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Agenzia sanitaria e sociale regionale

RegioneEmilia-Romagna

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA

Criteria for appropriate use of FDG-PET in malignant lymphoma

ORIentamenti 8

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
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
HL/HD	Hodgkin's lymphoma/disease
IF-RT	involved-field radiotherapy
LR	likelihood ratio
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NHL/NHD	Non-Hodgkin's lymphoma/disease
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 linfomi maligni

Linfoma di Hodgkin

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

- stadiazione del linfoma di Hodgkin -
  Appropriato (livello di evidenza: moderato)
- definizione del *dose painting* nella radioterapia *involved-field* nel linfoma di Hodgkin -
  Indeterminato a causa della mancanza di studi
- valutazione, durante il trattamento, della risposta precoce alla terapia del linfoma di Hodgkin -
  Appropriato (livello di evidenza: moderato)
- valutazione della risposta alla fine del trattamento del linfoma di Hodgkin -
  Appropriato (livello di evidenza: moderato)
- *follow up* dei pazienti trattati per linfoma di Hodgkin senza sospetto di ricaduta -
  Inappropriato (livello di evidenza: basso)
- stadiazione della ricaduta nei pazienti trattati per linfoma di Hodgkin -
  Appropriato (livello di evidenza: molto basso)

Per tutte le indicazioni sopra riportate il panel ha raggiunto un accordo.

STADIAZIONE DEL LINFOMA DI HODGKIN - APPROPRIATO

Durante la prima riunione il *panel* ha concordato nel giudicare appropriato (voto mediano 8; range 6-9) l'uso della FDG-PET per la stadiazione dei pazienti con linfoma di Hodgkin, al fine di distinguere la malattia precoce e localizzata (stadi I e II) da quella avanzata ed estesa (stadi III e IV) e avviare i pazienti al trattamento più appropriato. Il livello di evidenza per le stime di accuratezza diagnostica della FDG-PET è stato giudicato moderato, con la FDG-PET che mostra una migliore accuratezza rispetto al comparatore nell'individuazione del coinvolgimento a livello sia nodale che extranodale.

Tutti gli esiti clinici riguardanti i pazienti sono stati considerati critici dal *panel* (voti mediani: 8 e 7).

DEFINIZIONE DEL *DOSE PAINTING* NEL TRATTAMENTO RADIOTERAPICO *INVOLVED-FIELD* DEI PAZIENTI CON LINFOMA DI HODGKIN - INDETERMINATO

Durante la prima riunione il *panel* ha discusso il potenziale ruolo diagnostico della FDG-PET nella pianificazione del trattamento radioterapico e ha concordato di focalizzare l'analisi sull'impiego della FDG-PET nella definizione del "dose painting" anziché del *target volume*. Relativamente al quesito clinico individuato dal *panel* la revisione sistematica della letteratura non ha reperito alcuno studio e, durante il secondo incontro, il *panel* ha giudicato il quesito clinico indeterminato per la mancanza di studi. Le conseguenze cliniche dell'accuratezza della FDG-PET nella definizione del *dose painting* sono state giudicate importanti.

VALUTAZIONE, DURANTE IL TRATTAMENTO, DELLA RISPOSTA PRECOCE ALLA TERAPIA DEL LINFOMA DI HODGKIN - APPROPRIATO

Dopo un lieve disaccordo iniziale, con voti che variavano dall'incerto all'appropriato (voto mediano: 7; *range* 4-8), durante il secondo incontro il *panel* ha concordato nel votare appropriato l'uso della FDG-PET nella valutazione, durante il trattamento, della risposta precoce alla terapia del linfoma di Hodgkin (voto mediano: 7, *range* 7-8). La perplessità iniziale era dovuta alla mancanza di evidenze riguardo l'impatto che un cambio precoce di terapia potrebbe avere sugli esiti clinici. Tuttavia, il livello di evidenza relativo all'accuratezza della FDG-PET nel prevedere la risposta alla terapia è risultato moderato e tutti gli esiti clinici dei pazienti sono stati votati critici.

VALUTAZIONE DELLA RISPOSTA ALLA FINE DEL TRATTAMENTO DEL LINFOMA DI HODGKIN - APPROPRIATO

Durante la prima riunione, il *panel* ha concordato nel giudicare appropriato l'uso della FDG-PET nella valutazione della risposta dei pazienti alla terapia alla fine del trattamento per il linfoma di Hodgkin. Il livello di evidenza relativo all'accuratezza diagnostica della FDG-PET è risultato moderato, con una performance diagnostica della FDG-PET migliore di quella della CT, soprattutto relativamente alla specificità. Tutti gli esiti clinici sono stati giudicati critici, con voti mediani uguali o maggiori di 7.

FOLLOW UP DEI PAZIENTI TRATTATI PER LINFOMA DI HODGKIN, SENZA SOSPETTO DI RICADUTA - INAPPROPRIATO

Durante il primo incontro, i membri del *panel* erano fortemente in disaccordo sul ruolo della FDG-PET durante il *follow up* dei pazienti trattati per linfoma di Hodgkin e senza sospetto di ricaduta. Durante la prima votazione i voti espressi sono ricaduti in tutte e tre le regioni dell'appropriatezza (inappropriato, incerto e appropriato) con un valore mediano di 4 (*range* 2-7). I risultati ricavati da un recente studio che include la popolazione più ampia di tutti gli studi precedentemente pubblicati hanno influenzato la discussione durante il secondo incontro e la scarsa specificità della FDG-PET è stata determinante nel condurre il panel al giudizio di inappropriatezza (voto mediano: 2; *range* 1-3). Il livello di evidenza è stato giudicato basso e tutti gli esiti clinici sono stati giudicati

importanti (voto mediano: 6; *range* 3-9), tranne che per i pazienti con un test falso negativo per i quali l'esito è stato considerato critico.

STADIAZIONE DELLA RICADUTA NEI PAZIENTI TRATTATI PER LINFOMA DI HODGKIN - APPROPRIATO

Durante la prima votazione si è verificato un lieve disaccordo tra i componenti del *panel* con voti nella regione dell'incerto e dell'appropriato (voto mediano: 7; *range* 5-8). Il livello di evidenza per l'accuratezza diagnostica della FDG-PET è stato giudicato molto basso a causa di *sparse data*. Tuttavia, durante la seconda riunione, i membri del *panel* hanno giudicato le stime di accuratezza diagnostica della FDG-PET nella stadiazione iniziale del linfoma di Hodgkin sufficientemente attendibili, anche se indirette, ed applicabili alla stadiazione di pazienti con ricaduta. Durante la seconda votazione si è quindi raggiunto un accordo nel giudicare appropriato l'impiego della FDG-PET per la conferma diagnostica e la stadiazione della ricaduta nei pazienti trattati per linfoma di Hodgkin (voto mediano 8; *range* 7-8). L'importanza della stadiazione è stata ulteriormente evidenziata dall'importanza degli esiti clinici per i pazienti con malattia estesa che è stata giudicata critica (con un voto mediano di 7 per i pazienti con malattia estesa individuata dal test e di 8 per i pazienti con malattia estesa che il test non è in grado di individuare). Le conseguenze per i pazienti con malattia limitata sono state giudicate importanti (voto mediano: 6).

Linfoma non-Hodgkin aggressivo

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

- stadiazione del linfoma non-Hodgkin aggressivo -
  Appropriato (livello di evidenza: moderato)
- definizione del *dose painting* nella radioterapia *involved-field* nel linfoma non-Hodgkin aggressivo -
  Indeterminato a causa della mancanza di studi
- valutazione, durante il trattamento, della risposta precoce alla terapia del linfoma non-Hodgkin aggressivo -
  Inppropriato (livello di evidenza: moderato)
- valutazione della risposta alla fine del trattamento del linfoma non-Hodgkin aggressivo -
  Appropriato (livello di evidenza: moderato)
- *follow up* dei pazienti trattati per linfoma non-Hodgkin aggressivo, senza sospetto di ricaduta -
  Inappropriato (livello di evidenza: molto basso)
- stadiazione della ricaduta nei pazienti trattati per linfoma non-Hodgkin aggressivo -
  Appropriato (livello di evidenza: molto basso)

Per tutte le indicazioni sopra riportate il panel ha raggiunto un accordo.

