), or rectum (n = 38). Histological diagnosis was performed in all patients by colonoscopy

Pre-test probability	51.4%
Results	N staging (37 patients) FDG-PET sensitivity: 37% specificity: 83% PPV: 70% NPV: 43% MDCT sensitivity: 58% specificity: 67% PPV: 65% NPV: 60% Macroscopic diagnosis during surgery sensitivity: 68% specificity: 72% PPV: 72% NPV: 68%
Authors' recommendations and conclusions	FDG-PET is not superior to routine MDCT in the initial staging of primary CRC

Author, year	**Llamas-Elvira 2007**
Country	Spain
Technology	FDG-PET
Disease	colorectal cancer
Objective	to assess diagnostic accuracy in pre-operative N and M staging
Index test	FDG-PET
Comparator	CT
Reference standard	• pathological study of tumors and lymph nodes obtained during surgery; or • surgical exploration and biopsy (liver metastases, abdominal implantations, involvement of other abdominal organs); or • in the case of extra-abdominal metastases, pathological study after biopsy or (when pathology was not available) by clinical follow up for at least 1 year or by CT study after at least 2 months demonstrating lesion growth (>0.5 cm) in comparison with the initial examination; or • in cases of death, autopsy examination
Outcomes considered	sensitivity, specificity, PPV, NPV, accuracy
Study design	diagnostic cross sectional study with prospective recruitment
spectrum of patients representative of the individuals who will receive the test in practice	yes
patients selection criteria clearly described	yes
verification by reference standard of all subjects	yes
time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	yes
execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
execution of the reference standard described	yes
independent and blind interpretation of index test and	yes

reference standard results	
withdrawals from the study explained	yes (14 patients for N staging)
Pre-test probability	53% N staging 17.3% M staging
Patients' characteristics	104 consecutive patients with a histological diagnosis of colorectal carcinoma were enrolled in this prospective study: 53 males and 51 females aged from 28 to 83 years (mean age 66.76 years, standard deviation 12.36 years). At the time of the initial diagnosis, tumors were located in the rectum (n = 56), sigmoid colon (n=20), ascending colon (n = 2), transverse colon (n = 6), descending colon (n = 4), caecum (n = 10) and splenic flexure (n = 6). The large number of rectal carcinomas may have been caused by the admission of patients from centres that do not offer surgical treatment of this type of tumor.
Results	N staging (90 patients) FDG-PET sensitivity 21% [11-35%] specificity 95% [83-99%] overall accuracy 56% [45-66%] PPV 83% [51-97%] NPV 51% [40-63%] CT sensitivity 25% [14-40%] specificity 100% [83-99%] overall accuracy 60% [49-70%] PPV 100% [70-99%] NPV 54% [42-65%] M staging (104 patients) FDG-PET sensitivity 89% [64-98%] specificity 93% [85-97%] overall accuracy 92% [85-96%] PPV 73% [50-88%] NPV 98% [91-100%] CT sensitivity 44% [22-69%] specificity 95% [88-98%] overall accuracy 87% [78-92%] PPV 67% [35-89%] NPV 89% [80-94%]
Authors' recommendations and conclusions	Compared with conventional techniques, FDG-PET appears to be useful in pre-surgical staging of CC, revealing unsuspected disease and impacting on the treatment approach

Author, year	**Kosugi 2008**
Country	Japan
Technology	FDG-PET
Disease	colorectal cancer with advanced or metastatic disease
Objective	to assess diagnostic accuracy in pre-operative N staging
Index test	FDG-PET
Comparator	CT
Reference standard	following surgery detailed histopathology
Outcomes considered	sensitivity, specificity, PPV, NPV, accuracy
Study design	diagnostic cross sectional study with prospective recruitment
spectrum of patients representative of the individuals who will receive the test in practice	no
patients selection criteria clearly described	yes
verification by reference standard of all subjects	yes
time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	yes
execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
execution of the reference standard described	yes
independent and blind interpretation of index test and reference standard results	unknown
withdrawals from the study explained	no
Pre-test probability	not computable
Patients' characteristics	53 patients with locally advanced colorectal adenocarcinoma (20 colon, 33 rectal). 46 received curative operation, 7 palliative operation. Mean age (SD) 60.1 ± 10.9 years

Results	N staging (lesion based analysis) N1 FDG-PET sensitivity 52.2% specificity 87.5% accuracy 70.2% CT sensitivity 91.3% specificity 41.6% accuracy 65.9% N2-N3 FDG-PET sensitivity 75% specificity 94.4% accuracy 89.6% CT sensitivity 91.7% specificity 72.2% accuracy 77.1% N4 FDG-PET sensitivity 100% specificity 100% accuracy 100% CT sensitivity 100% specificity 17.6% accuracy 41.7%
Authors' recommendations and conclusions	While FDG-PET is markedly more sensitive than CT for detection of N4 LN involvement, the number of metastatic LNs is difficult to determine.

Author, year	**Tsunoda 2008**
Country	Japan
Technology	FDG-PET/CT
Disease	colorectal cancer
Objective	to assess diagnostic accuracy in pre-operative N staging
Index test	FDG-PET/CT
Comparator	none
Reference standard	following surgery detailed histopathology
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with prospective recruitment
spectrum of patients representative of the individuals who will receive the test in practice	yes
patients selection criteria clearly described	yes
verification by reference standard of all subjects	yes
time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	yes
execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
execution of the reference standard described	yes
independent and blind interpretation of index test and reference standard results	unknown
withdrawals from the study explained	no
Pre-test probability	48.9% (patient based analysis)
Patients' characteristics	88 consecutive patients who were scheduled for surgical treatment. There were 52 males and 36 females, and their mean age was 60.6 years (range 23-89 years). The location of the primary colorectal cancer was the colon in 37 patients, and the rectum in 51 patients.

Results	N staging (lesion based analysis) FDG-PET/CT visual analysis sensitivity 28.6% specificity 92.9% accuracy 75% FDG-PET/CT by nodal diameter using cutoff value of 10 mm sensitivity 30.6% specificity 95.3% accuracy 74.4% FDG-PET/CT by SUV using cutoff value of 1.5 sensitivity 53.1% specificity 90.6% accuracy 80.1%
Authors' recommendations and conclusions	FDG-PET/CT is useful for pre-operative diagnosis of distant LN metastases of colorectal cancers

Author, year	**Akiyoshi 2009**
Country	Japan
Technology	FDG-PET
Disease	colorectal cancer
Objective	to assess diagnostic accuracy in pre-operative N and liver M staging
Index test	FDG-PET
Comparator	multidetector row CT (MDCT)
Reference standard	following surgery histopathology
Outcomes considered	sensitivity, specificity, PPV, NPV, accuracy
Study design	diagnostic cross sectional study with prospective recruitment
spectrum of patients representative of the individuals who will receive the test in practice	no
patients selection criteria clearly described	yes
verification by reference standard of all subjects	not clear
time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	yes
execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	not clear
execution of the reference standard described	no
independent and blind interpretation of index test and reference standard results	not clear
withdrawals from the study explained	yes (9 patients on N staging)
Pre-test probability	62.5% N staging 33.8% liver M staging

Patients' characteristics	65: 36 men, 29 women with primary colorectal cancer histologically proven by colonoscopy underwent. FDG-PET was performed on patients as follows: • patients with suspected metastases of lymph nodes or liver on MDCT • patients with pre-operative serum carcinoembryonic antigen ≥5 ng/ml • patients with lower rectal cancer who were planned to pre-operative chemoradiotherapy or laparoscopic resection to check lateral lymph node metastasis. mean age was 62 years (range 37-84 years). tumors were located predominantly in the anal canal (n = 1), rectum (n = 27), rectosigmoid colon (n = 6), sigmoid colon (n = 13), descending colon (n = 2), transverse colon (n = 6), ascending colon (n = 8), caecum (n = 1) and appendix (n = 1)
Results	N staging (patient based analysis) FDG-PET sensitivity 43% (15/35; 95% CI 26-61%) specificity 95% (20/21; 95% CI 76-100%) MDCT sensitivity 89% (31/35; 95% CI 73-97%) specificity 52% (11/21; 95% CI 30-74%) Liver M staging (patient based analysis) FDG-PET sensitivity 91% (20/22; 95% CI 91-99%) specificity 100% (43/43; 95% CI: 92-100%) MDCT sensitivity 100% (22/22; 95% CI 85-100%) specificity 98% (42/43; 95% CI 88-100%)
Authors' recommendations and conclusions	Pre-operative FDG-PET is not superior to MDCT for detection of primary tumor, lymph node involvement or liver metastases, but may have potential clinical value in patients with advanced colorectal cancer by detecting extrahepatic distant metastases.

Author, year	**Ono 2009**
Country	Japan
Technology	FDG-PET
Disease	dolorectal cancer
Objective	to assess diagnostic accuracy in pre-operative N staging
Index test	FDG-PET
Comparator	diffusion-weighted MRI
Reference standard	histopathological results on surgical specimens (23 patients) or with both clinical and imaging follow up studies (endoscopic mucosal resection, N 1; polypectomy, N 1)
Outcomes considered	sensitivity, specificity, PPV, NPV, accuracy
Study design	diagnostic cross sectional study with retrospective recruitment
spectrum of patients representative of the individuals who will receive the test in practice	no
patients selection criteria clearly described	no
verification by reference standard of all subjects	no
time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	yes
execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	not clear
execution of the reference standard described	no
independent and blind interpretation of index test and reference standard results	yes
withdrawals from the study explained	yes (2 - no explanation)
Pre-test probability	43.5% N staging

Patients' characteristics	25 patients with 27 surgically proven colorectal cancers ranging from 10 to 70 mm (mean 40.4 mm). They were 9 women and 16 men ranging in age from 51 to 84 years (mean 67.3 years) and were treated between September 2004 and February 2007. All underwent DW-MRI and FDG-PET study within 9 days
Results	Nstaging (patient based analysis) FDG-PET sensitivity 30% (3/10) specificity 100% (13/13) accuracy 69.6% (16/23) DW-MRI sensitivity 80% (8/10) specificity 76.9% (10/13) accuracy 78.3% (18/23)
Authors' recommendations and conclusions	DW-MRI is inferior for the detection of primary lesions, but superior to FDG-PET for the detection of lymph node metastases. The DW-MRI study returned some false-negative results attributable to a small tumor size and susceptibility artifacts. Nonetheless, we suggest that DW-MRI is as useful as FDG-PET for the detection of both primary colorectal cancers and lymph node metastases.

