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RegioneEmilia-Romagna

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA

Criteria for appropriate use of FDG-PET in head and neck cancer

ORIentamenti 7

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
FDG	fluoro-deoxyglucose
FN	false negatives
FP	false positives
GVT	gross target volume
LR	likelihood ratio
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
PET	positron emission tomography
PVT	planned target volume
RCT	randomized controlled trial
RER	Regione Emilia-Romagna
RT	radiotherapy
SIGN	Scottish Intercollegiate Guidelines Network
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) nei tumori del testa-collo

Il ruolo della FDG-PET nei tumori del testa-collo è stato valutato in nove indicazioni cliniche. La ricerca in letteratura ha identificato un ragguardevole numero di studi con un gran numero di pazienti inclusi. Il livello di evidenza riscontrato è stato quindi spesso moderato, pur in presenza di problemi di qualità metodologica comuni alla maggior parte degli studi di diagnosi (incerta lettura in cieco, *bias* di verifica, ecc.). Nei tumori del testa-collo la FDG-PET sembra avere migliore *performance* rispetto agli altri test di *imaging*, soprattutto in termini di sensibilità. Per questa ragione il panel ha ritenuto di posizionare il test come esame di secondo livello rispetto alla diagnostica convenzionale, con l'obiettivo di recuperare i possibili falsi negativi. Le conseguenze per i falsi positivi sono state considerate gestibili, dal momento che la maggior parte dei pazienti viene sottoposta a biopsia di conferma, che, pur non essendo priva di rischi per i pazienti, riduce il rischio di decisioni terapeutiche inappropriate o errate.

Il panel ha esaminato e valutato il ruolo della FDG-PET nelle seguenti indicazioni cliniche:

- diagnosi di tumore del testa-collo -
  Inappropriato per mancanza di ruolo diagnostico della FDG-PET
- individuazione di tumore primitivo occulto del testa-collo in pazienti con metastasi linfonodali cervicali -
  Appropriato (livello di evidenza: moderato)
- stadiazione N di pazienti con tumore del testa-collo -
  Appropriato (livello di evidenza: moderato)
- stadiazione M e individuazione di secondo tumore primitivo sincrono in pazienti con tumore avanzato del testa-collo -
  Appropriato (livello di evidenza: moderato)
- definizione del *target volume* nel trattamento curativo radiante di tumore del testa-collo -
  Incerto (livello di evidenza: molto basso)
- valutazione della risposta precoce alla terapia neo-adiuvante/di induzione -
  Indeterminato per mancanza di studi

- valutazione della risposta ai regimi di chemioterapia o radioterapia al termine del trattamento -
  Incerto (livello di evidenza: basso)
- *follow up* di pazienti trattati per tumore del testa-collo senza sospetto di recidiva -
  Inappropriato (livello di evidenza: basso)
- diagnosi e stadiazione di sospetto di recidiva a distanza -
  Appropriato (livello di evidenza: moderato)

DIAGNOSI DI TUMORE DEL TESTA-COLLO - INAPPROPRIATO

Sebbene alcuni studi abbiano valutato l'accuratezza diagnostica della FDG-PET nella diagnosi del tumore del testa-collo, il panel ha concordato alla prima votazione di giudicare l'uso della FDG-PET nella diagnosi del tumore del testa-collo inappropriato, per mancanza di ruolo diagnostico della FDG-PET.

INDIVIDUAZIONE DI TUMORE PRIMITIVO OCCULTO DEL TESTA-COLLO IN PAZIENTI CON METASTASI DEI LINFONODI CERVICALI - APPROPRIATO

Alla prima votazione il panel ha raggiunto l'accordo nel giudicare appropriato l'utilizzo della FDG-PET nell'individuazione di tumore primitivo occulto del testa-collo in pazienti con metastasi dei linfonodi cervicali e con risultatiti negativi alla diagnostica convenzionale. Il livello di evidenza per l'accuratezza diagnostica della FDG-PET è stato giudicato moderato, con stime di sensibilità più alte rispetto alla diagnostica convenzionale, suggerendo che l'aggiunta dell'esame PET nei pazienti con risultati negativi o dubbi possa risultare in un maggior numero di tumori primari individuati. Il trattamento mirato del tumore primitivo è clinicamente molto rilevante e le conseguenze per i pazienti che ricevono trattamenti appropriati sono state considerate "critiche" (mediana 8; *range* 7-9). I pazienti per i quali il tumore primario rimane occulto ricevono una combinazione di radioterapia e chirurgia, possibilmente seguite da chemioterapia, e gli esiti clinici per i pazienti con risultati negativi (veri o falsi) o falsi positivi sono stati giudicati "importanti".

STADIAZIONE N DI PAZIENTI CON TUMORE DEL TESTA-COLLO - APPROPRIATO

L'utilizzo della FDG-PET nella stadiazione N dei pazienti con tumore del testa-collo e risultati dubbi alle metodiche di primo livello (TC, RM, ecografia) è stato votato appropriato dal panel alla prima votazione. Il livello di evidenza per l'accuratezza diagnostica della FDG-PET è stato giudicato moderato, con stime di sensibilità e specificità lievemente superiori rispetto alle altre metodiche diagnostiche. Gli esiti per i pazienti correttamente stadiati al livello superiore (veri positivi) sono stati votati "critici" (mediana 8, *range* 6-9), evidenziando l'importanza attribuita all'identificazione dei pazienti con linfonodi positivi non individuati dalla diagnostica convenzionale. Anche le conseguenze per i pazienti con risultati negativi (veri e falsi negativi) e per i falsi positivi sono state considerate di critica importanza, ma con un voto mediano più basso e un *range* di voti più ampi.

STADIAZIONE M E INDIVIDUAZIONE DI SECONDO TUMORE PRIMITIVO SINCRONO IN PAZIENTI CON TUMORE LOCALMENTE AVANZATO DEL TESTA-COLLO - APPROPRIATO

Alla prima votazione il panel ha raggiunto l'accordo nel giudicare appropriato l'utilizzo della FDG-PET nella stadiazione M dei pazienti con tumore localmente avanzato del testa-collo e risultato negativo o incerto ai test standard di *imaging*. Il livello di evidenza per l'accuratezza diagnostica della FDG-PET è stato giudicato moderato con stime di sensibilità più alte rispetto a quelle della diagnostica convenzionale. Tutti gli esiti clinici sono stati considerati "critici" (voto mediano 8), con un *range* più stretto (tra 7 e 8) per i pazienti correttamente stadiati al livello superiore, evidenziando il valore aggiunto della FDG-PET nell'identificare metastasi a distanza o tumore primitivo sincrono nei casi non individuati dalla diagnostica tradizionale.

DEFINIZIONE DEL *TARGET VOLUME* NEL TRATTAMENTO CURATIVO RADIANTE DI TUMORE DEL TESTA-COLLO - INCERTO

In entrambe le votazioni è stato registrato un leggero disaccordo tra i membri del panel, con i singoli punteggi compresi tra inappropriato e incerto (voto mediano 3). Pertanto l'uso della FDG-PET per la definizione del *target volume* nel trattamento radiante con intento curativo in sostituzione alla TC è risultato incerto per disaccordo. Vi sono evidenze coerenti che dimostrano una discordanza di risultato tra FDG-PET e TC nella definizione del campo da irradiare. Il livello delle evidenze è risultato molto basso, e in nessun caso è stato possibile evidenziare una migliore *performance* da parte della FDG-PET. Nonostante queste premesse, la discussione tra i membri del panel non ha risolto il disaccordo, il quale probabilmente origina dalla rilevanza della radioterapia nella cura dei tumori del testa-collo. A riprova, tutti gli esiti clinici sono stati infatti considerati "critici" (voto mediano 7).

Il panel ha evidenziato il fatto che, dato l'uso appropriato della FDG-PET per la stadiazione N dei pazienti con tumore del testa-collo, l'immagine ottenuta a tale scopo può essere utilizzata anche per supportare la definizione del campo da irradiare. Tuttavia queste informazioni vanno interpretate con molta cautela e le decisioni non possono essere basate solo su di esse.

VALUTAZIONE DELLA RISPOSTA PRECOCE ALLA TERAPIA NEO-ADIUVANTE/DI INDUZIONE - INDETERMINATO PER MANCANZA DI STUDI

La ricerca in letteratura non ha rilevato alcuno studio, né linea guida per la pratica clinica, sul possibile ruolo diagnostico della FDG-PET nella valutazione della risposta precoce al trattamento dei tumori del testa-collo. Tuttavia il panel ha espresso la necessità, nella pratica clinica, di un test adeguato a valutare la risposta precoce al trattamento radiante radicale a scopo curativo del tumore primario. Dal momento che nella malattia di stadio I-II e in pazienti con linfonodi negativi sia la chirurgia conservativa sia la radioterapia (radioterapia esterna o brachiterapia) offrono un simile controllo loco-regionale, un test accurato potrebbe individuare i pazienti che non rispondono al trattamento radiante e che beneficerebbero di un cambio di approccio passando al trattamento chirurgico.

Il panel ha concordato di classificare questo quesito indeterminato per mancanza di studi, e di proporlo come possibile futuro quesito di ricerca clinica.

VALUTAZIONE DELLA RISPOSTA AI REGIMI DI CHEMIOTERAPIA O RADIOTERAPIA AL TERMINE DEL TRATTAMENTO - INCERTO

In entrambe le votazioni è stato registrato un forte disaccordo tra i membri del panel, con i singoli punteggi distribuiti in tutte le categorie di voto appropriato, incerto e inappropriato (prima votazione punteggio mediano 6, seconda votazione punteggio mediano 5). Pertanto l'uso della FDG-PET come esame di secondo livello dopo risposta dubbia ai test standard di *imaging* (TC, RM) per valutare la risposta ai regimi di chemioterapia o radioterapia al termine del trattamento allo scopo di decidere una eventuale biopsia eco-guidata e un possibile intervento chirurgico di salvataggio, è risultato incerto per disaccordo.

Il livello di evidenza dell'accuratezza diagnostica della FDG-PET è risultato basso, a causa della eterogeneità della specificità. Dopo discussione il panel ha ritenuto utile analizzare i risultati, restringendo il quesito nel sottogruppo di pazienti sottoposti a FDG-PET entro 3 mesi dal termine del trattamento. Tuttavia le stime di accuratezza e il livello di evidenza non migliorano in questo sottogruppo.

Gli esiti sono stati votati come critici per tutte le categorie di pazienti, con punteggio superiore (mediana pari a 8) per i pazienti con malattia residua al termine della terapia - veri positivi e falsi negativi - a testimonianza dell'importanza di attribuire o negare correttamente l'intervento di salvataggio.

FOLLOW UP DI PAZIENTI TRATTATI PER TUMORE DEL TESTA-COLLO SENZA SOSPETTO DI RECIDIVA - INAPPROPRIATO

Dopo un iniziale leggero disaccordo tra giudizio inappropriato e incerto, il panel ha raggiunto l'accordo nel giudicare inappropriato l'uso della FDG-PET nel *follow up* dei pazienti con nessun sospetto di recidiva. Il livello di evidenza dell'accuratezza diagnostica della FDG-PET è risultato basso, in quanto basato su tre studi con stima eterogenea della specificità ed assenza di dati su test di comparazione adeguato.

Tutti gli esiti sono risultati "importanti" con lo stesso punteggio mediano pari a 4.

DIAGNOSI E STADIAZIONE DI SOSPETTO DI RECIDIVA A DISTANZA - APPROPRIATO

Alla prima votazione il panel ha concordato nel giudicare appropriato l'utilizzo della FDG-PET nella diagnosi e stadiazione della sospetta recidiva in pazienti con risultati dubbi alla diagnostica convenzionale. Il livello di evidenza per l'accuratezza diagnostica della FDG-PET è stato giudicato moderato, e la sensibilità della FDG-PET è risultata più alta rispetto alla specificità. Gli esiti clinici per i pazienti veri positivi hanno ricevuto il voto mediano più alto, 8, con un *range* tra 6 e 8. Anche le conseguenze per i pazienti che risultano veri o falsi negativi e falsi positivi sono stati considerate di critica importanza con un voto mediano di 7 ma range di voti più ampi.

Summary of results

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

The role of FDG-PET in head and neck cancer has been evaluated in nine clinical questions. The search in literature identified a large number of studies and overall a large number of patients have been included in the studies. Level of evidence was therefore often found to be moderate, although methodological flaws common to most studies on diagnostic accuracy were present (uncertain blinding, verification bias, etc.). In head and neck cancer FDG-PET seems to perform better than other imaging test especially in terms of sensitivity. For this reason the panel agreed in positioning the test in add on to conventional imaging, with the objective of uncovering false negative patients. Consequences for false positives were considered manageable, as most patients undergo confirmatory biopsies which - though involving some risks for the patients, reduce the risk of wrong or inappropriate therapeutic decisions.

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

- diagnosis of head and neck cancer -
  Inappropriate for lack of diagnostic role of FDG-PET
- detection of unknown primary head and neck cancer in patients with metastatic cervical lymph nodes -
  Appropriate (level of evidence: moderate)
- N staging of patients with head and neck cancer -
  Appropriate (level of evidence: moderate)
- M staging and detection of synchronous second primary tumor in patients with locally advanced head and neck cancer -
  Appropriate (level of evidence: moderate)
- target volume definition of curative radiation treatment -
  Uncertain (level of evidence: very low)
- evaluation of early response to neo-adjuvant/induction therapy -
  Indeterminate for lack of studies
- evaluation of response to chemotherapy or radiotherapy at the end of treatment -
  Uncertain (level of evidence: low)

- follow up in patients with no suspicion of recurrence - Inappropriate (level of evidence: low)
- diagnosis and staging of suspect distant recurrence - Appropriate (level of evidence: moderate)

DIAGNOSIS OF HEAD AND NECK CANCER - INAPPROPRIATE

Although some studies have evaluated the diagnostic accuracy of FDG-PET in the diagnosis of head and neck cancer, the panel agreed during the first round of voting to judge the use of FDG-PET in the diagnosis of head and neck as inappropriate, due to lack of diagnostic role for FDG-PET.

DETECTION OF UNKNOWN PRIMARY HEAD AND NECK CANCER IN PATIENTS WITH METASTATIC CERVICAL LYMPH NODES - APPROPRIATE

During the first round of voting the panel agreed to judge appropriate the use of FDG-PET for the detection of unknown primary head and neck cancer in patients with metastatic cervical lymph nodes and testing negative with conventional imaging. Level of evidence for diagnostic accuracy of FDG-PET has been judged moderate with estimates of sensitivity considerably higher than conventional imaging, suggesting that adding FDG-PET for patients with negative or unclear results would result in a higher number of detected primary tumors. Targeted treatment of primary tumor is of great clinical relevance and consequences for patients receiving appropriate treatment have been considered "critical" (median 8; range 7-9). Patients for whom primary tumor remains undetected receive a combination of radiation therapy and surgery, possibly followed by chemotherapy, and clinical outcomes for patients testing negative (true or false negative) or testing false positive have been voted "important".

N STAGING OF PATIENTS WITH HEAD AND NECK CANCER - APPROPRIATE

Use of FDG-PET for N staging of patients with primary head and neck cancer and with unclear results with conventional imaging (CT, MRI, ultrasound) has been judged appropriate by the panel during the first round of voting. Level of evidence for diagnostic accuracy of FDG-PET has been judged moderate, with estimates for sensitivity and specificity slightly higher than those of conventional imaging. Outcomes for patients correctly upstaged (true positives) have been voted "critical" (median score of 8, range 6-9), highlighting the importance attributed to the identification of node positive patients missed by conventional imaging. Consequences for patients testing negative (true and false negatives) and for false positives have also been judged critical, though with a lower median score and much wider range of votes.

M STAGING OF PATIENTS AND DETECTION OF SYNCHRONOUS SECOND PRIMARY TUMOR IN PATIENTS WITH LOCALLY ADVANCED HEAD AND NECK CANCER - APPROPRIATE

At the first voting round the panel agreed to judge appropriate the use of FDG-PET for M staging of advanced head and neck cancer in patients with negative or equivocal results from conventional imaging. Level of evidence for diagnostic accuracy of FDG-PET was judged moderate with estimates for sensitivity higher than conventional imaging. All clinical outcomes were considered "critical" (median score 8), with a closer range (between 7 and 8) for patients correctly upstaged, highlighting the added value of FDG-PET in identifying patients with distant metastases or second primary tumors missed by conventional imaging.

TARGET VOLUME DEFINITION OF CURATIVE RADIATION TREATMENT - UNCERTAIN

In neither voting rounds the panel reached an agreement on the appropriateness with votes (median score 3) falling between the inappropriate and uncertain regions. The use of FDG-PET in target volume definition of curative radiation treatment in replacement of CT resulted therefore uncertain due to disagreement.

There is consistent evidence of discordant radiation field definition between FDG-PET and CT. The level of evidence was judged to be very low and FDG-PET was not proven to provide a better pathological tumor coverage than CT. Nevertheless the discussion among panel members did not solve disagreement, that probably origins from the relevance of curative radiation treatment of head and neck cancer. In fact all clinical outcomes were considered "critical" (median score 7).

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

EVALUATION OF EARLY RESPONSE TO NEO-ADJUVANT/INDUCTION THERAPY - INDETERMINATE

The literature search resulted in no studies nor clinical practice guidelines addressing a possible diagnostic role of FDG-PET in the evaluation of early response to treatment of head and neck cancer. However the panel expressed the need, in clinical practice, for an adequate test evaluating early response to radical curative radiation treatment of early cancer. Since in early disease (stage I-II, i.e. node negative patients), either conservative surgery or radiotherapy (external radiotherapy or brachytherapy) give similar loco-regional control, an accurate test could identify patients who do not respond to radiation treatment and would benefit from a change of therapy and switch to radical surgery.

The panel unanimously agreed in classifying this clinical question as indeterminate, for lack of studies, and in proposing it as a future clinical research question.

EVALUATION OF RESPONSE TO CHEMOTHERAPY OR RADIOTHERAPY AT THE END OF TREATMENT - UNCERTAIN

In neither of voting rounds the panel reached an agreement on the appropriateness with votes falling in all regions of appropriateness, uncertainty and inappropriateness (first round median score 6, second round median score 5). The use of FDG-PET to evaluate end of treatment response to chemotherapy or radiotherapy, as add-on test in patients with equivocal results from conventional imaging (CT, MR), in order to proceed to confirmatory biopsy and salvage surgery, resulted therefore uncertain due to disagreement.

The level of evidence was judged low, due to heterogeneity of specificity estimates. After discussion the panel agreed to analyze data of the subgroup of patients undergoing FDG-PET within the first 3 months after the end of treatment. However the accuracy estimates and level of evidence did not change in this subgroup.

Clinical outcomes were voted critical in all cases, however outcomes concerning patients with residual disease at the end of treatment - true positive and false negative - had a higher score (median of 8), highlighting the importance of appropriate use of salvage aggressive treatment.

FOLLOW UP OF PATIENTS WITH NO SUSPISCION OF RECURRENCE - INAPPROPRIATE

After an initial slight disagreement between inappropriate and uncertain, the panel agreed to judge as inappropriate the use of FDG-PET for patients in follow up with no suspicion of recurrence. Level of evidence for diagnostic accuracy of FDG-PET in follow up was low and derived from three primary studies with heterogeneous estimate of specificity and absence of a fair comparator.

All outcomes were voted "important" (all median score of 4).

DIAGNOSIS AND STAGING OF SUSPECT DISTANT RECURRENCE - APPROPRIATE

During the first round of voting the panel agreed in judging appropriate the use of FDG-PET in the diagnosis and staging of suspect recurrence in patients with unclear results from conventional imaging. Level of evidence for diagnostic accuracy of FDG-PET was found moderate, and sensitivity of FDG-PET resulted higher than specificity. Clinical outcomes for patients resulting true positive received the highest median score of 8 with votes ranging from 6 to 8. Consequences for patients resulting true or false negative and false positive were also voted "critical" with a median score of 7 and wider ranges of votes.

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 head and neck cancer has been carried out between March and June 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 synthesize and present the evidence base, the logic and principles of the GRADE approach were applied and the consensus process was based on the RAND/UCLA Appropriateness Method.

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

1. Introduction and objectives

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

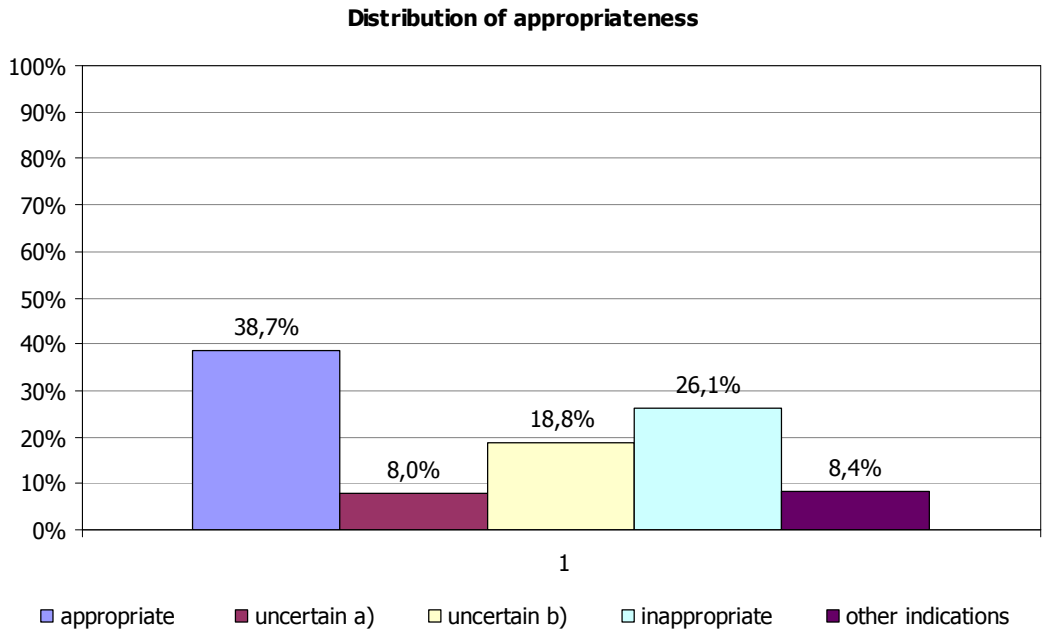
Since its introduction in the Emilia-Romagna Regional Health Service, the ASSR has been committed to promote and support regional research programs aimed at assessing clinical indications for PET and supporting programming policies.

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

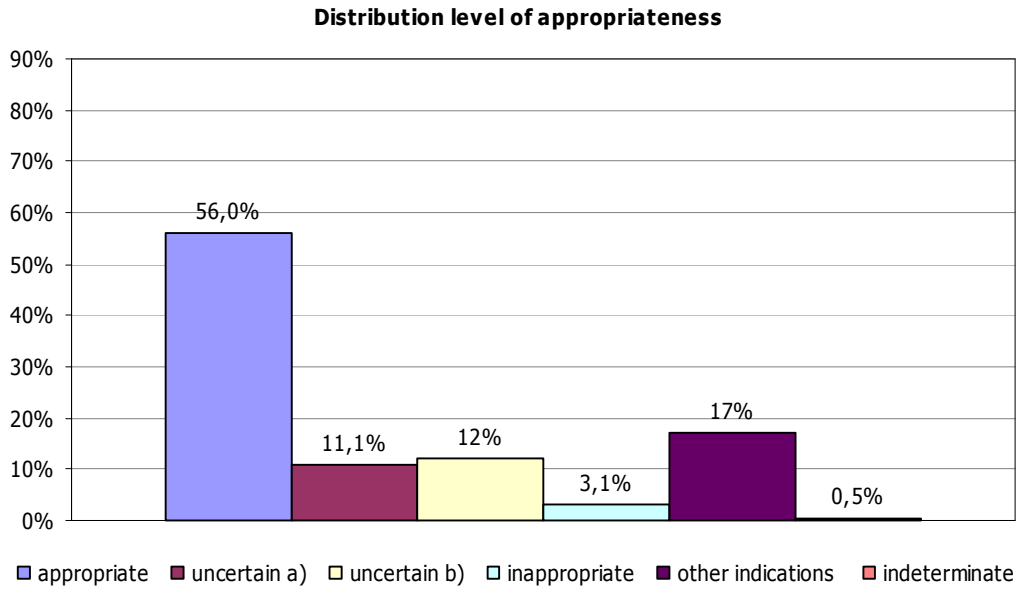
Following the increase in number of PET scanners (from 1 to 6) an update of the 2003 report was commissioned to a second regional panel and published in 2007. The second report addressed the role of FDG-PET in 18 types of cancer for a total of 65 clinical indications, and a second clinical audit was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

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

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



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



1.1. Use of FDG-PET in head and neck cancer: objectives

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

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

Under the definition of "head and neck cancer" we considered carcinoma of the larynx, oral cavity, oropharynx, hypopharynx, nasopharynx. Metastatic cervical lymph nodes of unknown primary cancer was taken into account with a specific clinical questions.

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

- supporting clinicians on the use of FDG-PET in head and neck 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 head and neck cancer.

1.2. Context

Incidence of head and neck cancer

Crude incidence rate of head and neck cancer in Emilia-Romagna Region in 2004 (RER 2009) was 25.1 per 100 000 male inhabitants per year and 6.9 per 100 000 female inhabitants per year.

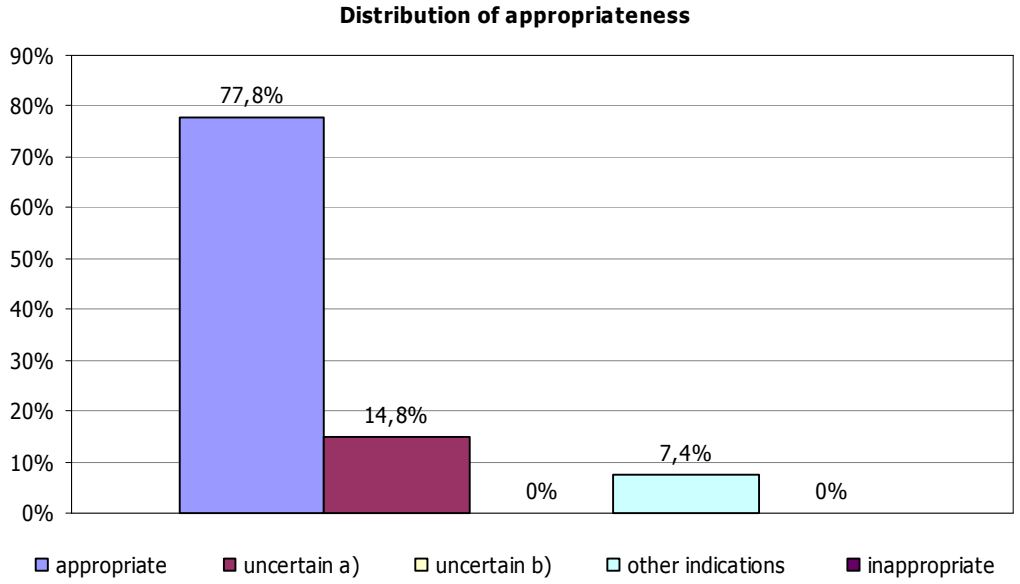
Prevalence of head and neck cancer

Cumulative 10 years prevalence estimate of head and neck cancer in Emilia-Romagna Region at 1/1/2005 (RER 2009) was 151 per 100 000 male inhabitants, corresponding to 3 047 cases in Emilia-Romagna region, and 32.5 per 100 000 female inhabitants, corresponding to 693 cases.

In the regional audit carried out in 2002, FDG-PET scans requested for patients with head and neck cancer represented 2.8% (n.13) of the total sample included, and 11 of these requests were considered uncertain, while the remaining 2 fell in the inappropriate category.

In the 2007 audit, following the criteria update in 2006, FDG-PET scans for head and neck cancer went up to 4.61% (n. 27) of the total sample and 78% of these fell in the appropriate category, 15% in the uncertain category, 7% were other clinical indications. There were no inappropriate requests (*Graph 3*).

Graph 3. Clinical audit 2006 - appropriate use of FDG-PET in head and neck cancer (27 FDG-PET scans)



2. Methods

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

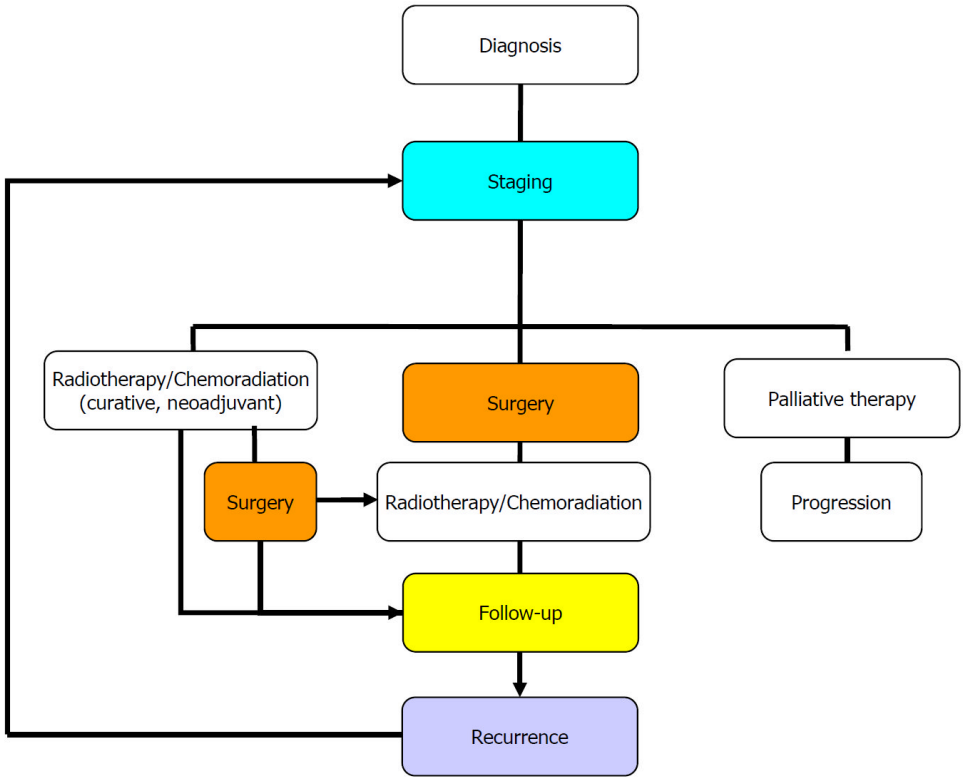
2.1. Clinical questions to be addressed

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

Table 2.1. Clinical indications selected by the panel

• Diagnosis of head and neck cancer
• Detection of unknown primary head and neck cancer in patients with metastatic cervical lymph nodes
• N staging of patients with head and neck cancer
• M staging and detection of synchronous second primary tumor in patients with locally advanced head and neck cancer
• Target volume definition of curative radiation treatment
• Evaluation of early response to neo-adjuvant/induction therapy
• Evaluation of response to chemotherapy or radiotherapy at the end of treatment
• Follow up in patients with no suspicion of recurrence
• Diagnosis and staging of suspect distant recurrence

Figure 2.1. Clinical pathway for head and neck cancer

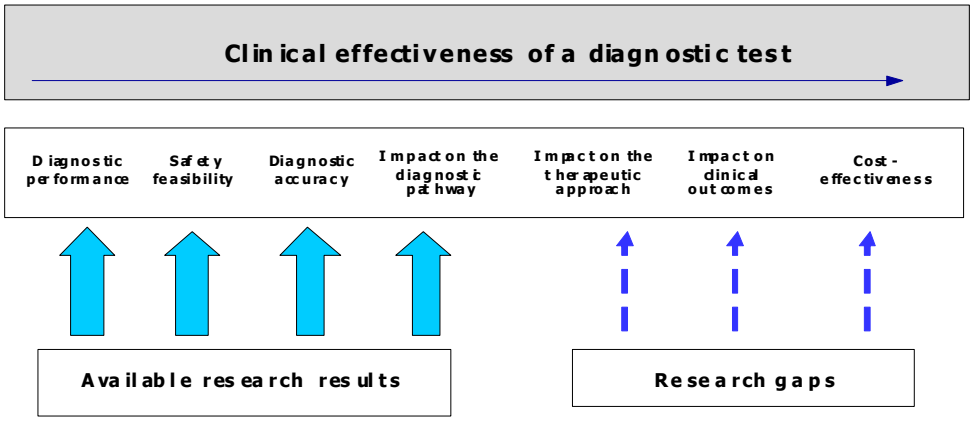


The starting point for the development of answerable "research questions", based on the PICO structure (Patient Intervention Comparator Outcome), has been the broad definition of appropriateness of a diagnostic test, which implies:

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

As for the previously published report (Liberati 2007), 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 clinical appropriateness, participants were identified as patients in one of the clinical situations selected by the panel (*Table 2.1*).

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

The intervention was either FDG-PET or CT/PET with a specific role within the diagnostic pathway and with a pre-defined position in relation to the comparator (replacement, triage, add-on) as defined by Bossuyt et al. (2006). The comparator was identified as the currently used or existing test for the diagnostic role under consideration. Diagnostic accuracy (sensitivity and specificity) of FDG-PET was identified as the outcome conveying the test's capacity to modify the initial diagnosis.

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

2.2. Systematic review of literature

Search methods for the identification of the studies

The following databases were searched for the period between January 2006 - date of the literature search for the previous update - and March 2011:

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

Language restrictions: English, Italian, French and Spanish.

Reference lists of identified articles were checked for additional references.

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

Selection criteria

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

Assessment of methodological quality of studies

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

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

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

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

Case control studies and cohort studies	criteria drawn from the New Castle-Ottawa checklist[1]
Case series	no standardized checklist has been published for the assessment of methodological quality of case series; the following two criteria have been used: prospective vs retrospective recruitment; consecutive recruitment

Data collection and analysis

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

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

Data synthesis

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

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

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

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

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

[1] http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (last access January 2012)

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 has been tested.