STADIAZIONE DEL LINFOMA NON-HODGKIN AGGRESSIVO- APPROPRIATO

Durante la prima riunione il *panel* ha unanimanente giudicato appropriato l'impiego della FDG-PET per la stadiazione dei pazienti con linfoma non-Hodgkin (voto mediano: 8; range 7-9) per distinguere la malattia precoce e localizzata (stadi I e II) da quella avanzata ed estesa (stadi III e IV) ed avviare i pazienti al trattamento più appropriato. Il livello di evidenza per le stime di accuratezza diagnostica della FDG-PET è stato giudicato moderato con la FDG-PET che mostra una migliore accuratezza rispetto al comparatore nell'individuare il coinvolgimento sia nodale ed extranodale sia del midollo osseo. Tuttavia il *panel* è stato d'accordo sul non proporre la FDG-PET in sostituzione alla TC che è spesso eseguita alla diagnosi e che fornisce uno strumento utile per il monitoraggio della risposta durante il trattamento.

Tutti gli esiti clinici riguardanti i pazienti sono stati considerati critici dal *panel* (voto mediano: 7).

DEFINIZIONE DEL *DOSE PAINTING* NELLA RADIOTERAPIA INVOLVED-FIELD NEL LINFOMA NON-HODGKIN AGGRESSIVO - INDETERMINATO

Durante la prima riunione il *panel* ha discusso il potenziale ruolo diagnostico della FDG-PET nella pianificazione del trattamento radioterapico e ha concordato di focalizzare l'analisi sull'analisi dell'impiego della FDG-PET nella definizione del *dose painting* piuttosto che in quella del *target volume*. Relativamente al quesito clinico individuato dal *panel* la revisione sistematica della letteratura non ha reperito alcuno studio e, durante il secondo incontro, il *panel* ha giudicato il quesito clinico indeterminato per mancanza di studi. Le conseguenze cliniche dell'accuratezza della FDG-PET nella definizione del *dose painting* sono state comunque giudicate non importanti.

VALUTAZIONE, DURANTE IL TRATTAMENTO, DELLA RISPOSTA PRECOCE ALLA TERAPIA DEL LINFOMA NON-HODGKIN AGGRESSIVO - INAPPROPRIATO

Durante la prima riunione il risultato della votazione ha mostrato un lieve disaccordo con voti che variavano dall'inappropriato all'incerto (voto mediano: 4; *range* 1-8). Durante il secondo incontro, il disaccordo iniziale è stato risolto attraverso la discussione ed è stato chiarito che la risposta durante il trattamento viene meglio valutata attraverso la riduzione della massa tumorale con l'esame TC. Pertanto, durante la seconda votazione, vi è stato accordo nel giudicare inappropriato l'utilizzo della FDG-PET per la valutazione, effettuata durante il trattamento, della risposta precoce alla terapia (voto mediano: 3, *range* 2-3). Il livello di evidenza relativo all'accuratezza diagnostica è stato giudicato moderato e gli esiti clinici sono stati considerati critici (voto mediano: 7, *range* 2-9) per i pazienti veri non responders, falsi non *responder* e falsi *responder* alla terapia. Gli esiti per i veri *responder* alla terapia sono stati votati importanti (voto mediano: 5, *range* 2-9).

VALUTAZIONE DELLA RISPOSTA ALLA FINE DEL TRATTAMENTO DEL LINFOMA NON-HODGKIN AGGRESSIVO - APPROPRIATO

Durante la prima riunione, il *panel* ha concordato nel giudicare appropriato l'uso della FDG-PET nella valutazione della risposta dei pazienti alla terapia alla fine del trattamento per il linfoma non-Hodgkin (voto mediano: 7; *range* 5-8). Il livello di evidenza relativo all'accuratezza diagnostica della FDG-PET è risultato moderato, con la FDG-PET che mostra una migliore specificità della TC. Gli esiti clinici sono stati giudicati critici (voto mediano di 7) tranne nel caso delle conseguenze per i pazienti falsi non responders che sono state giudicate importanti (voto mediano: 4; *range* 3-8).

FOLLOW UP DEI PAZIENTI TRATTATI PER LINFOMA NON-HODGKIN AGGRESSIVO, SENZA SOSPETTO DI RICADUTA - INAPPROPRIATO

Il livello di evidenza relativo all'accuratezza diagnostica della FDG-PET nell'identificare la ricaduta nei pazienti in follow up e senza sospetto di ricaduta è risultato molto basso.

La prima votazione ha registrato un lieve disaccordo tra l'inappropriato e l'incerto (voto mediano: 3; *range* 2-4) ma durante il secondo incontro il disaccordo è stato risolto attraverso la discussione e con la seconda votazione si è raggiunto un accordo sull'inappropriatezza (voto mediano: 3; *range* 1-3). Tutti gli esiti clinici dei pazienti sono stati giudicati importanti (voti mediani 4 e 5) tranne quelli dei pazienti che dovessero risultare falsamente positivi che sono stati giudicati non importanti (voto mediano: 3).

STADIAZIONE DELLA RICADUTA NEI PAZIENTI TRATTATI PER LINFOMA NON-HODGKIN AGGRESSIVO - APPROPRIATO

Durante la prima votazione si è verificato un lieve disaccordo tra i componenti del *panel* con voti nella regione dell'incerto e dell'appropriato (voto mediano: 7; range 5-8). Il livello di evidenza per l'accuratezza diagnostica della FDG-PET è stato giudicato molto basso a causa di *sparse data*. Tuttavia durante la seconda riunione, i membri del *panel* hanno giudicato le stime di accuratezza diagnostica della FDG-PET nella stadiazione iniziale sufficientemente attendibili, anche se indirette, e applicabili alla stadiazione di pazienti con ricaduta. Durante la seconda votazione si è pertanto registrato un accordo sull'appropriatezza (voto mediano: 7; *range* 6-8). L'importanza della stadiazione è stata ulteriormente evidenziata dall'importanza degli esiti clinici per i pazienti con malattia estesa che è stata giudicata critica con un voto mediano di 7 per i pazienti con malattia estesa individuata dal test e di 8 per i pazienti con malattia estesa che il test non è in grado di individuare (pazienti falsi negativi per malattia estesa). Le conseguenze per i pazienti con malattia limitata sono state giudicate importanti (voti mediani 6 e 5).

Summary of results

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

Hodgkin's lymphoma

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

- Staging of Hodgkin's lymphoma -
  Appropriate (level of evidence: moderate)
- Dose painting definition in involved-field radiation treatment of Hodgkin's lymphoma - Indeterminate due to lack of studies
- During treatment evaluation of early response to therapy in Hodgkin's lymphoma -
  Appropriate (level of evidence: moderate)
- End of treatment evaluation of response to therapy in Hodgkin's lymphoma -
  Appropriate (level of evidence: moderate)
- Follow up of patients treated for Hodgkin's lymphoma, with no suspicion of recurrence -
  Inappropriate (level of evidence: low)
- Staging of recurrence in patients treated for Hodgkin's lymphoma -
  Appropriate (level of evidence: very low)

For all the above clinical indications the panel reached an agreement.

STAGING OF HODGKIN'S LYMPHOMA - APPROPRIATE

During the first meeting the panel reached an agreement in judging appropriate (median score 8; range 6-9) the use of FDG-PET for staging patients with Hodgkin's lymphoma, in order to distinguish early, localised stage (I and II) from advanced, extended (stage III and IV) disease and direct patients to most appropriate treatment. The level of evidence for estimates of FDG-PET diagnostic accuracy was moderate, with FDG-PET performing better than comparator for detection of both linfonodal and extra-nodal involvement.