Chapter 6
M staging of patients with locally advanced primary colorectal cancer

Diagnostic accuracy

Systematic reviews

Author, year	Facey 2007
Technology	FDG-PET
Disease	colorectal cancer
Objective	to assess: ▪ primary diagnosis ▪ staging ▪ response to therapy (after treatment) ▪ diagnosis of suspected recurrence or restaging
Inclusion criteria	P patients with colorectal cancer I FDG-PET C all available R not specified O diagnostic accuracy for primary diagnosis, staging, re-staging after treatment, recurrence S retrospective and prospective studies
Years covered by the search	up to August 2005
Study selection data abstraction, quality assessment performed by two authors independently	not specified
Comprehensive bibliographic search: at least two databases searched	yes Medline, EMBASE, Cochrane Library, HTA database
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	no
Searched also unpublished studies	no
Language restriction	yes, only English literature
Overall number of references retrieved and n. of included studies reported	yes
N. and references of excluded studies reported, reason given	no

Characteristics of included studies clearly reported in tables	yes
Methodological quality of primary studies assessed; criteria reported	yes (QUADAS)
Results of quality assessment used to formulate results and conclusions	yes, qualitative report in the result section
Meta-analysis performed with appropriate statistic methods	not performed
Publication bias assessed	no
N. of included studies Study design	1 cross sectional diagnostic accuracy studies
N. of included patients	34
Reference standard	following surgery detailed histopathology or clinical follow up
Comparator	CT, US
Pre-test probability	N staging: 21.9% (1 study) liver metastasis: 26.5% (1 study)
Performance results	Liver metastasis staging FDG-PET sensitivity 78% specificity 96% CT sensitivity 67% specificity 100% US sensitivity 25% specificity 100%
Recommendations and conclusions	One diagnostic study of staging showed that PET (like other imaging methods) had poor sensitivity to detect regional lymph-node involvement, but better sensitivity for liver metastases. Specificity was high in all situations.
Comments of ASSR reviewers	metanalysis not performed

Synoptic table of primary studies on M staging of patients with primary colorectal cancer

Author, year	Patient number	Patient characteristics	Technology	Staging	Reference standard	Pre-test probability	Sensitivity (%)	Specificity (%)
Llamas-Elvira 2007	104	mean age 66.8 tumors were located in the rectum (56), sigmoid colon (20), ascending colon (2), transverse colon (6), descending colon (4), caecum (10) and splenic flexure (6)	FDG-PET	M staging (majority liver metastases)	surgery, following histopathology, biopsy of extra-abdominal metastases, clinical follow up, autopsy examination	17.3%	89	93
			CT				44	95
Akiyoshi 2009	65	mean age was 62 patients with: - suspected metastases of lymph nodes or liver on MDCT - pre-operative serum carcinoembryonic antigen ≥5 ng/ml - lower rectal cancer who were planned to pre-operative chemoradiotherapy or laparoscopic resection tumors located in the anal canal (1), rectum (27), rectosigmoid colon (6), sigmoid colon (13), descending colon (2), transverse colon (6), ascending colon (8), caecum (1) and appendix (1)	FDG-PET	liver M staging	following surgery histopathology	33.8%	91	100
			MDCT				100	98

Author, year	Patient number	Patient characteristics	Technology	Staging	Reference standard	Pre-test probability	Sensitivity (%)	Specificity (%)
Mainenti 2009	34	consecutive patients with histologically proven diagnosis of colo-rectal adenocarcinoma and scheduled for surgery (20 men and 14 women; age range, 29-81 years; mean age: 63 years)	FDG-PET/CT	liver M staging	surgical findings, intraoperative US, histopathology, and MDCT follow up	17.6%	100	96
			CE-MDCT				83	96
			MR gd				83	100
			MR spio				83	96
			CE-ECO				83	86

Primary studies

Author, year	Llamas-Elvira 2007
Country	Spain
Technology	FDG-PET
Disease	colorectal cancer
Objective	to assess diagnostic accuracy in pre-operative N and M staging
Index test	FDG-PET
Comparator	CT
Reference standard	▪ pathological study of tumors and lymph nodes obtained during surgery; or ▪ surgical exploration and biopsy (liver metastases, abdominal implantations, involvement of other abdominal organs); or ▪ in the case of extra-abdominal metastases, pathological study after biopsy or (when pathology was not available) by clinical follow up for at least 1 year or by CT study after at least 2 months demonstrating lesion growth (>0.5 cm) in comparison with the initial examination; or ▪ in cases of death, autopsy examination
Outcomes considered	sensitivity, specificity, PPV, NPV, accuracy
Study design	diagnostic cross sectional study with prospective recruitment
spectrum of patients representative of the individuals who will receive the test in practice	yes
patients selection criteria clearly described	yes
verification by reference standard of all subjects	yes
time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	yes
execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
execution of the reference standard described	yes

independent and blind interpretation of index test and reference standard results	yes
withdrawals from the study explained	yes (14 patients for N staging)
Pre-test probability	53% N staging 17.3% M staging
Patients' characteristics	104 consecutive patients with a histological diagnosis of colorectal carcinoma were enrolled in this prospective study: 53 males and 51 females aged from 28 to 83 years (mean age 66.76 years, standard deviation 12.36 years). At the time of the initial diagnosis, tumors were located in the rectum (n = 56), sigmoid colon (20), ascending colon (2), transverse colon (6), descending colon (4), caecum (10) and splenic flexure (n = 6). The large number of rectal carcinomas may have been caused by the admission of patients from centres that do not offer surgical treatment of this type of tumor.
Results	N staging (90 patients) FDG-PET sensitivity 21% (11-35%) specificity 95% (83-99%) overall accuracy 56% (45-66%) PPV 83% (51-97%) NPV 51% (40-63%) CT sensitivity 25% (14-40%) specificity 100% (83-99%) overall accuracy 60% (49-70%) PPV 100% (70-99%) NPV 54% (42-65%) M staging (104 patients) FDG-PET sensitivity 89% (64-98%) specificity 93% (85-97%) overall accuracy 92% (85-96%) PPV 73% (50-88%) NPV 98% (91-100%) CT sensitivity 44% (22-69%) specificity 95% (88-98%) overall accuracy 87% (78-92%) PPV 67% (35-89%) NPV 89% (80-94%)
Authors' recommendations and conclusions	Compared with conventional techniques, FDG-PET appears to be useful in pre-surgical staging of CC, revealing unsuspected disease and impacting on the treatment approach

Author, year	**Akiyoshi 2009**
Country	Japan
Technology	FDG-PET
Disease	colorectal cancer
Objective	to assess diagnostic accuracy in pre-operative N and liver M staging
Index test	FDG-PET
Comparator	multidetector row CT (MDCT)
Reference standard	following surgery histopathology
Outcomes considered	sensitivity, specificity, PPV, NPV, accuracy
Study design	diagnostic cross sectional study with prospective recruitment
spectrum of patients representative of the individuals who will receive the test in practice	no
patients selection criteria clearly described	yes
verification by reference standard of all subjects	not clear
time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	yes
execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	not clear
execution of the reference standard described	no
independent and blind interpretation of index test and reference standard results	not clear
withdrawals from the study explained	yes (9 patients on N staging)
Pre-test probability	62.5% N staging 33.8% liver M staging

Patients' characteristics	65 36 men, 29 women with primary colorectal cancer histologically proven by colonoscopy FDG-PET was performed on patients as follows: - patients with suspected metastases of lymph nodes or liver on MDCT - patients with pre-operative serum carcinoembryonic antigen ≥5 ng/ml - patients with lower rectal cancer who were planned to pre-operative chemoradiotherapy or laparoscopic resection to check lateral lymph node metastasis mean age was 62 years (range 37-84 years) tumors were located predominantly in the anal canal (n = 1), rectum (n = 27), rectosigmoid colon (n = 6), sigmoid colon (n = 13), descending colon (n = 2), transverse colon (n = 6), ascending colon (n = 8), caecum (n = 1), appendix (n = 1)
Results	N staging (patient based analysis) FDG-PET sensitivity 43% (15/35; 95% CI 26-61%) specificity 95% (20/21; 95% CI 76-100%) MDCT sensitivity 89% (31/35; 95% CI 73-97%) specificity 52% (11/21; 95% CI 30-74%) Liver M staging (patient based analysis) FDG-PET sensitivity 91% (20/22; 95% CI 91-99%) specificity 100% (43/43; 95% CI 92-100%) MDCT sensitivity 100% (22/22; 95% CI 85-100%) specificity 98% (42/43; 95% CI 88-100%)
Authors' recommendations and conclusions	Pre-operative FDG-PET is not superior to MDCT for detection of primary tumor, lymph node involvement or liver metastases, but may have potential clinical value in patients with advanced colorectal cancer by detecting extrahepatic distant metastases

Author, year	**Mainenti 2009**
Country	Italy
Technology	FDG-PET/CT
Disease	colorectal cancer
Objective	to assess diagnostic accuracy in pre-operative liver M staging
Index test	FDG-PET/CT
Comparator	contrast-enhanced US (CEUS), multidetector row CT (MDCT), 1.5 Tesla MR with extra-cellular (Gd-enhanced) and intracellular (SPIO enhanced) contrast agents
Reference standard	surgical findings, intraoperative US, histopathology, and MDCT follow up
Outcomes considered	sensitivity, specificity, ROC curve
Study design	diagnostic cross sectional study with prospective recruitment
spectrum of patients representative of the individuals who will receive the test in practice	yes
patients selection criteria clearly described	yes
verification by reference standard of all subjects	yes
time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	yes
execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
execution of the reference standard described	yes
independent and blind interpretation of index test and reference standard results	yes
withdrawals from the study explained	no
Pre-test probability	17.6% liver M staging

Patients' characteristics	34 consecutive patients with histologically proven diagnosis of colo-rectal adenocarcinoma and scheduled for surgery (20 men and 14 women; age range 29-81 years; mean age 63 years)
Results	Liver M staging (patient based analysis) FDG-PET/CT sensitivity 100% specificity 96% PPV 86% NPV 100% accuracy 97% CE-MDCT sensitivity 83% specificity 96% PPV 83% NPV 96% accuracy 94% MR gd sensitivity 83% specificity 100 % PPV 100 % NPV 97% accuracy 97% MR spio sensitivity 83% specificity 96 % PPV 83 % NPV 96% accuracy 94% CE-ECO sensitivity 83% specificity 86 % PPV 56 % NPV 96% accuracy 85%
Authors' recommendations and conclusions	Gd- and SPIO-enhanced MRI seem to be the most accurate modality in the identification of liver metastases from colo-rectal carcinoma. PET/CT shows a trend to perform better than the other modalities in the identification of patients with liver metastases

Chapter 7
Field definition of curative radiation treatment in patients with rectal cancer

Diagnostic accuracy

Systematic reviews

Author, year	Facey 2007
Technology	FDG-PET
Disease	colorectal cancer
Objective	to assess: ▪ primary diagnosis ▪ staging ▪ RT field-definition ▪ response to therapy (after treatment) ▪ diagnosis of suspected recurrence or restaging
Inclusion criteria	P patients with colorectal cancer I FDG-PET C all available R not specified O diagnostic accuracy for primary diagnosis, staging, re-staging after treatment, recurrence S retrospective and prospective studies
Years covered by the search	up to August 2005
Study selection data abstraction, quality assessment performed by two authors independently	not specified
Comprehensive bibliographic search: at least two databases searched	yes Medline, EMBASE, Cochrane Library, HTA database
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	no
Searched also unpublished studies	no
Language restriction	yes, only English literature
Overall number of references retrieved and n. of included studies reported	yes
N. and references of excluded studies reported, reason given	no

Characteristics of included studies clearly reported in tables	yes
Methodological quality of primary studies assessed; criteria reported	yes (QUADAS)
Results of quality assessment used to formulate results and conclusions	yes, qualitative report in the result section
Meta-analysis performed with appropriate statistic methods	not performed
Publication bias assessed	no
N. of included studies Study design	1 correlation study
N. of included patients	11
Reference standard	none
Comparator	CT
Pre-test probability	not applicable
Performance results	correlation between PET and CT GTV r2 = 0.84
Recommendations and conclusions	One small Swiss study showed that PET and CT produced similar RT planning regions.
Comments of ASSR reviewers	metanalysis not performed

Synoptic table of primary studies on M staging of patients with primary colorectal cancer

Author, year	Patient number	Patient characteristics	Technology	Comparator	Verification	Results
Anderson 2007	23	locally advanced (20 pts) rectal or anus cancer (3 pts)	FDG-PET	CT	none	PET volumes, on average, were smaller than CT volumes. The mean PET-GTV was 91.7 cm^3, and the mean CT-GTV was 99.6 cm^3. The mean OV was 46.7% and ranged from 11 to 99%. In 4 of 23 patients (17%) integration of the PET volume with the planning volumes resulted in a change in the PTV. 26% of patients (6 of 23) experienced a change in the radiation treatment-planning process. Changes included increasing field sizes because traditional fields would have cut through a contoured PET tumor volume or changing a treatment course from definitive to palliative because of the detection of distant metastases.
Bassi 2008	25	T3-4 or N+ rectal cancer	FDG-PET/CT	CT	none	The PET/CT-GTVand PET/CT-CTV were significantly greater than the CT-GTV (19.6 ± 29 cm^3; p = 0.00013) and CT-CTV (29 ± 15.2 cm^3; p = 0.00002), respectively. In 4 of 25 cases, PET/CT affected tumor staging or the treatment purpose (3 cases showed uptake in regional lymph nodes and in 1 case in the liver; in 1 patient with a single liver metastasis detected multiple lesions, changing the treatment intent from curative to palliative).