2.3. Level of evidence

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

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

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 head and neck cancer. Each member of the panel, except for the methodologists, voted each clinical question individually. When voting the level of appropriateness, panelists were asked to take into consideration:

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

Voting forms

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

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

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

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

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

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

Voting procedure

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

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

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

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

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

2.5. Definition of criteria of appropriateness

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

APPROPRIATE

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

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[2] http://www.rand.org/pubs/monograph_reports/MR1269.html
(last access January 2012)

UNCERTAIN

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

INAPPROPRIATE

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

or

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

INDETERMINATE

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

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

3. Systematic review of literature

3.1. Overall results

Methods and results of the systematic review of literature are reported in full in Appendix 2. The initial search identified 1 810 records; 464 were excluded because duplicates and a further 1 084 did not meet the inclusion criteria. Full text was acquired for the remaining potentially eligible 262 records, from which 140 studies were excluded on the basis of inclusion criteria while another 21 resulted already included in systematic reviews. One hundred and one studies were finally included.

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

The 101 included studies evaluated diagnostic accuracy of FDG-PET, and no studies evaluating impact on clinical outcomes were found.

Table 3.1. Number of included studies for questions and endpoints

Clinical question / Endpoint	Diagnosis	Diagnosis of unknown primary tumor	N staging	M staging and second primary cancer	TV definition for curative radiotherapy	Early response to therapy (during treatment)	Response to therapy (end of treatment)	Follow up	Diagnosis - staging of suspect of distant recurrence
Diagnostic accuracy	1 system. review 4 primary studies	2 systematic reviews 8 primary studies	2 systematic reviews 23 primary studies	2 systematic reviews 6 primary studies	1 systematic review 12 primary studies		2 systematic reviews 22 primary studies	6 primary studies	5 systematic reviews 14 primary studies
Impact on clinical outcomes	-	-	-	-	-	-	-	-	-
Results of ASSR Dossier 157/2007 (Liberati 2007)	not considered	appropriate	not considered	potentially useful (uncertain A)	appropriate	not considered	appropriate	not considered	appropriate

4. Diagnosis of head and neck cancer

Rationale

Diagnosis of head and neck cancer is placed with clinical examination, fibre optic endoscopy and fine needle aspiration or surgical biopsy of any neck mass (AIOM 2009, ESMO 2010a, SIGN 2006).

Diagnostic role of FDG-PET

Although some studies investigated the diagnostic accuracy of FDG-PET in primary head and neck, cancer diagnosis is always placed with biopsy and there is no diagnostic role of FDG-PET for this clinical indication.

Treatment effectiveness

For stage I and II head and neck cancer conservative surgery or radiotherapy give similar loco-regional control, while locally advanced stage III and IV cancers are treated with surgery and postoperative radiotherapy. Patients found at surgery to have high-risk features are also treated with post-operative chemo-radiotherapy (ESMO 2010a). Stage I nasopharyngeal cancer is treated with curative-intent radiotherapy, while advanced disease is treated with radiotherapy and concurrent chemotherapy (ESMO 2010b).

4.1. Systematic review of literature: results

Results from update of systematic review of literature from January 2006

Only studies evaluating diagnostic accuracy (1 systematic review and 4 primary studies) were found and included.

Systematic reviews

One systematic review has been retrieved (Facey 2007) on the accuracy of FDG-PET for the diagnosis of primary head and neck cancer. The methodological quality is low. Meta-analysis of data was not planned and results are provided only in narrative form (*Table 4.1*).

Table 4.1. Results from systematic reviews on diagnosis of primary head and neck cancer with FDG-PET

Reference	Facey 2007
Update to	August 2005
Number of studies	1 systematic review of 4 primary studies, 1 additional primary study
Number of patients	not reported for the systematic review; 45 patients included in the primary study
FDG-PET	sensitivity: not calculated: only descriptive results specificity: "PET was more sensitive and specific than CT/MRI for diagnosis. PET cannot currently replace these modalities because of the need for anatomical localization, but may be helpful where doubt exists"
Comparator	CT or MRI
Reference standard	not reported for the systematic review; neck dissection or biopsy of suspicious area in the additional primary study

Primary studies

One case-control study of 131 patients (Chen 2007), published after the above retrieved systematic review and evaluating accuracy of FDG-PET in the diagnosis of Waldeyer's ring (nasopharynx) cancer, reported a sensitivity of 72% and specificity of 80%.
Three more studies (Babin 2008, Gu 2010, Ma 2009) evaluated accuracy of FDG-PET in the diagnosis of mandibular bone involvement (T stage) in patients with squamous oral cancer (Babin 2008, Gu 2010) and suspected skull base invasion (T stage) in patients with nasopharyngeal carcinoma (Ma 2009). Results are reported in Table 4.2.

Table 4.2. Results from primary studies on T staging of primary cancer with FDG-PET

References	Babin 2008, Gu 2010, Ma 2009
Number of studies	3
Number of patients	86 (range 17-57)
FDG-PET/PET-CT	diagnosis of mandibular bone involvement in oral cancer (2 studies, 63 patients) sensitivity: 58.3-100% specificity: 85-97.1% diagnosis of skull base invasion in nasopharyngeal cancer (1 study, 23 patients) sensitivity: 100% specificity: 100%
Comparator	diagnosis of mandibular bone involvement in oral cancer CT (2 studies, 63 patients) sensitivity: 33-41.7% specificity: 100% MRI (1 study, 46 patients) sensitivity: 58.3% specificity: 97.1% diagnosis of skull base invasion in nasopharyngeal cancer (1 study, 23 patients) CT sensitivity: 73.7% specificity: 75% MRI sensitivity: 89.5% specificity: 75%
Reference standard	histopathology

Comments of ASSR reviewer

Only few studies dealt with the clinical question of the role of FGD-PET in the diagnosis of primary head and neck cancer. Any firm conclusion can not be drawn.

Diagnostic accuracy estimates

It is not possible to provide estimates.

LEVEL OF EVIDENCE: VERY LOW

4.2. Clinical outcomes

As the panel agreed on absence of diagnostic role of PET in diagnosis of head and neck 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 head and neck cancer as inappropriate.

FINAL RATING FOR THE USE OF FDG-PET FOR DIAGNOSIS OF HEAD AND NECK CANCER:

INAPPROPRIATE

4.4. Conclusions

Although some studies have evaluated the diagnostic accuracy of FDG-PET in the diagnosis of head and neck cancer, the panel agreed during the first round of voting to judge the use of FDG-PET in the diagnosis of head and neck as inappropriate, due to lack of diagnostic role for FDG-PET.

5. Detection of unknown primary head and neck cancer in patients with metastatic cervical lymph nodes

Rationale

Patients presenting with metastatic cervical lymph nodes undergo conventional diagnostic work up (clinical examination, fibre optic endoscopy, fine needle aspiration or surgical biopsy) and imaging tests (CT, MRI) in order to identify the unknown primary cancer (AIOM 2009, SIGN 2006).

Diagnostic role of FDG-PET

FDG-PET could be used as an add-on test in patients testing negative with conventional imaging in order to reduce the number ofpatients with undisclosed origin of disease and treat them specifically according to extension and type.

Treatment effectiveness

Indirect evidence - from studies including any site of lymph nodes metastasis of unknown primary tumor - supports the notion that the identification of the primary site improves the prognosis of patients (Dong 2008). Detected primary cancer is removed surgically and treated as advanced cancer (with radiotherapy with or without chemotherapy). Standard treatment of occult primary cancer is surgery (comprehensive neck dissection) followed by radiotherapy with or without chemotherapy, depending on the metastatic lymph nodes extension (AIOM 2009). The expected five-year risks of recurrent primary cancer and loco-regional recurrence are 5-10% and 10-20%, respectively (AIOM 2009).

Pre-test probability and change in management

The median pre-test probability of detection of unknown primary head and neck cancer in patients presenting with metastasis of neck lymph nodes is 33.3% (range 5.3-57.1%; from primary studies included in Dong 2008).

Evidence from 2 studies shows a change in management following FDG-PET exams in 23-25% of patients (Johansen 2008, Waltonen 2009).

Research question: FDG-PET as add-on test

Has FDG-PET sufficient sensitivity to be used as an add-on test to diagnose occult primary cancer in patients with negative results from conventional imaging (CT, MRI)?

5.1. Systematic review of literature: results

Results from update of systematic review of literature from Jan 2006

Only studies (2 systematic reviews and 8 primary studies) evaluating diagnostic accuracy were found and included.

Systematic reviews

Two systematic reviews have been retrieved (Facey 2007, Dong 2008) on the accuracy of FDG-PET in detecting occult primary cancer (Table 5.1). The methodological quality is low for Facey 2007 and medium for Dong 2008. Details on primary studies and meta-analysis of data were provided only by Dong (2008). The 13 primary studies included in this systematic review recruited patients presenting with cervical lymph node metastases and no detection of the presumed "occult" primary head and neck cancer according to the conventional diagnostic work up (that included CT or MRI in almost all studies, and panendoscopy in half of the studies).

Table 5.1. Results from systematic reviews on detection of occult primary cancer with FDG-PET

Reference	Facey 2007	Dong 2008
Update to	August 2005	September 2007
Number of studies	2 systematic reviews (total 9 primary studies) 2 additional primary studies	13 studies on patients with cervical lymph node metastases from occult primary head and neck cancer
Number of patients	210	300
FDG-PET/PET-CT	Only descriptive results "PET can detect occult primary tumors in patients with cervical lymph node metastases. Even in those where other imaging methods have failed, the true positive rate of PET is 30%. Tumors missed by PET in one study were smaller than 0.5 cm"	sensitivity: pooled 81% (95% CI 73-88%) heterogeneity test not reported specificity: pooled 82% (95% CI 76-87%) heterogeneity test not reported
Comparator	none	none
Reference standard	panendoscopy and biopsy or follow up	histology and/or follow up

Primary studies

Eight studies, published after the above systematic reviews, evaluating accuracy of FDG-PET in the detection of unknown primary cancer in patients with neck nodes metastasis were found (Cianchetti 2009, Ekberg 2007, Guntinas-Lichius 2006, Johansen 2008, Paul 2007, Roh 2009, Waltonen 2009, Wong 2007). Two studies (Paul 2007, Wong 2007) included only a specific subgroup of patients (palatine tonsil cancer or non squamous carcinoma) and they were excluded from the synoptic Table 5.2. Of the six remaining studies, five had an opportunistic retrospective design, i.e. they included patients that performed FDG-PET or FDG-PET/CT and some other tests (possibly CT, MRI, panendoscopy) with FDG-PET incorporated in the reference standard (probable incorporation bias). In all six studies, blind comparison between index test and reference standard was uncertain.

Table 5.2. Results from primary studies on detection of unknown primary cancer with FDG-PET

References	Cianchetti 2009, Ekberg 2007, Guntinas-Lichius 2006, Johansen 2008, Roh 2009, Waltonen 2009
Number of studies	6
Number of patients	282 (median 44, range 18-93)
FDG-PET/PET-CT	sensitivity: median 74.2% (range 21.4-87.5%) specificity: median 72.2% (range 66.7-88.8%)
Comparator	CT (3 studies, 143 patients) sensitivity: median 34% (range 21.5-72.2%) specificity: median 83.9% (range 43.7-91%) MRI (1 study, 46 patients) sensitivity: 50% specificity: 95% panendoscopy (1 study, 46 patients) sensitivity: 43% specificity: 88%
Reference standard	complete diagnostic work up, with or without histopathologic confirmation

The number of patients included in primary studies published after Dong's systematic review update (Dong 2008) is lower than the number of patients included in the meta-analysis, thus estimates for diagnostic accuracy of FDG-PET are drawn from the systematic review (*Table 5.3)* and data from primary studies are evaluated only for consistency. Estimates for diagnostic accuracy of comparators are based on data available from primary studies.

Table 5.3. Main results on diagnostic accuracy of studies on detection of unknown primary cancer with FDG-PET

Diagnostic accuracy	
Number of studies	1 systematic review including 13 primary studies (data on FDG-PET) further 3 primary studies (data on conventional imaging)
Number of patients	300 (FDG-PET), 143 (comparator)
Pre-test probability	median 33.3% (range 5.3-57.1%)
FDG-PET/PET-CT	sensitivity: pooled 81% (95% CI 73-88%) specificity: pooled 82% (95% CI 76-87%)
Comparator	CT/MRI sensitivity: range 22-50% specificity: range 72-95%
Reference standard	histology and/or follow up
References	Dong 2008, Guntinas-Lichius 2006, Roh 2009, Waltonen 2009

Comments of ASSR reviewer

The meta-analysis included studies on diagnostic accuracy of FDG-PET as add-on test, i.e. performed on patients with unknown primary cancer and inconclusive results from conventional diagnostic workup including CT or MRI. Primary studies published after show FDG-PET having a higher sensitivity but a slightly lower specificity than conventional imaging tests (CT, MRI).

Diagnostic accuracy estimates

FDG-PET sensitivity: (pooled) 81% (95% CI 73-88%)
specificity: (pooled) 82% (95% CI 76-87%)

Conventional work up (including CT and MRI)
sensitivity: (range) 22-50%
specificity: (range) 72-95%

LEVEL OF EVIDENCE: MODERATE

5.2. Clinical outcomes

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

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

Patient-important outcomes	**Median score (range)**
Consequences of test for patients with primary head and neck cancer	
• True positives - patients undergo confirmatory biopsy, primary cancer is detected and treated according to extension and type	8 (7-9)
• False negatives - primary cancer is not detected and patients are treated with a combination of more or less extended radiotherapy and surgery with or without chemo-radiotherapy	6 (2-8)
Consequences of test for patients without primary head and neck cancer	
• True negatives - patients are treated with a combination of more or less extended radiotherapy and surgery with or without chemo-radiotherapy	6 (2-8)
• False positives - patients undergo unnecessary biopsies which will prove negative and are treated with a combination of more or less extended radiotherapy and surgery with or without chemo-radiotherapy	5 (2-7)

The main benefit brought by the introduction of FDG-PET in patients testing negative with conventional imaging is finding the unknown primary tumor and clinical outcomes for true positives have been judged "critical" with a median score of 8 (range between 7 and 9). Consequences for patients testing true and false negative and false positive have all been voted "important", with wider ranges of scores. True and false negatives had a median score of 6 (range 2-8). Consequences for false positives, undergoing unnecessary biopsies, received a score of 5 (range 2-7). No studies investigating the impact of FDG-PET on the above clinical outcomes were found.

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

Table 5.5. Natural frequencies of patients tested for unknown primary head and neck cancer

		N of patients out of 100 submitted to the exam	
		According to FDG-PET	**According to conventional work up**
Patients with primary head and neck cancer	True positives	27	7-16
	False negatives	6	26-16
Patients without primary head and neck cancer	True negatives	55	48-64
	False positives	12	19-3
		100	100

5.3. Voting results

The panel agreed during the first round of voting on the judgment of appropriate with a median score of 8 (range 7-9).

FINAL RATING FOR THE USE OF FDG-PET FOR DETECTION OF PRIMARY CANCER IN PATIENTS WITH UNKNOWN PRIMARY HEAD AND NECK CANCER:

APPROPRIATE

5.4. Conclusions

During the first round of voting the panel agreed to judge appropriate the use of FDG-PET for the detection of unknown primary head and neck cancer in patients with metastatic cervical lymph nodes and testing negative with conventional imaging. Level of evidence for diagnostic accuracy of FDG-PET has been judged moderate with estimates of sensitivity considerably higher than conventional imaging, suggesting that adding FDG-PET for patients with negative or unclear results would result in a higher number of detected primary tumors. Targeted treatment of primary tumor is of great clinical relevance and consequences for patients receiving appropriate treatment have been considered "critical" (median 8; range 7-9). Patients for whom primary tumor remains undetected receive a combination of radiation therapy and surgery, possibly followed by chemotherapy, and clinical outcomes for patients testing negative (true or false negative) or testing false positive have been voted "important".

6. N staging of patients with head and neck cancer

Rationale

Accurate pre surgical N staging is necessary to correctly classify patients into early or advanced disease. Higher numbers and inferior levels of lymph nodes involved are adversely related to prognosis as is extracapsular nodal spread (microscopic or macroscopic) (SIGN 2006). Pre surgical N staging of neck nodes is made with physical examination and imaging tests (AIOM 2009, SIGN 2006). Some clinically node negative patients have a high risk of occult nodal metastases. The probability of occult nodal metastases depends mainly on the extension (T category) and the site of the primary tumor (from less than 20% in glottic laryngeal tumors to more than 50% in oropharyngeal and hypopharyngeal tumors) (AIOM 2009, SIGN 2006). CT and MRI, from skull base to sternoclavicular joints, may detect some occult nodal metastases that are missed by physical examination. CT is more accurate in detecting infrahyoid node metastasis and MRI is more accurate in detecting perivisceral nodal involvement (SIGN 2006).

Diagnostic role of FDG-PET

It is suggested that FDG-PET could represent a less invasive diagnostic test - compared to biopsy - in patients with equivocal nodal staging following conventional imaging tests (CT, MRI) in order to correctly differentiate patients with early disease from those with advanced disease and decide therapeutic approach accordingly.

Treatment effectiveness

Curative treatment strategies mainly depend on the stage of disease.

Standard options for locally advanced stage III and IV tumors are surgery (primary tumor and neck dissection) plus postoperative radiotherapy or chemo-radiotherapy (with single-agent platinum) in case of high-risk features of local recurrence (nodal extracapsular extension and/or R1 resection) (AIOM 2009, ESMO 2010a)

In early disease (stage I-II, i.e. node negative patients), either conservative surgery or radiotherapy (external radiotherapy or brachytherapy) give similar loco-regional control (AIOM 2009, ESMO 2010a). In node negative patients with a risk of micro metastases higher than 20% prophylactic treatment of the neck (either by appropriate selective or modified radical neck dissection or by external beam radiotherapy) is proposed (SIGN 2006, NCCN 2011, SEOM 2010) as data from retrospective studies suggest that in patients who do not have prophylactic therapy of the clinically node negative neck there is a higher risk of disease recurrence (SIGN 2006).

The expected local recurrence and 5-year survival rate after curative treatment in each stage class depend also on the site of cancer. The incidence of postoperative moderate to severe complications ranges between 13 and 24%; the risk of death is about 1-3% (Mendenhall 2002).

Pre-test probability and change in management

The median pre-test probability of cancer involvement of regional nodes is 53.7% (range 10.5-95%; data from primary studies: Burri 2008, Chen 2006a, Fleming 2007, Iyer 2010, Kim 2007a, Kim 2008, Krabbe 2010, Kubicek 2010, Meller 2006, Minovi 2007, Murakami 2007, Nahmias 2007, Pentenero 2008, Piao 2009, Richard 2010, Rodrigues 2009, Roh 2007a, Schroeder 2008, Veit-Haibach 2007, Yamazaki 2008, Yoon 2009, Yoshida 2009, Zytoon 2007). In the subgroup of patients with clinically node negative neck the median pre-test probability is 29.9% (range 19.9-35.3%; data from primary studies included data from primary studies: Iyer 2010, Kim 2008, Nahmias 2007, Richard 2010, Schroeder 2008).

Evidence from 4 studies (Goyal 2008, Ha 2006, Jeong 2007, Veit-Haibach 2007) on change in management following FDG-PET scan shows a median estimate of 3% (range 2-22%), with an upstaging of almost all patients leading to a new or more extensive neck surgery dissection.

Research question: FDG-PET as add-on test

Has FDG-PET sufficient accuracy to be used as an add-on test to diagnose lymph nodes metastases in patients with unclear results from conventional imaging (CT or MRI)?

6.1. Systematic review of literature: results

Results from update of systematic review of literature from January 2006

Two systematic reviews and 23 primary studies evaluating diagnostic accuracy were found and results are reported below.

Systematic reviews

Two systematic reviews have been retrieved (Facey 2007, Kyzas 2008) on the diagnostic accuracy of FDG-PET in staging cervical lymph nodes (*Table 6.1*). The methodological quality is low for Facey 2007 and high for Kyzas 2008. Meta-analysis of data was provided only by Kyzas (2008), where 10 of the studies included recruited only patients with clinically negative neck. All but five of the studies had an uncertain or absent blinding.

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

Reference	Facey 2007	Kyzas 2008
Update to	August 2005	July 2007
Number of studies	3 systematic reviews (including 11, 17, 7 primary studies respectively), 12 additional primary studies	32 studies (4 in common with Facey 2007) 10 studies including only patients with clinically negative neck
Number of patients	3 systematic reviews: 369 and 229 (1 systematic review not reported any number) additional primary studies (4 in common with Kyzas 2008): 498	1 236 (311 patients included in clinically negative neck studies)
FDG-PET/ PET-CT	only descriptive results. "Four studies in patients with clinically N0 necks showed that PET sensitivity was much lower than that of fine needle aspiration biopsy. Eight studies in populations of mixed or unspecified stage patients showed that PET or PET + CT had sensitivity of approximately 80% and specificity of 80-97%"	all patients sensitivity pooled 79% (95% CI 72-85%) heterogeneity test not reported specificity pooled 86% (95% CI 83-89%) heterogeneity test not reported clinically neck negative patients sensitivity pooled 50% (95% CI 37-63%) heterogeneity test not reported specificity pooled 87% (95% CI 76-93%) heterogeneity test not reported
Comparator	"This was comparable to or better than CT or MRI in most studies"	CT, MRI, ultrasound-guided fine-needle aspiration biopsy and conventional methods gathered all patients sensitivity pooled 75% (95% CI 65-83%) heterogeneity test not reported specificity pooled 79% (95% CI 72-85%) heterogeneity test not reported clinically neck negative patients (a comparator test performed in 204 patients) sensitivity pooled 45% (95% CI 25-67%) heterogeneity test not reported specificity pooled 87% (95% CI 72-95%) heterogeneity test not reported
Reference standard	neck dissection and histopathology; some studies also follow up	histopathology

Primary studies

Twenty-three studies, published after the above reported systematic reviews and evaluating diagnostic accuracy of FDG-PET in the N staging of patients with head and neck cancer were found (Burri 2008, Chen 2006a, Fleming 2007, Iyer 2010, Kim 2007a, Kim 2008, Krabbe 2010, Kubicek 2010, Meller 2006, Minovi 2007, Murakami 2007, Nahmias 2007, Pentenero 2008, Piao 2009, Richard 2010, Rodrigues 2009, Roh 2007a, Schroeder 2008, Veit-Haibach 2007, Yamazaki 2008, Yoon 2009, Yoshida 2009, Zytoon 2007) (*Table 6.2*). Five of them (Iyer 2010, Kim 2008, Nahmias 2007, Richard 2010, Schroeder 2008) reported separate data also for patients with clinically node negative neck.

With the exception of one study, all included patients proceeded to surgical curative or elective neck dissection (in order to perform histopathology). This kind of design leads to a serious selection bias as only patients with known lymph node involvement or at high risk of occult micro metastases were recruited. Other possible sources of bias are the retrospective design and the uncertain blind comparison between index test and reference standard in the majority of studies.

Table 6.2. Results from primary studies on N staging of patients with head and neck cancer, published after Kyzas' systematic review (2008)

References	Burri 2008, Chen 2006a, Fleming 2007, Iyer 2010, Kim 2007a, Kim 2008, Krabbe 2010, Kubicek 2010, Meller 2006, Minovi 2007, Murakami 2007, Nahmias 2007, Pentenero 2008, Piao 2009, Richard 2010, Rodrigues 2009, Roh 2007a, Schroeder 2008, Veit-Haibach 2007, Yamazaki 2008, Yoon 2009, Yoshida 2009, Zytoon 2007
Number of studies	23
Number of patients	966 (median 36, range 15-110)
FDG-PET/PET-CT	sensitivity: median 87% (range 0-100%) specificity: median 90% (range 76.7-100%)
Comparator	CT (12 studies, 440 patients) sensitivity: median 77% (range 57-100%) specificity: median 83.5% (range 50-100%) MRI (7 studies, 270 patients) sensitivity: median 77% (range 65.6-87.5%) specificity: median 90% (range 9.1-100%) US (2 studies, 103 patients) sensitivity: 78.4-95.2% specificity: 40-98.5% clinical examination (1 study, 23 patients) sensitivity: 93.3% specificity: 75%
Reference standard	histopathology after neck dissection

The number of patients included in primary studies published after Kyzas' systematic review update (Kyzas 2008) is lower than the number of patients included in the meta-analysis, thus data from primary studies are checked only for consistency. The results from Kyzas 2008 are used to provide diagnostic accuracy (*Table 6.3*).

Table 6.3. Main results on diagnostic accuracy of studies on N staging of head and neck cancer with FDG-PET

Diagnostic accuracy	
Number of studies	1 systematic review including 32 primary studies (10 studies with only patients with clinically negative neck)
Number of patients	1 236 (311 patients included in clinically negative neck studies)
Pre-test probability	non reported and not computable
FDG-PET/PET-CT	all patients sensitivity: pooled 79% (95% CI 72-85%) specificity: pooled 86% (95% CI 83-89%) clinically neck negative patients sensitivity: pooled 50% (95% CI 37-63%) specificity: pooled 87% (95% CI 76-93%)
Comparator	CT, MRI, ultrasound-guided fine-needle aspiration biopsy and conventional methods gathered all patients sensitivity: pooled 75% (95% CI 65-83%) specificity: pooled 79% (95% CI 72-85%) clinically neck negative patients (204 patients) sensitivity: pooled 45% (95% CI 25-67%) specificity: pooled 87% (95% CI 72-95%)
Reference standard	histopathology
References	Kyzas 2008

Comments of ASSR reviewer

Pooled diagnostic accuracy estimates for FDG-PET given by Kyzas 2008 show slightly lower values than those from primary studies. Conventional imaging tests (CT, MRI) overall seem to have slightly lower sensitivity and specificity than FDG-PET.

Diagnostic accuracy estimates

All patients

FDG-PET sensitivity: (pooled) 79% (95% CI 72-85%)
specificity: (pooled) 86% (95% CI 83-89%)

Conventional methods
sensitivity: (pooled) 75% (95% CI 65-83%)
specificity: (pooled) 79% (95% CI 72-85%)

Clinically neck negative patients

FDG-PET sensitivity: (pooled) 50% (95% CI 72-85%)
specificity: (pooled) 87% (95% CI 83-89%)

Conventional methods
sensitivity: (pooled) 45% (95% CI 65-83%)
specificity: (pooled) 87% (95% CI 72-85%)

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 for each outcome. Median scores and ranges are reported for each outcome.

Consequences for patients correctly upstaged, after unclear results from previous tests, have been voted "critical" and received the highest mean score of 8 (range 6-9). Clinical outcomes for patients scoring negative were also voted "critical" (median score of 8 with range between 3 and 9 for true negatives and median score of 7 with range 4-8 for false negatives). Outcomes for patients testing false positives and undergoing unnecessary biopsy were rated "critical" with a lower median score of 7 (range 4-9).

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 involvement of regional nodes	
• True positives - patients correctly upstaged to advanced disease are candidate to surgery plus postoperative radiotherapy or chemo-radiotherapy	8 (6-9)
• False negatives - patients incorrectly downstaged to early disease receive a less aggressive treatment (conservative surgery or radiotherapy) with possible negative impact on recurrence	7 (4-8)
Consequences of test for patients without involvement of regional nodes	
• True negatives - patients correctly staged for early disease can undergo either conservative surgery or radiotherapy for loco-regional control	8 (3-9)
• False positives - patients incorrectly upstaged undergo unnecessary biopsy or unnecessarily aggressive treatment, with risk of postoperative complications and no major gain in loco-regional control	7 (4-9)

Table 6.5. Natural frequencies of patients staged for neck node involvement

		N of patients out of 100 submitted to the exam	
		According to FDG-PET	**According to CT**
Patients with neck node involvement	True positives	43	40
	False negatives	11	14
Patients without neck node involvement	True negatives	40	36
	False positives	6	10
		100	100

6.3. Voting results

The panel agreed during the first round of voting on the judgment of appropriate with a median score of 7 (range 7-9).

FINAL RATING FOR THE USE OF FDG-PET FOR N STAGING OF HEAD AND NECK CANCER:

APPROPRIATE

6.4. Conclusions

Use of FDG-PET for N staging of patients with primary head and neck cancer and with unclear results with conventional imaging (CT, MRI, ultrasound) has been judged appropriate by the panel during the first round of voting. Level of evidence for diagnostic accuracy of FDG-PET has been judged moderate, with estimates for sensitivity and specificity slightly higher than those of conventional imaging. Outcomes for patients correctly upstaged (true positives) have been voted "critical" (median score of 8, range 6-9), highlighting the importance attributed to the identification of node positive patients missed by conventional imaging. Consequences for patients testing negative (true and false negatives) and for false positives have also been judged critical, though with a lower median score and much wider range of votes.

7. M staging and detection of synchronous second primary tumor in patients with locally advanced head and neck cancer

Rationale

Distant (mainly pulmonary) metastases usually occur late during the course of head and neck cancer (AIOM 2009). Due to risk factors involved in the etiology of head and neck cancer (smoking, alcohol consumption) patients are also prone to synchronous second primary malignant tumors (pulmonary or esophageal). Higher rates (15-33%) of synchronous tumors and pulmonary metastases are seen in patients with more advanced (T3/T4) primary tumors, or where there is level IV nodal involvement (SIGN 2006). M staging is made by CT of the thorax in high risk patients (SIGN 2006). For the investigation of synchronous second primary cancer esophagoscopy or bronchoscopy can be added (SIGN 2006).

In the case of nasopharyngeal cancer, skeleton is the most frequent site of metastasis and scintigraphy is added to the diagnostic work up.

M staging and research of synchronous second primary cancer have a role in identifying and selecting patients candidate to curative treatment.

Diagnostic role of FDG-PET

It is suggested that FDG-PET could help in detecting distant metastases or synchronous primary cancer in patients with equivocal or negative conventional imaging results in order to discriminate patients eligible for curative treatment from patients eligible for palliative treatment.

Treatment effectiveness

Standard options for locally advanced stage III and IV tumors are surgery plus postoperative radiotherapy. Post-operative chemo-radiotherapy is the standard for patients found at surgery to have high-risk features for local recurrence (nodal extracapsular extension and/or R1 resection). Patients with advanced larynx and hypopharynx cancer - requiring total laryngectomy - can undergo induction chemotherapy followed by radiotherapy in order to preserve the organ. Palliative treatment is the treatment of choice for patients with distant and not resectable

metastases (NCCN 2011, SEOM 2010, SIGN 2006). Palliation - with chemotherapy, radiotherapy, surgery - aims at debulking tumor mass and reducing symptoms (pain, bleeding, breathing problems) associated with tumor expansion.

Synchronous second primary cancer will be treated according to stage, with a curative intent if the first primary cancer is curable.

Pre-test probability and change in management

The median pre-test probability of occurrence of distant metastases or presence of second primary cancer is 13% (range 6.1-25%; data from studies on FDG-PET in Xu 2011).

Evidence from 8 studies on change in management following FDG-PET exams shows a median estimate of 15.1% (range 1.9-40.8%), with almost all patients being upstaged (median 12.9%, range 0-22.4%), and a change from curative to palliative intent treatment (Dietl 2006, Dietl 2008, Fleming 2007, Goyal 2008, Ha 2006, Jeong 2007, King 2008, Liu 2007a).

Research question: FDG-PET as add-on test

Has FDG-PET sufficient accuracy to be used as an add-on test in patients with advanced head and neck cancer to detect distant metastases or synchronous second primary cancer when conventional imaging tests (CT of thorax, esophagoscopy, bronchoscopy) are equivocal or negative?

7.1. Systematic review of literature: results

Results from update of systematic review of literature from January 2006

Two systematic reviews and 6 primary studies evaluating diagnostic accuracy were found. One additional primary study with historical controlled design (Rothschild 2007), evaluating the impact on clinical outcomes of the staging with FDG-PET/CT, was found but excluded because the case group received a different treatment from the historical control group (intensity-modulated radiotherapy, IMRT, vs conventional radiotherapy).

Diagnostic accuracy

Systematic reviews

Two systematic reviews have been retrieved on the diagnostic accuracy of FDG-PET in the detection of synchronous second primary cancer (Facey 2007) or in M staging and detection of synchronous second primary cancer (Xu 2011) (*Table 7.1*). The systematic review by Xu (2011) is judged of intermediate methodological quality and performed a meta-analysis of primary studies without describing the clinical characteristics of recruited patients. According to the authors virtually all primary studies included could have been

biased by incomplete verification and blinding. The systematic review by Facey (2007) is judged of low methodological quality and reported only descriptive results of the studies included (*Table 7.1*).

Table 7.1. Results from systematic reviews on M staging and/or detection of synchronous primary cancer with FDG-PET in patients with head and neck cancer

Reference	Facey 2007	Xu 2011
Update to	August 2005	September 2009
Number of studies	1 systematic review of 4 primary studies 1 additional primary study	12 studies (7 with data on FDG-PET and 7 with data on FDG-PET/CT)
Number of patients	198	1 445 (median 94.5, range 12-349); FDG-PET studies 797 patients, FDG-PET/CT studies 795 patients
FDG-PET/PET-CT	pooled sensitivity and specificity were not calculated. Only descriptive results were reported "PET could detect some, but not all synchronous primaries that other methods failed to detect"	FDG-PET sensitivity 85% (95% CI 78-90%) heterogeneity test chi square 7.12 (p = 0.417) specificity 95% (95% CI 93-97%) heterogeneity test chi square 4.46 (p = 0.725) FDG-PET/CT sensitivity 88% (95% CI 79-94%) heterogeneity test chi square 11.02 (p = 0.088) specificity 95% (95% CI 93-96%) heterogeneity test chi square 9.18 (p = 0.164)
Comparator	none	none
Reference standard	histopathology or follow up	histopathology and/or follow up of at least 6-24 months

Primary studies

Six studies (Haerle 2010, Kaida 2009, Liu 2006, Roh 2007b, Senft 2008, Wallowy 2009) evaluating diagnostic accuracy of FDG-PET in M staging of patients with head and neck cancer published after the above reported systematic reviews were included (*Table 7.2*). The studies show heterogeneity with respect to selection criteria of patients (head and neck cancer or some kind of cancer such as oral, oropharyngeal, nasopharyngeal or hypopharyngeal), type of clinical question (metastasis, second primary or both), type of metastasis (bone, intrathoracic, any kind). Almost all studies are limited by incomplete or

uncertain blinding and two of them (Roh 2007b, Wallowy 2009) are burdened by a probable selection bias (pre-selection of FDG-PET positive patients).