All patients' important outcomes were considered by the panel to be critical (median scores 8 and 7).

DOSE PAINTING DEFINITION IN INVOLVED FIELD RADIATION TREATMENT OF HODGKIN'S LYMPHOMA - INDETERMINATE

During the first meeting the panel discussed the potential diagnostic role of FDG-PET in radiation treatment planning and agreed to focus on dose painting definition, rather than on Target Volume definition. For the clinical question identified by the panel, the systematic review of the literature retrieved no studies and, during the second meeting, the panel judged this clinical indication as indeterminate due to lack of studies. Clinical consequences of accuracy of dose painting definition were voted important.

DURING TREATMENT EVALUATION OF EARLY RESPONSE TO THERAPY IN HODGKIN'S LYMPHOMA - APPROPRIATE

After an initial slight disagreement, with votes ranging from uncertain to appropriate (median score 7; range 4-8) the panel agree, during the second round, in voting the use of FDG-PET for during treatment evaluation of patients' response to therapy as appropriate (median score 7, range 7-8). The initial perplexity was due to the lack of evidence for impact on clinical outcomes following early switch of therapy. However level of evidence for FDG-PET accuracy in predicting response to treatment resulted to be moderate, and all patients' important outcomes were voted critical.

END OF TREATMENT EVALUATION OF RESPONSE TO THERAPY IN HODGKIN'S LYMPHOMA

The panel reached an agreement during the first voting round in judging appropriate the use of FDG-PET for the evaluation of patients' response to therapy at the end of treatment for Hodgkin's lymphoma. The level of evidence for FDG-PET diagnostic accuracy was found to be moderate, with FDG-PET performing better than CT, especially in specificity. All clinical outcomes were judged to be critical, with median votes equal to or higher than 7.

FOLLOW UP OF PATIENTS TREATED FOR HODGKIN'S LYMPHOMA, WITH NO SUSPICION OF RECURRENCE - INAPPROPRIATE

At the first meeting the panellists strongly disagreed about the role of FDG-PET during follow up of patients treated for Hodgkin's lymphoma and with no suspicion of recurrence. In the first round votes fell in all three region of appropriateness (inappropriate, uncertain, appropriate) with a median score of 4 (range 2-7). Results from a recently acquired and included study, recruiting a much larger sample of patients than all previously published studies, influenced the discussion of the second meeting and the poor specificity of FDG-PET was determinant in bringing the panel to agree on the judgment of inappropriateness (median score 2; range 1-3). The level of evidence was considered low and all outcomes were voted important (median score 6; range 3-9), except for consequences for patients testing false negative, which were considered critical.

STAGING OF RECURRENCE IN PATIENTS TREATED FOR HODGKIN'S LYMPHOMA - APPROPRIATE

The first voting round registered a slight disagreement among panellists with votes falling in the uncertain and appropriate regions (median score 7; range 5-8). Level of evidence for FDG-PET diagnostic accuracy was judged very low due to sparse data. However during the second meeting panellists agreed to judge the estimates for FDG-PET diagnostic accuracy for the initial staging of patients sufficiently reliable, although indirect, and applicable to staging of relapsing patients. The second voting round therefore registered an agreement on appropriateness (median score 8; *range* 7-8). Importance of staging was further highlighted by the critical importance assigned to clinical consequences of patients with extended disease, with a median score of 7 for detected extended disease and median score of 8 for undetected extended disease. Consequences for patients with limited disease were judged important (median score of 6).

Aggressive non-Hodgkin's lymphoma

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

- Staging of aggressive non-Hodgkin's lymphoma -
  Appropriate (level of evidence: moderate)
- Dose painting definition in involved-field radiation treatment of aggressive non-Hodgkin's lymphoma -
  Indeterminate due to lack of studies
- During treatment evaluation of early response to therapy in aggressive non-Hodgkin's lymphoma -
  Inappropriate (level of evidence: moderate)
- End of treatment evaluation of response to therapy in aggressive non-Hodgkin's lymphoma -
  Appropriate (level of evidence: moderate)
- Follow up of patients treated for aggressive non-Hodgkin's lymphoma, with no suspicion of recurrence -
  Inappropriate (level of evidence: very low)
- Staging of recurrence in patients treated for aggressive non-Hodgkin's lymphoma -
  Appropriate (level of evidence: very low)

For all the above clinical indications the panel reached an agreement.

STAGING OF AGGRESSIVE NON-HODGKIN'S LYMPHOMA - APPROPRIATE

During the first meeting the panel reached an agreement in judging appropriate (median score 8; range 7-9) the use of FDG-PET for staging patients with aggressive Non-Hodgkin's lymphoma, in order to distinguish early, localised stage (I and II) from

advanced, extended (stage III and IV) disease and direct patients to most appropriate treatment. The level of evidence for estimates of FDG-PET diagnostic accuracy was moderate, with FDG-PET performing better than comparators for detection of both linfonodal/extra-nodal involvement and bone marrow involvement. Nevertheless the panel agreed not to propose FDG-PET in replacement of CT, which is often performed at diagnosis and provides a useful basis for monitoring response to therapy during treatment.

All patients' important outcomes were considered by the panel to be critical (median scores 7).

DOSE PAINTING DEFINITION IN INVOLVED FIELD RADIATION TREATMENT OF AGGRESSIVE NON-HODGKIN'S LYMPHOMA - INDETERMINATE

During the first meeting the panel discussed the potential diagnostic role of FDG-PET in radiation treatment planning and agreed to focus on dose painting definition, rather than on target volume definition. For the clinical question identified by panel the systematic review of the literature retrieved no studies and, during the second meeting, the panel judged this clinical indication as indeterminate due to lack of studies. Clinical consequences of accuracy of dose painting definition were, however, voted not important.

DURING TREATMENT EVALUATION OF EARLY RESPONSE TO THERAPY IN AGGRESSIVE NON-HODGKIN'S LYMPHOMA - INAPPROPRIATE

During the first meeting the voting results showed a slight disagreement, with votes ranging from inappropriate to uncertain (median score 4; range 1-8). During the second meeting disagreement was resolved through discussion, as it was clarified that response during treatment is better assessed in terms of mass reduction using CT scans. The second voting round found panellists in agreement in judging inappropriate the use of FDG-PET for the evaluation of patients' early response to therapy during treatment (median score 3; range 2-3). Level of evidence for diagnostic accuracy was judged moderate and clinical outcomes were rated critical (median score 7; range 2-9) for true non responders, false non responders and false responders. Outcomes for true responders were voted important (median 5; range 2-9).

END OF TREATMENT EVALUATION OF RESPONSE TO THERAPY IN AGGRESSIVE NON-HODGKIN'S LYMPHOMA

The panel reached an agreement during the first voting round in judging appropriate the use of FDG-PET for the evaluation of patients' response to therapy at the end of treatment for Hodgkin's lymphoma (median score 7; range 5-8). The level of evidence for FDG-PET diagnostic accuracy was found to be moderate, with FDG-PET showing a higher specificity than CT. Clinical outcomes were judged to be critical, (median score of 7) except for consequences for patients testing as false non responders which were voted important (median score 4; range 3-8)

FOLLOW UP OF PATIENTS TREATED FOR AGGRESSIVE NON-HODGKIN'S LYMPHOMA, WITH NO SUSPICION OF RECURRENCE - INAPPROPRIATE

Level of evidence for FDG-PET diagnostic accuracy in identifying relapse in patients in follow up and with no suspicion of recurrence was found to be very low. The first voting round registered a slight disagreement between inappropriate and uncertain ratings (median score 3; range 2-4), but during the second meeting disagreement was resolved through discussion and the second voting round registered an agreement on inappropriate (median score 3; range 1-3).