Author, year	Patient number	Patient characteristics	Technology	Comparator	Verification	Results
Roels 2009	15	T2/T3 rectal cancer	FDG-PET	MRI	pathologic specimen after surgery	MRI showed larger TVs than FDG-PET. There was an approximately 50% mismatch between the FDG-PET TV and the MRI TV at baseline and during CRT.
Paskeviciute 2009	36	T3-4 or N+ rectal cancer	FDG-PET/CT	CT	none	PET/CT-GTVs were smaller than CT-GTVs ($p < 0.05$). In 16 of 35 patients (46%), PET/CT resulted in a need for modification of the usual target volumes (CT-PTV) because of detection of a geographic miss. 8% of change of management
Yavuz 2009	23	rectal adenocarcinoma candidates for radiotherapy in a pre-operative setting with concomitant chemotherapy	FDG-PET/CT	CT	none	The median GTV PET-CT (40 cm^3) was significantly greater than the GTV CT (25.7 cm^3) ($p= 0.0001$). The median difference between GTV measured by the two methods was 65%. The common volume measured by the two methods (intersected tumor volume) was 19.7 cm^3, and tumor volumes remaining outside CT was 15.2 cm^3. The median volume identified by PET but not by CT (PEToutCT) was 35% of GTVPET-CT, indicating the possibility of a geographic miss in GTV.

Primary studies

Author, year	**Anderson 2007**
Country	USA
Technology	FDG-PET
Disease	anorectal cancer
Objective	to assess: ▪ curative intent RT field definition
Patients characteristics	23 20 patients (87%) were diagnosed with rectal cancer, and 3 patients (13%) were treated for tumors of the anus. Thirteen patients (56.5%) were male, and mean age was 58 years (range, 30-81 years). Of the patients with rectal primaries, 12 (60%) were staged T3N0 (IIA); 2 (10%) were T4N0 (IIB); 3 (15%) were T3NxM1 (IV), and T3N1 (IIIB), T2N2 (IIIC), and TxNxM1 (IV) were each represented with 1 patient (5% each). Two patients (67%) with cancer of the anus were staged as T3N0 (II), and the third (33%) was staged T3N2 (IIIB). Patients with rectal cancer were treated with pre-operative chemoradiotherapy, whereas patients with anus cancer with definitive chemoradiation.
Index test	FDG-PET, FDG-PET/CT
Comparator	CT
Verification test	none
Outcomes considered	Mean GTV and overlap volumes (OVs) from the CT and PET were calculated. The impact of PET on formation of GTV and PTV and its ability to correspond to OV were analyzed. Additional analyses included changes in treatment strategy based on PET data and correlation of posttreatment PET imaging with pathologic response when appropriate

Results	PET volumes, on average, were smaller than CT volumes. The mean PET-GTV was 91.7 cm^3 (median 37.1 cm^3; range 2.9-859 cm^3), and the mean CT-GTV was 99.6 cm^3 (median 66 cm^3; range >17-570 cm^3). The mean OV was 46.7% and ranged from 11 to 99%. As tumor volume increased on CT or PET imaging, so too did OV in a statistically significant fashion ($p < 0.001$). This result was observed and remained significant if the outlier patient was excluded ($p < 0.001$). In addition, as the size of the tumor increased, there was a significant correlation between the PET and CT volumes ($R2 = 0.94$, $p < 0.0001$) that was still present without the outlier ($R2 = 0.75$, $p < 0.0001$). In 4 of 23 patients (17%; one anal canal tumor and three rectal tumors), integration of the PET volume with the planning volumes resulted in a change in the PTV. Twenty-six percent of patients (6 of 23) experienced a change in the radiation treatment-planning process. Changes included increasing field sizes because traditional fields would have cut through a contoured PET tumor volume or changing a treatment course from definitive to palliative because of the detection of distant metastases.
Study design	prospective and retrospective cohort
Consecutive recruitment	uncertain
independent and blind interpretation of index test, comparator and verification test results	uncertain
Authors recommendations and conclusions	Variation in volume was significant, with 17% and 26% of patients requiring a change in treatment fields and patient management, respectively. Positron emission tomography can change the management for anorectal tumors by early detection of metastatic disease or disease outside standard radiation fields.

Author, year	**Bassi 2008**
Country	Italy
Technology	FDG-PET/CT
Disease	rectal cancer
Objective	to assess: ▪ curative intent RT field definition
Patients characteristics	25 patients diagnosed with rectal cancer T3-4 N0-1 M0-1 and candidates for pre-operative radiotherapy. Male 19, female 6. Age (y) median 65 (range 44-79), Karnofsky performance status median 90 (range 70-100).
Index test	FDG-PET/CT
Comparator	CT
Verification test	none
Outcomes considered	PET-GTV and PET-CTV were respectively compared with CT-GTV and CT-CTV
Results	The PET/CT-GTVand PET/CT-CTV were significantly greater than the CT-GTV (19.6 ± 29 cm^3; p = 0.00013) and CT-CTV (29 ± 15.2 cm^3; p = 0.00002), respectively. The mean difference between PET/CT-GTV and CT-GTV was 25.4% and between PET/CT-CTV and CT-CTV was 4.1%. In 4 of 25 cases (24%), PET/CT affected tumor staging or the treatment purpose. In 3 of 25 cases (12%) staged N0 M0, PET/CT showed FDG uptake in regional lymph nodes and in a case also in the liver. In a patient with a single liver metastasis PET/CT detected multiple lesions, changing the treatment intent from curative to palliative.
Study design	prospective cohort
Consecutive recruitment	yes
independent and blind interpretation of index test, comparator and verification test results	not known
Authors recommendations and conclusions	Imaging with PET/CT for pre-operative radiotherapy of rectal cancer may lead to a change in staging and target volume delineation. Stage variation was observed in 12% of cases and a change of treatment intent in 4%. The GTV and CTV changed significantly, with a mean increase in size of 25% and 4%, respectively.

Author, year	**Roels 2009**
Country	Belgium
Technology	FDG-PET
Disease	rectal cancer
Objective	to assess: ▪ curative intent RT field definition
Patients characteristics	15 11 men (mean age 63 years; range 48-82 years) and 4 women (mean age 62 years; range 49-77 years) were enrolled in the study. All patients had biopsy-proven resectable adenocarcinoma of the rectum, clinical stage T2/3-N1/2M0 on MRI and/or rectal endosonography. All patients were treated with a long course of CRT, consisting of 25 fractions of 1.8 Gy, 5 days per week for 5 weeks, in combination with a continuous infusion of 5-fluorouracil (225 mg/m^2)
Index test	FDG-PET/CT
Comparator	MRI
Verification test	pathologic specimen after surgery
Outcomes considered	A mismatch analysis of TVs was performed between MRI and FDG-PET and between the different time points. The mismatch of a given volume A to a given volume B is defined as the percentage of A that does not belong to B. It is 0 if A falls entirely inside B and is 100% if A and B do not overlap. For the FDG-PET TVs the gradient-based segmentation was used. To quantify the distance of the mismatches, we calculated the maximum and mean value of the shortest distances between the FDG-PET TV and MRI TV.
Results	MRI showed larger TVs than FDGPET. There was an approximately 50% mismatch between the FDG-PET TV and the MRI TV at baseline and during CRT. Sixty-one percent of the FDG-PET TV and 76% of the MRI TV obtained after 10 fractions of CRT remained inside the corresponding baseline TV. On MRI, residual tumor was still suspected in all 6 patients with a pathologic complete response, whereas FDG-PET showed a metabolic complete response in 3 of them. The FDG-PET TVs delineated with the gradient-based method matched closest with pathologic findings
Study design	prospective cohort
Consecutive recruitment	not known
independent and blind interpretation of index test, comparator and verification test results	not known

Authors recommendations and conclusions	Integration of MRI and FDG-PET into radiotherapy seems feasible. Gradient-based segmentation is recommended for FDG-PET. Spatial variance between MRI and FDG-PET TVs should be taken into account for target definition

Author, year	**Paskeviciute 2009**
Country	Germany
Technology	FDG-PET/CT
Disease	locally advanced rectal cancer
Objective	to assess: ▪ curative intent RT field definition
Patients characteristics	36 median age of 56 years (range 31-72 years). All patients enrolled in the present study had a biopsy proven rectal adenocarcinoma and were considered candidates for radiotherapy in a pre-operative setting. Patients with clinical T3-4 or N+ tumors involving the rectal wall in the endoscopic segment from 0 to 15 cm were enrolled
Index test	FDG-PET/CT
Comparator	CT
Verification test	none
Outcomes considered	Gross tumor volume (GTV), clinical target volume (CTV) and planning target volume (PTV). The CT- and PET/CT-based GTVs were quantitatively compared and percentage of overlap (OV%) was calculated and analyzed. The impact of PET/CT on radiation treatment planning and overall patient management was evaluated.
Results	PET/CT-GTVs were smaller than CT-GTVs ($p < 0.05$). PET/CT imaging resulted in a change of overall management for three patients (8 %). In 16 of 35 patients (46 %), PET/CT resulted in a need for modification of the usual target volumes (CT-PTV) because of detection of a geographic miss.
Study design	retrospective cohort
Consecutive recruitment	not known
independent and blind interpretation of index test, comparator and verification test results	yes
Authors recommendations and conclusions	FDG-PET/CT had significant impact on radiotherapy planning and overall treatment of patients with locally advanced rectal cancer

Author, year	**Yavuz 2009**
Country	Turkey
Technology	FDG-PET/CT
Disease	rectal cancer
Objective	to assess: ▪ curative intent RT field definition
Patients characteristics	23 patients with pathologically confirmed rectal adenocarcinoma and candidates for radiotherapy in a pre-operative setting with concomitant chemotherapy Eastern Cooperative Oncology Group performance status (PS) of 0 to 2; median age 58 years, range between 18 and 75 years
Index test	FDG-PET/CT
Comparator	CT
Verification test	none
Outcomes considered	gross tumor volume (GTV)
Results	A comparison of the tumor volumes estimated by the two methods showed that the median GTVPET-CT (40 cm^3) was significantly greater than the GTVCT (25.7 cm^3) ($p = 0.0001$). The median difference between GTV measured by the two methods was 65%. The common volume measured by the two methods (intersected tumor volume) was 19.7 cm^3, and tumor volumes remaining outside CT was 15.2 cm^3. The median volume identified by PET but not by CT (PEToutCT) was 35% of GTVPET-CT, indicating the possibility of a geographic miss in GTV
Study design	prospective cohort
Consecutive recruitment	not known
independent and blind interpretation of index test, comparator and verification test results	not known
Authors recommendations and conclusions	Co-registration of PET and CT information in localized rectal cancer may improve the delineation of GTV and theoretically reduce the likelihood of geographic misses, thus potentially having a positive impact on treatment planning.