As results of primary studies are based on a lower number than that of patients included in systematic reviews and address heterogeneous diagnostic questions, they have been assessed only for overall consistency with results from the above reported systematic reviews. Estimates for diagnostic accuracy of FDG-PET were drawn from the pooled estimates reported in the Xu's systematic review (2011) (*Table 7.3*). Estimates for diagnostic accuracy of comparators were extracted from primary studies with available data included in the same systematic review.

Table 7.2. Results from primary studies on M staging of patients with head and neck cancer

References	Haerle 2010, Kaida 2009, Liu 2006, Roh 2007b, Senft 2008, Wallowy 2009
Number of studies	6
Number of patients	845 (median 89, range 70-311)
FDG-PET	intrathoracic metastasis (1 study, 86 patients) sensitivity: 84% specificity: 85% bone metastasis (1 study, 202 patients) sensitivity: 70% specificity: 98.8% distant metastasis (1 study, 84 patients) sensitivity: 38.5% specificity: 100% distant metastasis or second primary cancer (1 study, 92 patients) sensitivity: 58% specificity: 93% second primary (2 studies, 381 patients) sensitivity: 91.7-100% specificity: 93.8-94.8%
Comparator	intrathoracic metastasis (1 study, 86 patients) CT sensitivity: 53% specificity: 77% bone metastasis (1 study, 202 patients) scintigraphy sensitivity: 36.7% specificity: 97.7% distant metastasis or second primary cancer (1 study, 92 patients) CT sensitivity: 39% specificity: 94% second primary (1 study, 311 patients) panendoscopy sensitivity: 74% specificity: 99.7%
Reference standard	histopathology after neck dissection

Table 7.3. Main results on diagnostic accuracy of studies on M staging of head and neck cancer and detection of second primary with FDG-PET

Diagnostic accuracy	
Number of studies	12 studies (7 with data on FDG-PET and 7 with data on FDG-PET/CT)
Number of patients	1 445 (median 94.5, range 12-349) FDG-PET studies 797 patients FDG-PET/CT studies 795 patients
Pre-test probability of metastasis or second primary cancer	median 13% (range 6.1-25%)
FDG-PET/PET-CT	FDG-PET sensitivity: 85% (95% CI 78-90%); chi square 7.12 (p = 0.417) specificity: 95% (95% CI 93-97%); chi square 4.46 (p = 0.725) FDG-PET/CT sensitivity: 88% (95% CI 79-94%); chi square 11.02 (p = 0.088) specificity: 95% (95% CI 93-96%); chi square 9.18 (p = 0.164)
Comparator (our calculation)	CT or MRI (6 studies, 606 patients) sensitivity: median 70.4% (range 50-100%) specificity: median 96.1% (range 63-100%) conventional work up without CT or MRI (6 studies, 638 patients) sensitivity: median 33.1% (range 25-41%) specificity: median 94.4% (range 90.3-98.9%)
Reference standard	histopathology and or follow up of at least 6-24 months
References	Xu 2011 and primary studies included in it

Comments of ASSR reviewer

Results from the systematic review for diagnosis of distant metastasis and detection of second primary cancer show a higher sensitivity and similar specificity for FDG-PET when compared to the conventional diagnostic work up including CT or MRI. Due to possible incomplete verification and blinding all results could overestimate diagnostic accuracy.

Diagnostic accuracy estimates

FDG-PET/CT sensitivity: (pooled) 88%
specificity: (pooled) 95%

Diagnostic work up (with CT or MRI)* sensitivity: (median) 70.4%
specificity: (median) 96.1%

* data from studies evaluating PET

LEVEL OF EVIDENCE: MODERATE

7.2. Clinical outcomes

To evaluate the balance between benefits and risks, the panel agreed to consider the presumed patient-important outcomes reported below (*Table 7.4*), and voted on the level of importance for each outcome. Median scores and ranges are reported for each outcome.

All clinical outcomes have been voted "critical" by the panel receiving a median score of 8. A narrower range of voting was registered for true positive (between 7 and 8) confirming the need to "retrieve" patients with distant metastases or second primary tumor not identified by conventional imaging.

No studies were found evaluating the above clinical outcomes.

The following matrix of "natural frequencies" was provided (*Table 7.5*).

Table 7.4. Patient-important clinical outcomes and median scores of importance

Patient-important outcomes	**Median score (range)**
Consequences of test for patients with distant metastases or second primary cancer	
• True positives - patients are correctly upstaged and proceed to palliative treatment, aimed at improving quality of life	8 (7-8)
• False negatives - patients are incorrectly downstaged and do not receive palliative treatment, which might have improved quality of life	8 (5-9)
Consequences of test for patients without distant metastases or second primary cancer	
• True negatives - patients correctly proceed to curative radical treatment, aimed at improving survival	8 (3-9)
• False positives - patients are incorrectly upstaged and denied necessary radical curative treatment, which could have improved survival	8 (5-9)

Table 7.5. Natural frequencies of patients staged for distant metastases or second primary cancer

		N of patients out of 100 submitted to the exam	
		According to FDG-PET	**According to CT**
Patients with distant metastases / second primary	True positives	11	9
	False negatives	2	4
Patients without distant metastases / second primary	True negatives	83	84
	False positives	4	3
		100	100

7.3. Voting results

The panel agreed during the first round of voting on the judgment of *appropriate* with a median score of 7 (range 7-9).

FINAL RATING FOR THE USE OF FDG-PET FOR M STAGING AND DETECTION OF SECOND PRIMARY TUMOR IN HEAD AND NECK ADVANCED CANCER:

APPROPRIATE

7.4. Conclusions

At the first voting round the panel agreed to judge appropriate the use of FDG-PET for M staging of advanced head and neck cancer in patients with negative or equivocal results from conventional imaging. Level of evidence for diagnostic accuracy of FDG-PET was judged moderate with estimates for sensitivity higher than conventional imaging. All clinical outcomes were considered "critical" (median score 8), with a closer range (between 7 and 8) for patients correctly upstaged, highlighting the added value of FDG-PET in identifying patients with distant metastases or second primary tumors missed by conventional imaging.

8. Target volume definition of curative radiation treatment

Rationale

Radiotherapy has several indications in the treatment of head and neck cancer, including curative intent radical radiotherapy in early disease. Adjuvant radiotherapy can improve local control following surgery in locally advanced disease. Moreover patients with advanced larynx and hypopharynx cancer - requiring total laryngectomy - can undergo induction chemotherapy followed by radiotherapy or concomitant chemo-radiotherapy in order to preserve the organ (AIOM 2009, ESMO 2010a). Finally radiation treatment is an essential component of curative-intent treatment of non-disseminated nasopharyngeal cancer. Stage I disease is treated by radiation treatment alone, while stage III, IVA, B diseases are treated with radiation treatment and concurrent chemotherapy.

Diagnostic role of FDG-PET

A more precise diagnostic tool allowing a better definition of field could reduce adverse effects of radiation treatment or allow higher and safe dose delivery.

Treatment effectiveness

In early disease radical radiotherapy is reported to have similar effectiveness to radical surgery (AIOM 2009, ESMO 2010a, NCCN 2011).

Patients with advanced larynx and hypopharynx cancer - requiring total laryngectomy - can undergo induction chemotherapy followed by radiotherapy in order to preserve the organ (AIOM 2009, ESMO 2010a).

Research question: FDG-PET as replacement test

Does FDG-PET imaging lead to a better target volume definition of curative RT in patients with head and neck cancer than CT?

8.1. Systematic review of literature: results

Results from update of systematic review of literature from January 2006

One systematic review and 12 primary studies on target volume definition were found.

Systematic reviews

One systematic review assessing the role of FDG-PET in tumor volume definition for radiation treatment planning in head and neck cancer was included (Facey 2007). Methodological quality was judged low (*Table 8.1*).

Table 8.1. Results of systematic review on the role of FDG-PET in tumor volume definition in head and neck cancer

Reference	Facey 2007
Update to	August 2005
Number of studies	6
Number of patients	135
Results	only descriptive results "… change in GTV or dose or the number of irradiated nodes in several patients, compared with CT"
Reference standard	none

GTV = gross target volume

Primary studies

Twelve studies (Ashamalla 2007, Deantonio 2008, Dirix 2009, El Bassiouni 2007, Geets 2006, Geets 2007, Guido 2009, Schinagl 2007, Schinagl 2009, Seitz 2009, Wang 2006, Zheng 2007), not included in the systematic review by Facey 2007, were found. Nine studies included any type of head and neck cancer patients and three studies included only patients with pharyngolaryngeal cancer (Geets 2007) or oropharyngeal cancer (Seitz 2009) or nasopharyngeal cancer (Zheng 2007). Ten studies compared target volume defined with CT with that defined with FDG-PET (4 studies) or FDG-PET/CT (6 studies) for radiotherapy planning of the primary tumor. One study (Seitz 2009) compared the target volume definition of FDG-PET/CT and MRI with that obtained from the pathologic specimen. Another study (Schinagl 2009) considered the performance in identifying metastatic lymph nodes for radiotherapy planning.

Studies adopted different measures for the target volume definition: 9 studies used the mean difference of GTV between FDG-PET and CT (*Table 8.2*), 5 studies used the percentage of patients with increase/decrease of GTV with FDG-PET compared to CT (*Table 8.3*), 1 study the mean difference of GTV between FDG-PET/CT, MRI and

pathologic specimen (*Table 8.4*), 3 studies reported the mean difference of planned target volume (PTV) between FDG-PET and CT (*Table 8.5*), 1 study reported the difference of V50 and V95 between FDG-PET and CT (*Table 8.6*), 1 study used the difference of detected lymph nodes between FDG-PET and CT (*Table 8.7*).

All studies, with the exception of one (Seitz 2009), had no verification tests and 6 had uncertain or no blinding of imaging lecture.

Table 8.2. Primary studies on the role of FDG-PET in GTV definition in head and neck cancer reporting mean reduction

Reference	Deantonio 2008, Dirix 2009, El Bassiouni 2007, Geets 2006, Geets 2007, Guido 2009, Schinagl 2007, Wang 2006, Zheng 2007
Number of studies	9
Number of patients	261; median 22 (range 10-78)
Mean reduction of GTV	FDG-PET compared to CT: median 6.42 cm^3 (range 1.2-33.6)
Reference standard	none

GTV = gross target volume

Table 8.3. Primary studies on the role of FDG-PET in GTV in head and neck cancer reporting % of change

Reference	Ashamalla 2007, El Bassiouni 2007, Guido 2009, Schinagl 2007, Wang 2006, Zheng 2007
Number of studies	5
Number of patients	143; median 25 (range 13-39)
Percentage of patients with GTV modified	reduction with FDG-PET compared to CT: median 69% (range 44-92%) increase with FDG-PET compared to CT: median 28% (range 0-31%)
Reference standard	none

GTV = gross target volume

Table 8.4. Primary studies on the role of FDG-PET in GTV in head and neck cancer reporting mean difference from pathologic specimen

Reference	Seitz 2009
Number of studies	1
Number of patients	55
Mean reduction of GTV	FDG-PET compared to pathologic specimen: mean reduction of 2 ± 0.5 cm^3 MRI compared to pathologic specimen: mean reduction of 1 ± 0.5 cm^3
Reference standard	none

GTV = gross target volume

Table 8.5. Primary studies on the role of FDG-PET in PTV definition in head and neck cancer

Reference	El Bassiouni 2007, Geets 2006, Geets 2007
Number of studies	3
Number of patients	53; median 18 (range 10-25)
Mean reduction of PTV	FDG-PET compared to CT: median 40.8 cm^3 (range 38.1-56.1)
Reference standard	none

PTV = planned target volume

Table 8.6. Primary studies on the role of FDG-PET in fraction of volume definition in head and neck cancer

Reference	Geets 2006
Number of studies	1
Number of patients	18
Difference of V50	CT 100% vs FDG-PET 87% p = 0.005
Difference of V95	CT 100% vs FDG-PET 82% p = 0.001
Reference standard	none

V50 = fraction of volume receiving a dose higher than 50% of the isocenter dose
V95 = fraction of volume receiving a dose higher than 95% of the isocenter dose

Table 8.7. Primary studies on the role of FDG-PET in detection of enlarged nodes in head and neck cancer

Reference	Schinagl 2009
Number of studies	1
Number of patients	78
Results	FDG-PET (with different detecting method) identified 40-75% of enlarged nodes identified by CT FDG-PET (with different detecting method) identified 7-50% of "marginally enlarged" nodes identified by CT
Reference standard	none

Comments of ASSR reviewer

There seems to be consistent evidence of discordant GTV definition between FDG-PET and CT. Consistently FDG-PET leads to a reduction of GTV in 2/3 of patients and to an increase of GTV in the remaining 1/3. Data from one study suggest that FDG-PET could detect less metastatic lymph nodes compared to CT, and another study disclosed a mean reduction of GTV with FDG-PET (larger than that with MRI) compared to pathologic specimen. There are no data providing evidence that FDG-PET-based changes in target volume represent better pathological tumor coverage than CT-based volume delineation.

Diagnostic accuracy estimates

It was not possible to provide estimates.

LEVEL OF EVIDENCE: VERY LOW

8.2. Clinical outcomes

To evaluate the balance between benefits and risks, the panel agreed to consider the presumed patient-important outcomes reported below (*Table 8.8*), and voted on the level of importance for each outcome. Median scores and ranges are reported for each outcome.

All patient important outcomes have been voted "critical" with a median score of 7, but with a wide range of votes from "non important" to "critical".

Table 8.8. Patient-important clinical outcomes and median scores of importance

Patient-important outcomes	Median score (range)
Consequences of test for patients with large target volume	
• True increase of target volume - patients correctly receive irradiation on an increased target volume with benefit on their survival / local control	7 (3-8)
• False reductions of target volume - patients incorrectly irradiated on a reduced target volume, which might not improve local control and survival	7 (2-8)
Consequences of test for patients with small target volume	
• True reductions of target volume - patients correctly irradiated on a reduced target volume, suffer less adverse effects and obtain benefit on survival / local control	7 (2-8)
• False increase of target volume- patients incorrectly receive irradiation on an increased target volume and suffer unnecessary adverse effects	7 (2-8)

8.3. Voting results

Both voting rounds registered a disagreement with a median score of 3 (range 2-4) in the first round and a median score of 3 (range 2-4) in the second round.

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

UNCERTAIN

8.4. Conclusions

In neither voting rounds the panel reached an agreement on the appropriateness with votes (median score 3) falling between the inappropriate and uncertain regions. The use of FDG-PET in target volume definition of curative radiation treatment in replacement of CT resulted therefore uncertain due to disagreement.

There is consistent evidence of discordant radiation field definition between FDG-PET and CT. The level of evidence was judged to be very low and FDG-PET was not proven to provide a better pathological tumor coverage than CT. Nevertheless the discussion among panel members did not solve disagreement, that probably origins from the relevance of curative radiation treatment of head and neck cancer. In fact all clinical outcomes were considered "critical" (median score 7).

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

9. Evaluation of early response to neo-adjuvant/induction therapy

9.1. Conclusions

The literature search resulted in no studies nor clinical practice guidelines addressing a possible diagnostic role of FDG-PET in the evaluation of early response to treatment of head and neck cancer. However the panel expressed the need, in clinical practice, for an adequate test evaluating early response to radical curative radiation treatment of early cancer. Since in early disease (stage I-II, i.e. node negative patients), either conservative surgery or radiotherapy (external radiotherapy or brachytherapy) give similar loco-regional control, an accurate test could identify patients who do not respond to radiation treatment and would benefit from a change of therapy and switch to radical surgery.

The panel unanimously agreed in classifying this clinical question as indeterminate, for lack of studies, and in proposing it as a future clinical research question.

10. Evaluation of response to regimens of chemotherapy or radiotherapy at the end of treatment

Rationale

Patients potentially benefiting from evaluation of treatment response are those with locally advanced disease (stage III and IV), curable with different regimens of chemotherapy, radiotherapy or concomitant chemo-radiotherapy and possibly surgery.

Response to chemotherapy, radiotherapy or concomitant chemo-radiotherapy are evaluated with CT, MRI, US and fine-needle biopsy of primary tumor and neck nodes (NCCN 2011, SIGN 2006). In case of non response of the primary tumor a salvage surgery can be performed. If response of neck nodes is detected, node dissection can be spared or limited.

Diagnostic role of FDG-PET

It is suggested that FDG-PET could represent a diagnostic test to evaluate the response to chemotherapy, radiotherapy or concomitant chemo-radiotherapy in case of equivocal results from conventional imaging tests (CT, MRI, US and fine-needle biopsy) in order to discriminate patients candidate to further aggressive treatment (salvage surgery) from those eligible for follow up.

Treatment effectiveness

Five-year survival rate following salvage surgery in patients which do not respond to radiation treatment - with laryngeal, pharyngeal and oral cavity tumors - is 39% (Goodwin 2000). Site-specific five-year survival is 43.4% (oral cavity), 26% (pharynx), and 47.5% (larynx). Following salvage surgery for head and neck cancer, the total complication rate varies from 39% to 53% (Agra 2003, Goodwin 2000). Significant complications have been reported in 18.5-27% of patients undergoing salvage surgery, with an operative mortality rate of 3.2-5.2% (Agra 2003).

In patients with N2 or N3 disease without a complete clinical response to chemo-radiotherapy, neck dissection improves loco-regional control, neck progression-free survival and overall survival compared to observation only (Argiris 2004, Clayman 2005).

Pre-test probability and change in management

The median pre-test probability of residual disease after treatment is 18.4% (range 3.8-57.1%) for primary site (Chan 2006, Chen 2006b, Fakhry 2006, Moeller 2009, Oe 2007, Wang 2009, Yao 2009) and 12.2% (range 4.6-91.7%) for node site (Chan 2006, Chen 2006b, Fakhry 2006, Gourin 2009b, Inohara 2009, Lyford-Pike 2009, Moeller 2009, Nayak 2007, Ong 2008, Rabalais 2009, Wang 2009, Yao 2009).

Four studies (Connell 2007, Nayak 2007, Shintani 2008, Zheng 2006), reporting data on change in management, disclosed a wide range of change - from 12% to 86% - with patients avoiding either neck dissection for absence of neck recurrence or salvage therapy for diffuse disease.

Research question: FDG-PET as add-on test

Has FDG-PET sufficient accuracy to evaluate end of treatment response to chemotherapy, radiotherapy or concomitant chemo-radiotherapy in patients with equivocal results from conventional imaging?

10.1. Systematic review of literature: results

Results from update of systematic review of literature from January 2006

Three systematic reviews and 22 following primary studies evaluating diagnostic accuracy were found.

Systematic reviews

Three systematic reviews have been retrieved (Facey 2007, Isles 2008, Liu 2007b). Estimates of FDG-PET sensitivity and specificity from Facey 2007 and Liu 2007b could not be used as they did not differentiate patients tested for residual disease from those tested for recurrence. In Isles 2008 results of each included study are reported allowing to extract results from studies evaluating residual disease after up to 6 months from treatment. They have been included among the primary studies (*Table 10.1*).

Primary studies

Twenty-one studies were found (Andrade 2006, Chan 2006, Chen 2006b, Fakhry 2006, Gourin 2009b, Hoshikawa 2009, Inohara 2009, Inohara 2010, Ito 2010, Lyford-Pike 2009, Malone 2009, Martin 2009, Moeller 2009, Nayak 2007, Oe 2007, Ong 2008, Passero 2010, Rabalais 2009, Wang 2009, Yao 2009, Zytoon 2007), published after the above reported systematic reviews, on diagnostic accuracy of FDG-PET in the evaluation of patients' response to regimens of chemotherapy or radiotherapy at the end of treatment. Twelve more studies from the Isles' systematic review (Brkovich 2006, Goerres 2004, Greven 1994, Hanasono 1999, Horiuchi 2008, Kim 2007b, Kitagawa 2003, McCollum

2004, Rogers 2004, Tan 2007, Yao 2005, Yao 2007) dealing with the same clinical question were also included. The majority of studies included patients with any type of advanced head and neck cancer undergoing FDG-PET in the first 6 months after radiotherapy or chemo-radiotherapy. Almost all studies are limited by incomplete or uncertain blinding and by an uncertain or not consecutive recruitment of patients.

Estimates of all primary studies have been pooled and heterogeneity of diagnostic estimates of FDG-PET tested (*Table 10.2*).

Table 10.1. Results from primary studies on evaluation of response to regimens of chemotherapy or radiotherapy at the end of treatment

References	Andrade 2006, Brkovich 2006, Chan 2006, Chen 2006b, Fakhry 2006, Goerres 2004, Gourin 2009b, Greven 1994, Hanasono 1999, Horiuchi 2008, Hoshikawa 2009, Inohara 2009, Inohara 2010, Ito 2010, Kim 2007b, Kitagawa 2003, Lyford-Pike 2009, Malone 2009, Martin 2009, McCollum 2004, Moeller 2009, Nayak 2007, Oe 2007, Ong 2008, Passero 2010, Rabalais 2009, Rogers 2004, Tan 2007, Wang 2009, Yao 2005, Yao 2007, Yao 2009, Zytoon 2007
Number of studies	31
Number of patients	1 623 (median 32, range 12-188)
FDG-PET/PET-CT	primary site residual disease (18 studies, 985 patients) sensitivity: median 84.5% (range 50-100%) specificity: median 90.2% (range 54-100%) node residual disease (22 studies, 1 211 patients) sensitivity: median 85.7% (range 25-100%) specificity: median 88.9% (range 36.4-100%) residual disease at any site (3 studies, 246 patients) sensitivity: median 88.9% (range 88.2-93.8%) specificity: median 78% (range 69.4-96.6%)
Comparator	any comparator (CT, MRI, conventional work up) primary site residual disease (7 studies, 427 patients) sensitivity: median 80% (range 50-100%) specificity: median 89.3% (range 46.7-92.1%) any comparator (CT, MRI, conventional work up) node residual disease (8 studies, 412 patients) sensitivity: median 85.4% (range 50-100%) specificity: median 72.1% (range 46.7-93.6%) any comparator (CT, MRI, conventional work up) residual disease at any site (1 study, 131 patients) sensitivity: 50% specificity: 94.4%
Reference standard	histopathology or follow up or both

Table 10.2. Main results on diagnostic accuracy of studies on evaluation of response to regimens of chemotherapy or radiotherapy at the end of treatment

Diagnostic accuracy		
Number of studies	primary site residual disease: node residual disease: residual disease at any site:	18 studies 22 studies 3 studies
Number of patients	primary site residual disease: node residual disease: residual disease at any site:	985 (median 31; range 18-188) 1 211 (median 43.5; range 12-188) 246 (median 61; range 54-131)
Pre-test probability	primary site residual disease: node residual disease: residual disease at any site:	median 11.2% (range 3.8-57.1%) median 12% (range 4.6-37.8%) median 17.3% (4.1-30.5%)
FDG-PET/PET-CT	primary site residual disease sensitivity: median 84.5% (range 50-100%) heterogeneity chi-squared p = 0,186 specificity: range 54-100% heterogeneity chi-squared p = 0,000 node residual disease sensitivity: range 25-100% heterogeneity chi-squared p = 0,006 specificity: range 36.4-100% heterogeneity chi-squared p = 0,000 residual disease at any site (3 studies, 246 patients) sensitivity: median 88.9% (range 88.2-93.8%) heterogeneity chi-squared (only 2 studies available for test) p = 0,614 specificity: range 69.4-96.6% heterogeneity chi-squared (only 2 studies available for test) p = 0,000	
Comparator	CT or MRI (7 studies, 427 patients) primary site residual disease sensitivity: median 80% (range 50-100%) heterogeneity chi-squared p = 0,326 specificity: range 46.7-92.1% heterogeneity chi-squared p = 0,001 CT or MRI (8 studies, 412 patients) node residual disease sensitivity: median 84.5% (range 50-100%) heterogeneity chi-squared p = 0,159 specificity: range 46.7-93.6% heterogeneity chi-squared p = 0,000 any comparator (CT, MRI, conventional work up) residual disease at any site (1 study, 131 patients) sensitivity: 50% specificity: 94.4%	

(continues)

Reference standard	histopathology or follow up or both
References	Andrade 2006, Brkovich 2006, Chan 2006, Chen 2006b, Fakhry 2006, Goerres 2004, Gourin 2009b, Greven 1994, Hanasono 1999, Horiuchi 2008, Hoshikawa 2009, Inohara 2009, Inohara 2010, Ito 2010, Kim 2007b, Kitagawa 2003, Lyford-Pike 2009, Malone 2009, Martin 2009, McCollum 2004, Moeller 2009, Nayak 2007, Oe 2007, Ong 2008, Passero 2010, Rabalais 2009, Rogers 2004, Tan 2007, Wang 2009, Yao 2005, Yao 2007, Yao 2009, Zytoon 2007

Comments of ASSR reviewer

A large number of patients have been studied in the evaluation of response after treatment both in primary site and neck nodes. Heterogeneity in the estimates of sensitivity and specificity was found, except for sensitivity on primary site residual disease and residual disease at any site.

Diagnostic accuracy estimates

Primary site residual disease

FDG-PET sensitivity: (median) 84.5% (range 50-100%)
specificity: (heterogeneous) range 54-100%

comparator (CT or MRI)
sensitivity: median 80% (range 50-100%)
specificity: (heterogeneous) range 46.7-92.1%

Node residual disease

FDG-PET sensitivity: (heterogeneous) range 25-100%
specificity: (heterogeneous) range 36.4-100%

comparator (CT or MRI)
sensitivity: (median) 84.5% (range 50-100%)
specificity: (heterogeneous) range 46.7-93.6%

Residual disease at any site

FDG-PET sensitivity: median 88.9% (range 88.2-93.8%)
specificity: (heterogeneous) range 69.4-96.6%

comparator (CT or MRI)
sensitivity: 50%
specificity: 94.4%

LEVEL OF EVIDENCE: LOW

Diagnostic accuracy of FDG-PET performed up to the third month after the end of treatment

During the first meeting the panel discussed the best timing of FDG-PET scan for detection of residual disease avoiding misinterpretation of inflammatory reaction often caused by treatment. Thus it was decided to investigate diagnostic accuracy of FDG-PET exam performed within 3 months after the end of treatment.

Six primary studies published after Isles' systematic review (Fakhry 2006, Inohara 2010, Malone 2009, Martin 2009, Moeller 2009, Oe 2007) and seven more studies extracted from the same systematic review (Goerres 2004, Greven 1994, Hanasono 1999, Horiuchi 2008, Kim 2007b, Kitagawa 2003, McCollum 2004) evaluated the diagnostic accuracy of FDG-PET - performed within 3 months after the end of treatment - in order to assess patients' response to regimens of chemotherapy or radiotherapy.

Table 10.3. Main results on diagnostic accuracy of studies evaluating response to chemotherapy or radiotherapy at the end of treatment within 3 months

Diagnostic accuracy	
Number of studies	13 studies (residual disease in primary site)
Number of patients	574 (median 31; range 22-98)
Pre-test probability	median 19.4% (range 11.2-57.1%)
FDG-PET/PET-CT	sensitivity: median 83% (range 50-100%) heterogeneity chi-squared p = 0,402 specificity: range 54-100% heterogeneity chi-squared p = 0,017
Comparator	CT or MRI (3 studies, 237 patients) sensitivity: range 60-80% heterogeneity not computable specificity: range 66-92.1% heterogeneity not computable
Reference standard	histopathology or follow up or both
References	Fakhry 2006, Goerres 2004, Greven 1994, Hanasono 1999, Horiuchi 2008, Inohara 2010, Kim 2007b, Kitagawa 2003, Malone 2009, Martin 2009, McCollum 2004, Moeller 2009, Oe 2007

Diagnostic accuracy estimates

Residual disease in primary site within 3 months after the end of treatment

FDG-PET sensitivity: (median) 83% (range 50-100%)
specificity: (heterogeneous) range 54-100%

comparator (CT or MRI) sensitivity: (heterogeneity not computable) range 60-80%
specificity: (heterogeneity not computable) range 66-92.1%

LEVEL OF EVIDENCE: 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 10.4*), and voted on the level of importance for each outcome. Median scores and ranges are reported for each outcome.

All patient clinical outcomes have been judged "critical". Consequences for patients with residual disease received the highest median score of 8, with votes ranging just from 6 to 8, whether they are correctly diagnosed, receiving appropriate treatment, or incorrectly diagnosed and denied appropriate treatment. Outcomes for patients without residual disease had a median score of 7, with a wider range of votes (from 3 to 8).

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

The following matrix of "natural frequencies" was provided for patients with residual disease at primary site (*Table 10.5*)

Table 10.4. Patient-important clinical outcomes and median scores of importance

Patient-important outcomes	Median score (range)
Consequences of test for patients with residual disease	
• True positives - patients with residual disease after initial treatment proceed to confirmatory biopsy and further more aggressive therapeutic regimes, which might improve local control	8 (6-8)
• False negatives - patients with residual disease after initial treatment do not receive further more aggressive therapy which could have improved local control	8 (7-8)
Consequences of test for patients without residual disease	
• True negatives - patients without residual disease after initial treatment proceed to follow up	7 (3-8)
• False positives - patients without residual disease at initial treatment undergo unnecessary biopsies which entail serious risks.	7 (3-8)

Table 10.5. Natural frequencies of patients evaluated for primary site residual disease

		N of patients out of 100 submitted to the exam	
		According to FDG-PET	**According to conventional work up**
Patients with residual disease	True positives	15	14
	False negatives	3	4
Patients without residual disease	True negatives	44-82	39-76
	False positives	38-0	43-6
		100	100

10.3. Voting results

Both voting rounds registered a disagreement with a median score of 6 (range 3-8) in the first round and a median score of 5 (range 3-7) in the second round.

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

UNCERTAIN

10.4. Conclusions

In neither of voting rounds the panel reached an agreement on the appropriateness with votes falling in all regions of appropriateness, uncertainty and inappropriateness (first round median score 6, second round median score 5). The use of FDG-PET to evaluate end of treatment response to chemotherapy or radiotherapy, as add-on test in patients with equivocal results from conventional imaging (CT, MR), in order to proceed to confirmatory biopsy and salvage surgery, resulted therefore uncertain due to disagreement.

The level of evidence was judged low, due to heterogeneity of specificity estimates. After discussion the panel agreed to analyze data of the subgroup of patients undergoing FDG-PET within the first 3 months after the end of treatment. However the accuracy estimates and level of evidence did not change in this subgroup.

Clinical outcomes were voted critical in all cases, however outcomes concerning patients with residual disease at the end of treatment - true positive and false negative - had a higher score (median of 8), highlighting the importance of appropriate use of salvage effective treatment.

11. Follow up in patients with no suspicion of recurrence

Rationale

Seventy-six percent of recurrences for head and neck occur within the first two years after treatment with curative intent, and 11% occur in the third year (SIGN 2006). Thirty-nine percent of patients with recurrence have no symptoms (Boysen 1992).

Guidelines recommend regular active follow up, with physical exam, at least in the first three (SIGN 2006) or five years (NCCN 2011). In selected cases CT or MRI could be required. The aim of follow up is the early detection of potentially curable loco-regional recurrence and second primary tumors.

Diagnostic role of FDG-PET

To anticipate detection of recurrence or second primary tumors in patients treated for head and neck cancer in order to start appropriate therapy earlier.

Treatment effectiveness

There is no consistent evidence that surveillance with imaging alters outcome following treatment for head and neck cancer (SIGN 2006), however the risk of recurrence after treatment with curative intent is very high in the first three years.

Pre-test probability and change in management

The median pre-test probability of any kind of recurrence is 33% (range 30-37.5%; Abgral 2009, Kao 2009, Krabbe 2009) in the first 12-24 months after a curative treatment.

Change in management estimates following the application of FDG-PET (Kao 2009, Krabbe 2009, Perie 2007) range between 10 and 19%. Curative salvage treatment was the specified change in one study (Krabbe 2009).

Research question: FDG-PET as replacement test

Has FDG-PET higher diagnostic accuracy than the available comparator (physical exam, with CT or MRI) in detecting recurrence during follow up of patients with no suspicion of recurrence of head and neck cancer?

11.1. Systematic review of literature: results

Results from update of systematic review of literature from January 2006

Only 4 primary studies, evaluating diagnostic accuracy, and no systematic reviews were found.

Primary studies

Four studies (Abgral 2009, Kao 2009, Krabbe 2009, Lee 2007) were included; 3 studies applied FDG-PET and 1 FDG-PET/CT. Patients included had a primary head and neck cancer (any kind of cancer in 3 studies, oral or oropharyngeal in 1 study; any stage in 2 studies, II-IV stage only in 2 studies) and had been treated with any kind of curative therapy. FDG-PET evaluation was performed once during follow up (at the 12th month in 1 study, at any time in 1 study but with majority of patients after 6 months) or according to a scheduled program (every 3 months until the 12th month in 1 study, every 4-6 months until the 24th month in 1 study). All studies used biopsy of the suspected recurrence and clinical follow up (6 months after the last FDG-PET exam) as reference standard. FDG-PET was performed to detect any recurrence (3 studies, *Table 11.1*), loco-regional recurrence (2 studies, *Table 11.2*), local recurrence (1 study, *Table 11.3*), neck recurrence (1 study, *Table 11.4*), distant metastasis or second primary cancer (2 studies, *Table 11.5*). The studies were limited by absence of appropriate comparator, retrospective design or not consecutive recruitment of patients, possible verification bias, absence of or uncertain blinding during tests evaluation.

Primary studies had different diagnostic questions (any recurrence, loco-regional recurrence, local recurrence, neck recurrence, metastasis or second primary tumor). For the purpose of this dossier, diagnostic accuracy of the most consistent and representative diagnostic question - any recurrence - was chosen. In Table 11.6 estimates and heterogeneity of results are reported.