Patients' important outcomes were judged important (median score 4 and 5), except for patients testing false positives which were considered not important (median score 3).

STAGING OF RECURRENCE IN PATIENTS TREATED FOR AGGRESSIVE NON-HODGKIN'S LYMPHOMA - APPROPRIATE

The first voting round registered a slight disagreement among panellists with votes falling in the uncertain and appropriate regions (median score 7; range 5-8). Level of evidence for FDG-PET diagnostic accuracy was judged very low due to sparse data. However during the second meeting panellists agreed to judge the estimates for FDG-PET diagnostic accuracy for the initial staging of patients sufficiently reliable, although indirect, and applicable to staging of relapsing patients. The second voting round therefore registered an agreement on appropriateness (median score 7; range 6-8). Importance of staging was further highlighted by the critical importance assigned to clinical consequences for patients with extended disease, with a median score of 7 for detected extended disease and median score of 8 for undetected extended disease. Consequences for patients with limited disease were judged important (median scores of 6 and 5).

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 malignant lymphoma has been carried out between February 2011 and February 2012.

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.

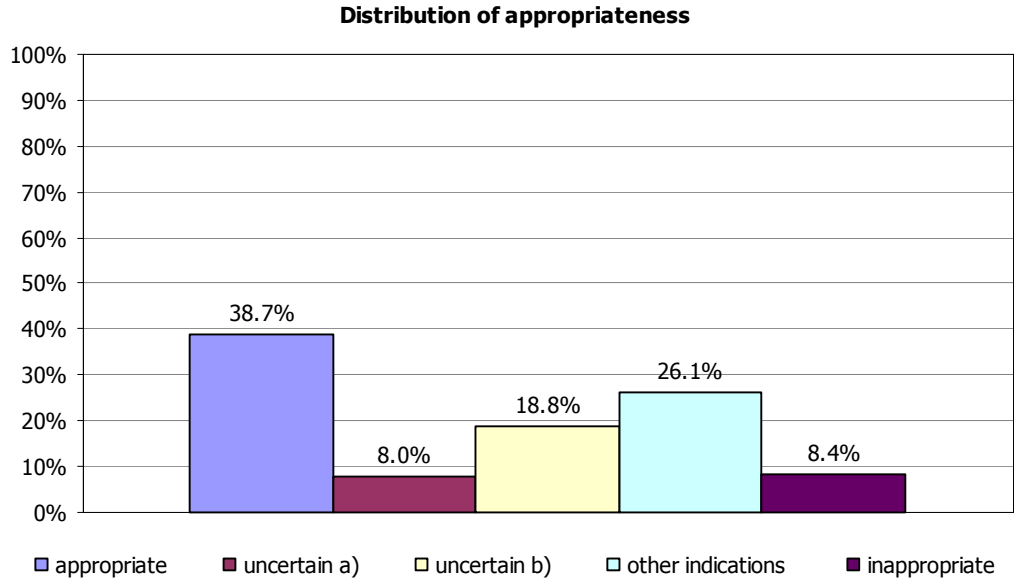
Since its introduction in the Emilia-Romagna Regional Health Service, the Regional Health and Social Agency of Emilia-Romagna (Agenzia sanitaria e sociale regionale - ASSR) has been committed to promote and support regional research programmes aimed at assessing clinical indications for PET and supporting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

The first research 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*).

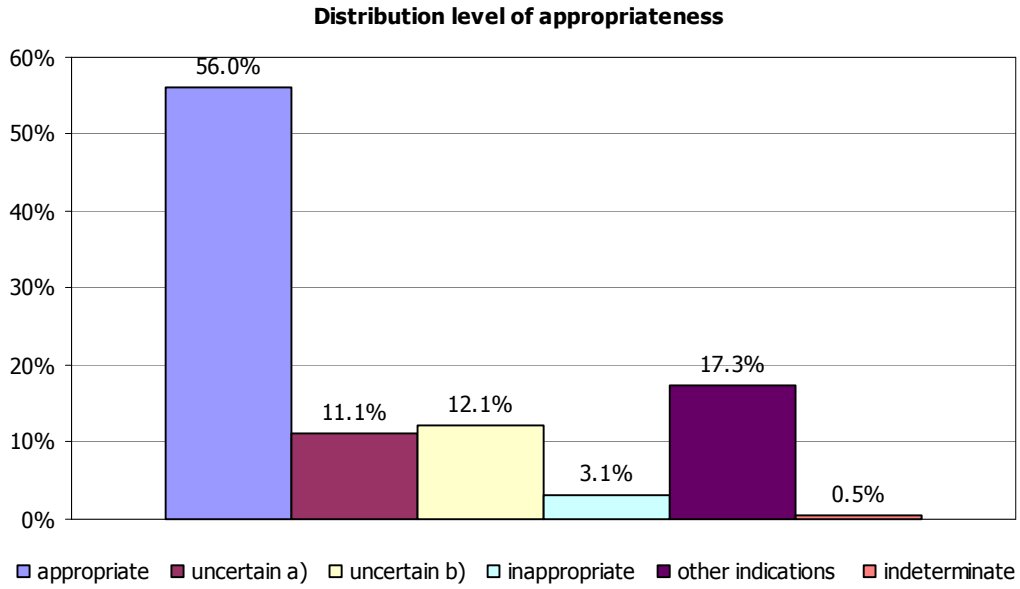
Following the increase in number of PET scanners (from 1 to 6) an update of the 2003 report was commissioned to a second regional panel and published in 2007 (Liberati 2007). The second report addressed the role of FDG-PET in 18 types of cancer for a total of 65 clinical indications, and a second clinical 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 malignant lymphoma: objectives

This work is part of a wider research programme 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 affected by Hodgkin's lymphoma or aggressive non-Hodgkin's lymphoma.

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
- post hoc analyses of appropriate use of FDG-PET
- contributing to the planning of the regional health service

in Hodgkin's lymphoma or aggressive non-Hodgkin's lymphoma.

The purpose of this report is not to produce clinical recommendations for the use of FDG-PET in Hodgkin's lymphoma or aggressive non-Hodgkin's lymphoma.

1.2. Context

Incidence of malignant lymphoma

In Emilia-Romagna Region, in 2007 (RER 2011), crude incidence rate of Hodgkin's lymphoma was 3.2 per 100 000 male inhabitants per year and 3.0 per 100 000 female inhabitants per year whilst for non-Hodgkin's lymphoma was 27.7 per 100 000 male inhabitants per year and 23.0 per 100 000 female inhabitants per year.

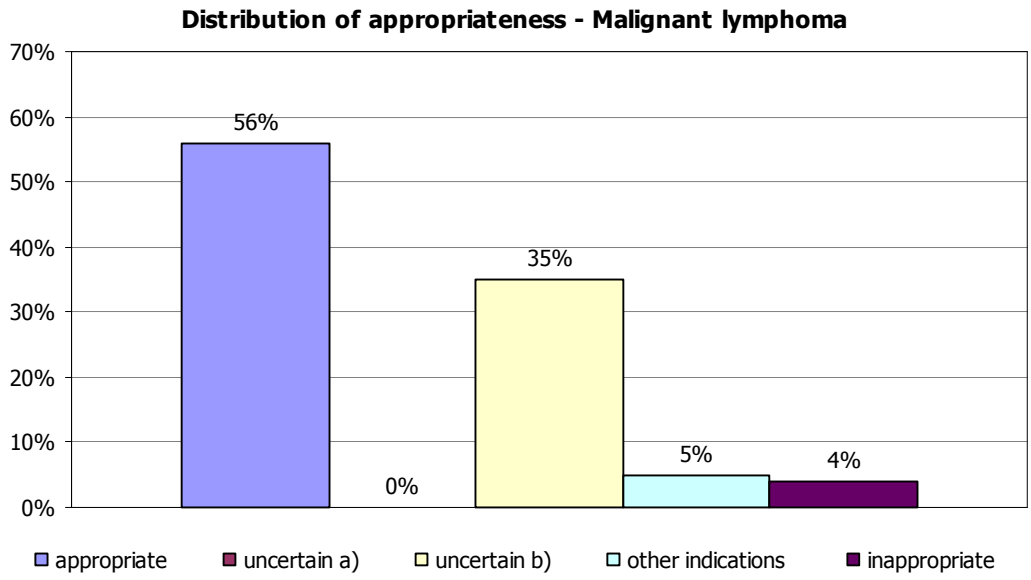
Prevalence of malignant lymphoma

Estimated cumulative prevalence in Emilia-Romagna Region at 1/1/2006 (RER 2009) was 2 958 cases of Hodgkin's lymphoma and 9 242 cases of non-Hodgkin's lymphoma.