Chapter 8
Role of FDG-PET in evaluating response to therapy in patients with colorectal cancer

Diagnostic accuracy

Systematic reviews

Author, year	Facey 2007
Technology	FDG-PET
Disease	colorectal cancer
Objective	to assess: ▪ primary diagnosis ▪ staging ▪ response to therapy (after treatment) ▪ diagnosis of suspected recurrence or restaging
Inclusion criteria	P patients with colorectal cancer I FDG-PET C all available R not specified O diagnostic accuracy for primary diagnosis, staging, re-staging after treatment, recurrence S retrospective and prospective studies
Years covered by the search	up to August 2005
Study selection data abstraction, quality assessment performed by two authors independently	not specified
Comprehensive bibliographic search: at least two databases searched	yes Medline, EMBASE, Cochrane Library, HTA database
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	no
Searched also unpublished studies	no
Language restriction	yes, only English literature
Overall number of references retrieved and n. of included studies reported	yes
N. and references of excluded studies reported, reason given	no
Characteristics of included studies clearly reported in tables	yes

Methodological quality of primary studies assessed; criteria reported	yes (QUADAS)
Results of quality assessment used to formulate results and conclusions	yes, qualitative report in the result section
Meta-analysis performed with appropriate statistic methods	not performed
Publication bias assessed	no
N. of included studies Study design	6 cross sectional diagnostic accuracy studies
N. of included patients	192
Reference standard	histopathology from resection
Comparator	US
Pre-test probability	not reported
Performance results	Only descriptive results of single studies. 5 studies included patients with advanced rectal cancer and submitted to neoadjuvant therapy 1 study included patients with advanced metastatic colorectal cancer submitted to adjuvant therapy.
Recommendations and conclusions	Six studies, one in more than 80 patients, provided evidence that changes in SUV between pretherapy and post-therapy scans may predict response in the majority of patients. One small study reported changes in patient management.
Comments of ASSR reviewers	metanalysis not performed

Author, year	**Geus-Oei 2009**
Technology	FDG-PET
Disease	colorectal cancer
Objective	to assess: ▪ response to therapy (after treatment)
Inclusion criteria	P patients with colorectal cancer I FDG-PET C all available R not specified O diagnostic accuracy for primary diagnosis, staging, re-staging after treatment, recurrence S retrospective and prospective studies
Years covered by the search	December 2008
Study selection data abstraction, quality assessment performed by two authors independently	not specified
Comprehensive bibliographic search: at least two databases searched	yes Medline, EMBASE, Cochrane Library, HTA database
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	no
Searched also unpublished studies	no
Language restriction	yes, only English literature
Overall number of references retrieved and n. of included studies reported	partially: only number of included studies reported
N. and references of excluded studies reported, reason given	no
Characteristics of included studies clearly reported in tables	yes
Methodological quality of primary studies assessed; criteria reported	no
Results of quality assessment used to formulate results and conclusions	no
Meta-analysis performed with appropriate statistic methods	not performed
Publication bias assessed	no

N. of included studies Study design	5 studies on chemotherapy response monitoring in advanced colorectal cancer 5 studies on response after local ablative therapy of liver metastases 19 studies on pre-operative radiotherapy and multimodality treatment response in primary rectal cancer cross sectional diagnostic accuracy studies or longitudinal prognostic studies
N. of included patients	chemotherapy response monitoring in advanced colorectal cancer: 127 patients response after local ablative therapy of liver metastases: 114 patients pre-operative radiotherapy and multimodality treatment response in primary rectal cancer: 603 patients
Reference standard	histopathology when present
Comparator	none reported
Pre-test probability	not reported
Performance results	only descriptive results o single studies
Recommendations and conclusions	The available studies on chemotherapy response monitoring in advanced colorectal cancer and on pre-operative radiotherapy and multimodality treatment response evaluation in primary rectal cancer indicate that 18F-FDG PET is a significant predictor of therapy outcome in both situations. In primary rectal cancer, 18F-FDG PET is applicable after neoadjuvant treatment in a pre-operative setting (important for the pre-operative selection for an individually tailored surgical approach) and correlates better with pathology than morphologic imaging modalities. Interestingly, when 18F-FDG PET is able to predict the final outcome, it may be used to guide adjuvant chemotherapy for rectal cancer after optimal neoadjuvant and local treatments. 18F-FDG PET could play a central role in optimizing the use of local ablative treatment of liver metastases because it recognizes, at early times, incomplete tumor ablation that is not detectable by CT. 18F-FDG PET could play a pivotal role in determining the need for further investigations and in guiding the reading of CT scans; the interpretation of the latter alone at early times after local ablative therapy appears to be difficult. Furthermore, 18FFDG PET may be helpful in shortening the duration of early clinical trials assessing new antineoplastic agents. Therefore, therapy response assessment with 18F-FDG PET remains a very worthwhile research topic.
Comments of ASSR reviewers	metanalysis not performed

Primary studies

Author, year	Capirci 2009
Country	Italy
Technology	FDG-PET/CT
Disease	rectal cancer
Objective	to assess the accuracy of PET (performed at baseline and repeated 5-6 weeks after chemoradiotherapy) to detect the response (complete pathological response = TRG1-2 scores were considered indicators of a response) to neoadjuvant chemoradiation therapy
Index test	FDG-PET/CT
Comparator	none
Reference standard	A tumor regression grade (TRG) score induced by the neoadjuvant CRT was defined as follows: TRG1 (complete regression), TRG2 (presence of rare residual cancer cells scattered through fibrotic tissue), TRG3 (increased number of residual cancer cells but fibrosis still predominant), TRG4 (residual cancer outgrowing fibrosis), and TRG5 (no regressive changes detectable) (10). Only the TRG1-2 scores were considered indicators of a response
Outcomes considered	sensitivity, specificity, PPV, NPV, accuracy
Study design	diagnostic cross sectional study with prospective recruitment
spectrum of patients representative of the individuals who will receive the test in practice	yes
Reference standard likely to classify correctly	yes
Reference standard independent of the index test	yes
patients selection criteria clearly described	no
verification by reference standard of all subjects	yes
time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	yes
execution of the index and comparator tests adequately described	yes

Did patients receive the same reference standard regardless of the index test result	yes
execution of the reference standard described	yes
independent and blind interpretation of index test and reference standard results	not reported
withdrawals from the study explained	yes (6 patients)
Patients' characteristics	81 patients with histologically proved LARC were prospectively enrolled. All patients were suitable for radical surgery. All patients were scheduled to undergo surgery treatment 8-10 weeks after completion of CRT. M:F was 58:23, the median age was 68 years (range, 37-83). Tumor was in the lower rectum in 52%, midrectum in 29%, and upper rectum in 19% of patients. The tumor infiltrated the rectal circumference in less than half the circumference of 19 patients, two thirds of 23 patients, and the complete circumference of 22 patients; it caused stenosis in 15 patients. The grading distribution was as follows: G1 = 10 patients, G2 = 43 patients, G3 = 14 patients, mucinous = 14 patients. At staging workup, 36 patients were in clinical Stage IIa, 3 in IIb, 34 in IIIb, and 8 in IIIc
Pre-test probability	40 out of 81 patients
Results	ROC analysis identified a 45.9% RI as the cutoff value to predict ypCR (AUC = 0.786, p <0.0001), relative specificity, and negative predictive value (NPV) were 81%, whereas sensibility and positive predictive value (PPV) were 50.8% and 39.2%, respectively; total accuracy was 63%. ROC analysis found RI as the best predictor of response. Using RI value of 63.4% as the cutoff threshold, (AUC = 0.862, p <0.0001) for defining response to therapy, it is possible to discriminate responders from nonresponders with a sensitivity of 84.5%, specificity of 80%, and PPV and NPV of 81.4%, and 84,2% respectively. The overall accuracy was 81%. Using RI value of 51.3% as the cutoff threshold to predict the presence of pathologic lymph node metastases, it is possible to discriminate (AUC = 0.718, p <0.0001) Stage III with a sensitivity of 72%, specificity of 71.4%, PPV, NPV, and accuracy of 52.9%, 85.1%, and 72% respectively.
Authors' recommendations and conclusions	These results suggest the potential role of [18F]FDG-PET in the restaging workup after pre-operative CRT in LARC. RI seems the best predictor to identify CRT response.

Author, year	**Martoni 2011**
Country	Italy
Technology	FDG-PET/CT
Disease	rectal cancer
Objective	to assess the accuracy of PET (performed at baseline and repeated 1-2 weeks before surgery) to detect the response (complete pathological response = TRG4) to neoadjuvant chemoradiation therapy (delivered for 6-week period)
Index test	FDG-PET/CT
Comparator	none
Reference standard	Pathological analysis of surgical specimens. Tumor regression after NCRT was evaluated with the semiquantitative 5-point tumor regression grading (TRG) system proposed by Dworak evaluating histological changes in the tumor. It identifies several different grade of pR ranging from no regression to complete disappearance of tumor cells: TRG0 as no regression, TRG1 as minor regression with fibrosis in only 25% or less of the tumor mass, TRG2 as dominant tumor mass with obvious fibrosis in 26%-50% of the tumor mass, TRG3 as dominant fibrosis outgrowing the tumor mass and TRG4 as total regression, total fibrotic mass and no viable tumor cells
Outcomes considered	sensitivity, specificity, PPV, NPV, accuracy
Study design	diagnostic cross sectional study with prospective recruitment
spectrum of patients representative of the individuals who will receive the test in practice	yes
Reference standard likely to classify correctly	yes
Reference standard independent of the index test	yes
patients selection criteria clearly described	no
verification by reference standard of all subjects	yes
time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	yes
execution of the index and comparator tests adequately described	yes

Did patients receive the same reference standard regardless of the index test result	yes
execution of the reference standard described	yes
independent and blind interpretation of index test and reference standard results	not reported
withdrawals from the study explained	no
Patients' characteristics	80 consecutive patients with clinical T3/4, N-/+ rectal cancer, located <12 cm from anal margin, suitable for receiving NCRT. NCRT consisted of radiotherapy, delivered at a total dose of 5040 cGy in daily 28 fractions of 1.8 Gy in combination with concurrent chemotherapy regimens with 5-fluorouracil (5-FU) continuous infusion at 225 mg/m^2 daily for 6 weeks alone or in combination with oxaliplatin at 60 mg/m^2 weekly infusion for six times or panitumumab at a dose of 6 mg/Kg, 2 weeks before the start of chemoradiotherapy (CRT), and then three times every 2 weeks. All the patients underwent rectal surgery with curative intent 7-8 weeks after the end of neoadjuvant treatment. Male 55 (68.7) Female 25 (31.3). Age (years) median 65, range 33-80. Clinical stage at diagnosis cT3N0 34 (42.5) cT3N+ 35 (43.7) cT4N0 6 (7.5) cT4N+ 5 (6.3). Post-CRT surgical treatment Sphincter preserving 66 (82.5) Non-sphincter preserving 14 (17.5). Completeness of local resection R0 72 (90) R1 8 (10). Sixty-eight patients (85%) received post-surgical adjuvant chemotherapy.
Pre-test probability	20% (16 patients with TRG4 = total regression)

Results	FDG-PET SUV at baseline (≤27) sensitivity 100% (79.4-100) specificity 10.9% (4.5-21.2) PPV 21.9% NPV 100% accuracy 28.75% SUV at end of NCRT (≤5) sensitivity 87.5% (61.6-98.4) specificity 34.4% (22.9-47.3) PPV 25% NPV 91.7% accuracy 45% D-SUV (<66.1) sensitivity 93.7% (69.8-99.8) specificity 31.2% (20.2-44.1) PPV 25.4% NPV 95.2% accuracy 43.75%
Authors' recommendations and conclusions	Dual-time FDG-PET/CT in patients with LARC treated with NCRT and radical surgery supplies limited predictive information. However, an optimal metabolic response appears associated with a favourable patient outcome.