Table 11.1. Results of primary studies on diagnostic accuracy of follow up with FDG-PET in the detection of any kind of recurrence

References	Abgral 2009, Kao 2009, Krabbe 2009
Number of studies	3
Number of patients	219; median 80 (range 48-91)
FDG-PET/PET-CT	sensitivity: median 100% (range 92-100%) specificity: median 78% (range 43.3-85.2%)
Comparator	physical examination (1 study, 48 patients) sensitivity: 0% specificity: 60%
Reference standard	biopsy of the suspected lesion or clinical follow up

Table 11.2. Results of primary studies on diagnostic accuracy of follow up with FDG-PET in the detection of loco-regional recurrence

References	Kao 2009, Lee 2007
Number of studies	2
Number of patients	236; range 80-156
FDG-PET/ PET-CT	sensitivity: median 91.2% (range 90.3-92%) specificity: median 86.6% (range 82-91.2%)
Comparator	none
Reference standard	biopsy of the suspected lesion or clinical follow up

Table 11.3. Results of primary studies on diagnostic accuracy of follow up with FDG-PET in the detection of local recurrence

References	Kao 2009
Number of studies	1
Number of patients	80
FDG-PET/ PET-CT	sensitivity: 88% specificity: 88%
Comparator	none
Reference standard	biopsy of the suspected lesion or clinical follow up

Table 11.4. Results of primary studies on diagnostic accuracy of follow up with FDG-PET in the detection of neck recurrence

References	Kao 2009
Number of studies	1
Number of patients	80
FDG-PET/ PET-CT	sensitivity: 100% specificity: range 91%
Comparator	none
Reference standard	biopsy of the suspected lesion or clinical follow up

Table 11.5. Results of primary studies on diagnostic accuracy of follow up with FDG-PET in the detection of distant metastasis or second primary tumor

References	Kao 2009, Lee 2007
Number of studies	2
Number of patients	236; range 80-156
FDG-PET/ PET-CT	sensitivity: range 93-100% specificity: range 96-96.6%
Comparator	none
Reference standard	biopsy of the suspected lesion or clinical follow up

Table 11.6. Diagnostic accuracy of follow up with FDG-PET in the detection of any kind of recurrence

Diagnostic accuracy	
Number of studies	3
Number of patients	219; median 80 (range 48-91)
Pre-test probability	median 33% (range 30-37.5%)
FDG-PET/PET-CT	sensitivity: median 100% (range 92-100%) heterogeneity chi-squared = 4.51 (d.f. = 2) p = 0,105 inconsistency (I-square) = 55.7% specificity: median 78% (range 43.3-85.2%) heterogeneity chi-squared = 17.72 (d.f. = 2) p = 0,000 inconsistency (I-square) = 88.7%
Comparator	none
Reference standard	biopsy of the suspected lesion or clinical follow up
References	Abgral 2009, Kao 2009, Krabbe 2009

Comments of ASSR reviewer

A sufficiently broad spectrum of patients in terms of type of cancer, stage and treatment was represented in studies evaluating diagnostic accuracy of FDG-PET performed during follow up in absence of suspicion of recurrence. Studies included report a high sensitivity but a heterogeneous specificity - possibly due to the differences in terms of follow up programs (opportunistic, one-exam-only, more than 1 exam in the first 12-24 months after treatment) - and the level of evidence is low. Another important limitation is the absence of data on a fair comparator for the follow up with FDG-PET.

Diagnostic accuracy estimates

FDG-PET sensitivity: median 100%
specificity: range 43.3-85.2%

Comparator: no estimate available

LEVEL OF EVIDENCE: 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 11.7*), and voted on the level of importance for each outcome. Median scores and ranges are reported for each outcome.

All patient important outcomes were voted important with a median score of just 4 with votes ranging from 3 to 8/7. No studies investigating the impact of FDG-PET on the above clinical outcomes were found.

The matrix of "natural frequencies" was not possible for the absence of data on comparator.

Table 11.7. Patient-important clinical outcomes and median scores of importance

Patient-important outcomes	Median score (range)
Consequences of test for patients with any recurrence	
• True positives - patients undergo biopsy to confirm positive results and proceed to possible salvage treatment	4 (3-8)
• False negatives - patients remain in follow up until symptoms/suspicion of recurrence occur, and delay a possible salvage treatment	4 (3-8)
Consequences of test for patients without recurrence	
• True negatives - patients remain in follow up and are reassured	4 (3-7)
• False positives - patients undergo unnecessary biopsy to prove negative and are exposed to additional unnecessary risks and anxiety	4 (3-8)

11.3. Voting results

The first voting round registered a disagreement among panelists between inappropriate and uncertain, with a median score of 2 (range 1-4). During the second round the panel agreed on the judgment of inappropriate with a median score of 2 (range 1-2).

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

INAPPROPRIATE

11.4. Conclusions

After an initial slight disagreement between inappropriate and uncertain, the panel agreed to judge as inappropriate the use of FDG-PET for patients in follow up with no suspicion of recurrence. Level of evidence for diagnostic accuracy of FDG-PET in follow up was low and derived from three primary studies with heterogeneous estimate of specificity and absence of a fair comparator.

All outcomes were voted "important" (all median score of 4).

12. Diagnosis and staging of suspect distant recurrence

Rationale

Residual or recurrent head and neck squamous cell carcinoma, either at the primary site or in neck nodes, occurs in up to 50% of patients treated for advanced tumor (Isles 2008). Seventy-six percent of recurrences occur within the first two years post-treatment, and 11% occur in the third year (SIGN 2006). Sixty-one percent of patients with recurrence report symptoms (Boysen 1992). Local recurrence at the site of the primary tumor is the most common cause of treatment failure and disease-related death in patients with head and neck cancer (SIGN 2006). Suspicion of recurrence is evaluated with conventional imaging tests (CT, MRI) (SIGN). The aim of a correct diagnosis is to direct patients to salvage surgery or re-irradiation, in case of localized recurrence, or to palliative treatment in case of non curable local recurrence or metastatic recurrence (ESMO 2010a, SIGN 2006).

Diagnostic role of FDG-PET

A more accurate test could resolve ambiguities resulting from conventional imaging (CT, MRI), particularly after combined chemoradiation, and correctly identify relapsing patients in order to direct them to appropriate treatment (local curative treatment, salvage surgery or palliative treatment).

Effectiveness of treatment

Therapeutic options for patients with head and neck cancer for whom first line treatment has failed include: surgery (salvage), radiotherapy (including re-irradiation) with or without chemotherapy, palliative treatment only (SIGN 2006).

Five-year survival following salvage surgery for recurrent, previously irradiated laryngeal, pharyngeal and oral cavity tumors is 39% (Goodwin 2000). Site-specific five-year survival is 43.4% (oral cavity), 26% (pharynx), and 47.5% (larynx). Disease-free survival following salvage therapy decreases with increase of stage of recurrence. Following salvage surgery for head and neck cancer, the total complication rate varies from 39 to 53% (Agra 2003, Goodwin 2000). Significant complications have been reported in 18.5-27% of patients undergoing salvage surgery, with an operative mortality rate of 3.2-5.2%. An increased rate of postoperative complications is seen with increasing stage of recurrent tumor (Agra 2003).

In patients with small, early (T1N0 and T2N0) recurrences or new primaries in previously irradiated oropharynx, interstitial brachytherapy alone can be administered, resulting in a five-year local control rate of 69-80%, with a five-year overall survival of 30%, most deaths being due to causes other than cancer (SIGN 2006).

In patients with unresectable recurrent disease following previous radiotherapy, re-irradiation with potentially curative doses of external beam radiotherapy with or without concurrent chemotherapy has obtained - in a small case series of highly selected patients - a five-year survival of 9-20% and local control rates of 11-48%. However normal tissue toxicity may be considerable. Severe late radiation toxicity is reported in 9-18% of patients. In one large case series, 41% of patients had cervical fibrosis, 41% mucosal necrosis and 30% trismus following re-irradiation, and an 11% fatal complication rate has been reported (SIGN 2006).

Pre-test probability and change in management

The median pre-test probability of any recurrence after suspicion is 45.5% (range 8.5-86.7%; Alvarez Perez 2006, Chen 2006a, Ekberg 2007, Ishikita 2010, Ng 2010, Wang 2009).

Five studies (Alvarez Perez 2006, Connell 2007, Ekberg 2007, Pasamontes Pingarrón 2006, Wang 2009), reporting data on change in management, show a median change of 44% (range from 21-63%), with about half of patients avoiding invasive salvage surgery for detection of metastases and half of patients switching to more targeted treatment (change between radiotherapy and chemo-radiotherapy, avoidance of node dissection, etc).

Research question: FDG-PET as add-on test

Has FDG-PET sufficient accuracy to be used as an add-on test to diagnose any recurrence in patients with unclear results from conventional imaging (CT, MRI)?

12.1. Systematic review of literature: results

Results from update of systematic review of literature from January 2006

Five systematic reviews and 14 primary studies evaluating diagnostic accuracy of FDG-PET in suspected recurrence were found. Results are reported below.

Systematic reviews

Five systematic reviews have been retrieved (Brouwer 2008a, Facey 2007, Isles 2008, Liu 2007b, Pasamontes Pingarrón 2008). Isles 2008 included patients with different diagnostic questions, and results from studies evaluating FDG-PET for detection of suspect recurrence were extracted and included among the primary studies.

The methodological quality is medium for Brouwer 2008a and Liu 2007b, low for Facey 2007 and Pasamontes Pingarrón 2008.

Meta-analysis of data was provided by all systematic reviews, except Facey 2007 that reported only descriptive results (*Table 12.1)*. Two systematic reviews (Facey 2007, Liu 2007b) included mixed population of studies assessing FDG-PET accuracy in re-staging patients with advanced cancer after curative treatment or with suspect recurrence patients. Facey 2007 included any kind of head and neck cancer; Liu 2007b included only studies with nasopharyngeal cancer patients. Other two systematic reviews (Brouwer 2008a, Pasamontes Pingarrón 2008) assessed FDG-PET accuracy only for suspect recurrence in patients with any kind of head and neck cancer (Pasamontes Pingarrón 2008) or laryngeal cancer patients after radiotherapy (Brouwer 2008a).

All but one systematic review (Facey 2007) assessed the methodological quality of studies and disclosed recurrent risks of bias (invalidity of verification and uncertainty or absence of blinding of readers' of tests results).

Table 12.1. Results from systematic reviews on accuracy of FDG-PET in re-staging after curative treatment or for suspected recurrence

Reference	Facey 2007	Pasamontes Pingarrón 2008	Liu 2007b	Brouwer 2008a
Update to	August 2005	May 2007	May 2007	April 2006
Number of studies	3 systematic reviews (including respectively 15, 10, 15 primary studies; some of them in common) 8 additional primary studies (6 re-staging; 2 suspected recurrence) 3 studies in common with Isles 2008	19 6 studies in common with Isles 2008 1 study in common with Brouwer 2008a 1 study in common with Liu 2007b	33 studies (21 articles, 11 on FDG-PET, 13 on CT, 9 on MRI) 1 study in common with Pasamontes Pingarrón 2008	8 studies 3 studies in common with Isles 2008 1 study in common with Pasamontes Pingarrón 2008
Number of patients	1 systematic review 350 patients; data not reported in the others primary studies: 381 (re-staging 290; suspected recurrence 91)	666 (median 30.5, range 12-143)	1 813 (only patients with nasopharyngeal cancer) 578 in FDG-PET studies 681 in CT studies 470 in MRI studies	191 (median 12, range 7-75) (only patients with laryngeal cancer)
FDG-PET/ PET-CT	only descriptive results "PET sensitivity was approximately 80%, with specificity at least 90%"	sensitivity: pooled 94% (95% CI 91-96%) test for heterogeneity χ^2 = 19.13; d.f. = 18 (P = .3836) specificity: pooled 80% (95% CI 76-84%) χ^2 = 41.12; d.f. = 18 (P =.0015)	sensitivity: pooled 95% (95% CI 90-97%) test for heterogeneity not reported specificity: pooled 90% (95% CI 87-93%) test for heterogeneity not reported	sensitivity: pooled 89% (95% CI 80-94%) Q test for heterogeneity p = 0.73 specificity: pooled 74% (95% CI 64-83%) Q test for heterogeneity p = 0.05

Comparator	none	none	CT sensitivity: pooled 76% (95% CI: 70-81%) test for heterogeneity not reported specificity: pooled 59% (95% CI: 55-63%) test for heterogeneity not reported for CT, the sensitivity, specificity, diagnostic OR, and the Q* index for dual-section helical and multi-section helical were all significantly higher than non-helical and single-section helical (P <0.01) MRI sensitivity: pooled 78% (95% CI 71-84%) test for heterogeneity not reported specificity: pooled 76% (95% CI 71-80%) test for heterogeneity not reported	CT (1 study, 23 patients) sensitivity: 58% specificity: 100%
Reference standard	not specified	histopathology and/or follow up	histopathology and/or follow up	histopathology and/or follow up

Primary studies

Fourteen studies were found (Alvarez Perez 2006, Brouwer 2008b, Chen 2006a, Connell 2007, Ekberg 2007, Fakhry 2007, Gourin 2009a, Halpern 2007, Ishikita 2010, Kunkel 2006, Ma 2009, Ng 2010, Wang 2009, Yen 2009), published after the above reported systematic reviews, on diagnostic accuracy of FDG-PET for the evaluation of patients with suspect recurrence. Eleven more studies from the Isles' systematic review (Bongers 2002, Chaiken 1993, Farber 1999, Gandhi 2005, Greven 1997, Kubota 2004, Li 2001, Rege 1994, Stokkel 1998, Stokkel 1999, Terhaard 2001) dealing with the same clinical question were also included. Fifteen studies included patients with any type of advanced head and neck cancer, 7 studies patients with nasopharyngeal cancer, 2 studies patients with laryngeal cancer, 1 study patients with oral cancer. Four studies included only patients with advanced disease. Almost all studies are limited by incomplete or uncertain blinding and by an uncertain or not consecutive recruitment of patients. The studies have been retrieved and assessed only for overall consistency with results on diagnostic accuracy of systematic reviews.

Diagnostic accuracy estimates for FDG-PET were drawn from the larger meta-analysis (Pasamontes Pingarrón 2008), as a test for heterogeneity was performed. Data on the best comparator were available from Liu 2007b (*Table 12.3)*.

Table 12.2. Results from primary studies on diagnostic accuracy of FDG-PET in the evaluation of patients with suspect of recurrence

References	Alvarez Perez 2006, Bongers 2002, Brouwer 2008b, Chaiken 1993, Chen 2006a, Connell 2007, Ekberg 2007, Fakhry 2007, Farber 1999, Gandhi 2005, Gourin 2009a, Greven 1997, Halpern 2007, Ishikita 2010, Kubota 2004, Kunkel 2006, Li 2001, Ma 2009, Ng 2010, Rege 1994, Stokkel 1998, Stokkel 1999, Terhaard 2001,Wang 2009, Yen 2009
Number of studies	25
Number of patients	1 101 (median 33, range 10-179)
FDG-PET/PET-CT	any recurrence (5 studies, 406 patients) sensitivity: median 93.9% (range 87.3-100%) specificity: median 94.4% (range 70-100%) local recurrence (17 studies, 585 patients) sensitivity: median 92% (range 80-100%) specificity: median 77.8% (range 50-100%) neck recurrence (6 studies, 181 patients) sensitivity: median 94.4% (range 87.5-100%) specificity: median 97.1% (range 81.8-100%) distant metastasis (3 studies, 155 patients) sensitivity: median 73% (range 70-100%) specificity: median 95.6% (range 87-97%) skull invasion in nasopharyngeal cancer (2 studies, 61 patients) sensitivity: 86.7-96% specificity: 33.3-75%
Comparator	CT any recurrence (1 study, 50 patients) sensitivity: 75.9% specificity: 75.7% MRI any recurrence (1 study, 179 patients) sensitivity: 90.9% specificity: 91.1%
Reference standard	histopathology or follow or both

Table 12.3. Main results on diagnostic accuracy of studies on accuracy of FDG-PET for suspected recurrence

Diagnostic accuracy	
Number of studies	19 studies on FDG-PET * 9 studies on MRI §
Number of patients	666 from studies on FDG-PET * 470 from studies on MRI §
Pre-test probability	median 45.5% (range 8.5-86.7%) #
FDG-PET/PET-CT*	sensitivity: pooled 94% (95% CI 91-96%) specificity: pooled 80% (95% CI 76-84%)
Comparator#	MRI sensitivity: pooled 78% (95% CI 71-84%) specificity: pooled 76% (95% CI 71-80%)
References	* Pasamontes Pingarrón 2008 § Liu 2007b # Alvarez Perez 2006, Chen 2006a, Ekberg 2007, Ishikita 2010, Ng 2010, Wang 2009

Comments of ASSR reviewer

Accuracy of FDG-PET in the diagnosis of suspect of recurrence has been investigated in a remarkable number of studies and in several clinical subgroups. Systematic reviews consistently report high estimates of sensitivity but lower specificity. Primary studies subsequently published show similar sensitivity but higher specificity.

Diagnostic accuracy estimates

Any recurrence

FDG-PET	sensitivity: (pooled) 94% (95% CI 91-96%) specificity: (pooled) 80% (95% CI 76-84%)
Comparator (MRI)	sensitivity: (pooled) 78% (95% CI 71-84%) specificity: (pooled) 76% (95% CI 71-80%)

LEVEL OF EVIDENCE: MODERATE

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

Table12.4. Patient-important clinical outcomes and median scores of importance

Patient-important outcomes	**Median score (range)**
Consequences of test for patients with recurrence	
• True positives - after confirmatory biopsy patients proceed to salvage surgery or radiotherapy with/without chemotherapy which could improve survival / quality of life	8 (6-8)
• False negatives - patients delay start of treatment until disease progresses, with a possible negative impact on survival / quality of life	7 (6-9)
Consequences of test for patients without recurrence	
• True negatives - patients remain in follow up, after a considerable amount of stress	7 (3-8)
• False positives - patients undergo unnecessary biopsy and risks, with a possible negative impact on quality of life.	7 (3-8)

The panel considered "critical", with a median score of 8 (range 6-8), the consequences for patients truly diagnosed for recurrence, after unclear results from other imaging tests. Consequences for patients resulting negative (true or false) or false positive were also considered "critical" with a slightly lower median score of 7 (range 6- 9 for false negatives and wider range of 3-8 for true negatives and false positives).

The following matrix of "natural frequencies" was provided for patients diagnosed and staged for recurrence (*Table 12.5*).

Table 12.5. Natural frequencies of patients tested for recurrence

		N of patients out of 100 submitted to the exam	
		According to FDG-PET	**According to MRI**
Patients with recurrence	True positives	42	35
	False negatives	3	10
Patients without recurrence	True negatives	44	42
	False positives	11	13
		100	100

12.3. Voting results

The panel voted the use of FDG-PET in the diagnosis and staging of suspect recurrence in patients with unclear results from conventional imaging *appropriate* at the first voting round (median score 8, range 7-8).

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

APPROPRIATE

12.4. Conclusions

During the first round of voting the panel agreed in judging appropriate the use of FDG-PET in the diagnosis and staging of suspect recurrence in patients with unclear results from conventional imaging. Level of evidence for diagnostic accuracy of FDG-PET was found moderate, and sensitivity of FG-PET resulted higher than specificity. Clinical outcomes for patients resulting true positive received the highest median score of 8 with votes ranging from 6 to 8. Consequences for patients resulting true or false negative and false positive were also voted "critical" with a median score of 7 and wider ranges of votes.

Conclusions

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

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

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Appendices

Appendix 1. Voting forms

ORI
Osservatorio Regionale per l'Innovazione

CRITERIA FOR APPROPRIATE USE OF FDG-PET IN ONCOLOGY

2010-2011

HEAD AND NECK CANCER

VOTING FORMS

NAME

_____

Agenzia sanitaria e sociale regionale

RegioneEmilia-Romagna

CLINICAL QUESTION

Diagnosis of head and neck cancer

Rationale

Diagnosis of head and neck cancer is made by clinical examination, fibre optic endoscopy and fine needle aspiration or surgical biopsy of any neck masses (AIOM 2009, ESMO 2010a, SIGN 2006).

Diagnostic role of FDG-PET

There is no diagnostic role for FDG-PET in the diagnosis of head and neck cancer.

Treatment effectiveness

For stage I and II head and neck cancer conservative surgery or radiotherapy give similar loco-regional control, while locally advanced stage III and IV cancers are treated with surgery and postoperative radiotherapy. Patients found at surgery to have high-risk features are treated with post-operative chemo-radiotherapy.

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

Detection of unknown primary head and neck cancer in patients with metastatic cervical lymph nodes

Rationale

Patients presenting with metastatic cervical lymph nodes undergo the conventional diagnostic work up (clinical examination, fibre optic endoscopy, fine needle aspiration or surgical biopsy) and imaging diagnostic tests (CT, MRI) in order to identify the unknown primary cancer (AIOM 2009, SIGN 2006).

Diagnostic role of FDG-PET

FDG-PET could be used as an add-on test in patients testing negative with conventional imaging in order to reduce the number of undisclosed primary cancers.

Treatment effectiveness

The identification of the primary site improves the prognosis of patients (Dong 2008). Detected primary cancer is removed surgically and treated as advanced cancer (with radiotherapy with or without chemotherapy). Standard treatment of occult primary cancer is surgery (comprehensive neck dissection) followed by radiotherapy with or without chemotherapy, depending on the metastatic lymph nodes extension (AIOM 2009). The expected five-year risks of recurrent primary cancer and loco-regional recurrence are 5-10% and 10-20%, respectively (AIOM 2009).

Pre-test probability

33.3% of unknown primary head and neck cancer in patients presenting with metastasis of neck lymph nodes

Research question: FDG-PET as add-on test

Has FDG-PET sufficient sensitivity to be used as an add-on test to diagnose occult primary cancer in patients with negative results from conventional imaging (CT, MRI)?

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

FDG-PET
- sensitivity: (pooled) 81%
- specificity: (pooled) 82%

Conventional work up (including CT and MRI)
- sensitivity: (range) 22-50%
- specificity: (range) 72-95%

Patient-important outcomes	Level of importance* (1-9)
Consequences of test for patients with primary head and neck cancer	
True positives - patients undergo confirmatory biopsy, primary cancer is detected and treated according to extension and type	
False negatives - primary cancer is not detected and patients are treated with a combination of more or less extended radiotherapy and surgery with or without chemo-radiotherapy	
Consequences of test for patients without primary head and neck cancer	
True negatives - patients are treated with a combination of more or less extended radiotherapy and surgery with or without chemo-radiotherapy	
False positives - patients undergo unnecessary biopsies which will prove negative and are treated with a combination of more or less extended radiotherapy and surgery with or without chemo-radiotherapy	

* 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 conventional work up**
Patients with primary head and neck cancer	True positives	27	7-16
	False negatives	6	26-16
Patients without primary head and neck cancer	True negatives	55	48-64
	False positives	12	19-3
		100	100

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 head and neck cancer

Rationale

Accurate pre-surgical N staging is necessary to correctly classify patients into early or advanced disease. Pre surgical N staging of neck nodes is made with physical examination and imaging tests (AIOM 2009, SIGN 2006). Some clinically node negative patients have a high risk of occult nodal metastases. The probability of occult nodal metastases depends mainly on the extension (T category) and the site of the primary tumor (AIOM 2009, SIGN 2006).

Diagnostic role of FDG-PET

It is suggested that FDG-PET could represent an add-on diagnostic test in case of negative nodal staging with conventional imaging tests (CT, MRI).

Treatment effectiveness

Standard options for locally advanced stage III and IV tumors are surgery (primary tumor and neck dissection) plus postoperative radiotherapy or chemo-radiotherapy in case of high-risk features of local recurrence (AIOM 2009, ESMO 2010a). In early disease (stage I-II, i.e. node negative patients), either conservative surgery or radiotherapy (external radiotherapy or brachytherapy) give similar loco-regional control (AIOM 2009, ESMO 2010a). In node negative patients with risk of micro metastases higher than 20% prophylactic treatment of the neck (selective or modified radical neck dissection or external beam radiotherapy) is proposed (SIGN 2006, NCCN 2011, SEOM 2010). The expected local recurrence and 5-year survival rate after curative treatment in each stage class further depend on the site of cancer. The incidence of postoperative moderate to severe complications ranges between 13% and 24%; the death risk is about 1-3% (Mendenhall 2002).

Pre-test probability

53.7% (cancer involvement of regional nodes)

Research question: FDG-PET as add-on test

Has FDG-PET sufficient accuracy to be used as an add-on test to diagnose lymph nodes metastases in patients with unclear results from conventional imaging (CT or MRI)?

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

FDG-PET

sensitivity: (pooled) 79%

specificity: (pooled) 86%

Conventional work up

sensitivity: (pooled) 75%

specificity: (pooled) 79%

Patient-important outcomes	**Level of importance* (1-9)**
Consequences of test for patients with involvement of regional nodes	
True positives - patients correctly upstaged to advanced disease are candidate to surgery plus postoperative radiotherapy or chemo-radiotherapy	
False negatives - patients incorrectly downstaged to early disease receive a less aggressive treatment (conservative surgery or radiotherapy) with possible negative impact on recurrence	
Consequences of test for patients without involvement of regional nodes	
True negatives - patients correctly staged for early disease can undergo either conservative surgery or radiotherapy for loco-regional control	
False positives - patients incorrectly upstaged undergo unnecessary biopsy or unnecessarily aggressive treatment, with risk of postoperative complications and no major gain in loco-regional control	

* 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 conventional work up**
Patients with neck node involvement	True positives	43	40
	False negatives	11	14
Patients without neck node involvement	True negatives	40	36
	False positives	6	10
		100	100

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 and detection of synchronous second primary tumor in patients with locally advanced head and neck cancer

Rationale

Distant (mainly pulmonary) metastases usually occur late during the course of head and neck cancer (AIOM 2009). Due to risk factors involved in the etiology of head and neck cancer patients are also prone to synchronous second primary malignant tumors (pulmonary or esophageal). Higher rates (15-33%) of synchronous tumors and pulmonary metastases are seen in patients with more advanced (T3/T4) primary tumors, or where there is level IV nodal involvement (SIGN 2006). M staging is made by CT of the thorax in high risk patients (SIGN 2006). For the investigation of synchronous second primary cancer esophagoscopy or bronchoscopy can be added (SIGN 2006). M staging and research of synchronous second primary cancer have a role in identifying and selecting patients candidate to curative treatment.

Diagnostic role of FDG-PET

It is suggested that FDG-PET could help in detecting distant metastases or synchronous primary cancer in patients with equivocal or negative conventional images results.

Treatment effectiveness

Standard options for locally advanced stage III and IV tumors are surgery plus postoperative radiotherapy. Post-operative chemo-radiotherapy is the standard for patients found at surgery to have high-risk features for local recurrence. Patients with advanced larynx and hypopharynx cancer - requiring total laryngectomy - can undergo induction chemotherapy followed by radiotherapy in order to preserve the organ. Palliative treatment is the treatment of choice for patients with distant and not resectable metastases (NCCN 2011, SEOM 2010, SIGN 2006). Palliation aims at debulking tumor mass and reducing symptoms (pain, bleeding, breathing problems) associated with tumor expansion. Synchronous second primary cancer will be treated according to stage, with a curative intent if the first primary cancer is curable.

Pre-test probability

13% (occurrence of distant metastasis)

Research question: FDG-PET as add-on test

Has FDG-PET sufficient accuracy to be used as an add-on test in patients with advanced head and neck cancer to detect distant metastases or synchronous second primary cancer if conventional imaging tests (CT of thorax, esophagoscopy, bronchoscopy) are equivocal or negative?

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

FDG-PET
- sensitivity: (pooled) 88%
- specificity: (pooled) 95%

Conventional work up (with CT or MRI)
- sensitivity: (median) 70.4%
- specificity: (median) 96.1%

Patient-important outcomes	**Level of importance* (1-9)**
Consequences of test for patients with distant metastases or second primary cancer	
True positives - patients are correctly upstaged and proceed to receive palliative treatment, aimed at improving quality of life	
False negatives - Patients are incorrectly downstaged and do not receive palliative treatment, which might have improved quality of life	
Consequences of test for patients without distant metastases or second primary cancer	
True negatives - patients correctly proceed to curative radical treatment, aimed at improving survival	
False positives - patients are incorrectly upstaged and denied necessary radical curative treatment, 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 conventional work up**
Patients with distant metastases / second primary	True positives	11	9
	False negatives	2	4
Patients without distant metastases / second primary	True negatives	83	84
	False positives	4	3
		100	100

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 curative radiation treatment

Rationale

Radiotherapy has several indications in the treatment for head and neck cancer, including curative intent radical radiotherapy in early disease. Adjuvant radiotherapy can improve local control following surgery in locally advanced disease. Patients with advanced larynx and hypopharynx cancer - requiring total laryngectomy - can undergo induction chemotherapy followed by radiotherapy or concomitant chemo-radiotherapy in order to preserve the organ (AIOM 2009, ESMO 2010a). Radiation therapy is an essential component of curative-intent treatment of non-disseminated nasopharyngeal cancer.

Diagnostic role of FDG-PET

A more precise diagnostic tool allowing a better definition of field could reduce adverse effects of radiation treatment or permit higher and safe dose delivery.

Treatment effectiveness

In early disease radical radiotherapy is reported to have similar effectiveness to radical surgery (AIOM 2009, ESMO 2010a, NCCN 2011). Patients with advanced larynx and hypopharynx cancer - requiring total laryngectomy - can undergo induction chemotherapy followed by radiotherapy in order to preserve the organ (AIOM 2009, ESMO 2010a).

Pre-test probability

It is not possible to provide estimates

Research question: FDG-PET in replacement

Does FDG-PET imaging lead to a better target volume definition of curative RT in patients with head and neck cancer than CT?

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

Not possible to provide estimates

There seems to be consistent evidence of discordant GTV definition between FDG-PET and CT. Consistently FDG-PET leads to a reduction of GTV in 2/3 of patients and to an increase of GTV in the remaining 1/3. Data from one study suggest that FDG-PET has a worst delineation of metastatic lymph nodes compared to CT, and another study

disclosed a mean reduction of GTV with FDG-PET (larger than that with MRI) compared to pathologic specimen.

There are no data providing evidence that FDG-PET-based changes in target volume represent better pathological tumor coverage than CT-based volume delineation.

Patient-important outcomes	**Level of importance* (1-9)**
Consequences of test for patients with large target volume	
True increase of target volume - patients correctly receive irradiation on an increased target volume with benefit on their survival / local control	
False reduction of target volume - patients incorrectly irradiated on a reduced target volume, which might not improve local control and survival	
Consequences of test for patients with small target volume	
True reduction of target volume - patients correctly irradiated on a reduced target volume, suffer less adverse effects and obtain benefit on survival / local control	
False increase of target volume- patients incorrectly receive irradiation on an increased target volume and suffer unnecessary adverse effects	

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

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

CLINICAL QUESTION

Evaluation of early response to neo-adjuvant/induction therapy

Rationale

The literature search resulted in no studies nor clinical practice guidelines addressing a possible diagnostic role of FDG-PET in the evaluation of early response to treatment of head and neck cancer. However the panel expressed the need, in clinical practice, for a test sufficiently adequate in evaluating early response to radical curative radiation treatment or early cancer. Since in early disease (stage I-II, i.e. node negative patients), either conservative surgery or radiotherapy (external radiotherapy or brachytherapy) give similar loco-regional control (AIOM 2009, ESMO 2010a), an accurate test could identify patients who do not respond to radiation treatment and would benefit from a change of therapy switching to radical surgery

The panel unanimously agreed in classifying this clinical question as indeterminate, for lack of studies, and in proposing it as a future research question.

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

CLINICAL QUESTION

Evaluation of response to chemotherapy or radiotherapy at the end of treatment

Rationale

Patients potentially benefiting from an evaluation of treatment response are those with locally advanced disease (stage III and IV), curable with different regimens of chemotherapy, radiotherapy or concomitant chemo-radiotherapy and possibly surgery. Response to chemotherapy, radiotherapy or concomitant chemo-radiotherapy are evaluated, with CT, MRI, US and FNB of primary tumor and neck nodes (NCCN 2011, SIGN, 2006). In case of non response of the primary tumor a salvage surgery can be performed. If response of neck nodes is detected, node dissection can be spared or limited.

Diagnostic role of FDG-PET

It is suggested that FDG-PET could represent an add-on diagnostic test to evaluate the response to chemotherapy, radiotherapy or concomitant chemo-radiotherapy in case of equivocal results from conventional imaging tests (CT, MRI, US and FNB).

Treatment effectiveness: Five-year survival rate following salvage surgery in patients which do non respond to radiation treatment - with laryngeal, pharyngeal and oral cavity tumors - is 39% (Goodwin 2000). Significant complications have been reported in 18.5-27% of patients undergoing salvage surgery, with an operative mortality rate of 3.2-5.2% (Agra 2003). In patients with N2 or N3 disease without a complete clinical response to chemo-radiotherapy, neck dissection improves loco-regional control, neck progression-free survival and overall survival compared to observation only (Argiris 2004, Clayman 2005).

Pre-test probability

17.9% (residual disease at primary site)
13.3% (residual disease at node site)
17.3% (residual disease at any site)

Research question: FDG-PET as add-on test

Has FDG-PET sufficient accuracy to evaluate end of treatment response to chemotherapy, radiotherapy or concomitant chemo-radiotherapy in patients with equivocal results from conventional imaging (CT, MRI, US)?

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

Primary site residual disease

FDG-PET

sensitivity: (median) 84.5%

specificity: (heterogeneous) range 54-100%

Comparator (CT or MRI)

sensitivity: (median) 80%

specificity (heterogeneous) range 46.7-92.1%

Node residual disease

FDG-PET

sensitivity: (heterogeneous) range 25-100%

specificity: (heterogeneous) range 36.4-100%

Comparator (CT or MRI)

sensitivity: (median) 84.5%

specificity: (heterogeneous) range 46.7-93.6%

Residual disease at any site

FDG-PET

sensitivity: median 88.9%

specificity: (heterogeneous) range 69.4-96.6%

Comparator (conventional work up including, CT and MRI)*

sensitivity: 50%

specificity: 94.4%

* data from 1 study

Subgroup of studies with FDG-PET performed within the third month after the end of treatment

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

FDG-PET

sensitivity (median) 83% (range 50-100%)

specificity (heterogeneous) range 54-100%

Comparator (CT or MRI)

sensitivity (heterogeneity not computable) range 60-80%

specificity (heterogeneity not computable) range 66-92.1%

Patient-important outcomes	Level of importance* (1-9)
Consequences of test for patients with residual disease	
True positives - patients with residual disease after initial treatment proceed to confirmatory biopsy and further more aggressive therapeutic regimes, which might improve local control	
False negatives - patients with residual disease after initial treatment do not receive further more aggressive therapy which could have improved local control	
Consequences of test for patients without residual disease	
True negatives - patients without residual disease after initial treatment proceed to follow up	
False positives - patients without residual disease at initial treatment undergo unnecessary biopsies which entail serious risks	

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

Matrix of natural frequencies

Primary site residual disease (all studies)

		N of patients out of 100 submitted to the exam	
		According to FDG-PET	**According to conventional work up**
Patients with residual disease	True positives	11	9
	False negatives	2	4
Patients without residual disease	True negatives	44-82	39-76
	False positives	38-0	43-6
		100	100

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 in patients with no suspicion of recurrence

Rationale

Seventy-six percent of recurrences for head and neck occur within the first two years after treatment with curative intent, and 11% occur in the third year (SIGN 2006). Thirty-nine percent of patients with recurrence have no symptoms (Boysen 1992).