In the regional audit carried out in 2002, FDG-PET scans requested for patients with malignant lymphoma represented 18.5% (n. 85) of the total sample included: 50 scans (11.1% of the total sample) were requested for Hodgkin's lymphoma patients (41 of these requests were considered appropriate whilst the remaining 9 fell in the inappropriate category) and 35 scans (7.7% of the total sample) were requested for non-Hodgkin's lymphoma patients (22 being considered appropriate, 12 uncertain and 1 inappropriate).

In the 2007 audit, following the criteria update in 2006, FDG-PET scans for malignant lymphoma went up to 28.4% (n. 167) of the total sample and 56% of these fell in the appropriate category, 35% in the uncertain category, 4% in the inappropriate category and 5% were for clinical indications not addressed by the report (*Graph 3*).

Graph 3. Clinical audit 2007 - appropriate use of FDG-PET in malignant lymphoma (167 FDG-PET scans)



2. Methods

A panel of 25 experts, comprising methodologists, nuclear physicians, radiologists, radiotherapists, oncologists, hematologists, internists, surgeons, pneumologists 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.

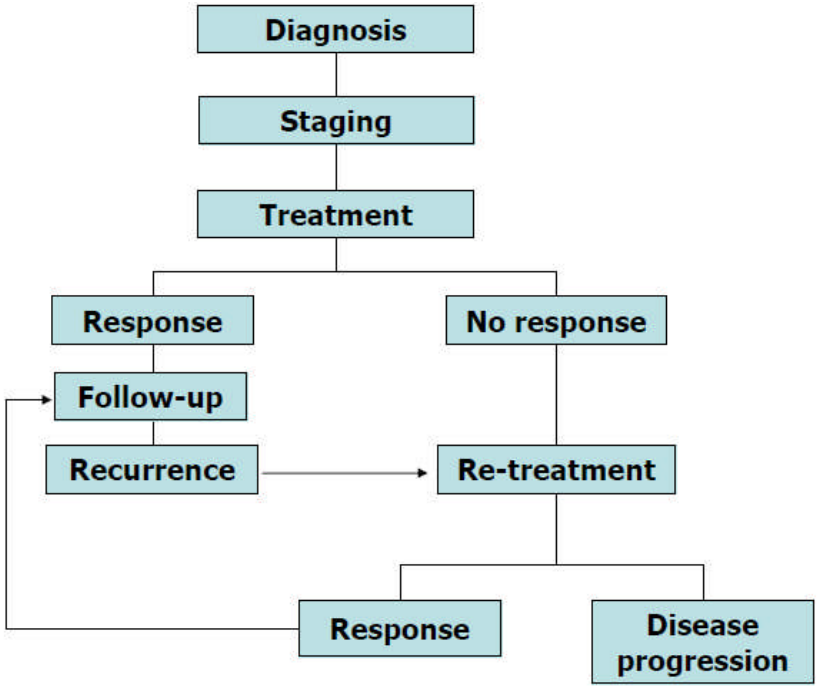
2.1. Clinical questions to be addressed

Based on the clinical pathway of the disease (*Figure 2.1*) the panel agreed on the clinical questions to address (*Table 2.1*). Considering the different clinical nature of the two diseases clinical questions were tackled separately for Hodgkin's lymphoma and for aggressive non-Hodgkin's lymphoma. For each disease the panel examined and assessed the role of FDG-PET for 6 clinical indications (for a total of 12 clinical questions).

Table 2.1. Clinical indications selected by the panel for Hodgkin's lymphoma and aggressive non-Hodgkin's lymphoma

• Staging
• Dose painting definition in involved-field radiation treatment
• During treatment evaluation of early response to therapy
• End of treatment evaluation of response to therapy
• Follow up of patients with no suspicion of recurrence
• Staging of recurrence

Figure 2.1. Clinical pathway for Hodgkin's lymphoma and aggressive non-Hodgkin's lymphoma

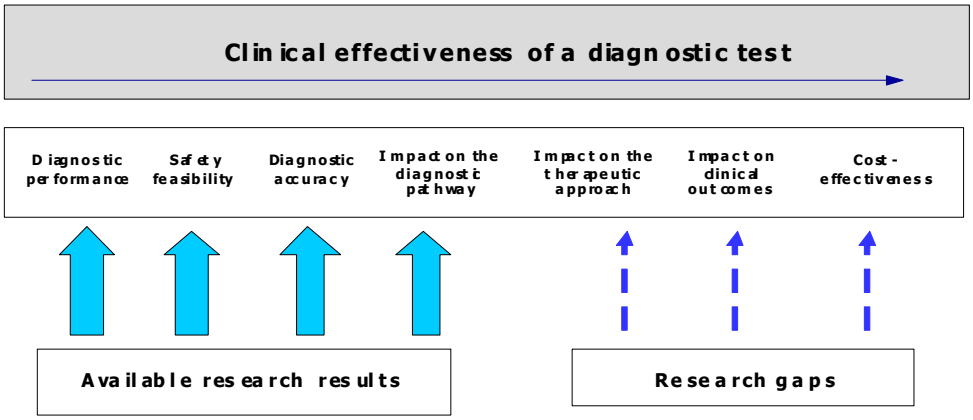


The starting point for the development of answerable "research questions", based on the PICO structure (Patient Intervention Comparator Outcome), has been the broad definition of appropriateness of a diagnostic test, which implies:

- 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 - which 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 affected by Hodgkin's lymphoma or aggressive non-Hodgkin's lymphoma and 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 PET/CT with a specific role within the diagnostic pathway and with a pre-defined position in relation to the comparator (replacement, triage, add on) as defined by Bossuyt *et al*. (Bossuyt 2006). The comparator was identified as the currently used or existing test for the diagnostic role under consideration.

Diagnostic accuracy (sensitivity and specificity) of FDG-PET or FDG-PET/CT 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 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 February 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. In addition, papers still in press at the time of literature search and/or brought to our attention by panel members were examined for inclusion in the systematic review.

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 either Hodgkin's or aggressive non-Hodgkin's lymphoma
Intervention	FDG-PET or FDG-PET/CT
Reference standard	histology or clinical follow up (for diagnostic accuracy studies)
Comparator	any other imaging technique
Outcomes	patient-based sensitivity and specificity, LR, accuracy in dose painting definition, metabolic/tumor response, quality of life, adverse events, time to recurrence, local, locoregional and distant recurrence, disease free survival, disease survival, overall survival

Assessment of methodological quality of studies

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

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

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

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

Case control studies and cohort studies:
criteria drawn from the New Castle-Ottawa checklist[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. Two reviewers analyzed all articles acquired in full text and assessed methodological quality for risk of bias addressing spectrum 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 studies included a mixed population (i.e. both patients with Hodgkin's lymphoma and patients with aggressive non-Hodgkin's lymphoma) data on single subpopulations of patients were also reported, whenever possible.

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.

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

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 than the patients included in the systematic reviews/meta-analyses, estimates of all studies have been pooled and median with range calculated.

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

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

Results from the voting rounds are reported for each clinical question addressed by the 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 good diagnostic accuracy of PET and the presumed benefit - resulting from the test results - is greater than the presumed harm.