Chapter 9
Role of FDG-PET in evaluating early response to treatment of metastatic colorectal cancer

Diagnostic accuracy

Systematic reviews

Author, year	Facey 2007
Technology	FDG-PET
Disease	colorectal cancer
Objective	to assess: ▪ primary diagnosis ▪ staging ▪ response to therapy (after treatment) ▪ diagnosis of suspected recurrence or restaging
Inclusion criteria	P patients with colorectal cancer I FDG-PET C all available R not specified O diagnostic accuracy for primary diagnosis, staging, re-staging after treatment, recurrence S retrospective and prospective studies
Years covered by the search	up to August 2005
Study selection data abstraction, quality assessment performed by two authors independently	not specified
Comprehensive bibliographic search: at least two databases searched	yes Medline, EMBASE, Cochrane Library, HTA database
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	no
Searched also unpublished studies	no
Language restriction	yes, only English literature
Overall number of references retrieved and n. of included studies reported	yes
N. and references of excluded studies reported, reason given	no
Characteristics of included studies clearly reported in tables	yes

Methodological quality of primary studies assessed; criteria reported	yes (QUADAS)
Results of quality assessment used to formulate results and conclusions	yes, qualitative report in the result section
Meta-analysis performed with appropriate statistic methods	not performed
Publication bias assessed	no
N. of included studies Study design	6 cross sectional diagnostic accuracy studies
N. of included patients	192
Reference standard	histopathology from resection
Comparator	US
Pre-test probability	not reported
Performance results	Only descriptive results of single studies. 5 studies included patients with advanced rectal cancer and submitted to neoadjuvant therapy 1 study included patients with advanced metastatic colorectal cancer submitted to adjuvant therapy.
Recommendations and conclusions	Six studies, one in more than 80 patients, provided evidence that changes in SUV between pretherapy and post-therapy scans may predict response in the majority of patients. One small study reported changes in patient management.
Comments of ASSR reviewers	metanalysis not performed

Author, year	**Geus-Oei 2009**
Technology	FDG-PET
Disease	colorectal cancer
Objective	to assess: ▪ response to therapy (after treatment)
Inclusion criteria	P patients with colorectal cancer I FDG-PET C all available R not specified O diagnostic accuracy for primary diagnosis, staging, re-staging after treatment, recurrence S retrospective and prospective studies
Years covered by the search	December 2008
Study selection data abstraction, quality assessment performed by two authors independently	not specified
Comprehensive bibliographic search: at least two databases searched	yes Medline, EMBASE, Cochrane Library, HTA database
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	no
Searched also unpublished studies	no
Language restriction	yes, only English literature
Overall number of references retrieved and n. of included studies reported	partially: only number of included studies reported
N. and references of excluded studies reported, reason given	no
Characteristics of included studies clearly reported in tables	yes
Methodological quality of primary studies assessed; criteria reported	no
Results of quality assessment used to formulate results and conclusions	no
Meta-analysis performed with appropriate statistic methods	not performed
Publication bias assessed	no

N. of included studies Study design	5 studies on chemotherapy response monitoring in advanced colorectal cancer 5 studies on response after local ablative therapy of liver metastases 19 studies on pre-operative radiotherapy and multimodality treatment response in primary rectal cancer cross sectional diagnostic accuracy studies or longitudinal prognostic studies
N. of included patients	chemotherapy response monitoring in advanced colorectal cancer: 127 patients response after local ablative therapy of liver metastases: 114 patients pre-operative radiotherapy and multimodality treatment response in primary rectal cancer: 603 patients
Reference standard	histopathology when present
Comparator	none reported
Pre-test probability	not reported
Performance results	only descriptive results o single studies
Recommendations and conclusions	The available studies on chemotherapy response monitoring in advanced colorectal cancer and on pre-operative radiotherapy and multimodality treatment response evaluation in primary rectal cancer indicate that 18F-FDG PET is a significant predictor of therapy outcome in both situations. In primary rectal cancer, 18F-FDG PET is applicable after neoadjuvant treatment in a pre-operative setting (important for the pre-operative selection for an individually tailored surgical approach) and correlates better with pathology than morphologic imaging modalities. Interestingly, when 18F-FDG PET is able to predict the final outcome, it may be used to guide adjuvant chemotherapy for rectal cancer after optimal neoadjuvant and local treatments. 18F-FDG PET could play a central role in optimizing the use of local ablative treatment of liver metastases because it recognizes, at early times, incomplete tumor ablation that is not detectable by CT. 18F-FDG PET could play a pivotal role in determining the need for further investigations and in guiding the reading of CT scans; the interpretation of the latter alone at early times after local ablative therapy appears to be difficult. Furthermore, 18FFDG PET may be helpful in shortening the duration of early clinical trials assessing new antineoplastic agents. Therefore, therapy response assessment with 18F-FDG PET remains a very worthwhile research topic.
Comments of ASSR reviewers	metanalysis not performed

Primary studies

Author, year	Bystrom 2009
Country	Sweden
Technology	FDG-PET
Disease	Metastastic colorectal cancer
Objective	to assess diagnostic accuracy of early evaluation with FDG-PET (was made 1-14 days before start of treatment and immediately before the third cycle) of response to first-line combination chemotherapy value
Index test	FDG-PET
Comparator	none
Reference standard	clinical tumor response with CT evaluated according to RECIST criteria
Outcomes considered	sensitivity, specificity, PPV, NPV, accuracy
Study design	diagnostic cross sectional study with prospective recruitment
spectrum of patients representative of the individuals who will receive the test in practice	no
Reference standard likely to classify correctly	no
Reference standard independent of the index test	yes
patients selection criteria clearly described	yes
verification by reference standard of all subjects	yes
time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	yes
execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
execution of the reference standard described	yes
independent and blind interpretation of index test and reference standard results	yes

withdrawals from the study explained	no
Patients characteristics	51 median age was 59 (range 42-75) years and 35% were females. 27 received FLIRI and 28 Lv5FU2-IRI. The majority of tumor lesions were located in the liver [involved organs; liver (n = 48), lungs (n = 13) and lymph nodes (n = 11)]
Pre-test probability	43.1%
Results	FDG-PET 17/22 patients metabolic responders: sensitivity 77% 22/29 patients metabolic non responders: specificity 76% 71% positive predictive value 81% negative predictive value
Authors recommendations and conclusions	Although metabolic response assessed by FDG-PET reflects radiological tumor volume changes, the sensitivity and specificity are too low to support the routine use of PET in mCRC. Furthermore, PET failed to reflect long-term outcome and can, thus, not be used as surrogate end point for hard endpoint benefit.

Chapter 10
Follow up of patients treated for colorectal cancer with no suspicion of recurrence

Diagnostic accuracy

Systematic reviews

Author, year	Kuehl 2008
Country	Germany
Technology	FDG-PET, FDG-PET/CT
Disease	Colorectal cancer
Objective	to assess diagnostic accuracy in follow up of patients with colorectal liver metastases treated with radiofrequency ablation
Index test	FDG-PET, FDG-PET/CT at 3 months, 6 months and then every 6 months after radiofrequency ablation (RFA)
Comparator	MRI
Reference standard	Follow up (mean 22 months) with biopsy, surgical specimens or other imaging
Outcomes considered	sensitivity, specificity, PPV, NPV, accuracy
Study design	diagnostic cross sectional study with retrospective recruitment
spectrum of patients representative of the individuals who will receive the test in practice	no
patients selection criteria clearly described	yes
verification by reference standard of all subjects	yes
time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	no
execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
execution of the reference standard described	yes

independent and blind interpretation of index test and reference standard results	yes
withdrawals from the study explained	not applicable
Patients characteristics	16 (13 male and 3 female, age range 34-76 years, mean age 62 years) with known colorectal liver metastases and preinterventional PET/CT as well as post-interventional PET/CT and MRI after RFA
Pre-test probability (of recurrence)	75% (4 patients remained free of intrahepatic tumor manifestations)
Results	lesion based analysis PET sensitivity 61% specificity 98% accuracy 79% PPV 98% NPV 70% PET/CT sensitivity 84% specificity 100% accuracy 92% PPV 100% NPV 86% MRI sensitivity 73% specificity 100% accuracy 91% PPV 100% NPV 88%
Authors recommendations and conclusions	In comparison to PET alone, PET/CT was significantly better for detecting LTP after RFA. There were no significant differences between MRI and PET/CT. These preliminary results, however, need further verification.

Impact on clinical outcomes

Primary studies

Author, year	Sobhani 2008
Country	France
Technology	FDG-PET
Disease	Colorectal cancer
Objective	to assess: ▪ the impact on clinical outcomes of FDG-PET in a systematic program of follow up ▪ the diagnostic accuracy of FDG-PET in a systematic program of follow up
Index test	FDG-PET after 9 and 15 months from curative surgery plus conventional work up
Comparator	conventional work up (physical examination, biomarker essays and US every three months, chest X ray every 6 months, abdominal CT scan after 9 and 15 months from curative surgery)
Reference standard	Recurrence was identified from histological samples (from biopsy or curative surgery) in all cases except in those with evidence of recurrence consisting of disseminated metastases or those for whom clinical examination, tumor markers and imaging procedures (routinely discussed during a multidisciplinary staff meeting) yielded consistently positive results. Patients requiring radiofrequency ablation of hepatic lesions underwent biopsy for histological analyses before treatment was started. Any discrepancy between the FDG-PET findings, and those obtained by other imaging procedures or a physical examination, were taken to be indicative of recurrence, and this was confirmed by a biopsy. There were several options in cases in which the FDG-PET results were consistent with recurrence: - continuing with surgery if the image showed one or a few localised lesions; any additional examinations required by the surgeon could be performed before surgery - biopsy of rectal, colonic, peritoneal, liver, pulmonary or nodular lesions - chemotherapy and/or palliative care if required for multiple recurrent tumors All imaging findings were correlated with the subsequent final histological diagnosis, based on findings at surgery and/or from biopsies.
Outcomes considered	recurrence, time to recurrence, time to therapy, surgery operation, R0 curative, death, sensitivity, specificity
Study design	randomized controlled trial

For the RCT design	
Allocation concealment	uncertain
Blindness	open study but detection blind
Attrition	no
Outcome reporting bias	no
Directness	yes
For the diagnostic accuracy design	
spectrum of patients representative of the individuals who will receive the test in practice	yes
patients selection criteria clearly described	yes
verification by reference standard of all subjects	yes
time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not applicable
execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
execution of the reference standard described	yes
independent and blind interpretation of index test and reference standard results	yes
withdrawals from the study explained	not applicable
Pre-test probability	35.4% (recurrence in 46 patients out of 130)
Patients characteristics	130 patients (65 PET group, 65 conventional work up group) from seven teaching hospitals underwent curative R0 surgery for colon or rectal cancer Age, mean (year) (s.d.) PET group 58.1 (11.2) conventional group 62 (12.1) Location of tumors % colon PET group 56.2 conventional group 59.4 % rectum PET group 43.8 conventional group 40.6

(to be continued)