Guidelines recommend regular active follow up, with physical exam, at least in the first three (SIGN 2006) or five years (NCCN 2011). In selected cases CT or MRI could be required. The aim of follow up is the early detection of potentially curable loco-regional recurrence and second primary tumors.

Diagnostic role of FDG-PET

To anticipate detection of recurrence or second primary tumors in patients treated for head and neck cancer in order to start appropriate therapy earlier.

Treatment effectiveness

There is no consistent evidence that surveillance with imaging alters outcome following treatment for head and neck cancer (SIGN 2006), however the risk of recurrence after treatment with curative intent is very high in the first three years.

Pre-test probability

33% (recurrence in the first 12-24 months after a curative treatment)

Research question: FDG-PET as replacement

Has FDG-PET higher diagnostic accuracy than the available comparator (physical exam, with CT or MRI) in detecting recurrence during follow up test of patients with no suspicion of recurrence of head and neck cancer?

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

FDG-PET

sensitivity: (median) 100%

specificity (heterogeneous): range 43.3-85.2%

Conventional work up (with CT or MRI)

no estimate available

Patient-important outcomes	**Level of importance* (1-9)**
Consequences of test for patients with any recurrence	
True positives - patients undergo biopsy to confirm positive results and proceed to possible salvage treatment	
False negatives - patients remain in follow up until symptoms/suspicion of recurrence occur, and delay a possible salvage treatment	
Consequences of test for patients without recurrence	
True negatives - patients remain in follow up and are reassured	
False positives - patients undergo unnecessary biopsy to prove negative and are exposed to additional unnecessary risks and anxiety	

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

The matrix of "natural frequencies" was not provided because of the absence of data on comparator.

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

CLINICAL QUESTION

Diagnosis and staging of suspect distant recurrence

Rationale

Residual or recurrent head and neck squamous cell carcinoma, either at the primary site or in neck nodes, occurs in up to 50% of patients treated for advanced tumor (Isles 2008). Seventy-six percent of recurrences occur within the first two years post-treatment, and 11% occur in the third year (SIGN 2006). Sixty-one percent of patients with recurrence report symptoms (Boysen 1992). Local recurrence at the site of the primary tumor is the most common cause of treatment failure and disease-related death in patients with head and neck cancer (SIGN 2006). Suspicion of recurrence is evaluated with conventional imaging tests (CT, MRI) (SIGN). The aim of a correct diagnosis is to direct patients to salvage surgery or re-irradiation, in case of localized recurrence, or to palliative treatment in case of non curable local recurrence or metastatic recurrence (ESMO 2010a, SIGN 2006).

Diagnostic role of FDG-PET

A more accurate test could resolve ambiguities resulting from conventional imaging (CT, MRI), particularly after combined chemoradiation, and correctly identify relapsing patients.

Treatment effectiveness

Therapeutic options for patients with head and neck cancer whose first line treatment has failed include: surgery (salvage), radiotherapy with or without chemotherapy, palliative treatment only (SIGN 2006). Five-year survival following salvage surgery for recurrent, previously irradiated laryngeal, pharyngeal and oral cavity tumors is 39% (Goodwin 2000). Significant complications have been reported in 18.5-27% of patients undergoing salvage surgery, with an operative mortality rate of 3.2-5.2%. In patients with early (T1N0 and T2N0) recurrences or new primaries in previously irradiated oropharynx, interstitial brachytherapy alone can be administered (five-year local control rate of 69-80%, five-year overall survival of 30%, SIGN 2006). In patients with unresectable recurrent disease following previous radiotherapy, re-irradiation with potentially curative doses of external beam radiotherapy with or without concurrent chemotherapy has obtained a five-year survival of 9-20% and local control rates of 11-48%. Severe late radiation toxicity is reported in 9-18% of patients.

Pre-test probability

45.5% (any recurrence after suspicion)

Research question: FDG-PET as add-on test

Has FDG-PET sufficient accuracy to be used as an add-on test to diagnose any recurrence in patients with unclear results from conventional imaging (CT, MRI)?

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

FDG-PET

sensitivity: (pooled) 94%

specificity: (pooled) 80%

MRI

sensitivity: (pooled) 78%

specificity: (pooled) 76%

Patient-important outcomes	**Level of importance* (1-9)**
Consequences of test for patients with recurrence	
True positives - after confirmatory biopsy patients proceed to salvage surgery or radiotherapy with/without chemotherapy which could improve survival / quality of life	
False negatives - patients delay start of treatment until disease progresses, with a possible negative impact on survival / quality of life	
Consequences of test for patients without recurrence	
True negatives - patients remain in follow up, after a considerable amount of stress	
False positives - patients undergo unnecessary biopsy and risks, with a possible negative impact on quality of life	

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

		N of patients out of 100 submitted to the exam	
		According to FDG-PET	**According to MRI**
Patients with recurrence	True positives	42	35
	False negatives	3	10
Patients without recurrence	True negatives	44	42
	False positives	11	13
		100	100

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

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

ORI
Osservatorio Regionale per l'Innovazione

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

SEARCH STRATEGY AND TABLES OF EVIDENCE

Agenzia sanitaria e sociale regionale

RegioneEmilia-Romagna

SEARCH STRATEGY

The following databases were searched for the period between January 2006 and March 2011:

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

Language restrictions: English, Italian, French and Spanish.

Reference lists of identified articles were checked for additional references.

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. "Head and Neck Neoplasms" [MeSH descriptor explode all trees]
10. **8 AND 9**

Publication date: 2006-2011

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. "head and neck cancer"[Title/Abstract]
26. head and neck cancers"[Title/Abstract]
27. "head and neck neoplasms"[Title/Abstract])
28. "head and neck neoplasm"[Title/Abstract])
29. "oral neoplasm"[Title/Abstract]
30. "oral neoplasms"[Title/Abstract]
31. "cancer of mouth"[Title/Abstract]
32. "oral cancer"[Title/Abstract]
33. "oral cancers"[Title/Abstract]
34. "gingival neoplasms"[Title/Abstract]
35. "gingival neoplasm"[Title/Abstract]
36. "congenital epulides"[Title/Abstract]
37. "congenital epulis"[Title/Abstract]
38. leukokeratoses[Title/Abstract]
39. leukokeratosis[Title/Abstract]
40. leukoplakia[Title/Abstract]
41. leukoplakias[Title/Abstract
42. "lip cancer"[Title/Abstract]
43. "lip cancers"[Title/Abstract]
44. "lip neoplasms"[Title/Abstract]
45. "lip neoplasm"[Title/Abstract]
46. "palatal neoplasm" [Title/Abstract]
47. "palatal neoplasms"[Title/Abstract]
48. "salivary gland neoplasm"[Title/Abstract]
49. "salivary gland neoplasms"[Title/Abstract]
50. "salivary gland cancer"[Title/Abstract]
51. "salivary gland cancers"[Title/Abstract]
52. "parotid neoplasm"[Title/Abstract]
53. "parotid neoplasms"[Title/Abstract]
54. "parotid cancer"[Title/Abstract]
55. "parotid cancers"[Title/Abstract]
56. "parotid carcinomas"[Title/Abstract]
57. "gland neoplasm"[Title/Abstract]
58. "gland neoplasms"[Title/Abstract]

59. "tongue neoplasm"[Title/Abstract]
60. "tongue neoplasms"[Title/Abstract]
61. "tongue cancer"[Title/Abstract]
62. "tongue cancers"[Title/Abstract]
63. "otorhinolaryngological neoplasms"[Title/Abstract]
64. "otorhinolaryngological neoplasm"[Title/Abstract]
65. "otorhinolaryngological cancer"[Title/Abstract]
66. "otorhinolaryngological cancers"[Title/Abstract]
67. "auricular cancer"[Title/Abstract]
68. "auricular cancers"[Title/Abstract]
69. "auricular carcinoma"[Title/Abstract]
70. "ear neoplasm"[Title/Abstract]
71. "ear neoplasms"[Title/Abstract]
72. "ear cancer"[Title/Abstract]
73. "ear cancers"[Title/Abstract]
74. "laryngeal neoplasm"[Title/Abstract]
75. "laryngeal neoplasms"[Title/Abstract]
76. "laryngeal cancer"[Title/Abstract]
77. "laryngeal cancers"[Title/Abstract]
78. "larynx neoplasm"[Title/Abstract]
79. "larynx neoplasms"[Title/Abstract]
80. "larynx cancer"[Title/Abstract]
81. "larynx cancers"[Title/Abstract]
82. "nose neoplasms"[Title/Abstract]
83. "nose neoplasm"[Title/Abstract]
84. "nose cancer"[Title/Abstract]
85. "nose cancers"[Title/Abstract]
86. "sinus neoplasm"[Title/Abstract]
87. "sinus neoplasms"[Title/Abstract]
88. "paranasal sinus cancer"[Title/Abstract]
89. "paranasal sinus cancers"[Title/Abstract]
90. "sinus cancer"[Title/Abstract]
91. "sinus cancers"[Title/Abstract]
92. "pharyngeal neoplasm"[Title/Abstract]
93. "pharyngeal neoplasms"[Title/Abstract]
94. "pharyngeal cancer"[Title/Abstract]

95. "pharyngeal cancers"[Title/Abstract]
96. "pharynx cancer"[Title/Abstract]
97. "pharynx cancers"[Title/Abstract]
98. "hypopharyngeal cancer"[Title/Abstract]
99. "hypopharyngeal cancers"[Title/Abstract]
100. "nasopharynx cancer"[Title/Abstract]
101. "nasopharynx cancers"[Title/Abstract]
102. "oropharyngeal neoplasm"[Title/Abstract]
103. oropharyngeal neoplasms"[Title/Abstract]
104. "oropharyngeal cancer"[Title/Abstract]
105. "oropharyngeal cancers"[Title/Abstract]
106. "oropharynx cancer"[Title/Abstract]
107. "oropharynx cancers"[Title/Abstract]
108. "tonsil cancer"[Title/Abstract]
109. "tonsil cancers"[Title/Abstract]
110. "tonsillar neoplasm"[Title/Abstract
111. "tonsillar neoplasms"[Title/Abstract
112. "tonsillar cancer"[Title/Abstract
113. "tonsillar cancers"[Title/Abstract
114. "Mouth Neoplasms"[Mesh]
115. "Head and Neck Neoplasms"[Mesh:noexp]
116. "Otorhinolaryngologic Neoplasms"[Mesh]
117. **25/116 OR**
118. **24 AND 117**

Limit: Humans

Languages: English, French, Italian, Spanish

Publication date: 2006-2011

EMBASE search strategy

1. "positron emission tomography"/syn
2. "positron emission tomography"/exp
3. "fluorodeoxyglucose f 18"/exp
4. "fluorodeoxyglucose f 18"/syn
5. "computer assisted emission tomography"/exp
6. "computer assisted emission tomography"/tw
7. pet/tw
8. "pet scans"/tw
9. "pet scanner"/tw
10. "pet scan"/tw
11. "pet/ct scan"/tw
12. "pet/ct scans"/tw
13. "pet/ct"/tw
14. "positron emission tomography/computed tomography"/tw
15. pet NEAR/4 scan*
16. pet NEAR/4 ct
17. **1/15 OR**
18. "head and neck cancer"/exp
19. "head and neck cancer"/syn
20. "head and neck cancer"/tw
21. "head cancer"/de
22. "head cancer"/tw
23. "nose cancer"/exp
24. "nose cancer"/tw
25. "lip cancer"/exp
26. "lip cancer"/tw
27. "mouth cancer"/exp
28. "mouth cancer"/syn
29. mouth cancer"/tw
30. "neck cancer"/exp
31. "neck cancer"/tw
32. "paranasal sinus cancer"/tw
33. "paranasal sinus cancer"/exp
34. "pharynx cancer"/exp
35. "pharynx cancer"/tw

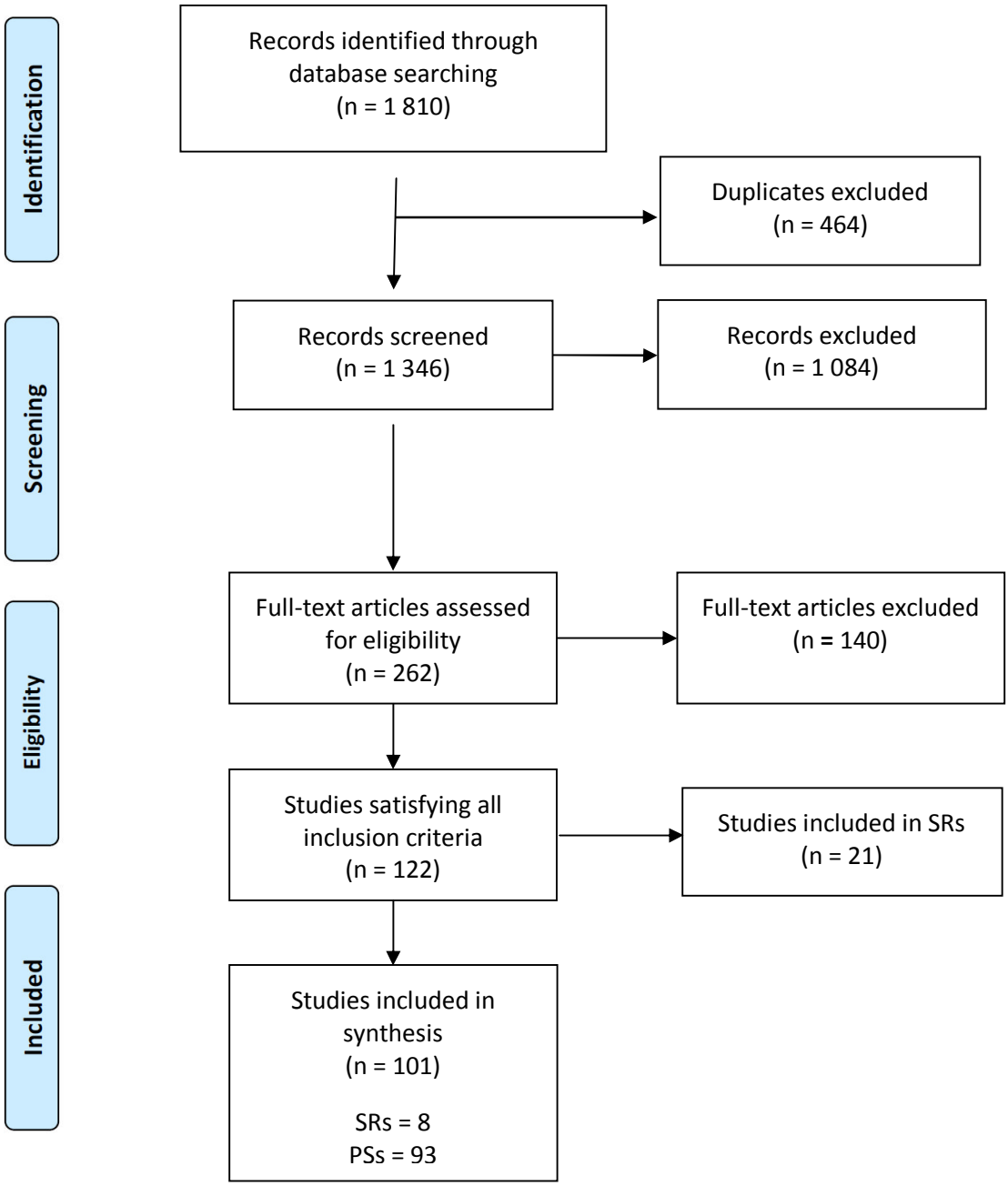
36. "salivary gland cancer"/exp
37. "salivary gland cancer"/tw
38. "tongue cancer"/exp
39. "tongue cancer"/tw
40. "tonsil cancer"/exp
41. "tonsil cancer"/tw
42. **18/42 OR**
43. **17 AND 42**

Limit: Humans

Languages: English, French, Italian, Spanish

Publication date: 2006-2011

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



CHAPTER 4
Diagnosis of head and neck cancer
Diagnostic accuracy
Systematic reviews

Author, year	**Facey 2007**
Technology	FDG-PET
Disease	head and neck cancer
Objective	to assess: ▪ **X** primary diagnosis ▪ **X** staging ▪ **X** RT planning ▪ **X** response to therapy (after treatment) ▪ **X** diagnosis of suspected recurrence or re-staging
Inclusion criteria	P patients with head and neck cancer I FDG-PET C all available R not specified O diagnostic accuracy for primary diagnosis, staging, re-staging after treatment, recurrence; change in management for RT planning 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	primary diagnosis: 1 systematic review (including 4 primary studies), 1 additional primary study cross sectional diagnostic accuracy studies, with prospective or retrospective recruitment
N. of included patients	primary diagnosis: not reported
Reference standard	primary diagnosis: not reported
Comparator	primary diagnosis: CT or MRI
Pre-test probability	not reported
Performance results	Not calculated: only descriptive results. One systematic review of four primary studies, and one additional primary study showed that PET was more sensitive and specific than CT/MRI for diagnosis. PET cannot currently replace these modalities because of the need for anatomical localization, but may be helpful where doubt exists. One systematic review with four primary studies, and one additional four primary study. There is some evidence of change in patient management. This is not clearly documented, but savings in panendoscopy and multiple biopsies are suggested.
Recommendations and conclusions	none reported
Comment of ASSR reviewers	meta-analysis not performed

Primary studies

Author, year	Babin 2008
Country	France
Technology	FDG-PET/CT
Disease	squamous cell carcinoma of the oral cavity and/or of the oropharynx adjacent to the mandibular bone
Objective	to assess diagnostic accuracy in detecting mandible involvement
Index test	FDG-PET/CT
Comparator	CT
Reference standard	histopathology
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with prospective design
Spectrum of patients representative of the individuals who will receive the test in practice	uncertain
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
Reference standard independent of the index test	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	no
Independent and blind interpretation of index test and reference standard results	not reported
Withdrawals from the study explained	no withdrawals

Patients number and characteristics	17 (15 men and 2 women) all presented with localized cancer of the oral cavity (10) or oropharynx (seven). Lesions included 7 T2, 8 T3 and 2 T4 with 7 N0, 5 N1, 3 N2 and 2 N3, using the UICC classification no patients presented with visceral metastases
Pre-test probability	17.6% (3/17)
Results	PET/CT sensitivity 100% specificity 85% CT sensitivity 33% specificity 100%
Authors' recommendations and conclusions	This study shows that PET/CT appears to be useful in stage planning for patients with tumors close to the mandible. Further investigation is warranted to confirm these results

Author, year	**Chen 2007**
Country	Taiwan
Technology	FDG-PET/CT
Disease	patients with benign or malignant lesions in lateral pharyngeal recess of nasopharynx (Waldeyer's ring)
Objective:	to assess diagnostic accuracy in differentiating benign from malignant lesions
Index test	FDG-PET/CT
Comparator	none
Reference standard	histology, follow up
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with retrospective design and case-control 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
Reference standard independent of the index test	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	no
Independent and blind interpretation of index test and reference standard results	not reported
Withdrawals from the study explained	no withdrawals
Patients number and characteristics	131: 80 subjects with benign lesions (53 without and 27 with symptoms of upper airway discomfort), 30 healthy controls, 21 patients with newly diagnosed nasopharyngeal carcinoma

Pre-test probability	16% (21 out of 131)
Results	When the LPR SUV was used to differentiate benign from malignant lesions on receiver-operating-characteristic curve analysis, the AUC of 18F-FDG-PET was 0.81 (95% CI 0.72-0.88), with a sensitivity of 72% and specificity of 80%. When the N/P ratio was used, the AUC was 0.87 6 0.05 (95% CI 0.79-0.93), with a sensitivity of 67% and specificity of 95%.
Authors' recommendations and conclusions	The intensity and patterns of 18F-FDG uptake in various regions of Waldeyer's ring along with CT scan findings provide a feasible modality to differentiate benign from malignant nasopharyngeal lesions.
Comment of ASSR reviewers	very low quality study

Author, year	**Gu 2010**
Country	Korea
Technology	FDG-PET/CT
Disease	squamous cell carcinoma of the oral cavity adjacent to the mandibular bone
Objective	to assess diagnostic accuracy in detecting mandible involvement
Index test	FDG-PET/CT
Comparator	CT, MRI
Reference standard	histopathology
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with retrospective design
Spectrum of patients representative of the individuals who will receive the test in practice	uncertain
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
Reference standard independent of the index test	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	no
Independent and blind interpretation of index test and reference standard results	yes
Withdrawals from the study explained	no withdrawals

Patients number and characteristics	46 patients (39 men and 7 women) mean age 59.4 ± 11.4 years; age range 39-89 years Of these patients, two had recurrent perioral SCCs after previous surgical resection, radiation therapy, chemotherapy, or combinations of the above (but did not receive mandibulectomy). The primary sites of SCC in these patients included tonsils (n. 23), retromolar trigone (n. 8), tongue base (n. 6), floor of mouth (n. 5), buccal space (n. 3), and gingiva (n. 1). All patients were treated with complete or near complete surgical resections of the tumor, which were determined by the surgeon based on the clinical, imaging, intraoperative, and fast-frozen histological findings. Of the 46 patients, 5 underwent segmental mandibulectomy and 10 underwent marginal mandibulectomy.
Pre-test probability	twelve (26.1%) of the 46 tumors had histopathologic evidence of mandibular invasion
Results	PET sensitivity 58.3% specificity 97.1% CT sensitivity 41.7% specificity 100% MRI sensitivity 58.3% specificity 97.1%
Authors' recommendations and conclusions	The combined analysis of CT, MR and PET/CT can improve sensitivity in the detection of mandibular invasion by SCC of the oral cavity.

Author, year	**Ma 2009**
Country	China
Technology	FDG-PET/CT
Disease	patients with nasopharyngeal carcinoma and suspected of skull base invasion by clinical symptoms or MRI or CT imaging
Objective:	to assess diagnostic accuracy in detecting skull base invasion
Index test	FDG-PET/CT
Comparator	CT, MRI
Reference standard	pathology or at least 6 months of clinical and imaging follow up
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with retrospective design; not consecutive recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	uncertain
Patients selection criteria clearly described	no
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not applicable
Execution of the index and comparator tests adequately described	yes
Reference standard independent of the index test	yes
Did patients receive the same reference standard regardless of the index test result	uncertain
Execution of the reference standard described	no
Independent and blind interpretation of index test and reference standard results	not reported
Withdrawals from the study explained	no withdrawals

Patients number and characteristics	57, 47 males, 10 females median age 46 years All cases had pathological confirmation before beginning the investigation, 23 among which were primary cases of nasopharyngeal carcinomas, 34 were post-radiation recurrences (4-68 months after radiation). Pathological type: poorly differentiated carcinoma in 45 cases and well-differentiated carcinoma in 3 cases, undifferentiated carcinoma in 9 cases
Pre-test probability	primary patients: 82.5% recurrent patients: 73.5%
Results	For detecting skull base invasion of NPC, the sensitivity of enhanced CT, MRI and PET-CT were 68.18%, 84.09%, 97.67% respectively; specificity were 76.92%, 69.23%, 57.14% respectively. Primary patients PET sensitivity: 100% specificity: 100% CT sensitivity: 73.7% specificity: 75% MRI sensitivity: 89.5% specificity: 75% Recurrent patients PET sensitivity: 96% specificity: 33.3% CT sensitivity: 64% specificity: 77.8% MRI sensitivity: 80% specificity: 66.7%
Authors' recommendations and conclusions	PET-CT has obvious advantages in sensitivity over CT ($P < 0.05$) and MRI, better than the two methods in accuracy and NPV and may be more valuable for new patients in detecting skull base invasion of NPC patients
Comment of ASSR reviewers	We calculated estimates in the two subgroups (primary patients, recurrence patients). Raw data (2x2 table) in the primary patients group from the original paper are incorrect

CHAPTER 5
Detection of unknown primary head and neck cancer in patients with metastatic cervical lymph nodes

Systematic reviews

Author, year	**Dong 2008**
Technology	FDG-PET
Disease	all kind of unknown primary tumors (including the subgroup of patients with cervical lymph node metastases from suspected primary head and neck cancer)
Objective	to assess: ▪ **X** primary diagnosis: detection of unknown primary tumor
Inclusion criteria	P all kind of unknown primary tumors (including the subgroup of patients with cervical lymph node metastases from suspected primary head and neck cancer); unknown primary tumor was defined according to conventional work up I FDG-PET, FDG-PET/CT C none R histology and/or follow up O diagnostic accuracy S retrospective and prospective studies
Years covered by the search	up to September 2007
Study selection data abstraction, quality assessment performed by two authors independently	yes
Comprehensive bibliographic search: at least two databases searched	yes Medline, EMBASE, Cancerlit
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	no
Searched also unpublished studies	no
Language restriction	not specified
Overall number of references retrieved and n of included studies reported	yes
N. and references of excluded studies reported, reason given	yes
Characteristics of included studies clearly reported in tables	yes

Methodological quality of primary studies assessed; criteria reported	yes (criteria from previously published systematic reviews in this field)
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	28 studies, including 13 studies with cervical lymph node metastases Unknown primary tumor was defined according to conventional work up; almost all studies included CT and MRI in the diagnostic work up Cross sectional diagnostic accuracy studies, with prospective or retrospective recruitment
N. of included patients	910, including 300 patients with cervical lymph node metastases
Reference standard	histopathology and/or follow up
Comparator	none
Pre-test probability	median 33.3%, range 5.3-57.1% (from the 13 studies with cervical lymph node metastases)
Performance results	13 studies detecting occult primaries in patients with cervical lymph node metastases pooled sensitivity 0.81 (95% CI 0.73-0.88) pooled specificity 0.82 (95% CI 0.76-0.87) pooled lnDOR 3.11 (95% CI 2.35-3.87) pooled SROC (± SE) 0.889 (± 0.028) FDG-PET exhibited lower sensitivity with respect to the tumors at the base of the tongue and the tonsils
Recommendations and conclusions	Our findings indicate that FDG-PET and FDG-PET-CT could be valuable imaging modalities in patients with carcinoma of unknown primary beyond what was provided from a conventional workup, and these findings simply provide data for modeling cost-effectiveness.

Author, year	**Facey 2007**
Technology	FDG-PET
Disease	head and neck cancer
Objective	to assess: ▪ **X** primary diagnosis ▪ **X** staging ▪ **X** RT planning ▪ **X** response to therapy (after treatment) ▪ **X** diagnosis of suspected recurrence or re-staging
Inclusion criteria	P patients with head and neck cancer I FDG-PET C all available R not specified O diagnostic accuracy for primary diagnosis, staging, re-staging after treatment, recurrence; change in management for RT planning 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	diagnosis of occult primary tumor: 2 systematic reviews (including 8 primary studies), 2 additional primary studies cross sectional diagnostic accuracy studies, with prospective or retrospective recruitment
N. of included patients	diagnosis of occult primary tumor: 210
Reference standard	diagnosis of occult primary tumor: panendoscopy and biopsy or follow up
Comparator	diagnosis of occult primary tumor: none
Pre-test probability	not reported
Performance results	Not calculated: only descriptive results. Two systematic reviews (total 9 primary studies) and two additional primary studies showed that PET can detect occult primary tumors in patients with cervical lymph node metastases. Even in those where other imaging methods have failed, the true positive rate of PET is 30%. Tumors missed by PET in one study were smaller than 0.5 cm. There is some evidence of change in patient management. This is not clearly documented, but savings in panendoscopy and multiple biopsies are suggested.
Recommendations and conclusions	none reported
Comment of ASSR reviewers	meta-analysis not performed

Synoptic table of primary studies on detection of cancer of unknown primary

Author, year	Technology	Patient number	Study characteristics or limits	Pre-test probability	Sensitivity	Specificity
Cianchetti 2009	FDG-PET, FDG-PET/CT	21	retrospective design and not consecutive recruitment; incorporation bias, incomplete verification	66.7%	21.4%	71.4%
Ekberg 2007	FDG-PET	18	incorporation bias; retrospective design	50.0%	77.7%	88.8%
Guntinas-Lichius 2006	FDG-PET	69	incorporation bias; retrospective design; non consecutive recruitment	33.0%	69.0%	79.0%
	panendoscopy	not reported			43.0%	88.0%
	CT of neck	69			36.0%	87.0%
	CT of thorax	53			32.0%	91.0%
	MRI of neck	not reported			50.0%	95.0%
Johansen 2008	FDG-PET, FDG-PET/CT	60	prospective design and consecutive recruitment; incorporation bias, incomplete verification	35.0%	86.0%	69.0%
Roh 2009	FDG-PET/CT	44	retrospective design and consecutive recruitment	36.4%	87.5%	82.1%
	CT				43.7%	89.3%
Waltonen 2009	FDG-PET	41	retrospective design and opportunistic recruitment	not considered	42.9%	72.4%
	FDG-PET/CT	52			74.2%	72.0%
	CT	146			21.5%	80.7%

Primary studies

Author, year	Cianchetti 2009
Country	USA
Technology	FDG-PET or FDG-PET/CT
Disease	metastatic cervical adenopathy and an unknown primary site
Objective:	to assess diagnostic accuracy in detecting carcinoma of unknown primary
Index test	FDG-PET or FDG-PET/CT
Comparator	none
Reference standard	the complete diagnostic work up (see below)
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with retrospective design and not consecutive recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	no
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not applicable
Execution of the index and comparator tests adequately described	yes
Reference standard independent of the index test	no
Did patients receive the same reference standard regardless of the index test result	no
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	not reported
Withdrawals from the study explained	no withdrawals

Patients number and characteristics	21 (those underwent to FDG-PET or FDG-PET/CT) Two hundred thirty-six patients were deemed eligible for the analysis. Mean age was 59 years (range 25-92 years). The conventional work up included: a complete history and physical examination, including a head and neck examination by multiple examiners, chest radiography, and CT and/or MRI. Select patients underwent FDG-SPECT or, in more recent years FDGPET, to clarify questionable findings on CT and/or MRI. An FDG-PET and/or chest CT was also used to detect distant metastases thought to be at high risk, such as those with N3 neck disease extending below the level of the thyroid notch. Following the diagnostic evaluation, all patients underwent panendoscopy with directed biopsies. Patients with adequate lymphoid tissue in the tonsillar region usually underwent a unilateral or bilateral tonsillectomy at the discretion of the attending otolaryngologist. Forty-four of the patients (73%) had metastatic neck disease from a squamous cell carcinoma, 12 from an undifferentiated carcinoma (20%), while 2 patients had adenosquamous carcinoma, and 2 patients had unspecified histology. Nine patients had N1 disease, 34 had N2 disease, and 17 had N3 disease.
Pre-test probability	66.7% (14 out of 21)
Results	no patient had a biopsy-proven primary site detected only on FDG-PET or FDG-PET/CT sensitivity 21.4% (3/14) specificity was 71.4% (5/7) change of treatment was possible in 0 patients (0%)
Authors' recommendations and conclusions	Diagnostic evaluation should include a thorough physical examination, CT and/or MRI of the head and neck, and panendoscopy with directed biopsies. Unilateral or bilateral tonsillectomy should be performed on patients with adequate lymphoid tonsillar tissue. FDG-PET or FDG-PET/CT should be considered for those with indeterminate findings on physical examination and/or head and neck CT and/or MRI if those sites are located outside of the oropharynx.
Comment of ASSR reviewers	very low quality study

Author, year	**Ekberg 2007**
Country	Sweden
Technology	FDG-PET
Disease	patients with metastases from an unknown primary tumor
Objective:	to assess diagnostic accuracy in detecting primary tumor
Index test	FDG-PET
Comparator	none
Reference standard	not specified (probably an opportunistic diagnostic work up: physical examinations, endoscopy, CT, MRI, FDG-PET, follow up, biopsy, cytology)
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with retrospective design
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	not applicable
Execution of the index and comparator tests adequately described	yes
Reference standard independent of the index test	no
Did patients receive the same reference standard regardless of the index test result	no
Execution of the reference standard described	no
Independent and blind interpretation of index test and reference standard results	not reported
Withdrawals from the study explained	no withdrawals

Patients number and characteristics	18 The histopathologic diagnoses were SCC (10), adenocarcinoma (3), poorly differentiated cancer (3), malignant melanoma (1) and carcinosarcoma (1). Besides physical examination and endoscopies, all patients underwent radiological evaluation with CT (12), MRI (3) or both (3)
Pre-test probability	50% (9/18 patients)
Results	FDG-PET sensitivity: 77.7% specificity: 88.8%
Authors' recommendations and conclusions	The results suggest an important role for FDGPET in staging, on suspicion of recurrence, and for detecting occult primary tumors. For reasons of economy PET for follow up might have to be reserved for patients with a high risk of cancer recurrence. A prospective study might further clarify how best to select patients for PET.
Comment of ASSR reviewers	very low quality study

Author, year	**Guntinas-Lichius 2006**
Country	Germany
Technology	FDG-PET
Disease	patients with cervical lymph node metastases without apparent primary
Objective:	to assess diagnostic accuracy in detecting primary tumor
Index test	FDG-PET
Comparator	the single components of the diagnostic work up
Reference standard	the complete diagnostic work up: physical examinations, ultrasonography of the neck and abdomen, chest X-ray, CT scan of the neck, bone scintigraphy, panendoscopy, CT scan of the brain, CT scan of the thorax, CT scan of the abdomen, MRI scan of the head, whole-body FDG-PET
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with retrospective design
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	not applicable
Execution of the index and comparator tests adequately described	yes
Reference standard independent of the index test	no
Did patients receive the same reference standard regardless of the index test result	no
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	not reported
Withdrawals from the study explained	no withdrawals