[2] http://www.rand.org/pubs/monograph_reports/MR1269.html (last access May 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 2 863 records; 765 records were excluded because duplicates and a further 1 837 did not meet the inclusion criteria. Full text was acquired for the remaining potentially eligible 261 records, from which 206 studies were excluded on the basis of inclusion criteria while another 19 resulted already included in systematic reviews. Six additional studies were identified through references of already included papers and/or because brought to attention by panel members.

Nine systematic reviews and 33 primary studies, for a total of 42 papers were finally included. Figure 3.1 reports the studies selection process.

Tables 3.1 and 3.2 report 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 41 included studies evaluated diagnostic accuracy of FDG-PET. Only two studies evaluating impact of FDG-PET on clinical outcomes were found.

Figure 3.1. Malignant lymphoma: study selection process according to PRISMA Flow Diagram (Moher 2009)

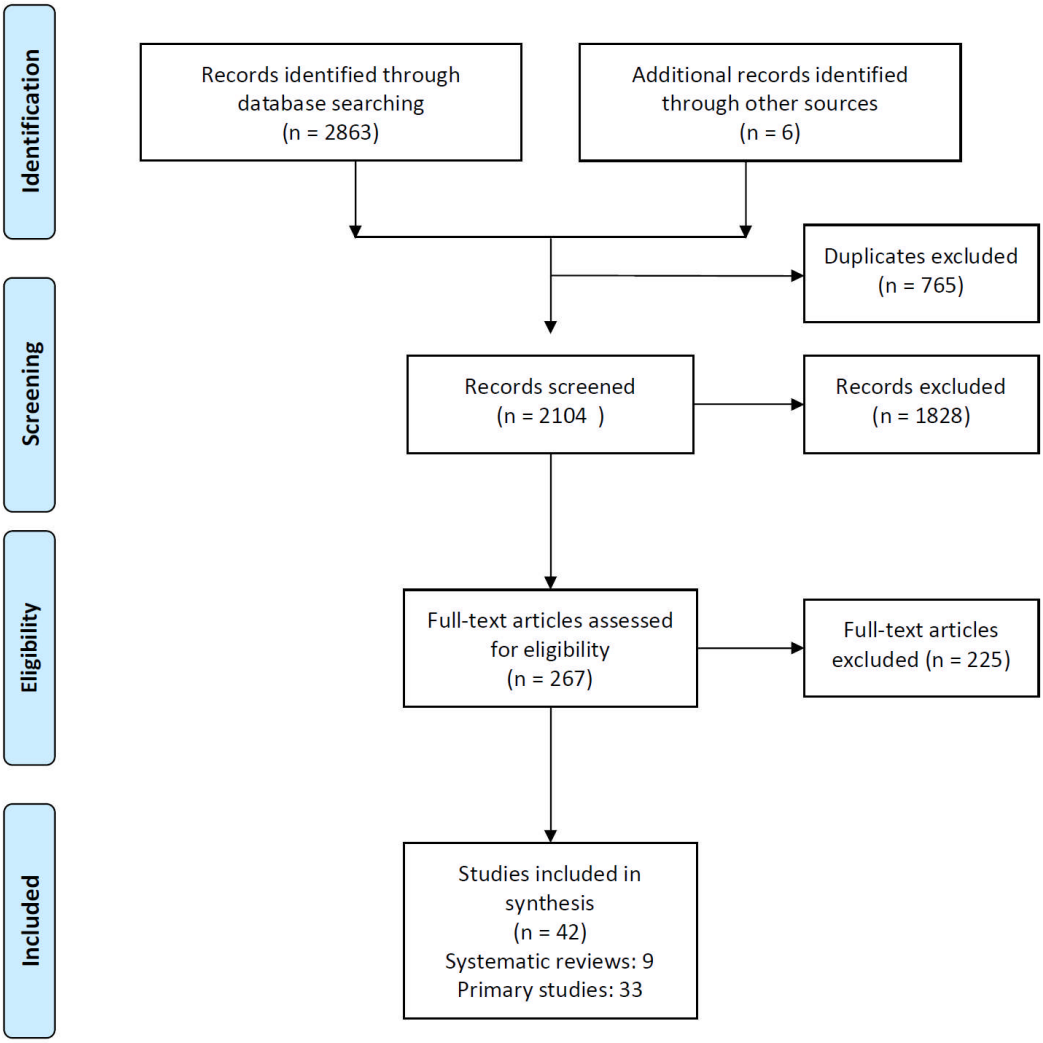

Table 3.1. Number of included studies for questions and endpoints: Hodgkin's lymphoma

Clinical question / Endpoint	Staging	Dose painting definition	Early response to therapy (during treatment)	Response to therapy (end of treatment)	Follow up	Staging of suspect of recurrence
Diagnostic accuracy	systematic reviews: 3 primary studies: 7	systematic reviews: 0 primary studies: 0	systematic reviews: 5 primary studies: 7	systematic reviews: 6 primary studies: 9	systematic reviews: 1 primary studies: 6*	systematic reviews: 2 primary studies: 3
Impact on clinical outcomes	systematic reviews: 0 primary studies: 0	systematic reviews: 0 primary studies: 0	systematic reviews: 0 primary studies: 0	systematic reviews: 0 primary studies: 0	systematic reviews: 0 primary studies: 0	systematic reviews: 0 primary studies: 0
Results of ASSR Dossier 157/2007 (Liberati 2007)	appropriate	not considered	appropriate only if baseline FDG-PET scan available (otherwise inappropriate)	appropriate	uncertain	appropriate

* including one study extracted from the systematic review

Table 3.2. Number of included studies for questions and endpoints: aggressive non-Hodgkin's lymphoma

Clinical question / Endpoint	Staging	Dose painting definition	Early response to therapy (during treatment)	Response to therapy (end of treatment)	Follow up	Staging of suspect of recurrence
Diagnostic accuracy	systematic reviews: 3 primary studies: 5	systematic reviews: 0 primary studies: 0	systematic reviews: 5 primary studies: 3	systematic reviews: 5 primary studies: 4	systematic reviews: 0 primary studies: 3	systematic reviews: 1 primary studies: 2
Impact on clinical outcomes	systematic reviews: 0 primary studies: 0	systematic reviews: 0 primary studies: 0	systematic reviews: 0 primary studies: 2	systematic reviews: 0 primary studies: 0	systematic reviews: 0 primary studies: 0	systematic reviews: 0 primary studies: 0
Results of ASSR Dossier 157/2007 (Liberati 2007)	appropriate	not considered	appropriate only if baseline FDG-PET scan available (otherwise inappropriate)	appropriate	uncertain	appropriate

Hodgkin’s lymphoma

4. Staging of Hodgkin's lymphoma

Rationale

Hodgkin's lymphoma (HL) is an uncommon malignancy involving lymph nodes and the lymphatic system. Most patients are diagnosed when between 15 and 30 years of age, with another peak in adults aged 55 years or older (NCCN 2010).

The gold standard for the diagnosis of lymphoma is an excisional lymph node biopsy (NCCN 2010, ESMO 2010a, AIOM 2009).

Once the diagnosis of lymphoma has been established by biopsy of a particular site, the accurate staging of dissemination is still a mainstay of the initial evaluation as it gives information on the prognosis, guides treatment management and predicts response to treatment and potential for cure (Namberger 2007).

Staging for Hodgkin's lymphoma is based on Ann Arbor staging system and according to spread of disease, extra nodal involvement and presence of systemic symptoms.

CT total body still forms the cornerstone of imaging for the assessment of disease status; however, CT fails to identify a considerable number of sites (especially abdominal ones, Hutchings 2006) leading to a possible underestimation of clinical stage. Staging of lymphomas usually includes a bone marrow biopsy to judge bone marrow involvement (Namberger 2007, Kwee 2008, NCCN 2010).