	Differentiation of the tumor (%) good PET group 67.2 conventional group 57.8 intermediate PET group 1.6 conventional group 4.7 poor PET group 31.2 conventional group 37.5 Stage IV (%) PET group 12.1 conventional group 13.8 Adjuvant treatment (%) yes PET group 90.5 conventional group 89.2 no PET group 9.5 conventional group 10.8
Results	Recurrence 15 out of the 60 (25%) patients in the PET-group, and 12 out of the 65 (18.5%) patients in the Con group (p = 0.19). Kaplan-Meier curves for the time from baseline until the detection of a recurrence of the disease during follow up were obtained, and ITT analysis performed. There was no significant difference between the PET and Con groups with regard to actuarial curves of recurrence (log-rank, p = 0.55); however, for all the patients with a recurrence, the time from baseline until detection of the recurrence was significantly shorter (p = 0.01) in the PET group (12.1 ± 3.6 months) than in the Con group (15.4 ± 4.9 months). However, if we consider only asymptomatic patients without elevated serum tumor markers, then a recurrence was detected in 34 patients (20 PET group patients and 14 in the Con group) by imaging procedures. In this case, the time from baseline until the detection of a recurrence was shorter (although not significantly so) in the PET group than in the Con group (log-rank test, p = 0.25) Curative surgical tumor resection 17 out of 44 patients (PP analysis): 2 in the Con arm and 15 in the PET arm (p <0.0001) Curative R0 surgery performed in 12 cases, more frequently (p <0.01) in patients in the PET group (10 out of 23; 43.5%) than in those in the Con group (2 out of 21; 9.5%). Chemotherapy administered in 39 cases (19 and 20), and palliative therapy in 5 cases (2 and 3) in the PET and Con groups, respectively Curative surgery (R0) performed or a new course of chemotherapy was started sooner after baseline in the PET group (14.8 ± 4.1 months) than in the Con group (17.5 ± 6 months; p =0.09). At 24 months, 9 out of 44 patients had died: 3 in the PET-group and 6 in the Con group Sensitivity FDG-PET 96% conventional work up 91% Specificity FDG-PET 93% conventional work up 92.1%

Authors recommendations and conclusions	In summary, using this new follow up strategy increased the rate of curative resection (R0) in patients by allowing us to detect CRC recurrences at an earlier stage. We would therefore expect improved patient survival if such a follow up programme was undertaken. We now need to assess the cost-effectiveness of strategies including the systematic use of FDG PET/CT in patients who have developed stage III and VI colon and rectum cancer following curative surgery.

Chapter 11
Diagnosis of suspected recurrence and staging of recurrence in patients treated for colorectal cancer

Diagnostic accuracy

Systematic reviews

Author, year	Facey 2007
Technology	FDG-PET
Disease	colorectal cancer
Objective	to assess: ▪ primary diagnosis ▪ staging ▪ response to therapy (after treatment) ▪ diagnosis of suspected recurrence or restaging
Inclusion criteria	P patients with colorectal cancer I FDG-PET C all available R not specified O diagnostic accuracy for primary diagnosis, staging, re-staging after treatment, recurrence S retrospective and prospective studies
Years covered by the search	up to August 2005
Study selection data abstraction, quality assessment performed by two authors independently	not specified
Comprehensive bibliographic search: at least two databases searched	yes Medline, EMBASE, Cochrane Library, HTA database
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	no
Searched also unpublished studies	no
Language restriction	yes, only English literature
Overall number of references retrieved and n. of included studies reported	yes
N. and references of excluded studies reported, reason given	no

Characteristics of included studies clearly reported in tables	yes
Methodological quality of primary studies assessed; criteria reported	yes (QUADAS)
Results of quality assessment used to formulate results and conclusions	yes, qualitative report in the result section
Meta-analysis performed with appropriate statistic methods	not performed
Publication bias assessed	no
N. of included studies Study design	7 cross sectional diagnostic accuracy studies 1 systematic review of 13 primary studies
N. of included patients	510 (from 7 primary studies)
Reference standard	not reported
Comparator	not reported
Pre-test probability	not reported
Performance results	Only descriptive results. One systematic review with 13 primary studies, and two additional primary studies showed that PET was more accurate than CT for detecting recurrence, with sensitivity at least 85% and wide-ranging specificities. The primary studies suggested similar accuracy to MRI, but one PS showed that PET identified a small number of sites that MRI did not detect. In two studies it was noted that the sensitivity of PET to detect lesions smaller than 1 cm was poor. Change in therapy as a result of PET was recorded in two studies as two out of 49 patients (4%) and 17 out of 114 patients (15%). There were two studies of PET used in monitoring for recurrence. One found that PET detected recurrence more quickly than CT. In the other, PET identified recurrence that led to management changes in two out of 49 patients. There were three retrospective primary studies of PET/CT versus PET in 157 patients. One study showed that both assessed recurrence accurately, while another showed slightly better sensitivity of PET/CT (96% versus 88%) and higher specificity (89% versus 74%). In the other trial 88% of patients were correctly staged with PET/CT versus 71% of patients with PET.
Recommendations and conclusions	not reported
Comments of ASSR reviewers	metanalysis not performed

Author, year	**Zhang 2009**
Technology	FDG-PET
Disease	colorectal cancer
Objective	to assess: ▪ diagnosis of suspected recurrence or restaging
Inclusion criteria	P patients with colorectal cancer I FDG-PET C all available R not specified O diagnostic accuracy for primary diagnosis, staging, re-staging after treatment, recurrence S retrospective and prospective studies
Years covered by the search	up to January 2008
Study selection data abstraction, quality assessment performed by two authors independently	yes
Comprehensive bibliographic search: at least two databases searched	yes Medline, EMBASE
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	only reference list of retrieved studies
Searched also unpublished studies	no
Language restriction	yes, only English
Overall number of references retrieved and n. of included studies reported	yes
N. and references of excluded studies reported, reason given	yes
Characteristics of included studies clearly reported in tables	yes
Methodological quality of primary studies assessed; criteria reported	yes (Huebner et al. 2000 criteria)
Results of quality assessment used to formulate results and conclusions	yes: qualitative report in the result section
Meta-analysis performed with appropriate statistic methods	yes
Publication bias assessed	no
N. of included studies Study design	27 cross sectional diagnostic accuracy studies

N. of included patients	1 639; median 42 (range 18-303)
Reference standard	pathology (histology or biopsy) and/or clinical follow up
Comparator	not reported
Pre-test probability	not reported
Performance results	Metanalysis for distant metastasis or whole body recurrence (19 studies) sensitivity 0.91 (95% CI 0.88-0.92) specificity 0.83 (95% CI 0.79-0.87) There existed heterogeneity for sensitivity and specificity (p <0.0000 and 0.0001). A clear influence of studies by 3 studies was noted as they have contributed most toward heterogeneity; values were seen to be outside Galbraith's plot confidence bands. The calculated area under SROC curves and Q* value were 0.9309 and 0.8662. Metanalysis for hepatic metastasis (16 studies) sensitivity 0.97 (95% CI 0.95-0.98) specificity 0.98 (95% CI 0.97-0.99) There existed heterogeneity for specificity (p <0.0004) not for sensitivity (p<0.4505). The calculated area under SROC curves and Q* value were 0.9904 and 0.9594. Metanalysis for pelvic metastasis or local regional recurrence (14 studies) sensitivity 0.94 (95% CI 0.91-0.97) specificity 0.94 (95% CI 0.92-0.96) There existed no heterogeneity for sensitivity and specificity (p <0.2716 and 0.090). The calculated area under SROC curves and Q* value were 0.9776 and 0.9328.

Recommendations and conclusions	Our study suggests a positive influence of PET on the management of recurrent colorectal carcinoma. Most of patients could avoid inappropriate exploratory surgery because of its introduction. Although currently the initial cost of FDG PET is substantial, a decrease in the cost of FDG PET or in the number of FDG PET scans per study population might lead to cost savings. By avoiding medical expenses from these unnecessary surgeries through the increased ability to detect recurrent or metastasis disease throughout the entire body, these initial FDG PET costs might be overshadowed, potentially leading to national medical cost savings of millions of dollars per year. With the exponential development, PET offer numerous advantages over more traditional methods of radiologic diagnosis, and provide essential information not only for initial diagnosis, but also for management, follow up and detection of potential complications. Will PET replace conventional imaging modalities in the future? We do not believe so at present. However, combined with several derivative techniques on the horizon involving CT, MRI and other modalities, these techniques may further improve the specificity and sensitivity of imaging modalities in CRC screening and save the colonoscopy resource for the patients who need treatment. Nevertheless, our research utilized the available sources of included articles to make an object assessment of the role of FDGPET in the recognition of recurrent colorectal carcinoma and to analyze relevant reasons of the misdiagnosis or missed diagnosis to some extent. This offered precious information for the clinical practice and medical treatment or sanitary decision-making.

Author, year	**Floriani 2010**
Technology	FDG-PET
Disease	colorectal cancer
Objective	to assess: ▪ diagnosis of suspected recurrence or restaging
Inclusion criteria	P patients with colorectal cancer I FDG-PET C all available R not specified O diagnostic accuracy for primary diagnosis, staging, re-staging after treatment, recurrence S retrospective and prospective studies
Years covered by the search	up to August 2008
Study selection data abstraction, quality assessment performed by two authors independently	yes
Comprehensive bibliographic search: at least two databases searched	yes Medline, EMBASE
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	only reference list of retrieved studies
Searched also unpublished studies	no
Language restriction	no
Overall number of references retrieved and n. of included studies reported	yes
N. and references of excluded studies reported, reason given	yes
Characteristics of included studies clearly reported in tables	yes
Methodological quality of primary studies assessed; criteria reported	yes (QUADAS tool)
Results of quality assessment used to formulate results and conclusions	yes: qualitative report in the result and discussion sections
Meta-analysis performed with appropriate statistic methods	yes; some doubts about the inclusion of studies with only affected or unaffected patients (specificity and sensitivity not computable respectively)
Publication bias assessed	yes
N. of included studies	25 cross sectional diagnostic accuracy studies

Study design	24 studies CT 14 studies FDG-PET 11 studies MRI 6 studies US
N. of included patients	1 816; median 55.5 (range 8-365) CT studies 1 716; median 53 (range 8-365) FDG-PET studies 699; median 50 (range 19-100) MRI studies 670; median 50 (range 8-125) US studies 661; median 100 (range 38-365)
Reference standard	pathology (histology or biopsy), intraoperative US and/or clinical follow up
Comparator	US, CT, MRI
Pre-test probability	median 36.2% (range 15-63.4%); data from 8 studies (738 patients)
Performance results	Per-patient analysis (metanalysis) CT (12 studies; 884 patients) sensitivity (95% CI) 74.8% (71.2-78.3%) specificity (95% CI) 95.6% (93.4-97.8%) LR+ (95% CI) 11.66 (7.74-17.55) LR- (95% CI) 0.38 (0.25-0.58) FDG-PET (7 studies; 546 patients) sensitivity (95% CI) 93.8% (90-97.7%) specificity (95% CI) 98.7% (97.2-100%) LR+ (95% CI) 51.53 (31.99-82.99) LR- (95% CI) 0.008 (0.005-0.013) MRI (5 studies; 384 patients) sensitivity (95% CI) 81.1% (76-86.1%) specificity (95% CI) 97.2% (94.5-99.9%) LR+ (95% CI) 29.16 (15.04-56.56) LR- (95% CI) 0.35 (0.18-0.69) US (5 studies; 459 patients) sensitivity (95% CI) 63% (56-70%) specificity (95% CI) 97.6% (95.6-99.5%) LR+ (95% CI) 16.88 (9.85-28.92) LR- (95% CI) 0.34 (0.20-0.58) Methodological quality of studies showed that major source of bias in the meta-analysis could be verification bias, which could not be excluded in 8 of 25 studies the blinding of interpretation of results, which was not adopted in 15 of 25 studies.
Recommendations and conclusions	In conclusion, based on the available data on literature, the most through evidence suggests that MRI is the modality with more data supporting its use for the detection of CRC liver metastases