Patients number and characteristics	46 (those underwent to FDG-PET or FDG-PET/CT) patients admitted from 1987 to 2002 with cervical lymph node metastases without apparent primary. Diagnostic management included careful otolaryngological and physical examinations followed by standard imaging procedures such as ultrasonography of the neck and abdomen, chest X-ray, CT scan of the neck, and bone scintigraphy. If this diagnostic work up did not detect the primary tumor, a panendoscopy under general anesthesia was performed, and the diagnostic work up was extended individually. A CT scan of the brain was performed in 6 patients (9%), a CT scan of the thorax in 53 patients (77%), a CT scan of the abdomen in 24 patients (35%), an MRI scan of the head in 9 patients (13%) and a whole-body FDG-PET in 46 patients (67%).
Pre-test probability	33% (23 patients) The most frequent origin of the primary tumor was the palatine tonsil (n 8, 35%). Other localizations were, in order of frequency, the base of the tongue (n 6, 26%), lung (n 4, 17%), nasopharynx (n 2, 9%), followed by esophagus, parotid gland, skin, supraglottic larynx and tongue (n 1, 4%, for each)
Results	sensitivity specificity FDG-PET 69% 79% panendoscopy 48% 88% CT of neck 36% 87% CT of thorax 32% 91% MRI of neck 50% 95% primary tumor detected only by PET: 2 patients (9%)
Authors' recommendations and conclusions	not reported
Comment of ASSR reviewers	very low quality study

Author, year	**Johansen 2008**
Country	Denmark
Technology	FDG-PET or FDG-PET/CT
Disease	patients with neck node metastases from a suspected carcinoma of unknown primary
Objective	to assess diagnostic accuracy in detecting carcinoma of unknown primary
Index test	FDG-PET or FDG-PET/CT
Comparator	none
Reference standard	the complete diagnostic work up (see below)
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with prospective design and consecutive recruitment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	no
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not applicable
Execution of the index and comparator tests adequately described	yes
Reference standard independent of the index test	no
Did patients receive the same reference standard regardless of the index test result	no
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	not reported
Withdrawals from the study explained	no withdrawals

Patients number and characteristics	60 Sixty-seven patients entered the study, 48 men and 19 women with a median age of 56.5 years (range 32-78 years). Three patients did not have a PET scan: 2 patients abstained, and 1 patient's scan was cancelled due to obesity. Another 4 patients were ineligible for the data analysis: 1 with lymphoma, 1 with adenocarcinoma, and 2 patients with benign branchiogenic cysts. This left 60 patients for the data analysis The conventional diagnostic work up included panendoscopies of the pharynx, larynx, bronchi, and esophagus, random mucosal biopsies from sites of predilection of a primary tumor. This included ipsilateral tonsillectomy, and a base of tongue biopsy. Diagnostic imaging included a chest X-ray or a CT scan, ultrasonography of the neck, and CT or MRI of the head and neck. The CUP patients were allowed to have a PET scan either before or after panendoscopy at the oncology centers. This divided the patients into 2 groups, namely a pre-endoscopy PET group (n 19) and a post-endoscopy PET group (n 41). Forty-four patients (73%) had metastatic neck disease from a squamous cell carcinoma, 12 from an undifferentiated carcinoma (20%), while 2 patients had adenosquamous carcinoma, and 2 patients had unspecified histology. Nine patients had N1 disease, 34 had N2 disease, and 17 had N3 disease.
Pre-test probability	35% (21 out of 60)
Results	sensitivity 86% specificity 69% change of treatment was possible in 15 patients (25%)
Authors' recommendations and conclusions	FDG-PET is a valuable tool in addition to conventional extensive workup in CUP and neck metastases. Consequently, FDG-PET is now recommended as an early diagnostic modality in the workup of these patients.
Comment of ASSR reviewers	low quality study

Author, year	**Roh 2009**
Country	Korea
Technology	FDG-PET/CT
Disease	metastatic cervical adenopathy and an unknown primary site
Objective:	to assess diagnostic accuracy in detecting carcinoma of unknown primary to assess diagnostic accuracy in M staging
Index test	FDG-PET/CT
Comparator	CT (detection of carcinoma of unknown primary)
Reference standard	panendoscopy and biopsy histological findings or follow up imaging after therapy (M staging)
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with retrospective design and consecutive 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
Reference standard independent of the index test	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	not reported
Withdrawals from the study explained	no withdrawals

Patients number and characteristics	44 (37 men, 7 women), of median age 58 years (range 39-73 years) all consecutive patients with cervical metastases from cancer of unknown primary newly diagnosed between January 2004 and March 2007 at our institution. Patients presenting with palpable malignant neck masses underwent careful physical and endoscopic examinations of the upper aerodigestive tract and fine-needle aspiration cytology of the neck masses. All patients were evaluated by head and neck computed tomography (CT) and whole-body FDGPET/CT prior to panendoscopy and guided biopsy of the tonsils, base of the tongue, nasopharynx, and other sites suspected of harboring primary tumors. Pathology of the metastatic neck diseases included squamous cell carcinoma in 33 patients (75%), adenocarcinoma in 6, undifferentiated carcinoma in 3, salivary ductal carcinoma in 1, and anaplastic carcinoma in 1. Six patients had N1 disease, 29 had N2, and 9 had N3.
Pre-test probability	36.4% (16 out of 44)
Results	primary tumors were detected in 16 patients (36.4%): 9 tumors in the palatine tonsil; 2 in the nasopharynx; 2 at the base of the tongue; and 1 each in the hypopharynx, oral cavity, and thyroid gland Detection of primary tumor FDG-PET/CT sensitivity 87.5% (61-98) specificity 82.1% (63-93) CT sensitivity 43.7% (19-70) specificity 89.3% (71-97) M staging FDG-PET/CT sensitivity 100% (54-100) specificity 97.5% (86-99)
Authors' recommendations and conclusions	We found that combined FDG-PET/CT is useful as a primary screening method for detection of occult primary cancers, nodal staging, and distant metastases in patients with cervical metastases from cancer of unknown primary. In addition to its high sensitivity, combined FDG-PET/CT appears to improve the relatively low specificity of FDG-PET caused by poor spatial resolution. Improvements in the detection and staging of primary tumors may lead to proper therapeutic planning for cancer of unknown primary patients.

Author, year	**Waltonen 2009**
Country	USA
Technology	FDG-PET or FDG-PET/CT
Disease	patients with metastatic carcinoma of the neck from an unknown primary
Objective:	to assess diagnostic accuracy in detecting occult primary tumor location
Index test	FDG-PET or FDG-PET/CT
Comparator	CT of the neck
Reference standard	panendoscopy and biopsy
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with retrospective design and opportunistic 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
Reference standard independent of the index test	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	not applicable

Patients number and characteristics	93 patients underwent FDG-PET from a consecutive sample of 183 patients; 141 were male (77%) and 42 female (23%) age range from 17 to 86 years, median age: 55 years Patients diagnosed as having unknown primary cancer in our practice undergo, with few exceptions, imaging studies and examination under anesthesia with panendoscopy. If no primary tumor is evident during endoscopy, directed biopsies are obtained from the nasopharynx, tonsils (deep biopsies or unilateral or bilateral tonsillectomy), base of the tongue, and hypopharynx. When imaging studies detect suspicious primary tumor sites, we will carefully examine and obtain biopsy specimens from these areas during endoscopy. If no obvious primary tumor is evident, directed biopsy specimens are also obtained from the remainder of the foregoing locations. Patients were examined by 1 or more of 4 different radiological studies: CT scan of the neck (146 patients [79.8%]), MR imaging of the neck (13 [7.1%]), whole body fludeoxyglucose PET scan (41 [22.4%]), or whole body fludeoxyglucose PET-CT fusion scan (52 [28.4%]).
Pre-test probability	Not computable for FDG-PET
Results	CT of neck (146 patients) changes in management, 2 (1.4%) sensitivity 21.5% specificity 80.7% FDG-PET (41 patients) changes in management 4 (9.8%) sensitivity 42.9% specificity 72.4% FDG-PET/CT (52 patients) changes in management 12 (23%) sensitivity 74.2% specificity 72%
Authors' recommendations and conclusions	Diagnostic workup including PET-CT, alongside panendoscopy with directed biopsies including bilateral tonsillectomy, offers the greatest likelihood of successfully identifying occult primary tumor location
Comment of ASSR reviewers	low quality study

Synoptic table of primary studies on detection of cancer of unknown primary including only particular subgroups of patients (palatine tonsil cancer, non squamous carcinoma)

Author, year	Technology	Patient number	Study characteristics or limits	Pre-test probability	Sensitivity	Specificity
Paul 2007	FDG-PET, FDG-PET/CT	14	patients with cervical lymph node metastases without apparent primary, with biopsy positive for non squamous carcinoma; retrospective design	64.3%	77.8%	80.0%
Wong 2007	FDG-PET/CT	53	patients with cervical lymph node metastases with apparent primary from palatine tonsil cancer case-control design with retrospective recruitment and control obtained from patients with other cancer	18.9%	100%	81.0%

Primary studies on detection of cancer of unknown primary including only particular subgroups of patients

Author, year	Paul 2007
Country	Switzerland
Technology	FDG-PET, FDG-PET/CT
Disease	patients with cervical lymph node metastases without apparent primary, with biopsy positive for non squamous carcinoma
Objective:	to assess diagnostic accuracy in detecting non squamous primary tumor
Index test	FDG-PET, FDG-PET/CT
Comparator	none
Reference standard	cytology o r histology
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study with retrospective design
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	no
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not applicable
Execution of the index and comparator tests adequately described	yes
Reference standard independent of the index test	no
Did patients receive the same reference standard regardless of the index test result	no
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	not reported
Withdrawals from the study explained	no withdrawals

Patients number and characteristics	14 (5 women and 9 men) with a mean age of 63.2 years (range 29-85 years) The findings of the clinical evaluation and imaging including at least a chest X-ray was available in all patients. PET or PET/CT scanning was done in these patients as part of the work up before or after imaging with morphological methods (ultrasound, CT, MRI) of the head and neck area, thorax, and abdomen. In all patients with additional CT and MRI studies these structural imaging tests were acquired using standard protocols with contrast enhancement. The result of cytology or histology of the neck metastases was adenocarcinoma and undifferentiated adenocarcinoma (n 9), undifferentiated carcinoma (n. 3), undifferentiated neuroendocrine tumor (n. 1) and low-grade sarcoma (n. 1)
Pre-test probability	64.3% (9 out of 14)
Results	PET detected pathological FDG uptake suspicious for the primary in eight patients. PET or PET/CT findings were true positive in 7 patients, true negative in 4, false positive in 1, and false negative in 2 patients
Authors' recommendations and conclusions	The results suggest that whole body imaging with FDG-PET and PET/CT can be useful to identify unknown primaries of non-SCC origin. However, the work up of patients undergoing PET or PET/CT in our study was very heterogeneous and the primary was more likely found in patients without extensive imaging before PET scanning. Further studies should evaluate if the histology of a neck nodal metastasis should influence the choice of the imaging method and the role of PET and PET/CT imaging for the work up of patients with a non-SCC neck lymph node metastasis of an unknown primary.
Comment of ASSR reviewers	very low quality study

Author, year	**Wong 2007**
Country	United Kingdom
Technology	FDG-PET/CT
Disease	patients with cervical lymph node metastases with apparent primary from palatine tonsil cancer
Objective:	to assess diagnostic accuracy in detecting primary tumor
Index test	FDG-PET/CT
Comparator	none
Reference standard	only in the case group: flexible naso-endoscopy and head and neck CT/magnetic resonance (MR) and subsequent histological confirmation of pharyngeal palatine tonsil primary cancer
Outcomes considered	sensitivity, specificity
Study design	case-control design 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	no
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not applicable
Execution of the index and comparator tests adequately described	yes
Reference standard independent of the index test	no
Did patients receive the same reference standard regardless of the index test result	no
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	not reported
Withdrawals from the study explained	no withdrawals

Patients number and characteristics	53 The histologically proven occult pharyngeal palatine tonsil primary cancer patient group consisted of 10 consecutive patients (8 males and 2 females, aged 46-58 years, mean age 54 years) who presented with squamous cell carcinoma neck nodes where no primary site identified on full clinical assessment which included flexible naso-endoscopy and head and neck CT/magnetic resonance (MR) and had subsequent histological confirmation of pharyngeal palatine tonsil primary cancer The control group comprised 43 consecutive subjects (25 males and 18 females, aged 34-89 years, mean age 63 years) who had been referred for evaluation of known or suspected cancer and had no history or clinical suspicion of head and neck cancer.
Pre-test probability	18.9%
Results	ROC analysis showed that a SUV max difference cut off of 0.83 would achieve a 100% (95% CI 0.69-1.0) and specificity of 81% (95% CI 0.66-0.92)
Authors' recommendations and conclusions	There is considerable variation of pharyngeal palatine tonsil FDG uptake in patients with no pharyngeal palatine tonsil primary cancer. However, in the same patient there is generally only a small difference in uptake between left and right sides. The absolute difference in SUV max between left and right pharyngeal palatine tonsil is a potentially useful parameter for distinguishing between normal FDG uptake in pharyngeal palatine tonsil from occult pharyngeal palatine tonsil primary cancer.
Comment of ASSR reviewers	very low quality study

CHAPTER 6
N staging of patients with head and neck cancer

Diagnostic accuracy

Systematic reviews

Author, year	Facey 2007
Technology	FDG-PET
Disease	head and neck cancer
Objective	to assess: ▪ **X** N staging
Inclusion criteria	P patients with head and neck cancer I FDG-PET C all available R not specified O diagnostic accuracy for N staging 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 systematic reviews (including 11, 17, 7 primary studies respectively), 12 additional primary studies cross sectional diagnostic accuracy studies, with prospective or retrospective recruitment
N. of included patients	3 systematic reviews: 369 and 229 (1 systematic review not reported any number) primary studies: 498
Reference standard	systematic reviews: histopathology or not reported primary studies: neck dissection and histopathology; some studies also follow up
Comparator	CT, MRI, fine-needle aspiration biopsy (FNAB), US
Pre-test probability	not reported
Performance results	Only descriptive results. Three systematic reviews and 12 additional primary studies studied PET in staging regional lymph node involvement. Four studies in patients with clinically N0 necks showed that PET sensitivity was much lower than that of fine needle aspiration biopsy. Eight studies in populations of mixed or unspecified stage patients showed that PET or PET + CT had sensitivity of approximately 80% and specificity of 80-97%. This was comparable to or better than CT or MRI in most studies. One of these studies used SLNB on PET negative necks to improve sensitivity. There is little evidence of documented change in management, but one PS showed that PET + SLNB reduced the number of radical neck dissections from 45 out of 62 compared with 35 out of 62 on CT.
Recommendations and conclusions	none reported
Comment of ASSR reviewers	meta-analysis not performed

Author, year	**Kyzas 2008**
Technology	FDG-PET
Disease	all kind of unknown primary tumors (including the subgroup of patients with cervical lymph node metastases from suspected primary head and neck cancer)
Objective	to assess: ▪ **X** N staging
Inclusion criteria	P patients with head and neck squamous cell carcinoma at the initial staging before surgical treatment (both patients with and without cancerous lymph node infiltration according to histopathologic examination) I FDG-PET, FDG-PET/CT C CT, MRI, and ultrasound with fine-needle aspiration (USFNA) R histopathologic examination O diagnostic accuracy S retrospective and prospective studies
Years covered by the search	up to July 2007
Study selection data abstraction, quality assessment performed by two authors independently	yes
Comprehensive bibliographic search: at least two databases searched	No (only Medline)
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	no
Searched also unpublished studies	no
Language restriction	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 (design, blinding)
Results of quality assessment used to formulate results and conclusions	yes: subgroup analysis report in the result section and comments in the discussion section
Meta-analysis performed with appropriate statistic methods	yes

Publication bias assessed	no
N. of included studies study design	32 studies (10 studies including only patients with clinically negative neck) 13 studies prospective The evaluation of 18 F-FDG-PET results was stated to have been done in a blinded fashion in only five studies. Another five studies stated explicitly that evaluation was not blinded, whereas the others did not comment on this design aspect. In 19 studies, 18 F-FDG-PET positivity was stated to have been assessed in a qualitative manner, whereas in 8 studies it was stated to have been assessed by quantitative methods using standardized uptake values
N. of included patients	1 236 (311 patients included in clinically negative neck studies)
Reference standard	histopathology
Comparator	CT, MRI, ultrasound guided fine-needle aspiration biopsy and conventional methods gathered
Pre-test probability	not reported and not computable
Performance results	all patients FDG-PET sensitivity 79% (95% CI 72-85%) specificity 86% (95% CI 83-89%) all patients with a comparator test performed 18 F-FDG-PET sensitivity 80% (95% CI 72-87%) specificity 86% (95% CI 82-90%) conventional methods sensitivity 75% (95% CI 65-83%) specificity 79% (95% CI 72-85%) clinically neck negative patients 18 F-FDG-PET sensitivity 50% (95% CI 37-63%) specificity 87% (95% CI 76-93%) clinically neck negative patients with a comparator test performed (204 patients) F-FDG-PET sensitivity 52% (95% CI 39-65%) specificity 93% (95% CI 87-96%) conventional methods sensitivity 45% (95% CI 25-67%) specificity 87% (95% CI 72-95%)
Recommendations and conclusions	18 F-FDG-PET has good diagnostic performance in the overall pretreatment evaluation of patients with HNSCC but still does not detect disease in half of the patients with metastasis and cN0.

Synoptic table of primary studies on N staging of patients with head and neck cancer, published after Kyzas' systematic review (2008)

Author, year	Technology	Patient number	Cancer type	cN0 %	Neck dissection	Reference standard	Sources of bias	Pre test probability %	Sensitivity %	Specificity %
Burri 2008	PET	18	HN, stage 2-4	nr	all	histopathology	selection of patients on applicability of reference standard (neck dissection)	52.6	90.0	77.8
	CT								66.7	77.8
Chen 2006a	PET	20	nasopharyngeal, stage I-IV	nr	not reported	histopathology, follow up	retrospective design, not blinding	95.0	100	100
	CT								89.5	100
Fleming 2007	PET/CT	39	HN, stage II-IV	nr	all	histopathology	retrospective design, blinding not reported, selection of patients on applicability of reference standard (neck dissection)	56.4	86.4	94.1
Iyer 2010	PET/CT	80	HN	67	all	histopathology	retrospective design, blinding not reported, selection of patients on applicability of reference standard (neck dissection)	69.9	93.1	88.0

Author, year	Technology	Patient number	Cancer type	cN0 %	Neck dissection	Reference standard	Sources of bias	Pre test probability %	Sensitivity %	Specificity %
Kim 2007a	PET	32	oropharyngeal, stage III-IV	19	all	histopathology	retrospective design, blinding not reported, selection of patients on applicability of reference standard (neck dissection)	74.4	96.6	90.0
	CT/MRI								75.9	90.0
Kim 2008	PET	67	oral, stage I-IV	63	all	histopathology	retrospective design, selection of patients on applicability of reference standard (neck dissection)	42.7	84.4	76.7
	CT/MRI								65.6	81.4
Krabbe 2010	PET	27	oral, oropharyngeal, stage I-IV	nr	all	histopathology	blinding not reported, selection of patients on applicability of reference standard (neck dissection)	44.4	83.3	93.3
Kubicek 2010	PET/PET-CT	110	HN, stage I-IV	nr	all	histopathology	retrospective design, blinding not reported, selection of patients on applicability of reference standard (neck dissection)	60.9	92.5	90.7
Meller 2006	PET	36	HN, stage III-IV	0	all	histopathology	blinding not reported, selection of patients on applicability of reference standard (neck dissection)	58.3	85.7	80.0
	US								95.2	40.0

Author, year	Technology	Patient number	Cancer type	cN0 %	Neck dissection	Reference standard	Sources of bias	Pre test probability %	Sensitivity %	Specificity %
Minovi 2007	PET	23	HN, stage I-IV	44	nr	biopsy	blinding not reported, incomplete reference standard	30.4	100	87.5
	MRI								85.7	87.5
Murakami 2007	PET/CT	23	HN, stage II-IV	35	all	histopathology	retrospective design, blinding not reported, selection of patients on applicability of reference standard (neck dissection)	65.2	100	100
	clinical staging								93.3	75.0
Nahmias 2007	PET/CT	70	oral	67	all	histopathology	retrospective design, blinding not reported, selection of patients on applicability of reference standard (neck dissection)	52.9	89.2	78.8
Pentenero 2008	PET/CT	15	oral	nr	all	histopathology	selection of patients on applicability of reference standard (neck dissection)	10.5	0	82.4
Piao 2009	PET/CT	56	oropharyngeal	nr	all	histopathology	blinding not reported, incomplete reference standard	30.4	83.5	90.8

Author, year	Technology	Patient number	Cancer type	cN0 %	Neck dissection	Reference standard	Sources of bias	Pre test probability %	Sensitivity %	Specificity %
Richard 2010	PET/CT	50	HN, stage I-IV	42	all	histopathology	retrospective design, blinding not reported, selection of patients on applicability of reference standard (neck dissection)	20.8	83.0	94.0
Rodrigues 2009	PET/CT	44	HN	nr	all	histopathology	retrospective design, blinding not reported, selection of patients on applicability of reference standard (neck dissection)	54.5	70.0	82.0
	CECT								57.0	88.0
Roh 2007a	PET/CT	28	salivary glands, stage I-IV	nr	all	histopathology	retrospective design, blinding not reported, selection of patients on applicability of reference standard (neck dissection)	30.4	93.3	84.6
	CECT								80.0	76.9
Schroeder 2008	PET	17	oral, oropharyngeal, T1-T2, N0	100	all	histopathology	retrospective design, selection of patients on applicability of reference standard (neck dissection)	35.3	0	100
	CT								100	50.0
	MRI								83.3	9.1

Author, year	Technology	Patient number	Cancer type	cN0 %	Neck dissection	Reference standard	Sources of bias	Pre test probability %	Sensitivity %	Specificity %
Veit-Haibach 2007	PET/CT	55	HN	nr	all	histopathology	retrospective design, blinding not reported, selection of patients on applicability of reference standard (neck dissection)	not reported	87.0	79.0
	CT								77.0	75.0
Yamazaki 2008	PET	26	HN, T2-T4	nr	all	histopathology	blinding not reported, selection of patients on applicability of reference standard (neck dissection)	65.7	73.9	91.7
	CT			nr					78.3	58.3
Yoon 2009	PET/CT	67	HN, T1-T4	nr	all	histopathology	retrospective design, selection of patients on applicability of reference standard (neck dissection)	not reported	81.1	98.2
	MRI								77.0	99.4
	CT								77.0	99.4
	US								78.4	98.5
Yoshida 2009	PET/CT	40	HN, stage I-IV	nr	not reported	not reported	reference standard not reported	60.0	91.7	100
	CECT								82.6	100
	MRI								87.5	100
Zytoon 2007	PET/CT	23	HN	nr	not reported	not reported	reference standard not reported	not reported	88.9	78.6
	CT								66.7	85.7
	MRI								66.7	92.9

HN = head and neck cancer

Synoptic table of primary studies on N staging of patients with head and neck cancer and clinically node negative neck, published after Kyzas' systematic review (2008)

Author, year	Technology	Patient number	Cancer type	cN0 %	Neck dissection	Reference standard	Sources of bias	Pre test probability %	Sensitivity %	Specificity %
Iyer 2010	PET/CT	32	HN	100	all	histopathology	retrospective design, blinding not reported, selection of patients on applicability of reference standard (neck dissection)	19.9	65.5	96.6
Kim 2008	PET	46	oral, stage I-IV	100	all	histopathology	retrospective design, selection of patients on applicability of reference standard (neck dissection)	23.9	54.5	88.6
Nahmias 2007	PET/CT	47	oral	100	all	histopathology	retrospective design, blinding not reported, selection of patients on applicability of reference standard (neck dissection)	34.0	75.0	77.4
Richard 2010	PET/CT	21	HN, stage I-IV	100	all	histopathology	retrospective design, blinding not reported, selection of patients on applicability of reference standard (neck dissection)	not reported	88.0	62.0

Author, year	Technology	Patient number	Cancer type	cN0 %	Neck dissection	Reference standard	Sources of bias	Pre test probability %	Sensitivity %	Specificity %
Schroeder 2008	PET	17	oral, oropharyngeal, T1-T2, N0	100	all	histopathology	retrospective design, selection of patients on applicability of reference standard (neck dissection)	35.3	0	100
	CT								100	50.0
	MRI								83.3	9.1

HN = head and neck cancer

CHAPTER 7
M staging and detection of synchronous second primary tumor in patients with locally advanced head and neck cancer

Diagnostic accuracy

Systematic reviews

Author, year	Xu 2010
Technology	FDG-PET, FDG-PET/CT
Disease	any kind of head and neck cancer
Objective	to assess: ▪ M staging ▪ detection of second primary cancer
Inclusion criteria	P patients with any kind of head and neck cancer at the initial staging I FDG-PET, FDG-PET/CT C none R histopathologic examination and/or follow up O diagnostic accuracy in M staging or in detecting second primary cancer S retrospective and prospective studies
Years covered by the search	up to September 2009
Study selection data abstraction, quality assessment performed by two authors independently	yes
Comprehensive bibliographic search: at least two databases searched	yes Medline, Embase, Cochrane Library
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	no
Searched also unpublished studies	yes
Language restriction	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 (QUADAS tool)

Results of quality assessment used to formulate results and conclusions	yes: only descriptive data in the result section
Meta-analysis performed with appropriate statistic methods	yes
Publication bias assessed	no
N. of included studies study design	12 studies (7 with data on FDG-PET and 7 with data on FDG-PET/CT) 7 studies prospective design All studies had a suboptimal design in regard to the examination with the same reference standard (100% for "no" responses to question 6), and the interpretation of the reference standard results without knowledge of the index test results (100% for "no" responses to question 11)
N. of included patients	1 445 (median 94.5, range 12-349) FDG-PET studies 797 patients FDG-PET/CT studies 795 patients
Reference standard	histopathology and or follow up of at least 6-24 months
Comparator	none
Pre-test probability	median 13% (range 6.1-25%)
Performance results	FDG-PET sensitivity 85% (95% CI 78-90%) chi square 7.12 (p = 0.417) specificity 95% (95% CI 93-97%) chi square 4.46 (p = 0.725) FDG-PET/CT sensitivity 88% (95% CI 79-94%) chi square 11.02 (p = 0.088) specificity 95% (95% CI 93-96%) chi square 9.18 (p = 0.164)
Recommendations and conclusions	Whole-body PET and PET-CT have good diagnostic performance in initial M staging of head and neck cancer; although PET-CT tends to have higher accuracy than PET

Synoptic table of primary studies on M staging or detection of second primary of patients with head and neck cancer, published after Xu's systematic review (2011)

Author, year	Technology	Patient number	Cancer type	Target	Reference standard	Sources of bias	Pre test probability %	Sensitivity %	Specificity %
Liu 2006	PET	202	nasopharyngeal cancer; all stages	bone metastasis	at least 1 year of follow up	design and blinding not clear	18.3	70.0	98.8
	scintigraphy							36.7	97.7
Haerle 2010	PET/CT	311	any head and neck cancer; 90% of patients stage III or IV	second primary cancer	histopathology or follow up	not consecutive sample	4.5	100	93.8
	panendoscopy							74.0	99.7
Kaida 2009	PET	70	hypopharyngeal cancer; 86% of patients stage III or IV	second primary cancer	histopathology and follow up of at least 6 months	design not clear; partial blinding	17.1	91.7	94.8
Wallowy 2009	PET (with quantitative cut off)	84	oral or oropharyngeal cancer with a positive PET; 73% of patients stage III or IV	metastasis	histopathology and follow up of at least 6 months	selection of patients positive to PET; blinding not reported	31.0	38.5	100
Roh 2007b	PET	86	any head and neck cancer with a positive intrathoracic PET	intrathoracic metastasis	histopathology or follow up	selection of patients positive to PET	not reported	84.0	85.0
	CT							53.0	77.0

Author, year	Technology	Patient number	Cancer type	Target	Reference standard	Sources of bias	Pre test probability %	Sensitivity %	Specificity %
Senft 2008	PET	92	any head and neck cancer with a high risk of distant metastasis on the basis of a clinical score mainly based on the number of involved lymph nodes	metastasis or second primary cancer	histopathology or follow up of at least 12 months	partial blinding	41.3 (32.6 metastasis; 8.7 second primary)	58.0	93.0
	CT							39.0	94.0

Impact on clinical outcomes

Primary studies

Author, year	Rothschild 2007
Country	Switzerland
Technology	FDG-PET/CT
Disease	locally advanced oro- or hypopharyngeal carcinoma
Objective:	to assess the impact on clinical outcomes of PET/CT staging followed by Intensity-Modulated Radiotherapy (IMRT)
Index test	PET/CT staging followed by Intensity-Modulated Radiotherapy (IMRT)
Comparator	3D-conformal radiotherapy without PET/CT
Outcomes considered	1-year and 2-year overall survival and event-free survival rate
Study design	case-control study
Recruitment	retrospective; not reported if consecutive
Control of confounding factors	only partial; cases unbalanced with respect to chemotherapy (performed in 100% of cases and 79% of controls)
Patients characteristics	case were 45 patients with stage IVA oro- or hypopharyngeal carcinoma were staged with an integrated PET/CT and treated with definitive chemoradiation with IMRT from 2002 until 2005. Controls were 86 patients treated between 1991 and 2001 without PET/CT and 3D-conformal radiotherapy matched with respect to gender, age, stage, grade, and tumor location
Results	Overall survival of patients with PET/CT and IMRT was 97 and 91% at 1 and 2 years respectively, compared to 74 and 54% for patients without PET/CT or IMRT ($p = 0.002$). The event-free survival rate of PET/CT-IMRT group was 90 and 80% at 1 and 2 years respectively, compared to 72 and 56% in the control group ($p = 0.005$)
Authors' recommendations and conclusions	PET/CT in combination with IMRT and chemotherapy for pharyngeal carcinoma improve oncological therapy of pharyngeal carcinomas. Long-term follow up is needed to confirm these findings

CHAPTER 8
Target volume definition of curative radiation treatment

Systematic reviews

Author, year	Facey 2007
Technology	FDG-PET
Disease	head and neck cancer
Objective	to assess: ▪ **X** diagnosis ▪ **X** staging ▪ **X** target volume definition ▪ **X** diagnosis of suspected recurrence or re-staging
Inclusion criteria	P patients with head and neck cancer I FDG-PET C all available R not specified O change in volume, diagnostic accuracy, change in management 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 agreement studies
N. of included patients	135
Reference standard	none
comparator	CT
Pre-test probability	not applicable
Performance results	only descriptive results From the included studies resulted "change in GTV or dose or the number of irradiated nodes in several patients, compared with CT"
Recommendations and conclusions	no
Notes	meta-analysis not performed

Synoptic table of primary studies on role of FDG-PET in tumor volume definition for radiotherapy treatment planning in head and neck cancer, published after Facey's systematic review (2007)

Author, year	Patient number	Patient characteristics	Technology vs comparator	Blinding	GTV	PTV	Other outcomes
Ashmalla 2007	25	head and neck cancer	FDG-PET/CT CT no verification	yes	11/25 (44%) reduction with PET/CT 6/25 (24%) increase with PET/CT		
Deantonio 2008	22	head and neck cancer	FDG-PET/CT CT no verification	no	PET: mean 17.2 cm^3 (SD 16.8) CT: mean 20 cm^3 (SD 17.8) difference 2.8 cm^3 p = 0.2		
Dirix 2009	15	head and neck cancer	FDG-PET CT no verification	yes	PET: mean 18.7 cm^3 (range 5.2-81.1) CT: mean 33.6 cm^3 (range 14.5-85) difference 14.9 cm^3 p = 0.0005		
El-Bassiouni 2007	25	head and neck cancer	FDG-PET/CT CT no verification	yes	PET: mean 34.2 cm^3 (SD 34.1) CT: mean 41.6 cm^3 (SD 35.1) difference 7.4 cm^3 18/25 (72%) reduction with PET/CT 7/25 (28%) increase with PET/CT	PET: mean 165.9 cm^3 (SD 120.9) CT: mean 204.1 cm^3 (SD 119.7) difference: mean 38.1 cm^3 (SD 64), p = 0.0009	

Author, year	Patient number	Patient characteristics	Technology vs comparator	Blinding	GTV	PTV	Other outcomes
Geets 2006	18	head and neck cancer	FDG-PET CT no verification	not reported	PET: mean 17.5 cm^3 (SD 4.6) CT: mean 28.5 ml (SD 6.2) difference 11 cm^3 $p < 0.001$	PET 139.6 ± 16.7 ml CT 180.4 ± 22.5 ml difference: mean 40.8 cm^3 $p = 0.001$	V50: CT 100% vs PET 87% $p = 0.005$ V95: CT 100% vs PET 82% $p = 0.001$
Geets 2007	10	pharyngo-laryngeal cancer	FDG-PET CT no verification	not reported	PET: mean 30.1 cm^3 (SD 8.4) CT: mean 63.7 cm^3 (SD 19.7) difference 33.6 cm^3 $p <0.001$	mean PTV CT 256.9 ± 52.8 ml vs PTV PET 200.8 ± 31.6 ml difference: mean 56.1 ml	
Guido 2009	38	head and neck cancer	FDG-PET/CT CT no verification	not reported	PET: 29.38 cm^3 (range 2.87-95.02) CT: mean 34.54 cm^3 (range 3.56-109) difference 6.16 cm^3 $p <0.05$ 35/38 (92%) reduction with PET/CT	PET/CT-based boost PTV vs CT-based boost PTV increased in 3 (8%) of 38 cases and decreased in 35 (92%) of 38 cases	
Schinagl 2007	78	head and neck cancer	FDG-PET CT no verification	yes	PET: mean 21.5 cm^3 (95% CI 16.5-26.6) CT: mean 22.7 cm^3 (95% CI 17.4-27.9) difference 1.2 cm^3		

Author, year	Patient number	Patient characteristics	Technology vs comparator	Blinding	GTV	PTV	Other outcomes
Schinagl 2009	78 (108 nodes)	metastatic lymph nodes in head-and-neck cancer	FDG-PET CT some patients underwent verification with biopsy but results were not reported	no			PET (with different detecting method) identified 40-75% of enlarged nodes identified by CT PET (with different detecting method) identified 7-50% of "marginally enlarged" nodes identified by CT
Seitz 2009	55	oropharyngeal and oral cavity cancer	FDG-PET/CT MRI histopathologic verification	yes	mean difference from pathologic specimen GTV: MRI GTV: 1 ± 0.5 cm^3 PET/CT GTV: 2 ± 0.5 cm^3		
Wang 2006	16	head and neck cancer	FDG-PET/CT CT no verification	partial	difference (CT-PET/CT): mean 6.42 cm^3 9/16 reduction with PET/CT 5/16 increase with PET/CT		

Author, year	Patient number	Patient characteristics	Technology vs comparator	Blinding	GTV	PTV	Other outcomes
Zheng 2007	39	nasopharyngeal cancer	FDG-PET/CT CT no verification	not reported	PET: mean 13.7 cm^3 (range 1.3-31.3) CT: mean 15.9 cm^3 (range 3.1-37.4) difference 2.2 cm^3 27/39 (69%) reduction with PET/CT 12/39 (31%) reduction with PET/CT		volume difference ratio: 0.21 (range 0.05-0.76).