Clinical guidelines recommend an FDG-PET/CT scan for the appropriate staging of patients with Hodgkin's lymphoma and before treatment initiation (AIOM 2009, ISH-ISEH 2009, ESMO 2010a, NCCN 2010).

Diagnostic role of FDG-PET

To define disease extension and to distinguish between early, localised stage (I and II) from advanced, extended (stage III and IV) disease in order to direct patients to the most appropriate treatment.

Treatment effectiveness

Hodgkin's lymphoma's management has seen great improvement in the past few decades and the disease is now curable in at least 80% of patients (NCCN 2010). Therapeutic approach for Hodgkin's lymphoma is different according to the disease stage: patients in early stage (I and II) are usually treated with chemotherapy followed by radiation (involved-field radiation therapy, IFRT). Patients with advanced stage disease (III and IV) are usually treated with a prolonged course of chemotherapy, radiotherapy being limited to patients with bulky disease and with large residual masses after chemotherapy (AIOM 2009, NCCN 2010, ESMO 2010a).

Pre-test probability and change in management

Probability of diagnosis of stage I-II disease ranges approximately from 48 to 64.6% and form 35.4 to 52% for stage III-IV (Boisson 2007, Hutchings 2006, Cerci 2011).

Bone marrow involvement, that indicates stage IV disease, is usually present in 5-15% of patients (Wu 2012).

Research question: FDG-PET/CT as replacement test

Is FDG-PET/CT more accurate than CT in characterizing disease extension?

4.1. Systematic review of literature: results

Results from update of systematic review of literature from January 2006

Three systematic reviews and seven additional primary studies were included.

Systematic reviews

Four systematic reviews (Facey 2007, Kirby 2007, Kwee 2008, Wu 2012) that evaluated diagnostic accuracy of FDG-PET or FDG-PET/CT in staging patients with Hodgkin's lymphoma were retrieved. One review (Kwee 2008) was excluded as it reported diagnostic accuracy estimates using lesions as units of analysis. The three remaining reviews included studies on Hodgkin's lymphoma patients, non-Hodgkin's lymphoma patients or mixed population. Wu (Wu 2012) considered both staging of primary disease and staging of recurrence. Studies included in systematic reviews were of generally low quality: a large number was retrospective and not all prospective studies used a consecutive enrolment, leading to a possible spectrum bias. Only a limited number of studies used an appropriate reference standard test: additional sites identified by FDG-PET or areas negative according to FDG-PET but positive according to conventional imaging (predominately CT) often didn't receive histological confirmation of the presence or absence of disease. Lack of appropriate verification test carries a risk of misinterpretation of diagnostic accuracy estimates. The only review where a meta-analysis of data was performed (Wu 2012) suggests a higher sensitivity for FDG-PET and FDG-PET/CT in comparison to MRI and a higher specificity of FDG-PET/CT, when compared to FDG-PET and MRI, in detecting bone marrow involvement. However the authors of the review highlight that sensitivity and specificity of FDG-PET and sensitivity of FDG-PET/CT appear to be highly heterogeneous, affecting their diagnostic value in the assessment of bone marrow involvement in malignant lymphoma (Wu 2012).

The quality of the reviews was judged very low for Facey 2007 and Kirby 2007 (methods of review, criteria of studies' inclusion and quality appraisal of studies not fully described, poor results reporting) and high for Wu 2012. Results from systematic reviews on Hodgkin's lymphoma staging with FDG-PET or FDG-PET/CT are reported in Table 4.1.

Table 4.1 Results from systematic reviews on Hodgkin's lymphoma staging with FDG-PET or FDG-PET/CT

Reference	Facey 2007	Kirby 2007	Wu 2012
Update to	August 2005	September 2005	July 2010
Number of studies	total number of studies: 10 + a systematic review (on 7 studies) 1 on HL patients, 7 on a mixed population, 3 on NHL patients	total number of studies: 37 11 on HL patients, 17 on a mixed population, 2 on aggressive NHL, 7 on indolent NHL	total number of studies: 32 8 on HL pts, 16 on a mixed population, 8 on aggressive NHL patients
Number of patients	469 with HL or NHL (median: 42, range: 27-88) 188 with HL (median 18, range 4-88)	1 465 with HL or NHL (median: 38, range: 4-91) 681 with HL patients (median 26, range 4-88)	1 845 with HL or NHL (median: 45.5, range: 11-194) 690 with HL (median: 30, range: 6-88)
FDG-PET or FDG-PET/CT	Nodal and extra-nodal, staging, only narrative results: "Evidence from 1 SR reviewing seven PSs, and 7 additional PSs shows that PET had specificity of at least 90% and sensitivity of 79-100% (or ≥90% in the new studies). PET consistently showed superior sensitivity to Ga scanning. Two older studies suggested PET was more accurate than CT for staging lymph-node involvement, but one new study showed them to be comparable. There was evidence that all imaging methods may miss small disease foci."	Nodal and extra-nodal, staging **FDG-PET** HL sensitivity: median 94% (range: 87-100%) specificity: not reported HL+NHL sensitivity: median 93% (86-100%) specificity: median 99% (72-100%)	Bone marrow involvement, staging of primary disease and of recurrence **FDG-PET** HL+NHL sensitivity: mean 81.5% (95% CI 77.3-85.3%) specificity: mean 87.3% (95% CI 84.9-89.5%) **FDG-PET/CT** HL+NHL sensitivity: mean 91.6% (95% CI 85.1-95.9%) specificity: mean 90.3% (95% CI 85.9-93.7%)

(continues)

Reference	Facey 2007	Kirby 2007	Wu 2012
Update to	August 2005	September 2005	July 2010
Comparator	Nodal and extra-nodal, staging and restaging Only narrative results.	Nodal and extra-nodal, staging and restaging **Conventional imaging** HL sensitivity: median 77% (range, 20-93%) specificity: not calculated, only descriptive results **CT** HL+NHL sensitivity: median 81% (range not provided) specificity: median 93% (range not provided) **Ga scan** HL+NHL sensitivity: median 73% (range not provided) specificity: median 76% (range not provided)	Bone marrow involvement, staging of primary disease and of recurrence **MRI** HL+NHL sensitivity: mean 90.3% (95% CI 82.4-95.5%) specificity: mean 75.9% (95% CI 69.8-81.2%)
Reference standard	concordance between FDG-PET and other imaging techniques, follow up	none, histopathological confirmation, CT, CT + follow up + histology, clinical information and follow up, gallium versus conventional imaging	histopathology and/or close clinical and imaging follow up of at least 6 months

Primary studies

Five primary studies (Boisson 2007, Cerci 2011, de Jong 2009, Furth 2006, Picardi 2009) - for a total of 395 patients - assessed the accuracy of FDG-PET in the staging of Hodgkin's lymphoma patients; further 2 studies (Fuster 2006, Pinilla 2011) - for a total of 207 patients - assessed the accuracy of FDG-PET (both studies) or FDG-PET/CT (1 study) considering a mixed population of Hodgkin's lymphoma patients and non-Hodgkin's lymphoma patients and reporting only aggregate results.

The accuracy of FDG-PET was assessed in detecting nodal, extra-nodal or overall involvement (3 studies: Furth 2006, Pinilla 2011, Cerci 2011; *Table 4.2*), splenic involvement (2 studies: de Jong 2009, Picardi 2009; *Table 4.3*) or bone marrow involvement (4 studies: Boisson 2007, Fuster 2006, Pinilla 2011, Cerci 2011; *Table 4.4*).

Four studies had a prospective design (Furth 2006, Picardi 2009, Pinilla 2011, Cerci 2011); all but one study had an uncertain blinding of diagnostic imaging readers; the two studies assessing the splenic involvement (de Jong 2009, Picardi 2009) had the incorporation of FDG-PET in the reference standard. In one study discordant positive findings didn't receive histological confirmation leading to a possible verification bias (Cerci 2011) while another one (Furth 2006) included only pediatric patients.