Synoptic table of primary studies on whole body metastasis

Author, year	Patient characteristics	Technology	Patient number	Reference standard	Pre-test probability	Sensitivity	Specificity
Shen 2006	elevated CEA	PET	50	pathology or follow up	90%	95.6%	60%
Chen 2007	not specified (some elevated CEA)	PET/CT	68	pathology or follow up	82.4%	94.6%	83.3%
Sarikaya 2007	clinically and/or radiologically suspected recurrence and normal CEA	PET	39	histology	69.2%	81.5%	66.7%
Kitajima 2009	suspected metastases	PET/CT	170	pathology or follow up	43.5%	89.2%	94.8%
		PET/CECT				93.2%	95.8%
		CECT				79.7%	93.8%
Potter 2009	suspected metastases	PET/CT	50	pathology or follow up	46%	87%	96.3%
		CT OR MRI				82.6%	100 %
Kyoto 2010	elevated CEA	PET/CT	73	pathology or follow up	74%	92.6%	73.7%
Lee 2010	clinically and/or radiologically suspected recurrence and normal CEA	PET/CT	63	pathology or follow up	41.3%	96.3%	86.1%
Metser 2010	elevated CEA	PET/CT	55	pathology or follow up	67.3%	97.3%	94.4%
		64 MDCT				70.3%	94.4%
Shamim 2010	suspected metastases	PET/CT	269	pathology or follow up	63.2%	87.1%	89.9%

Synoptic table of primary studies on liver metastasis

Author, year	Patient characteristics	Technology	Patient number	Reference standard	Pre-test probability	Sensitivity	Specificity
Chua 2007	suspected liver metastasis	PET/CT	75	histology or follow up	89.3%	95.5%	75%
		CECT				91%	25%
Wiering 2007	selected for resection of liver metastases	PET	131	histology or IUS	97.7%	98.4%	100%
		CT				99.2%	0%
Kong 2008	known or suspected liver metastases	PET/CT	65	histology or follow up	93.8%	98.4%	100%
		MRI				98.4%	100%
Orlacchio 2009	suspected liver metastases	PET	467	histology or follow up	71.9%	94%	91.6%
		PET/CT				97.9%	97.7%
		CT				91.1%	95.4%
Glazer 2010	suspected liver metastases before resection	PET	138	laparotomy or IUS	93.5%	89.9%	22.2%

Synoptic table of primary studies on liver metastasis

Author, year	Patient characteristics	Technology	Patient number	Reference standard	Pre-test probability	Sensitivity	Specificity
Shyn 2010	not specified	PET/CT	79	histology or follow up	11.4%	100%	97.1%

Impact on clinical outcomes

Synoptic table of primary studies on futile/non therapeutic laparotomy in patients eligible to liver metastasis resection/ablation

Author, year	Design and methodological consideration	Population	Control group	FDG-PET group	Results control group	Results FDG-PET group	Absolute difference	GRADE level of evidence
Wiering 2007	historical series with controls with not adequate control of confounders	patients undergoing laparotomy for intended resection of colorectal liver metastases	100 participants conventional diagnostic imaging (CDM): CT of liver, abdomen and chest; and colon visualisation, either with colonoscopy or barium enema	103 participants CDM plus FDG-PET	28% (28/100)	19.4% (20/103)	8.6% (p = 0.186)	very low
Pawlik 2009	historical series with controls with not adequate control of confounders	patients undergoing laparotomy for intended resection of colorectal liver metastases	231 participants conventional diagnostic imaging (CDM) without FDG-PET	230 participants CDM with FDG-PET	12.4%	5.6%	6.8% (p = 0.009)	very low
Ruers 2009	open RCT with major concern on directness*	patients undergoing laparotomy for intended resection of colorectal liver metastases	75 participants conventional diagnostic imaging (CDM): CT of liver, abdomen and chest; and colon visualisation, either with colonoscopy or barium enema	75 participants CDM plus FDG-PET	45% (34/75)	26% (21/75)	19% (p = 0.042)	low

* Ruers 2009: too extensive definition of futile laparotomy: only 5 out 75 participants avoided laparotomy in the FDG-PET group

Synoptic table of primary studies on perioperative mortality for laparotomy in patients eligible to liver metastasis resection/ ablation

Author, year	Design and methodological consideration	Population	Control group	FDG-PET group	Results control group	Results FDG-PET group	Absolute difference	GRADE level of evidence
Wiering 2007	historical series with controls with not adequate control of confounders	patients undergoing to laparotomy for intended resection of colorectal liver metastases	100 participants conventional diagnostic imaging (CDM): CT of liver, abdomen and chest; and colon visualisation, either with colonoscopy or barium enema	103 participants CDM plus FDG-PET	3% (3/100)	3% (3/103)	0	very low

Synoptic table of primary studies on disease-free survival in patients eligible to liver metastasis resection/ablation

Author, year	Design and methodological consideration	Population	Control group	FDG-PET group	3-year survival control group	3-year survival FDG-PET group	Absolute difference	GRADE level of evidence
Wiering 2007	historical series with controls with not adequate control of confounders	patients undergoing laparotomy for intended resection of colorectal liver metastases	100 participants: conventional diagnostic imaging (CDM): CT of liver, abdomen and chest; and colon visualisation, either with colonoscopy or barium enema	103 participants CDM plus FDG-PET	OS: 57.1% DFS: 23%	OS: 60.1% DFS: 31.4%	3% (p = 0.678) 8.4% (p = 0.656)	very low
Ruers 2009	open RCT with imprecise data	patients undergoing laparotomy for intended resection of colorectal liver metastases	75 participants: conventional diagnostic imaging (CDM): CT of liver, abdomen and chest; and colon visualisation, either with colonoscopy or barium enema	75 participants CDM plus FDG-PET	OS: 65.8% DFS: 29.8%	OS: 61.3% DFS: 35.5%	-4.5% (p = 0.378) 5.7% (p = 0.194)	moderate

Synoptic table of primary studies on overall survival in patients undergoing resection of pulmonary metastasis from colorectal cancer

Author, year	Design and methodological consideration	Population	Control group	FDG-PET group	3-year survival control group	3-year survival FDG-PET group	Absolute difference	GRADE level of evidence
Muñoz Llarena 2007	historical series with controls with not adequate control of confounders	patients undergoing to resection of pulmonary metastasis	38 participants: conventional diagnostic imaging (CDM) with CT	16 participants CDM plus FDG-PET	31,5 months (95% CI 22.9-40.1)	41,4 months (95% CI 8.7-74.1)	9.9 months (p = 0.14)	very low

Primary studies

Author, year	Muñoz Llarena 2007
Country	Spain
Technology	FDG-PET
Disease	colorectal cancer
Objective	to assess: ▪ restaging
Patients characteristics	55 consecutive patients (36 males, 19 females) who had undergone resection of pulmonary metastases from colorectal adenocarcinoma between January 1993 and June 2004 mean age (± SD) 64.5 ± 10.2 years (range: 41-80)
Intervention	pre-operative CT and FDG-PET
Comparator	pre-operative CT
Outcomes considered	overall survival
Results	univariate analysis median survival CT + PET (N 16) 41,4 months (95% CI 8.7-74.1) CT (N 38) 31,5 months (95% CI 22.9-40.1) p = 0.14 In the multivariate analysis, only size of the largest pulmonary metastasis influenced overall survival (p = 0.036).
Study design	historical series with controls
Consecutive recruitment	yes
Directness	major concern
Control of confounders	not adequate
Sparse data	yes
Authors recommendations and conclusions	The pre-operative variables that best predicted survival in our patients were size of the largest pulmonary metastasis and the level of carcinoembryonic antigen. Prospective studies are needed to determine the usefulness of PET for tumor staging prior to resection of pulmonary metastases
Comment of ASSR reviewers	very low level of evidence according to GRADE

Author, year	**Wiering 2007**
Country	The Netherlands
Technology	FDG-PET
Disease	colorectal cancer
Objective	to assess: ▪ restaging
Patients characteristics	Between January 1995 and November 2003, a consecutive series of 203 patients was identified from our prospective colorectal liver metastases database who underwent laparotomy for intended resection of colorectal liver metastases. After diagnostic workup, 203 patients underwent laparotomy: 100 in group of conventional diagnostic imaging (CDM) (since 1995 till 1998) and 103 in group of CDM and additionally FDG-PET (since 1999 till 2003). For group comparison, tumor and patient characteristics were analysed according to the prognostic scoring system of Fong. The distribution of Fong criteria between groups was comparable.
Intervention	pre-operative CDM and FDG-PET
Comparator	pre-operative CDM: CT of liver, abdomen and chest; and colon visualisation, either with colonoscopy or barium enema.
Outcomes considered	overall survival (3 years of follow up) in patients undergoing surgical resection/ablation disease-free survival (3 years of follow up) in patients undergoing surgical resection/ablation non therapeutic laparotomy perioperative mortality
Results	univariate analysis At laparotomy, 28 patients (28%) in CDM group (n = 100) and 20 (19.4%) in FDG-PET group (n = 103) were considered ineligible for surgical treatment at laparotomy, and further treatment consisted of chemotherapy only (p = 0.186). Remarkably, futile laparotomy was due to extrahepatic disease in only two (1.9%) patients in FDG-PET group compared with 10 (10%) in CDM group (p = 0.017). Perioperative mortality in both groups was similar; three patients (3%) in CDM group and three (3%) in FDG-PET group patients in CDM group (n = 72) 1- and 3-year OS: 86.1% and 57.1% 1- and 3-year DFS: 54.4% and 23% patients in FDG-PET group (n = 83) 1- and 3-year OS: 94% and 60.1% 1- and 3-year DFS: 56.9% and 31.4% OS and DFS curves did not show any significant difference between groups (log rank, p = 0.678 and p = 0.656)

Study design	historical series with controls
Consecutive recruitment	yes
Directness	major concern
Control of confounders	not adequate
Sparse data	no
Authors recommendations and conclusions	In patients with colorectal liver metastases, FDG-PET may reduce the number of negative laparotomies. However, the effect size on the selection of these patients seems not sufficient enough to affect the overall and disease-free survival after treatment
Comment of ASSR reviewers	very low level of evidence according to GRADE

Author, year	**Pawlik 2009**
Country	USA
Technology	FDG-PET
Disease	colorectal cancer
Objective	to assess: ▪ restaging
Patients characteristics	461 patients, since 1994 till 2005, underwent 530 exploratory laparotomy procedures at the Johns Hopkins Hospital with curative intent to treat hepatic colorectal metastasis. Only patients with disease initially believed to be limited to the liver and that was amenable to complete curative treatment were included in the study. Median patient age 61 years (IQR 22-90 years); 66.2% were male. Most patients who underwent exploratory laparotomy with curative intent had hepatic metastases from a primary colon tumor (72.7%), while 27.3% had a primary rectal lesion. Most primary colorectal tumors were staged as T3/T4 (75.5%) and were associated with metastatic nodal disease (N1) (59.4%). Median carcinoembryonic antigen (CEA) level was 13 mg/dL; the majority of patients had clinical risk score greater than 2 (66.6%). Many patients (43.6%) received pre-operative systemic chemotherapy prior to liver-directed surgery with either oxaliplatin- (43.5%) or irinotecan-based (45.4%) regimens. Pre-operative imaging included CT scan (90%) and PET scan (49.9%) in most patients. Looking at the entire cohort, median number of treated hepatic metastases per patient was 2 (IQR 1-3) and median size of largest lesion was 3 cm (IQR 2-5 cm). On a quadrennial point of view (1994-1997, 1998-2001, 2002-2005) some factors had a different rate of occurrence: disease-free interval <12 months, clinical risk score >2 points, pre-operative chemotherapy, pre-operative PET imaging (0% in the first 4-year period, 45.5% in the second, 90.1% in the third)
Intervention	pre-operative FDG-PET
Comparator	not pre-operative FDG-PET
Outcomes considered	non therapeutic laparotomy