Primary studies

Author, year	Ashmalla 2007
Country	USA
Technology	FDG-PET/CT
Disease	head and neck cancer
Objective	to assess: ▪ **X** curative intent target volume definition
Patients characteristics	25 6 oropharynx, 4 nasopharynx/paranasal sinus 4 supraglottis, 4 lymph nodes with unknown primary 3 oral cavity, 2 thyroid 1 hypopharynx, 1 parotid median age was 68 years (range 57-81 years) intensity-modulated radiotherapy was used in 14 patients; the remaining patients were treated with standard radiation techniques
Index test	FDG-PET/CT
Comparator	CT
Verification test	none
Outcomes considered	GTV
Results	Overall (≥25%) modification of GTV using PET/CT planning vs CT-based planning was seen in 17 of 25 patients (68%). Of these 17, 11 demonstrated reduction in the GTV-CT. The reason for volume reduction was overstated lymph nodes in 9 cases (6 on the opposite side, and 3 on the same side), and the other 2 patients had volume reduction due to inclusion of postoperative scarring. Six patients demonstrated increase in volume with PET/CT; in 4 this was owing to unrecognized contralateral lymph nodes and in 2 to unsuspected base of skull involvement.
Study design	case series
Consecutive recruitment	not known
Independent and blind interpretation of index test, comparator and verification test results	yes
Authors' recommendations and conclusions	Using the "anatomic biologic halo" to contour GTV in PET/CT improves consistency among observers. The distinctive appearance of the described halo and its presence in all of the studied tumors make it attractive for GTV contouring in head and neck tumors. Additional studies are needed to confirm the correlation of the halo with presence of malignant cells

Author, year	**Deantonio 2008**
Country	Italy
Technology	FDG-PET/CT
Disease	head and neck cancer
Objective	to assess: ▪ **X** curative intent target volume definition
Patients characteristics	22 patients selected for radiotherapy. No patients were candidates for curative surgery. Fifteen patients were candidates for combined radiotherapy and platinum-based chemotherapy and 7 patients for radiotherapy alone
Index test	FDG-PET/CT
Comparator	CT
Verification test	none
Outcomes considered	GTV
Results	PET-GTV was smaller than CT-GTV (17.2 cc, with a standard deviation of 16.8 cc vs 20 cc, with a standard deviation of 17.8 cc) with a mean difference of 2.8 cc, that was not statistically significant ($p = 0.2$). However, PET/CT-GTV (26 cc), that was used for clinical purposes, was significantly greater than CT-GTV ($p < 0.0001$). These volumes had a mean difference of 6 cc. The mean PET out CT volume was 27% of the mean CT-GTV and resulted ≥10%, i.e. 2 cc, larger than the mean CT-GTV in 13/22 patients (59%)
Study design	case series
Consecutive recruitment	yes
Independent and blind interpretation of index test, comparator and verification test results	no
Authors' recommendations and conclusions	PET/CT fusion images could have a potential impact on both tumor staging and treatment planning

Author, year	**Dirix 2009**
Country	Belgium
Technology	FDG-PET
Disease	head and neck cancer
Objective	to assess: ▪ **X** curative intent target volume definition
Patients characteristics	15 patients with locally advanced HNSCC scheduled for primary radiotherapy. There were 13 male and 2 female patients, with a median age of 57 years (range 46-61 years). The patients had squamous cell carcinoma of the oropharynx (n. 6), larynx (n. 5), hypopharynx (n. 3), or oral cavity (n. 1). Treatment was decided by a multidisciplinary team according to institutional guidelines and consisted of concomitant chemo-radiotherapy in all 15 patients. Radiotherapy was delivered according to a hybrid fractionation schedule: 20 daily fractions of 2 Gy (40 Gy) followed by 20 fractions of 1.6 Gy twice daily (32 Gy) to a total dose of 72 Gy, as described previously (20). Patients also received cisplatinum (100 mg/m^2) intravenously, on the first day of weeks 1 and 4 (20)
Index test	FDG-PET
Comparator	CT
Verification test	none
Outcomes considered	GTV
Results	mean GTV CT was 33.6 mL (range 14.5-85 mL) mean GTV PET was 18.7 mL (range 5.2-81.1 mL). GTV_PET significantly smaller than the GTV CT (P = 0.0005)
Study design	case series
Consecutive recruitment	not reported
Independent and blind interpretation of index test, comparator and verification test results	yes
Authors' recommendations and conclusions	These results confirm the added value of 18F-FDG-PET and 18F-fluoromisonidazole PET for radiotherapy planning of HNSCC and suggest the potential of diffusion-weighted and dynamic enhanced MRI for dose painting and early response assessment.

Author, year	**El-Bassiouni 2007**
Country	Switzerland
Technology	FDG-PET/CT
Disease	head and neck cancer
Objective	to assess: ▪ **X** curative intent target volume definition
Patients characteristics	25 5 patients (20%) underwent surgical resection of their tumors with a gross residual (R1) before radiotherapy (IMRT), whereas the majority (80%) had a biopsy as the only surgical procedure. 11 patients (44%) had oropharyngeal carcinoma, 6 (24%) had nasopharyngeal carcinoma, 3 (12%) had carcinoma of the paranasal sinuses, 2 (8%) had hypopharyngeal carcinoma, 2 (8%) laryngeal carcinoma, and 1 patient (4%) had carcinoma of the floor of the mouth. 11 primary tumors (44%) were T2, 8 (32%) were T4, 2 (8%) were T1, and 1 (4%) was T3. 6 patients (24%) were node negative, 3 (12%) were N1, and 13 (52%) were N2. The majority of tumors (68%) were stage IV. Stage II and recurrent tumors accounted for 12% each, and stage I and III tumors accounted for 8% of cases.
Index test	FDG-PET/CT
Comparator	CT
Verification test	none
Outcomes considered	GTV, PTV
Results	The GTV CT had a median value of 29.6 mL (range 3.6-131.8 mL) and a mean of 41.6 ± 35.1 mL. This was larger ($p = 0.0022$) than the GTV PET, with a median of 23 mL (range 3-132.6 mL) and a mean of 34.2 ± 34.1 mL. The GTV CT was larger than the GTVPET in 18 cases (72%) and smaller in 7 cases (28%). The median PTV CT was 171.5 mL (range 36.4-492.5 mL) and the mean was 204.1-119.7 mL. The median PTV PET was 127.7 mL (range 36.1-472.5 mL), with a mean of 165.9 ± 120.9 mL ($p = 0.0009$). The mean reduction of PTV CT to PTV PET was 38.1 ± 64 mL. Using PTV PET for radiotherapy treatment planning resulted in a reduction of the high-dose PTV or the SIB volume in 72% of cases. In 55.6% of those cases, the reduction was 25-50%. On the other hand, it led to an increase in PTV in 28% of cases, of which 71.4% had an increase of <15% in volume.

Study design	case series
Consecutive recruitment	not reported
Independent and blind interpretation of index test, comparator and verification test results	yes
Authors' recommendations and conclusions	A case-specific PET signal threshold is optimal in PET-based radiotherapy treatment planning. Signal gating using a THR of 20% in tumors with S >30% ± 1.6% kBq/mL and 40% in tumors with S ≤30% ± 1.6% kBq/mL is suitable.

Author, year	**Geets 2006**
Country	Belgium
Technology	FDG-PET
Disease	head and neck cancer
Objective	to assess: ▪ **X** curative intent target volume definition
Patients characteristics	18 stage II-IV head and neck squamous cell carcinoma (HNSCC) 9 patients had an oropharyngeal tumor, 5 had a hypopharyngeal tumor and 4 had a laryngeal tumor. all patients were treated in the framework of organ preservation protocols using either a slightly accelerated schedule of radiotherapy (70 Gy in 6 weeks with a concomitant boost approach) or concomitant chemoradiation (70 Gy in 7 weeks; chemotherapy with carboplatine-5Fu on week 1, 4 and 7)
Index test	FDG-PET
Comparator	CT
Verification test	none
Outcomes considered	GTV, CTV, PTV dose distribution
Results	mean GTV CT 28.5 ± 6.2 ml vs PET 17.5 ± 4.6 ml, p <0.001 prophylactic CTV CT 97.7 ± 14.8 ml vs PET 72.7 ± 11.3 ml, p = 0.001 prophylactic PTV CT 180.4 ± 22.5 ml vs PET 139.6 ± 16.7 ml, p = 0.001 pre-treatment imaging modality on dose distribution V50: CT 100% vs PET 87% p = 0.005 V95: CT 100% vs PET 82% p = 0.001 mean (C/K SEM) dose to the ipsilateral parotid CT 38.6 ± 7.1% vs PET 30.7 ± 6.3% p = 0.004 mean (C/K SEM) dose to the contralateral parotid CT 14.4 +/- 3.4 %vs PET 11.2+/- 2.6% p = 0.014 maximum dose to the spinal cord CT 35.3 ± 2.5% vs PET 32.2 ± 3.6% p = 0.35
Study design	case series
Consecutive recruitment	not reported
Independent and blind interpretation of index test, comparator and verification test results	not reported

Authors' recommendations and conclusions	The use of pre-treatment FDG-PET and per-treatment CT or MRI significantly impacts on the delineation of TVs in pharyngo-laryngeal SCC, translating into more normal tissue sparing after conformal radiotherapy planning.

Author, year	**Geets 2007**
Country	Belgium
Technology	FDG-PET
Disease	pharyngo-laryngeal tumors
Objective	to assess: ▪ **X** curative intent target volume definition
Patients characteristics	10 mean age 57 years; range 45-80 years; stage III-IV cancer. 7 had hypopharyngeal tumors, 2 had laryngeal tumors and one had an oropharyngeal tumor. all patients were treated by radical concomitant chemoradiation (forward planning linac-based IMRT with a prophylactic dose of 50 Gy in 5 weeks and a therapeutic dose of 70 Gy in 7 weeks; chemotherapy with carboplatin/5-fluorouracil on weeks 1, 4 and 7). None of the additional imaging examinations interfered with the prescribed treatment and the results of the present study did not, in either way, modify patients' care
Index test	FDG-PET
Comparator	CT
Verification test	none
Outcomes considered	pre- and post-treatment GTV, CTV, PTV pre- and post-treatment imaging modality on dose distribution
Results	pre-treatment mean GTV CT 63.7 ± 19.7 ml vs GTV PET 30.1 ± 8.4 ml, p <0.001 mean CTV CT 156.6 ± 39.2 ml vs CTV PET 135.2 ± 36.3 ml mean PTV CT 256.9 ± 52.8 ml vs PTV PET 200.8 ± 31.6 ml Regarding the therapeutic primary tumor target volumes, for both CT and FDG-PET, a significant (ANOVA, p <0.01) progressive reduction in the CTVs and PTVs was observed throughout the course of treatment. At an average dose of 45 Gy, the mean CTV CT,45 Gy and PTV CT,45 Gy have decreased by 51% and 48%, respectively; corresponding value for FDG-PET reached 52% and 50%, respectively. Throughout the treatment course, the absolute mean CTVs and PTVs delineated from the GTVstat-PET,x Gy were always significantly smaller than the corresponding volumes delineated from the GTVCT,x Gy (ANOVA, p <0.001). *(continues)*

	Classical FDG-PET-based IMRT produced a significant (ANOVA, $p < 0.001$) tighter dose distribution compared to classical CT-based IMRT, but only for the high dose isodose volumes (i.e. PV90) Adaptive treatment with CT-based or PET-based IMRT further reduced the high dose volume isodoses, especially for FDG-PET-based IMRT. When various OARs or avoidance structures were compared, no difference between the various scenarios was observed. These findings are in agreement with the previous data that indicated that adaptive treatment and/or the use of FDG-PET only had an impact on the high dose volumes, i.e., above 60 Gy
Study design	case series
Consecutive recruitment	not reported
Independent and blind interpretation of index test, comparator and verification test results	not reported
Authors' recommendations and conclusions	Adaptive IMRT with FDG-PET images has a significant impact on the delineation of TVs and on the dose distribution in pharyngo-laryngeal tumors. Such an approach might thus be considered for dose escalation strategies.

Author, year	**Guido 2009**
Country	Italy
Technology	FDG-PET/CT
Disease	head and neck cancer
Objective	to assess: ▪ **X** curative intent target volume definition
Patients characteristics	38, 29 men and 9 women with head and-neck cancer mean age 59 years; range 35-82 7 had stage I, 11 had stage II, 10 had stage III, 8 had stage IVA, and 2 had stage IVB. primary tumor sites: 20 oropharyngeal tumors 4 laryngeal tumors 2 hypopharyngeal tumors 2 paranasal sinuses tumors 9 nasopharyngeal tumors 1 parotid gland
Index test	FDG-PET/CT
Comparator	CT
Verification test	none
Outcomes considered	GTV, PTV
Results	In 35 (92%) of 38 cases, the CT-based GTVs were larger than the PET/CT-based GTVs. The average total GTV from the CT and PET/CT scans was 34.54 cm3 (range 3.56-109) and 29.38 cm3 (range 2.87-95.02), respectively ($p < 0.05$). The PET/CT-based boost PTV compared with the CT-based boost PTV was increased in 3 (8%) of 38 cases and decreased in 35 (92%) of 38 cases. The comparison between the mean 18F-FDG-PET/CT-based boost PTVs and the mean CT-based boost PTVs did not show a statistically significant difference.
Study design	case series
Consecutive recruitment	yes
Independent and blind interpretation of index test, comparator and verification test results	not reported
Authors' recommendations and conclusions	GTVs, but not planning target volumes, were significantly changed by the implementation of combined PET/CT. Large multicenter studies are needed to ascertain whether combined PET/CT in target delineation can influence the main clinical outcomes

Author, year	**Schinagl 2007**
Country	Netherlands
Technology	FDG-PET/CT
Disease	head and neck cancer
Objective	to assess: ▪ **X** curative intent target volume definition
Patients characteristics	78, 59 men, 19 women median age 61 years; range 43-86 years stages II-IV squamous cell carcinoma of the head and neck area eligible for primary curative radiotherapy
Index test	FDG-PET
Comparator	CT
Verification test	none
Outcomes considered	GTV
Results	GTV CT (cm^3, 95% CI): 22.7 (17.4-27.9) PET (cm^3, 95% CI): GTVVIS 21.5 (16.5-26.6) GTV40% 16.4 (13.2-19.6) GTV50% 10.5 (8.2-12.7) GTVSBR 11.2 (8.2-12.9) The GTV method of applying an isocontour of a standardized uptake value of 2.5 failed to provide successful delineation in 45% of cases. For the other PET delineation methods, volume and shape of the GTV were influenced heavily by the choice of segmentation tool. On average, all threshold-based PET-GTVs were smaller than on CT. Nevertheless, PET frequently detected significant tumor extension outside the GTV delineated on CT (15-34% of PET volume)
Study design	case series
Consecutive recruitment	yes
Independent and blind interpretation of index test, comparator and verification test results	yes
Authors' recommendations and conclusions	The choice of segmentation tool for target-volume definition of head and neck cancer based on FDGPET images is not trivial because it influences both volume and shape of the resulting GTV. With adequate delineation, PET may add significantly to CT- and physical examination-based GTV definition.

Author, year	**Schinagl 2009**
Country	Netherlands
Technology	FDG-PET
Disease	metastatic lymph nodes in head-and-neck cancer
Objective	to assess: ▪ **X** curative intent target volume definition
Patients characteristics	78 patients (59 males and 19 females, median age 61 years, range 43-86 years) with stages II-IV SCC of the head and-neck area, eligible for primary curative radiotherapy, were prospectively enrolled from June 2003 until July 2006
Index test	FDG-PET
Comparator	CT
Verification test	some patients underwent biopsy but results are not reported
Outcomes considered	comparison of pathologic nodes between CT and PET for radiotherapy target volume definition of the neck
Results	Of 108 nodes classified as "enlarged" on CT, 75% were also identified by PETVIS, 59% by PET40%, 43% by PET50% and 43% by PETSBR. Of 100 nodes classified as "marginally enlarged", only a minority were visualized by FDG-PET. The respective numbers were 26%, 10%, 7% and 8% for PETVIS, PET40%, PET50% and PETSBR. PET40%N, PET50%N and PETSBRN, respectively, identified 66%, 82% and 96% of the PETVIS-positive nodes.
Study design	case series
Consecutive recruitment	yes
Independent and blind interpretation of index test, comparator and verification test results	no
Authors' recommendations and conclusions	Many lymph nodes that are enlarged and considered metastatic by standard CT-based criteria appear to be negative on FDG-PET scan. Alternately, a small proportion of marginally enlarged nodes are positive on FDG-PET scan. However, the results are largely dependent on the PET segmentation tool used, and until proper validation FDG-PET is not recommended for target volume definition of metastatic lymph nodes in routine practice.

Author, year	**Seitz 2009**
Country	Germany
Technology	FDG-PET/CT
Disease	oropharyngeal and oral cavity cancer
Objective	to assess: ▪ **X** curative intent target volume definition
Patients characteristics	55 (from a sample of 66 patients, 39 males, 27 females; mean age, 63 ± 14 years; age range 25-89 years) who fulfilled the following criteria: (a) clinical suspicion of a primary or recurrent carcinoma in the oropharynx and oral cavity (b) surgical excision of the tumor with histological diagnosis and calculation of the specimen volume, and (c) baseline whole-body 18F-FDG-PET/CT scan followed by head and neck MRI within 5 days and up to 5 days before surgery
Index test	FDG-PET/CT
Comparator	MRI
Verification test	histopathology
Outcomes considered	correlation of GTV
Results	The mean GTV in the pathologic specimen was 16.6 ± 18.6 ml, the mean volume derived by the MR imaging was 17.6 ± 19.1 ml, while the estimated by PET/CT volume was 18.8 ± 18.1 ml. Graph analysis showed the larger the tumor volume, the more pronounced the difference with the histopathologic specimen. The Bland-Altman analysis showed that the arithmetic mean of the difference between the pathologic and the MRI tumor volume estimation was -0.05 ± 0.14 (95% CI -0.08 to -0.009). The mean difference between the pathologic and the PET/ CT-based tumor volume calculation was -0.1 ± 0.19 (95% CI -0.14 to -0.04). MRI and PET/CT overestimated the tumor volume compared to the pathologic specimens. Moreover, PET/CT delivered higher volume results than MRI measurements.
Study design	case series
Consecutive recruitment	no
Independent and blind interpretation of index test, comparator and verification test results	yes
Authors' recommendations and conclusions	the diagnostic performance of FDG-PET/CT in the local staging of oral cancer is not superior to MRI

Author, year	**Wang 2006**
Country	USA
Technology	FDG-PET/CT
Disease	head and neck cancer
Objective	to assess: ▪ **X** curative intent target volume definition
Patients characteristics	28 patients with head and neck carcinoma (3 nasopharynx, 16 oropharynx, 6 hypopharynx, 2 oral cavities, 1 larynx) All underwent FDGPET/CT-guided IMRT The CT-based GTV and the PET/CT-based GTV are compared in a subset of 16 patients
Index test	FDG-PET/CT
Comparator	CT
Verification test	none
Outcomes considered	GTV
Results	In 9 cases, the CT-based GTVs are larger than the PET/CT-based GTVs by 11-40%. In 5 cases, the PET/CT-defined GTVs were larger than the CT-defined GTVs by 14-31%. Mean volume difference (GTV CT - GTV PET/CT): 6.42 cc
Study design	case series
Consecutive recruitment	not reported
Independent and blind interpretation of index test, comparator and verification test results	partial
Authors' recommendations and conclusions	Fused images were found to be useful to delineate GTV required in IMRT planning. PET/CT should be considered for both initial staging and treatment planning in patients with head and neck carcinoma.

Author, year	**Zheng 2007**
Country	China
Technology	FDG-PET/CT
Disease	nasopharyngeal cancer
Objective	to assess: ▪ **X** curative intent target volume definition
Patients characteristics	39 locally recurrent nasopharyngeal cancer
Index test	FDG-PET/CT
Comparator	CT
Verification test	none
Outcomes considered	GTV, volume difference ratio
Results	GTV CT 15.9 cm^3 (range 3.1-37.4 cm^3) GTV PET/CT 13.7 cm^3 (range 1.3-31.3 cm^3) GTV PET/CT was smaller and larger than the GTV CT in 27 (69%) and 12 (31%) cases, respectively. Additionally, the larger one did not always include the smaller one Volume difference ratio: 0.21 (range 0.05-0.76)
Study design	case series
Consecutive recruitment	not reported
Independent and blind interpretation of index test, comparator and verification test results	not reported
Authors' recommendations and conclusions	The addition of FDG-PET information might influence CT-based radiotherapy planning for locally recurrent nasopharyngeal carcinoma by altering the definition of the target volume, with the potential to avoid a geographic miss of true disease.

CHAPTER 10
Evaluation of response to chemotherapy or radiotherapy at the end of treatment

Diagnostic accuracy

Systematic reviews

Author, year	**Facey 2007**
Technology	FDG-PET
Disease	head and neck cancer
Objective	to assess: ▪ **X** primary diagnosis ▪ **X** staging ▪ **X** RT planning ▪ **X** response to therapy (after treatment) ▪ **X** diagnosis of suspected recurrence or re-staging
Inclusion criteria	P patients with head and neck cancer I FDG-PET C all available R not specified O diagnostic accuracy for primary diagnosis, staging, re-staging after treatment, recurrence; change in management for RT planning 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 systematic reviews (including respectively 15, 10, 15 primary studies; some of them in common), 8 additional primary studies (6 re-staging/early follow up [3 after CRT]; 2 true suspected recurrence) cross sectional diagnostic accuracy studies, with prospective or retrospective recruitment
N. of included patients	systematic reviews: 1 systematic review 350 patients; not reported in the others primary studies: 381 (re-staging/early follow up 290; suspected recurrence 91)
Reference standard	systematic reviews: not reported 1 systematic review; histopathology 1 systematic review; histopathology or follow up 1 systematic review primary studies: 6 studies combination of histopathologic results and follow up; 1 study only histopathology; 1 study only follow up
Comparator	primary diagnosis: CT or MRI
Pre-test probability	not reported
Performance results	not calculated: only descriptive results. "Two SRs with 15 and ten PSs, and seven additional PSs showed that PET sensitivity was approximately 80%, with specificity at least 90%, which was somewhat more accurate than CT/MRI for re-staging or recurrence. Another SR reported similar accuracy and eight studies with some evidence of change in patient management. The strongest evidence was detection of distant metastases in seven out of 22 patients. Most other changes were related to further diagnostic tests, were poorly documented, and no clear links with improvement in outcomes were made."
Recommendations and conclusions	none reported
Comment of ASSR reviewers	meta-analysis not performed

Author, year	**Isles 2008**
Technology	FDG-PET
Disease	head and neck squamous cell carcinoma after curative treatment, always including radiotherapy or chemo-radiotherapy
Objective	to assess: ▪ re-staging at the end of treatment ▪ diagnosis of suspected recurrence
Inclusion criteria	P suspicion of recurrent head and neck carcinoma or residual after radiotherapy or chemo-radiotherapy I FDG-PET C none R histopathologic examination and/or follow up O diagnostic accuracy in re-staging or detecting suspected recurrence both at the primary site and in the neck S retrospective and prospective studies
Years covered by the search	up to October 2007
Study selection data abstraction, quality assessment performed by two authors independently	yes
Comprehensive bibliographic search: at least two databases searched	yes Medline, Cochrane
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	no
Searched also unpublished studies	no
Language restriction	English
Overall number of references retrieved and n of included studies reported	yes
n. and references of excluded studies reported, reason given	only number of excluded studies
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: meta-regression and descriptive data in the result and discussion sections
Meta-analysis performed with appropriate statistic methods	yes (heterogeneity not reported)
Publication bias assessed	no

N. of included studies study design	27 studies; 20 for primary site recurrence and 13 for neck recurrence; 6 studies retrospective design; reference standards for included histology from biopsy or surgical specimen and length of disease free survival. Time from treatment to PET scan varied from 1 month to 13 years. Length of follow up was often not stated, and in some instances was too short for reliable extrapolation of results. 8 studies included patients with suspected recurrence; 15 studies included patients (usually with stage III-IV disease) after the curative treatment with radiotherapy or chemo-radiotherapy; 4 studies included only patients with cancer of larynx, 1 with oral cancer. Partial blinding (PET interpretation blinded to the other imaging tests) in the majority of studies.
N. of included patients	917 (median 12, range 8-97)
Reference standard	histopathology and/or follow up
comparator	none (in one table reported some studies on CT or MRI, retrieved without a systematic process)
Pre-test probability	not reported and not computable
Performance results	FDG-PET Primary site recurrence/residual disease sensitivity: pooled 94% (95% CI 87-97%) test for heterogeneity not reported specificity: pooled 82% (95% CI 76-86%) test for heterogeneity not reported When the QUADAS score is added as a term in the model, there is no effect on sensitivity for the primary site, but there is an effect on specificity, with a correlation between higher QUADAS scores and lower specificity (P-value 0.04). Recurrence/residual disease of nodal metastasis sensitivity: pooled 74% (95% CI 50-89%) test for heterogeneity not reported specificity: pooled 88% (95% CI 74-95%) test for heterogeneity not reported
Recommendations and conclusions	Positron emission tomography is highly accurate in this role. However it is less sensitive early after treatment and has poor anatomical detail. PET may reduce the requirement for check endoscopies and planned neck dissections. A protocol for its use in post-treatment surveillance is proposed.

Synoptic table of primary studies on evaluation of response to chemotherapy or radiotherapy at the end of treatment

Author, year	Technology	Patient number	Population	Reference standard	Sources of bias	Target	Pre test probability %	Sensitivity %	Specificity %
Andrade 2006	PET/CT 2-4 months after therapy	28	advanced head and neck cancer after IMRT	histopathology or follow up	uncertain design	primary site or node residual disease	46.4	76.9	93.3
	contrast-enhanced CT 2-4 months after therapy							92.3	46.7
Chan 2006	PET/CT 3 months after therapy	131	advanced nasopharyngeal cancer after curative chemo-radiotherapy with IMRT	histopathology or 6 months follow up after PET	prospective design	any residual disease	4.1	93.8	96.6
						primary site residual disease	3.8	100	98.4
						node residual disease	4.6	100	96.0
						metastases	3.8	80.0	95.2
	conventional work up 3 months after therapy					any residual disease	4.1	50.0	94.4
						primary site residual disease	3.8	60.0	92.1
						node residual disease	4.6	50.0	93.6
						metastases	3.8	40.0	98.4

Author, year	Technology	Patient number	Population	Reference standard	Sources of bias	Target	Pre test probability %	Sensitivity %	Specificity %
Chen 2006b	PET/CT 1-6 months after therapy	30	nasopharyngeal cancer after any curative treatment	histopathology or 6 months follow up after PET	uncertain design and blinding	primary site residual disease	6.7	50.0	84.6
	PET/CT 1-6 months after therapy					node residual disease	13.3	100	69.5
	contrast-enhanced CT 1-6 months after therapy					primary site residual disease	6.7	50.0	88.5
	contrast-enhanced CT 1-6 months after therapy					node residual disease	13.3	100	52.2
Fakhry 2006	PET/CT 3 months after therapy	61	advanced (stage III, IV) head and neck cancer after any curative treatment	histopathology or 6 months follow up after PET	prospective design, uncertain blinding	any residual disease	30.5	88.8	78.1
						primary site residual disease	24.6	86.7	82.6
						node residual disease	6.7	100	98.2
						metastasis	13.6	100	92.2

Author, year	Technology	Patient number	Population	Reference standard	Sources of bias	Target	Pre test probability %	Sensitivity %	Specificity %
Gourin 2009b	PET/CT 2-3 months after therapy	32	stage IV head and neck cancer after chemotherapy	neck dissection	retrospective design, consecutive recruitment, unblinding	node residual disease	31.3	60.0	36.4
Hoshikawa 2009	PET 0-4 months after therapy	27	advanced head and neck cancer after chemo-radiotherapy	histopathology	retrospective design, uncertain if consecutive recruitment, uncertain blinding	primary site or node residual disease	27.5	85.7	73.0
Inohara 2009	PET 2 months after therapy	48	node-positive head and neck cancer after chemo-radiotherapy	histopathology	uncertain design, uncertain if consecutive recruitment, uncertain blinding	node residual disease	30.0	50.0	88.1
	CT 2 months after therapy							72.2	78.6
Inohara 2010	PET (SUV max 2.7) 2 months after therapy	31	stage III-IV hypopharyngeal cancer after chemo-radiotherapy	not reported	prospective design, consecutive recruitment, partial blinding	primary site or node residual disease	not reported	71.0	76.0

Author, year	Technology	Patient number	Population	Reference standard	Sources of bias	Target	Pre test probability %	Sensitivity %	Specificity %
Ito 2010	PET/CT at <3 months after therapy	53	advanced head and neck cancer after with combined intra-arterial chemotherapy and concurrent radiotherapy	histopathology or 9 months follow up after PET	uncertain design, partial blinding	primary site or node residual disease	54.7	58.6	91.7
	C-Choline-PET at <3 months after therapy							55.2	75.0
Lyford-Pike 2009	PET/CT 2 months after therapy	38	advanced head and neck cancer after chemo-radiotherapy	histopathology	retrospective design, uncertain if consecutive recruitment, uncertain blinding	node residual disease	37.8	57.1	73.9
Malone 2009	PET/CT <2 months after therapy	31	III-IV stage head and neck cancer after chemo-radiotherapy	biopsy or follow up	retrospective design, uncertain if consecutive recruitment, uncertain blinding	primary site residual disease	not reported	83.0	54.0

Author, year	Technology	Patient number	Population	Reference standard	Sources of bias	Target	Pre test probability %	Sensitivity %	Specificity %
Martin 2009	PET or PET/CT 3 months after therapy	78	head and neck cancer after chemo-radiotherapy	histopathology or follow up	retrospective design, uncertain if consecutive recruitment, uncertain blinding	primary site residual disease	not reported	82.0	95.0
	conventional imaging 3 months after therapy							67.0	66.0
	clinical examination 3 months after therapy							65.0	87.0
Moeller 2009	PET/CT 2 months after therapy	98	III-IV stage head and neck cancer after radiotherapy	histopathology or follow up	prospective consecutive recruitment, unblinding, attrition of patients	primary site residual disease	11.2	70.0	93.7
						node residual disease	10.7	75.0	76.1
	CT					primary site residual disease	11.2	80.0	89.9
						node residual disease	10.7	87.5	65.7
Nayak 2007	PET/CT at < 6 months after therapy	43	IV stage head and neck cancer after chemo-radiotherapy with IMRT	histopathology or 5 months of follow up after PET	unclear design and recruitment, unblinding	node residual disease	18.6	87.5	91.4

Author, year	Technology	Patient number	Population	Reference standard	Sources of bias	Target	Pre test probability %	Sensitivity %	Specificity %
Oe 2007	PET "immediately" after therapy	total: 36 evaluated for end-of-treatment response 28	laryngeal cancer after any curative treatment	histopathology or 12 months of follow up after PET	retrospective design, uncertain if consecutive recruitment, uncertain blinding	local recurrence	57.1	93.8	91.7
Ong 2008	PET/CT at <6 months after therapy	65	N+ head and neck cancer after chemo-radiotherapy	histopathology or follow up	retrospective design, uncertain if consecutive recruitment, blinding	node residual disease	8.5	71.4	89.3
Passero 2010	PET/CT 2 months after therapy	53	stage III-IV head and neck cancer after chemo-radiotherapy	follow up	prospective design, not consecutive recruitment, blinding	any residual disease	not reported	88.2	69.4
Rabalais 2009	PET/CT at <7 months after therapy	52	head and neck cancer after chemo-radiotherapy with IMRT	histopathology or follow up	retrospective design, not consecutive recruitment, uncertain blinding	node residual disease	7.7	100	87.5

Author, year	Technology	Patient number	Population	Reference standard	Sources of bias	Target	Pre test probability %	Sensitivity %	Specificity %
Wang 2009	PET 4 months after therapy	44	stage III-IV head and neck cancer after chemo-radiotherapy	histopathology or follow up	prospective design, not consecutive recruitment, blinding	primary site residual disease	25.0	100	90.9
						node residual disease	22.7	100	97.1
						metastasis	11.4	100	97.4
	CT 4 months after therapy					primary site residual disease	25.0	100	67.0
						node residual disease	22.7	90.0	85.0
Yao 2009	PET 4 months after therapy	188	head and neck cancer after radiotherapy with IMRT with or without surgery	histopathology or follow up	retrospective design, not consecutive recruitment, uncertain blinding	primary site residual disease	7.4	85.7	85.6
						node residual disease	7.4	85.7	97.1

Author, year	Technology	Patient number	Population	Reference standard	Sources of bias	Target	Pre test probability %	Sensitivity %	Specificity %
Zytoon 2007	PET 2 months after therapy	18	head and neck cancer after any treatment	histopathology or follow up	retrospective design, not consecutive recruitment, blinding	primary site residual disease	not reported	100	90.9
						node residual disease		100	91.7
	CT 2 months after therapy					primary site residual disease		85.7	90.9
						node residual disease		83.3	91.7
	MRI 2 months after therapy					primary site residual disease		85.7	90.9
						node residual disease		83.3	91.7

CHAPTER 11

Follow up in patients with no suspicion of recurrence

Diagnostic accuracy

Synoptic table of primary studies on follow up of patients with head and neck cancer with no suspicion of recurrence

Author, year	Technology	Patient number	Population	Reference standard	Sources of bias	Target	Pre test probability %	Sensitivity %	Specificity %
Abgral 2009	PET/CT at 12-month follow up	91	head and neck cancer at any stage after any curative treatment, without any clinical evidence of recurrence	histopathology or 6 months follow up after PET	uncertain design and blinding	any recurrence	33.0	100	85.2
Kao 2009	PET/CT at 2/4-month after radiotherapy, then at 4- to 6-month intervals till 20-month follow up	80	head and neck cancer (stage II-IV) after any curative treatment (always including radiotherapy, definitive or adjuvant), without any clinical evidence of recurrence	histopathology or 6 months follow up after PET	retrospective design, uncertain blinding	any recurrence	30.0	92.0	78.0
						loco-regional recurrence		92.0	82.0
						local recurrence		88.0	88.0
						neck recurrence		100	91.0
						metastasis		93.0	96.0

Author, year	Technology	Patient number	Population	Reference standard	Sources of bias	Target	Pre test probability %	Sensitivity %	Specificity %
Krabbe 2009	PET/CT at set times (3, 6, 9, and 12 months) after the completion of curative treatment	48	advanced (stage III and IV) SCC of the oral cavity or oropharynx, without any clinical evidence of recurrence	histopathology or 6 months follow up after PET	prospective design, uncertain blinding	any recurrence	37.5	100	43.3
	physical examination (same schedule as PET)							0	60.0
Lee 2007	PET (at different times after therapy: 2-6 months: group I 6-12 mo: group II 12-24 mo: group III >24 mo: group IV)	159 (206 scans, 156 performed without and 50 for clinical suspicion)	head and neck cancer at any stage after any curative treatment, without any clinical evidence of recurrence	histopathology or 6 months follow up after PET	uncertain design, partial blinding	loco-regional recurrence (per-exam analysis)	19.9	90.3	91.2
						metastasis / second primary (per-exam analysis)	6.4	100	96.6

HN = head and neck cancer

Primary studies

Author, year	Abgral 2009
Country	France
Technology	FDG-PET/CT
Disease	head and neck squamous cell carcinoma without any clinical evidence of recurrence after any kind of treatment (surgical, radiotherapy, both)
Objective	to assess diagnostic accuracy in detecting recurrence (local or distant)
Index test	FDG-PET/CT at 12-month follow up
Comparator	none
Reference standard	histopathology or other imaging for true positive and 6-month follow up after PET for true negative
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study; not clear of retrospective or prospective design
Spectrum of patients representative of the individuals who will receive the test in practice	uncertain
Patients selection criteria clearly described	no
Reference standard likely to classify the target condition correctly	no
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not applicable
Execution of the index and comparator tests adequately described	yes
Reference standard independent of the index test	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	not reported

Withdrawals from the study explained	no withdrawals
Patients number and characteristics	91 (13 women and 78 men, with a mean age of 57.4 ± 9.4 years) All patients treated for histologically proven HNSCC from September 2005 to January 2008 at the University Hospital of Brest and at the Regional Hospital of Quimper and who did not show any findings suggestive of recurrence at 12 months of their usual follow up (consisting of a standard whole-body examination including inspection and palpation of all anatomic subsites of the head and neck [oral cavity, nasopharynx, oropharynx, hypopharynx and larynx] and an examination of internal structures by a mirror and a flexible endoscope) were included in the study. Patients with distant metastasis at the initial staging and with a previous history of recurrence were excluded.
Pre-test probability	33% (30/91)
Results	PET sensitivity 100% specificity 85.2%
Authors' recommendations and conclusions	The results of our study confirm the high effectiveness of 18F-FDG-PET/CT in the assessment of HNSCC recurrence and suggest that 18F-FDGPET/CT is more accurate than conventional follow up physical examination alone in the assessment of recurrence after previous curative treatment for HNSCC and could be proposed systematically at 12 months of the usual follow up.

Author, year	**Kao 2009**
Country	USA
Technology	FDG-PET/CT
Disease	head and neck cancer after treatment with radiotherapy, without any clinical evidence of recurrence
Objective:	to assess diagnostic accuracy in detecting loco-regional recurrence, distant metastases, and second primary tumors
Index test	FDG-PET/CT 2 to 4 months after the completion of RT and at 4-month to 6-month intervals thereafter
Comparator	physical examination at follow up appointments at 3-month intervals for the first 2 years and at 6-month intervals thereafter: collected data but not reported
Reference standard	biopsy for true positive, 6-month follow up after PET for true negative
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study; retrospective design; consecutive patients
Spectrum of patients representative of the individuals who will receive the test in practice	uncertain
Patients selection criteria clearly described	no
Reference standard likely to classify the target condition correctly	no
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not applicable
Execution of the index and comparator tests adequately described	yes
Reference standard independent of the index test	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	uncertain

Withdrawals from the study explained	9 withdrawals
Patients number and characteristics	80 (58 men, median age of 61 years, range 18-86 years) patients with stage II through IVB head and neck cancer who were treated with RT between July, 2005 and August, 2007 The median follow up was 20.5 months (range 6-38 months). All surviving patients had a minimum of 11 months of clinical follow up (median 22 months) after treatment and no patients were lost to follow up. The 2-year loco-regional control, distant control, progression-free survival, and overall survival rates were 86%, 83%, 77%, and 84%, respectively. Definitive RT was given to 41 patients and adjuvant RT was administered to 39 patients. A total of 62 patients received concurrent chemotherapy and/or cetuximab.
Pre-test probability	any recurrence 30% (24/80)
Results	any recurrence sensitivity 92% specificity 78% loco-regional sensitivity 92% specificity 82% local sensitivity 88% specificity 88% regional sensitivity 100% specificity 91% distant sensitivity 93% specificity 96% Eight patients (10%) developed disease recurrences or second primary tumors that were amenable to salvage surgery with negative surgical margins
Authors' recommendations and conclusions	Although post-therapy follow up using PET/CT is reportedly associated with a high false-positive rate in the irradiated head and neck, PET/CT appears to be a highly sensitive technique for the detection of recurrent disease. Furthermore, negative PET/CT results within 6 months of the completion of RT offer significant prognostic value.

Author, year	**Krabbe 2009**
Country	Netherlands
Technology	FDG-PET/CT
Disease	advanced squamous cell carcinoma in the oral cavity or oropharynx after completion curative treatment
Objective:	to assess diagnostic accuracy in detecting early tumor recurrence, distant metastases, and second primary tumors
Index test	FDG-PET/CT at set times (3, 6, 9, and 12 months) after the completion of initial therapy
Comparator	physical examination at follow up appointments at 3-month intervals for the first 18 months
Reference standard	biopsy additional diagnostic procedures for true positive, 6-month follow up after PET for true negative
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study; prospective design; consecutive patients
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	no
Reference standard likely to classify the target condition correctly	no
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not applicable
Execution of the index and comparator tests adequately described	yes
Reference standard independent of the index test	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	uncertain

Withdrawals from the study explained	no
Patients number and characteristics	48 (32 men, 16 women; mean age was 59.9 ± 9.7 years) Consecutive patients who had been treated curatively for an advanced (stage III and IV) SCC of the oral cavity or oropharynx were included after completion of their treatment (T0). Loco-regional recurrences, distant metastases, or a second primary tumor after a median follow up of 7.2 months (interquartile range 4.8-13.2) developed in 18 patients. During the study, 16 patients died after a median period of 1.6 years (interquartile range 0.7-1.9 years) after treatment; 15 deaths were due to malignancy, 1 was due to cardiac arrest.
Pre-test probability	any recurrence 37.5% (18/48)
Results	Incidence of recurrences and second primary tumors was 27% and 10%, respectively. 18F-FDG-PET was significantly (P = 0.035) more often in agreement with the gold standard than was regular follow up. 18F-FDG-PET showed a sensitivity, specificity, positive predictive value, and negative predictive value of 100%, 43%, 51%, and 100%, respectively. For regular follow up, these values were 0%, 60%, 0%, and 50%, respectively. 18F-FDG-PET accounted for a change in diagnostics or treatment in 63% of the patients and regular follow up in 25% of the patients. Sensitivity and specificity of 18F-FDG-PET were both irrespective of timing of 18F-FDG-PET. For the 3- and 6-months post-therapy results combined, 18F-FDG-PET detected malignancy in 16 of the 18 patients.
Authors' recommendations and conclusions	18F-FDG-PET is a suitable routine post treatment surveillance tool in oral and oropharyngeal SCC patients and detects malignancy before clinical suggestion by the regular follow up arises. The best timing of a systematic 18F-FDG-PET scan is between 3 and 6 mo after treatment.

Author, year	**Lee 2007**
Country	Korea
Technology	FDG-PET
Disease	head and neck squamous cell carcinoma
Objective:	to assess diagnostic accuracy in detecting loco-regional tumor recurrence, distant metastases, and second primary tumors
Index test	FDG-PET performed at different times (2-6 months, group I; 6-12 months, group II; 12-24 months, group III; >24 months, group IV) after the completion of initial therapy
Comparator	physical examination at follow up appointments at 3-month intervals for the first 18 months
Reference standard	biopsy additional diagnostic procedures for true positive, 6-month follow up after PET for true negative
Outcomes considered	sensitivity, specificity
Study design	diagnostic cross sectional study; uncertain design
Spectrum of patients representative of the individuals who will receive the test in practice	uncertain
Patients selection criteria clearly described	no
Reference standard likely to classify the target condition correctly	no
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not applicable
Execution of the index and comparator tests adequately described	yes
Reference standard independent of the index test	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes

Independent and blind interpretation of index test and reference standard results	yes for index test
Withdrawals from the study explained	yes
Patients number and characteristics	159 (median age 61 years, range 22-81 years, 87% men) all stages Patients who underwent to any treatment with curative intent: 71% radiation therapy and 69% the patients had surgical treatment. The median follow up period after completion of treatment was 24 months (range 3-65 months) We evaluated 206 post-treatment PET scans in these 159 patients; 112 patients had one scan, 33 patients had two scans, 12 patients had three scans, and 2 patients had four scans. The scans were classified into 4 groups according to time after completion of treatment: 2-6 months (group I), 6-12 months (group II), 12-24 months (group III), and >24 months (group IV). Each group was further subdivided by indication: those performed in the absence of any evidence of recurrence and those performed if there was any evidence of recurrence by conventional evaluation of symptoms, physical examination, chest radiograph, CT, and MRI. Of the 206 scans, 156 were performed without and 50 for clinical suspicion.
Pre-test probability	loco-regional recurrence 19.9% (per-exam denominator) metastasis/second primary 6.4% (per-exam denominator)
Results	loco-regional recurrence sensitivity 90.3% specificity 91.2% metastasis/second primary sensitivity 100% specificity 96%
Authors' recommendations and conclusions	PET scan may be a useful tool in routine surveillance for detection of recurrence in subclinical patients. For routine surveillance, the initial PET scan should be performed within 6 months after completion of treatment and the proper timing of next routine PET scan for subclinical patient with initial negative PET result might be 1 year after initial PET scan.

CHAPTER 12
Diagnosis and staging of suspect distant recurrence

Diagnostic accuracy

Systematic reviews

Author, year	Brouwer 2008a
Technology	FDG-PET
Disease	suspicion of recurrent laryngeal carcinoma after radiotherapy
Objective	to assess: ▪ diagnosis of suspected recurrence
Inclusion criteria	P suspicion of recurrent laryngeal carcinoma after radiotherapy I FDG-PET C CT, MRI, scintigraphy R histopathologic examination and/or follow up O diagnostic accuracy in detecting suspected recurrence S retrospective and prospective studies
Years covered by the search	up to April 2006
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	yes (reference list of retrieved studies)
Searched also unpublished studies	yes
Language restriction	English, German, French, Dutch
Overall number of references retrieved and n of included studies reported	yes
N. and references of excluded studies reported, reason given	only number of excluded studies
Characteristics of included studies clearly reported in tables	yes
Methodological quality of primary studies assessed; criteria reported	yes (Cochrane criteria list for diagnostic tests)
Results of quality assessment used to formulate results and conclusions	yes: descriptive data in the result and discussion sections

Meta-analysis performed with appropriate statistic methods	yes
Publication bias assessed	no
N. of included studies study design	8 studies (1 study excluded from meta-analysis); 4 studies prospective design, 2 with consecutive recruitment. 5 studies: not all patients had a valid reference standard. 7 patients had an uncertain blinding of index test
N. of included patients	191 (median 12, range 7-75); 180 patients included in the meta-analysis
Reference standard	histopathology and or follow up
Comparator	CT, MRI, scintigraphy
Pre-test probability	median 51% (range 14-53%)
Performance results	FDG-PET sensitivity: pooled 89% (95% CI 80-94%) Q test for heterogeneity p = 0.73 specificity: pooled 74% (95% CI 64-83%) Q test for heterogeneity p =0.05 CT (1 study, 23 patients) sensitivity: 58% specificity: 100%
Recommendations and conclusions	The diagnostic accuracy of 18FDG-PET is promising and warrants a randomized trial comparing a strategy based on conventional diagnostic work up to one based on 18FDG-PET.

Author, year	**Facey 2007**
Technology	FDG-PET
Disease	head and neck cancer
Objective	to assess: ▪ **X** primary diagnosis ▪ **X** staging ▪ **X** RT planning ▪ **X** response to therapy (after treatment) ▪ **X** diagnosis of suspected recurrence or re-staging
Inclusion criteria	P patients with head and neck cancer I FDG-PET C all available R not specified O diagnostic accuracy for primary diagnosis, staging, re-staging after treatment, recurrence; change in management for RT planning 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 systematic reviews (including respectively 15, 10, 15 primary studies; some of them in common), 8 additional primary studies (6 re-staging/early follow up [3 after CRT]; 2 true suspected recurrence) cross sectional diagnostic accuracy studies, with prospective or retrospective recruitment
N. of included patients	systematic reviews: 1 systematic review 350 patients; not reported in the others primary studies: 381 (re-staging/early follow up 290; suspected recurrence 91)
Reference standard	systematic reviews: not reported 1 systematic review histopathology 1 systematic review histopathology or follow up 1 systematic review primary studies: 6 studies combination of histopathologic results and follow up 1 study only histopathology 1 study only follow up
Comparator	primary diagnosis: CT or MRI
Pre-test probability	not reported
Performance results	not calculated: only descriptive results. "Two SRs with 15 and ten PSs, and seven additional PSs showed that PET sensitivity was approximately 80%, with specificity at least 90%, which was somewhat more accurate than CT/MRI for re-staging or recurrence. Another SR reported similar accuracy and eight studies with some evidence of change in patient management. The strongest evidence was detection of distant metastases in seven out of 22 patients. Most other changes were related to further diagnostic tests, were poorly documented, and no clear links with improvement in outcomes were made"
Recommendations and conclusions	none reported
Comment of ASSR reviewers	meta-analysis not performed

Author, year	**Isles 2008**
Technology	FDG-PET
Disease	head and neck squamous cell carcinoma after curative treatment, always including radiotherapy or chemo-radiotherapy
Objective	to assess: ▪ re-staging at the end of treatment ▪ diagnosis of suspected recurrence
Inclusion criteria	P suspicion of recurrent head and neck carcinoma or residual after radiotherapy or chemo-radiotherapy I FDG-PET C none R histopathologic examination and/or follow up O diagnostic accuracy in re-staging or detecting suspected recurrence both at the primary site and in the neck S retrospective and prospective studies
Years covered by the search	up to October 2007
Study selection data abstraction, quality assessment performed by two authors independently	yes
Comprehensive bibliographic search: at least two databases searched	yes Medline, Cochrane
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	no
Searched also unpublished studies	no
Language restriction	English
Overall number of references retrieved and n of included studies reported	yes
N. and references of excluded studies reported, reason given	only number of excluded studies
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: meta-regression and descriptive data in the result and discussion sections
Meta-analysis performed with appropriate statistic methods	yes (heterogeneity not reported)
Publication bias assessed	no

N. of included studies study design	27 studies; 20 for primary site recurrence and 13 for neck recurrence; 6 studies retrospective design; reference standards for included histology from biopsy or surgical specimen and length of disease free survival. Time from treatment to PET scan varied from 1 month-13 years. Length of follow up was often not stated, and in some instances was too short for reliable extrapolation of results. 8 studies included patients with suspected recurrence; 15 studies included patients (usually with stage III-IV disease) after the curative treatment with radiotherapy or chemo-radiotherapy. Four studies included only patients with cancer of larynx, 1 with oral cancer. Partial blinding (PET interpretation blinded to the other imaging tests) in the majority of studies.
N. of included patients	917 (median 12, range 8-97)
Reference standard	histopathology and/or follow up
Comparator	none (in one table reported some studies on CT or MRI, retrieved without a systematic process)
Pre-test probability	not reported and not computable
Performance results	FDG-PET primary site recurrence / residual disease sensitivity: pooled 94% (95% CI 87-97%) test for heterogeneity not reported specificity: pooled 82% (95% CI 76-86%) test for heterogeneity not reported When the QUADAS score is added as a term in the model, there is no effect on sensitivity for the primary site, but there is an effect on specificity, with a correlation between higher QUADAS scores and lower specificity (P-value 0.04). recurrence / residual disease of nodal metastasis sensitivity: pooled 74% (95% CI 50-89%) test for heterogeneity not reported specificity: pooled 88% (95% CI 74-95%) test for heterogeneity not reported
Recommendations and conclusions	Positron emission tomography is highly accurate in this role. However it is less sensitive early after treatment and has poor anatomical detail. PET may reduce the requirement for check endoscopies and planned neck dissections. A protocol for its use in post-treatment surveillance is proposed.

Author, year	**Liu 2007b**
Technology	FDG-PET
Disease	nasopharyngeal carcinoma after curative treatment with radiotherapy
Objective	to assess: ▪ re-staging at the end of treatment ▪ diagnosis of suspected recurrence
Inclusion criteria	P suspicion of residual or recurrent nasopharyngeal carcinoma after radiotherapy I FDG-PET C CT, MRI R histopathologic examination and follow up for at least 6 months O diagnostic accuracy in re-staging or detecting suspected recurrence at the primary site S retrospective and prospective studies
Years covered by the search	up to May 2007
Study selection data abstraction, quality assessment performed by two authors independently	yes
Comprehensive bibliographic search: at least two databases searched	yes Medline, Embase, Cochrane, CBMdisc databases (Chinese articles)
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	only references of retrieved studies
Searched also unpublished studies	no
Language restriction	English, Chinese
Overall number of references retrieved and n of included studies reported	yes
N. and references of excluded studies reported, reason given	only number of excluded studies
Characteristics of included studies clearly reported in tables	no
Methodological quality of primary studies assessed; criteria reported	yes (QUADAS tool)
Results of quality assessment used to formulate results and conclusions	yes: meta-regression and descriptive data in the result and discussion sections
Meta-analysis performed with appropriate statistic methods	yes (heterogeneity not reported)
Publication bias assessed	no

N. of included studies study design	33 studies (21 articles, 11 on PET, 13 on CT, 9 on MRI) Most studies had a suboptimal design in regard to the examination with the same reference standard (78% for "no" responses to question 6), the description of the execution of the reference standard (69% for "no" responses to question 9) and the interpretation of the reference standard results without knowledge of the index test results (100% for "no" responses to question 11). The reference standard was histopathologic analysis in 8 studies, both histopathologic analysis and close clinical and imaging follow up in the other 25 ones, no study used close clinical and imaging follow up alone as the reference standard. The time of follow up for all the 25 studies, whose reference standard was both histopathologic analysis and close clinical and imaging follow up was longer than 6 months. For almost all the studies, the time period after treatment when these examinations were performed was longer than 3 or 4 months (ranged from 3 to 70 months), except for one that ranged from 2.5 weeks to 12 years (average time was 23 months), and another that ranged from 2 to 6 months. There was no difference among the scan time of PET, CT, and MRI. Eighteen of the 33 studies were in English, and the other 15 were in Chinese. 1 study used PET/CT, while all the rest used PET. 5 studies used single-section helical, 2 non-helical, 3 dual-section helical, 1 four-section helical and 2 not presented clearly. For MRI, 4 studies used 1.5 T, 2 used 1 T, 1 used 0.5 T and the remaining one did not state clearly.
N. of included patients	1 813 578 in PET studies 681 in CT studies 470 in MRI studies
Reference standard	histopathology and or follow up
Comparator	CT, MRI
Pre-test probability	not reported and not computable
Performance results	FDG-PET sensitivity: pooled 95% (95% CI 90-97%) test for heterogeneity not reported specificity: pooled 90% (95% CI 87-93%) test for heterogeneity not reported *(continues)*

	CT sensitivity: pooled 76% (95% CI 70-81%) test for heterogeneity not reported specificity: pooled 59% (95% CI 55-63%) test for heterogeneity not reported For CT, The sensitivity, specificity, diagnostic OR, and the Q* index for dual-section helical and multi-section helical were all significantly higher than non-helical and single-section helical (P <0.01) MRI sensitivity: pooled 78% (95% CI 71-84%) test for heterogeneity not reported specificity: pooled 76% (95% CI 71-80%) test for heterogeneity not reported After single factor regression analysis, two variables were found to be explanatory, concluding modality category, question 14. (Questions 1-14 were questions about study design characteristic in the QUADAS tool.) Then we developed a multivariable regression model with which we used a backward stepwise algorithm, variables evaluated included modality category, question 8, question 13, and question 14. Finally we found that only the modality category was the most important characteristic.
Recommendations and conclusions	FDG-PET was the best modality for diagnosis of local residual or recurrent nasopharyngeal carcinoma. The type of analysis for PET imaging and the section thickness for CT would affect the diagnostic results. Dual-section helical and multi-section helical CT were better than non-helical and single-section helical CT.

Author, year	**Pasamontes Pingarrón 2008**
Technology	FDG-PET
Disease	head and neck squamous cell carcinoma after any curative treatment
Objective	to assess diagnosis of suspected recurrence
Inclusion criteria	P suspicion of recurrent head and neck carcinoma after radiotherapy or chemo-radiotherapy I FDG-PET C none R not specified O diagnostic accuracy detecting suspected recurrence (not specified if loco-regional or distant) S retrospective and prospective studies
Years covered by the search	up to May 2007
Study selection data abstraction, quality assessment performed by two authors independently	yes
Comprehensive bibliographic search: at least two databases searched	yes Medline
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	yes
Searched also unpublished studies	yes
Language restriction	English
Overall number of references retrieved and n of included studies reported	yes
N. and references of excluded studies reported, reason given	only number of excluded studies
Characteristics of included studies clearly reported in tables	no
Methodological quality of primary studies assessed; criteria reported	yes (an ad hoc checklist)
Results of quality assessment used to formulate results and conclusions	yes: meta-regression and descriptive data in the result and discussion sections
Meta-analysis performed with appropriate statistic methods	yes
Publication bias assessed	no

N. of included studies study design	19 studies
N. of included patients	666 (median 30.5, range 12-143) not reported clinical characteristics of single studies
Reference standard	not specified
Comparator	none
Pre-test probability	not reported and not computable
Performance results	FDG-PET sensitivity: pooled 94% (95% CI 91-96%) test for heterogeneity $\chi 2$ = 19.13; d.f. = 18 (P = .3836) specificity: pooled 80% (95% CI 76-84%) χ^2 = 41.12; d.f. = 18 (P = .0015) meta-regression: the methodological quality of the studies did not influence the heterogeneity (P = .03)
Recommendations and conclusions	The meta-analysis of the studies published on 18F-FDG-PET, in patients that are suspected of having head and neck tumor recurrence, provided the following conclusions: In the first place, the methodological quality was high and the differences in quality of the studies were not correlated with the differences it their results. In second place, there was homogeneity among the different types of studies seen, regarding the sensitivity, positive probability ratio, negative probability ratio, and the diagnostic odds ratio, which is why the results may be grouped together for a global or joint estimation. In third place the specificity did present heterogeneity among studies, due to the high pre-test probability of recurring disease. In fourth and last place, the diagnostic performance of the 18F-FDG-PET in diagnosing head and neck tumor recurrence suspicions, shown by the summary ROC curve, was high due the ABC being very close to 1.

Synoptic table of primary studies on diagnosis and staging of suspect distant recurrence, published after systematic reviews (Brouwer 2008a , Facey 2007, Liu 2007b, Pasamontes Pingarrón 2008)

Author, year	Technology	Patient number	Population	Reference standard	Sources of bias	Target	Pre test probability %	Sensitivity %	Specificity %
Alvarez Perez 2006	PET 3-36 months after treatment	15	laryngeal cancer after any curative treatment	histopathology or 12 months follow up after PET	retrospective design, uncertain recruitment, uncertain blinding	any recurrence	86.7	100	100
Brouwer 2008b	PET 2-47 months after treatment	30	laryngeal cancer after radiotherapy	histopathology or 12 months follow up after PET	consecutive recruitment, partial blinding	loco-regional recurrence	26.7	87.5	81.8
Chen 2006a	PET/CT after treatment	50	nasopharyngeal cancer after radiotherapy	histopathology or 6 months follow up after PET	uncertain design, partial blinding	any recurrence	45.5	100	94.4
						local recurrence	12.1	100	100
						neck recurrence	16.7	100	100
						metastasis	31.8	100	95.6
	CT after treatment					any recurrence	43.9	75.9	75.7
						local recurrence	12.1	87.5	94.8
						neck recurrence	15.2	80.0	89.3
						metastasis	30.3	80.0	95.7

Author, year	Technology	Patient number	Population	Reference standard	Sources of bias	Target	Pre test probability %	Sensitivity %	Specificity %
Connell 2007	PET/CT 1-66 months after treatment	35	head and neck cancer after radiotherapy	histopathology or 12 months follow up after PET	prospective design, uncertain recruitment, uncertain blinding	neck recurrence	25.7	88.9	96.2
Ekberg 2007	PET after treatment	33	head and neck cancer after any treatment	histopathology or 6 months follow up after PET	retrospective design, non consecutive recruitment, uncertain blinding	any recurrence	67.7	90.5	70.0
Fakhry 2007	PET/CT 6-95 months after treatment	32	head and neck cancer after any treatment	histopathology or 8 months follow up after PET	prospective design, consecutive recruitment, blinding	local recurrence	56.3	94.4	57.1
Gourin 2009a	PET/CT 3-42 months after treatment	64	stage III, IV head and neck cancer after any curative treatment	biopsy or follow up	retrospective design, uncertain recruitment, uncertain blinding	metastasis	15.6	70.0	87.0
Halpern 2007	PET/CT after treatment	49	head and neck cancer after any treatment	histopathology	retrospective design, uncertain recruitment, blinding	local recurrence	85.7	88.1	71.4
Ishikita 2010	PET/CT after treatment	129	head and neck cancer after any treatment	partial verification with histopathology	unclear design, partial blinding	any recurrence	8.5	93.9	97.2

Author, year	Technology	Patient number	Population	Reference standard	Sources of bias	Target	Pre test probability %	Sensitivity %	Specificity %
Kunkel 2006	PET 7-10-months after treatment	41	oral cancer after salvage surgery	follow up	retrospective design, uncertain recruitment, uncertain blinding	local recurrence	32.0	92.0	75.0
						neck recurrence	20.0	88.0	98.0
						metastasis	27.0	73.0	97.0
Ma 2009	PET/CT 4-68-months after treatment	34	nasopharyngeal cancer after radiotherapy	histopathology or 6 months follow up after PET	unclear design, uncertain blinding	skull base invasion	73.5	96.0	33.3
	CT 4-68-months after treatment							64.0	77.8
	MRI 4-68-months after treatment							80.0	66.7
Ng 2010	PET/CT 14-months (mean) after treatment	179	II-IV stage nasopharyngeal cancer after curative radiotherapy with IMRT	histopathology or 12 months follow up after PET	prospective design, uncertain recruitment, partial blinding	any recurrence	30.7	87.3	90.3
	MRI 14 months (mean) after treatment							90.9	91.1

Author, year	Technology	Patient number	Population	Reference standard	Sources of bias	Target	Pre test probability %	Sensitivity %	Specificity %
Wang 2009	PET after treatment	10	stage III, IV head and neck cancer after chemo-radiotherapy	histopathology or follow up	prospective design, uncertain recruitment, partial blinding	local recurrence	10.0	100.0	100.0
						neck recurrence	20.0	100.0	87.5
Yen 2009	PET/CT 40 months (mean) after treatment	27	any nasopharyngeal cancer after radiotherapy or chemotherapy	histopathology or 6 months follow up after PET	retrospective design, uncertain recruitment, uncertain blinding	skull base invasion	55.6	86.7	75.0
	SPECT/CT 40 months (mean) after treatment							66.7	100.0

COLLANA DOSSIER

a cura dell'Agenzia sanitaria e sociale regionale

1990

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

1991

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

1992

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. **(*)**
11. I Coordinamenti dei Servizi per l'Educazione sanitaria (CSES): funzioni, risorse e problemi. Sintesi di un'indagine svolta nell'ambito dei programmi di ricerca sanitaria finalizzata (1989 - 1990). Bologna. **(*)**
12. Epi Info versione 5. Un programma di elaborazione testi, archiviazione dati e analisi statistica per praticare l'epidemiologia su personal computer. Programma (dischetto A). Manuale d'uso (dischetto B). Manuale introduttivo. Bologna.
13. Catalogo collettivo dei periodici per la prevenzione in Emilia-Romagna. 2ª edizione. Bologna.

1993

14. Amianto 1986-1993. Legislazione, rassegna bibliografica, studi italiani di mortalità, proposte operative. Bologna. **(*)**
15. Rischi ambientali, alimentari e occupazionali, Attività di prevenzione e controllo nelle USL dell'Emilia-Romagna. 1991. Bologna. **(*)**
16. La valutazione della qualità nei Servizi di igiene pubblica delle USL dell'Emilia-Romagna, 1991. Bologna. **(*)**
17. Metodi analitici per lo studio delle matrici alimentari. Bologna. **(*)**

1994

18. Venti anni di cultura per la prevenzione. Bologna.
19. La valutazione della qualità nei Servizi di igiene pubblica dell'Emilia-Romagna 1992. Bologna. **(*)**
20. Rischi ambientali, alimentari e occupazionali, Attività di prevenzione e controllo nelle USL dell'Emilia-Romagna. 1992. Bologna. **(*)**
21. Atlante regionale degli infortuni sul lavoro. 1986-1991. 2 volumi. Bologna. **(*)**
22. Atlante degli infortuni sul lavoro del distretto di Ravenna. 1989-1992. Ravenna. **(*)**
23. 5ª Conferenza europea sui rischi professionali. Riccione, 7-9 ottobre 1994. Bologna.

(*) volumi disponibili presso l'Agenzia sanitaria e sociale regionale. Sono anche scaricabili dal sito http://asr.regione.emilia-romagna.it/wcm/asr/collana_dossier/archivio_dossier_1.htm

1995

24. La valutazione della qualità nei Servizi di igiene pubblica dell'Emilia-Romagna 1993. Bologna. **(*)**

25. Rischi ambientali, alimentari e occupazionali, Attività di prevenzione e controllo nelle USL dell'Emilia-Romagna. 1993. Bologna. **(*)**

1996

26. La valutazione della qualità nei Servizi di igiene pubblica dell'Emilia-Romagna. Sintesi del triennio 1992-1994. Dati relativi al 1994. Bologna. **(*)**

27. Lavoro e salute. Atti della 5a Conferenza europea sui rischi professionali. Riccione, 7-9 ottobre 1994. Bologna. **(*)**

28. Gli scavi in sotterraneo. Analisi dei rischi e normativa in materia di sicurezza. Ravenna. **(*)**

1997

29. La radioattività ambientale nel nuovo assetto istituzionale. Convegno Nazionale AIRP. Ravenna. **(*)**

30. Metodi microbiologici per lo studio delle matrici alimentari. Ravenna. **(*)**

31. Valutazione della qualità dello screening del carcinoma della cervice uterina. Ravenna. **(*)**

32. Valutazione della qualità dello screening mammografico del carcinoma della mammella. Ravenna. **(*)**

33. Processi comunicativi negli screening del tumore del collo dell'utero e della mammella (parte generale). Proposta di linee guida. Ravenna. **(*)**

34. EPI INFO versione 6. Ravenna. **(*)**

1998

35. Come rispondere alle 100 domande più frequenti negli screening del tumore del collo dell'utero. Vademecum per gli operatori di front-office. Ravenna.

36. Come rispondere alle 100 domande più frequenti negli screening del tumore della mammella. Vademecum per gli operatori di front-office. Ravenna. **(*)**

37. Centri di Produzione Pasti. Guida per l'applicazione del sistema HACCP. Ravenna. **(*)**

38. La comunicazione e l'educazione per la prevenzione dell'AIDS. Ravenna. **(*)**

39. Rapporti tecnici della Task Force D.Lgs 626/94 - 1995-1997. Ravenna. **(*)**

1999

40. Progetti di educazione alla salute nelle Aziende sanitarie dell'Emilia Romagna. Catalogo 1995 - 1997. Ravenna. **(*)**

2000

41. Manuale di gestione e codifica delle cause di morte, Ravenna.

42. Rapporti tecnici della Task Force D.Lgs 626/94 - 1998-1999. Ravenna. **(*)**

43. Comparto ceramiche: profilo dei rischi e interventi di prevenzione. Ravenna. **(*)**

44. L'Osservatorio per le dermatiti professionali della provincia di Bologna. Ravenna. **(*)**

45. SIDRIA Studi Italiani sui Disturbi Respiratori nell'Infanzia e l'Ambiente. Ravenna. **(*)**

46. Neoplasie. Rapporto tecnico per la definizione di obiettivi e strategie per la salute. Ravenna. **(*)**

2001

47. Salute mentale. Rapporto tecnico per la definizione di obiettivi e strategie per la salute. Ravenna. **(*)**

48. Infortuni e sicurezza sul lavoro. Rapporto tecnico per la definizione di obiettivi e strategie per la salute. Ravenna. **(*)**

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