Results	Univariate analysis Patients staged with a pre-operative PET scan had a non therapeutic laparotomy rate of 5.6% compared with 12.4% in those not undergoing pre-operative PET staging (OR = 0.42, 95% CI 0.2-0.8; p = 0.009) While the overall NTL rate was 9.2%, the NTL rate did show a significant decrease over time (14.9% for 1994-1997 versus 9.6% for 1998-2001 versus 4.7% for 2002-2005; p = 0.003) A significantly higher proportions of patients in later time periods underwent pre-operative PET scan staging (0% for 1994-1997 versus 30.2% for 1998-2001 versus 90.5% for 2002-2005; p <0.001). In addition, use of more extensive hepatic resection, as well as utilization of ablation, similarly had increased over time (p = 0.02 and p = 0.004, respectively)
Study design	historical series with controls
Consecutive recruitment	yes
Directness	major concern
Control of confounders	not adequate
Sparse data	no
Authors recommendations and conclusions	The prevalence of non therapeutic laparotomy for patients undergoing surgical exploration for hepatic colorectal metastases has decreased significantly in recent years with the NTL rate most recently being less than 5%. The reasons for this trend are probably multifactorial and include improved pre-operative assessment, such as PET imaging, as well as additional surgical options. Such low negative laparotomy rates call into question the utility of routine staging laparoscopy prior to open surgical exploration. Data from the current study should provide guidance in helping to identify patients at highest risk of non therapeutic laparotomy
Comment of ASSR reviewers	very low level of evidence according to GRADE

Author, year	**Ruers 2007**
Country	The Netherlands
Technology	FDG-PET
Disease	colorectal cancer
Objective	to assess: ▪ restaging
Patients characteristics	150 patients were enrolled in a trial between May 2002 and February 2006. Eligible patients were required to have a history of histologically documented colorectal cancer treated by R0 surgical resection (tumor-free resection margins); 1-4 suspected potentially resectable colorectal liver metastases, without evidence of extrahepatic metastatic disease (with the exception of a maximum of 2 resectable lung metastases) on contrast-enhanced CT of the abdomen, pelvis, and chest; no signs of recurrent or second colorectal carcinoma on barium enema or colonoscopy; and World Health Organization performance status 0-2. In addition, patients were required to be aged 18-75 y. No patients were lost to follow up. Patient and tumor characteristics were similar between the 2 strategy groups
Intervention	pre-operative CDM and FDG-PET
Comparator	pre-operative CDM: CT of liver, abdomen and chest; and colon visualisation, either with colonoscopy or barium enema
Outcomes considered	Primary outcome: the number of futile laparotomies. Futile laparotomy was defined as any laparotomy that did not result in complete tumor clearance either intrahepatically or extrahepatically or that revealed benign disease at laparotomy or histopathologic examination. Although arbitrary, laparotomy and surgical treatment were also considered futile when disease recurrence occurred within 6 mo after surgery. Overall survival (3 years of follow up) Disease-free survival (3 years of follow up)

Results	Univariate analysis Additional 18F-FDG PET findings resulted in cancellation of planned resection of the suspected liver metastases in 5 patients. Follow up of these patients showed that 18FFDG PET correctly predicted benign disease in 2 patients and unresectable extrahepatic disease in 3. So, in total 75 patients in the conventional arm without 18F-FDG PET and 70 patients in the experimental arm with 18F-FDG PET underwent laparotomy. Futile laparotomy control arm without 18F-FDG PET (75 pts): 45% experimental arm with 18F-FDG PET (75 pts): 28% p <0.042). Relative risk reduction: 38% (95% confidence interval, 4%-60%). The absolute difference of 17% means that 6 patients need to undergo 18F-FDG PET to avoid 1 futile laparotomy. patients in CDM group (n = 75) 3-year OS: 65.8% 3-year DFS: 29.8% patients in FDG-PET group (75 pts) 3-year OS: 61.3% 3-year DFS: 35.5% OS and DFS curves did not show any significant difference between groups (log rank, p = 0.378 and p = 0.194).
Study design	open randomized controlled trial
Consecutive recruitment	minor concern: unblinding of panel deciding elegibility to laparotomy
Directness	major concern: too extensive definition of futile laparotomy: see the difference with avoided laparotomy
Control of confounders	adequate
Sparse data	no
Authors recommendations and conclusions	The introduction of 18F-FDG PET in the pre-operative work-up of patients with colorectal liver metastases that are considered resectable on CT significantly reduces the number of futile laparotomies due to unexpected unresectable disease. When considering surgical intervention for liver metastases, one should not disregard suspected extrahepatic disease on 18F-FDG PET and PET-negative liver lesions. Therefore, 18F-FDG PET should be implemented in the diagnostic algorithm before laparotomy for resection of colorectal liver metastases is performed
Comment of ASSR reviewers	low level of evidence according to GRADE for the futile laparotomy outcome moderate level of evidence according to GRADE for OS and DFS outcomes

COLLANA DOSSIER

a cura dell'Agenzia sanitaria e sociale regionale

1990

1. Centrale a carbone "Rete 2": valutazione dei rischi. Bologna. **(*)**
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8. Educazione alimentare e tutela del consumatore "Seminario regionale Bologna 1-2 marzo 1990". Bologna. **(*)**

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9. Guida alle banche dati per la prevenzione. Bologna.
10. Metodologia, strumenti e protocolli operativi del piano dipartimentale di prevenzione nel comparto rivestimenti superficiali e affini della provincia di Bologna. Bologna. **(*)**
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15. Rischi ambientali, alimentari e occupazionali, Attività di prevenzione e controllo nelle USL dell'Emilia-Romagna. 1991. Bologna. **(*)**
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156. Atlante della mortalità in Emilia-Romagna 1998-2004. Bologna. **(*)**

157. FDG-PET in oncologia. Criteri per un uso appropriato. Bologna. **(*)**

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

159. L'audit per il controllo degli operatori del settore alimentare. Indicazioni per l'uso in Emilia-Romagna. Bologna. **(*)**

160. Politiche e piani d'azione per la salute mentale dell'infanzia e dell'adolescenza. Bologna. **(*)**

2008

161. Sorveglianza dell'antibioticoresistenza e uso di antibiotici sistemici in Emilia-Romagna. Rapporto 2006. Bologna. **(*)**

162. Tomografia computerizzata multistrato per la diagnostica della patologia coronarica. Revisione sistematica della letteratura e indicazioni d'uso appropriato. Bologna. **(*)**

163. Le Aziende USL dell'Emilia-Romagna. Una lettura di sintesi dei Bilanci di missione 2005 e 2006. Bologna. **(*)**

164. La rappresentazione del capitale intellettuale nelle organizzazioni sanitarie. Bologna. **(*)**

165. L'accreditamento istituzionale in Emilia-Romagna. Studio pilota sull'impatto del processo di accreditamento presso l'Azienda USL di Ferrara. Bologna. **(*)**

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

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

168. Educazione continua in medicina in Emilia-Romagna. Rapporto 2007. Bologna. **(*)**

169. Le opinioni dei professionisti della sanità sulla formazione continua. Bologna. **(*)**

170. Per un Osservatorio nazionale sulla qualità dell'Educazione continua in medicina. Bologna. **(*)**

171. Le segnalazioni dei cittadini agli URP delle Aziende sanitarie. Report regionale 2007. Bologna. **(*)**

2009

172. La produzione di raccomandazioni cliniche con il metodo GRADE. L'esperienza sui farmaci oncologici. Bologna. **(*)**

173. Sorveglianza dell'antibioticoresistenza e uso di antibiotici sistemici in Emilia-Romagna. Rapporto 2007. Bologna. **(*)**

174. I tutor per la formazione nel Servizio sanitario regionale dell'Emilia-Romagna. Rapporto preliminare. Bologna. **(*)**

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

176. Utilizzo di farmaci antibatterici e antimicotici in ambito ospedaliero in Emilia-Romagna. Rapporto 2007. Bologna. **(*)**

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. **(*)**

181. Le segnalazioni dei cittadini agli URP delle Aziende sanitarie. Report regionale 2008. Bologna. **(*)**

182. La ricerca come attività istituzionale del Servizio sanitario regionale. Principi generali e indirizzi operativi per le Aziende sanitarie dell'Emilia-Romagna. Bologna. **(*)**

183. I Comitati etici locali in Emilia-Romagna. Bologna. **(*)**

184. Il Programma di ricerca Regione-Università. 2007-2009. Bologna. **(*)**

185. Il Programma Ricerca e innovazione (PRI E-R) dell'Emilia-Romagna. Report delle attività 2005-2008. Bologna. **(*)**

186. Le medicine non convenzionali e il Servizio sanitario dell'Emilia-Romagna. Un approccio sperimentale. Bologna. **(*)**

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

2010

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. **(*)**

190. Infezioni delle vie urinarie nell'adulto. Linea guida regionale. Bologna. **(*)**

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

192. La *governance* delle politiche per la salute e il benessere sociale in Emilia-Romagna. Opportunità per lo sviluppo e il miglioramento. Bologna. **(*)**

193. Il *mobbing* tra istanze individuali e di gruppo. Analisi di un'organizzazione aziendale attraverso la tecnica del *focus group*. Bologna. **(*)**

194. Linee di indirizzo per trattare il dolore in area medica. Bologna. **(*)**

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

196. Evoluzione delle Unità di terapia intensiva coronarica in Emilia-Romagna. Analisi empirica dopo implementazione della rete cardiologica per l'infarto miocardico acuto. Bologna. **(*)**

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. **(*)**

200. Tredici anni di SIRS - Servizio informativo per i rappresentanti per la sicurezza. Bologna. **(*)**

201. Sorveglianza dell'antibioticoresistenza e uso di antibiotici sistemici in Emilia-Romagna. Rapporto 2008. Bologna. **(*)**

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

2011

203. Buone pratiche infermieristiche per il controllo delle infezioni nelle Unità di terapia intensiva. Bologna. **(*)**

204. Le segnalazioni dei cittadini agli URP delle Aziende sanitarie. Report regionale 2009. Bologna. **(*)**

205. L'informazione nella diagnostica pre-natale. Il punto di vista delle utenti e degli operatori. Bologna. **(*)**

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. **(*)**

209. Criteria for appropriate use of FDG-PET in esophageal cancer. ORIentamenti 4. Bologna. **(*)**

210. Sorveglianza dell'antibioticoresistenza e uso di antibiotici sistemici in Emilia-Romagna. Rapporto 2009. Bologna. **(*)**

211. Criteria for appropriate use of FDG-PET in colorectal cancer. ORIentamenti 5. Bologna. **(*)**

212. Mortalità e morbosità materna in Emilia-Romagna. Rapporto 2001-2007. Bologna. **(*)**

213. Atlante della mortalità in Emilia-Romagna 2003-2007. Bologna. **(*)**

214. Atlante della mortalità in Emilia-Romagna 2008-2009. Bologna. **(*)**

215. "Fidatevi dei pazienti". La qualità percepita nei Centri di salute mentale e nei Servizi per le dipendenze patologiche. Bologna. **(*)**

216. Piano programma 2011-2013. Agenzia sanitaria e sociale regionale. Bologna. **(*)**