Table 4.2. Results from primary studies on Hodgkin's lymphoma staging with FDG-PET assessing nodal and extra-nodal extension

Reference	Furth 2006	Pinilla 2011	Cerci 2011
Number of patients	33 (all HL patients)	101 (32 with HL, 69 with NHL)	210 (all HL patients)
FDG-PET/ PET-CT	FDG-PET sensitivity: 94% specificity: 94%	FDG-PET sensitivity: 73% specificity: 80% Low dose FDG-PET/CT sensitivity: 89% specificity: 89% Full dose FDG-PET/CT sensitivity: 90% specificity: 89%	FDG-PET sensitivity: 97.9% (95-98%) specificity: 95.3% (91-97%)
Comparator	Nodal and extra-nodal extension CIM (CT and MRI) sensitivity: 75% specificity: 94%	Nodal extension CT sensitivity: 90% specificity: 92% Extra-nodal extension CT sensitivity: 87% specificity: 91%	Nodal and extra-nodal extension CT sensitivity: 87.3% (84-89%) specificity: 96.8% (93-98%)
Reference standard	all clinical and imaging investigations and biopsy in a minority of discordant results between PET and CIM	clinical history; physical examination; laboratory work-up; iliac crest bone marrow biopsy; contrast-enhanced CT and other imaging findings (magnetic resonance imaging [MRI], Gallium scan); lumbar puncture; endoscopy; biopsies and surgery when clinically indicated; and follow up data	all clinical and imaging investigations and follow up (no histological confirmation)

Table 4.3. Results from primary studies on Hodgkin's lymphoma staging with FDG-PET assessing splenic involvement

Reference	De Jong 2009	Picardi 2009
Number of patients	15 (all HL patients)	100 (all HL patients)
FDG-PET/PET-CT	sensitivity: 70% specificity: 80%	sensitivity: 43% specificity: 100%
Comparator	CT sensitivity: 91% specificity: 96%	CT sensitivity: 43% specificity: 96% Contrast-enhanced US sensitivity: 100% specificity: 100%
Reference standard	coincidental findings of nodules positive for malignancy with at least 2 different imaging techniques (e.g. at both contrast-enhanced CT and FDG-PET) or, when malignancy was found with only one imaging technique (e.g. at contrast-enhanced harmonic compound US), to have or not to have nodule size decrease (>50% in the greatest diameter) after chemotherapy	follow up with PET/CT; a reference standard strongly suggestive of initial splenic involvement in lymphoma is reversal of progression of splenic size and the finding of splenic nodules or splenic uptake on follow up FDG-PET and CT in relation to other disease sites.

Table 4.4. Results from primary studies on Hodgkin's lymphoma staging with FDG-PET assessing bone marrow involvement

Reference	Boisson 2007	Cerci 2011	Fuster 2006	Pinilla 2011
Number of patients	37 (all HL patients)	210 (all HL patients)	106 (18 with HL, 88 with NHL)	101 (32 with HL, 69 with NHL)
FDG-PET/ PET-CT	FDG-PET/CT sensitivity: 80% specificity: 86%	FDG-PET sensitivity: 94.2% (79-99%) specificity: 98.2% (94-99%)	FDG-PET sensitivity: 85.7% specificity: 98.9%	FDG-PET sensitivity: 29% specificity: 84% Low dose FDG-PET/CT sensitivity: 29% specificity: 90% Full dose FDG-PET/CT sensitivity: 29% specificity: 90%
Comparator	no data available	biopsy sensitivity: 71.4% (53-84%) specificity: 100% (97-100%)	biopsy sensitivity: 57.1% specificity: 100%	no data available
Reference standard	bone marrow biopsy and MRI	bone marrow biopsy and follow up	bone marrow biopsy and follow up	clinical history; physical examination; laboratory work-up; iliac crest bone marrow biopsy; contrast-enhanced CT and other imaging findings (magnetic resonance imaging [MRI], Gallium scan); lumbar puncture; endoscopy; biopsies and surgery when clinically indicated; and follow up data

As the number of patient included in studies published after the systematic reviews added up to a smaller number than that of patients included in the systematic reviews, the latter's pooled estimates of FDG-PET accuracy in detecting nodal and extra-nodal extension (Kirby 2007) and bone marrow involvement (Wu 2012) were chosen and reported in Table 4.5.

Table 4.5. Diagnostic accuracy estimates of FDG-PET in detecting nodal and extra-nodal disease extension and bone marrow involvement in patients with Hodgkin's lymphoma

Diagnostic accuracy	Nodal and extra-nodal extension	Bone marrow involvement
Number of studies	37 (total) 11 on HL pts, 17 on a mixed population, 2 on aggressive NHL, 7 on indolent NHL	32 (total) 8 on HL pts, 16 on a mixed population, on NHL pts
Number of patients	1 465 with HL or NHL (median: 38, range: 4-91) (HL patients 681; range 4-88)	1 845 with HL or NHL (median: 45.5, range: 11-194) (HL patients 690: range 6-88)
Pre-test probability	stage III-IV ranges approximately form 35.4 to 52% (Boisson 2007, Hutchings 2006, Cerci 2011)	bone marrow involvement 5-15% (Wu 2012)
FDG-PET or FDG-PET/CT	**FDG-PET** HL+NHL sensitivity: median 93% (range 86-100%) specificity: median 99% (range 72-100%)	**FDG-PET/CT** HL+NHL sensitivity: mean 91.6% (95% CI 85.1-95.9) specificity: mean 90.3% (95% CI 85.9-93.7%)
Comparator	**CT** HL+NHL sensitivity: median 81% (range not provided) specificity: median 93% (range not provided)	**MRI** HL+NHL sensitivity: mean 90.3% (95% CI 82.4-95.5%) specificity: mean 75.9% (95% CI 69.8-81.2%)
	Ga scan HL+NHL sensitivity: median 73% (range not provided) specificity: median 76% (range not provided)	
Reference	Kirby 2007	Wu 2012

Comments of ASSR reviewer

Many studies have been retrieved on FDG-PET use for staging of Hodgkin's lymphoma patients. Most of them included patients with Hodgkin's lymphoma and patients with non-Hodgkin's lymphoma and didn't provide estimates for single populations. Studies were affected by some important limitations. Nevertheless FDG-PET seems to have slightly higher diagnostic accuracy performance than that of comparators (CT, MRI). The results of studies published after the systematic reviews do not modify these conclusions.

Diagnostic accuracy estimates

Nodal and extra-nodal disease extension

FDG-PET	sensitivity: median 93% (range 86-100%) specificity: median 99% (range 72-100%)
Comparator: CT:	sensitivity: median 81% (range not provided) specificity: median 93% (range not provided)

Bone marrow involvement

FDG-PET/CT	sensitivity: mean 91.6% (95% CI 85.1-95.9%) specificity: mean 90.3% (95% CI 85.9-93.7%)
Comparator: MRI:	sensitivity: mean 90.3% (95% CI 82.4-95.5%) specificity: mean 75.9% (95% CI 69.8-81.2%)

LEVEL OF EVIDENCE: MODERATE

4.2. Clinical outcomes

To evaluate the balance between benefits and risks, the panel agreed to consider the presumed patient-important outcomes reported below (*Table 4.6*), and voted on the level of importance for each outcome. All outcomes were considered by the panel to be critical. No studies evaluating the impact of FDG-PET on clinical outcomes were found.

The following matrices of "natural frequencies" were provided (*Tables 4.7* and *4.8*).

Table 4.6. Patient-important clinical outcomes and median scores of importance

Patient-important outcomes	**Median score (range)**
Consequences of test for patients with extended disease	
• True positives - Patients receive a more aggressive treatment that improves survival but increases adverse effects	8 (7-9)
• False negatives - Patients do not receive necessary aggressive treatment which could improve chance of cure, with possible negative impact on survival	8 (6-9)
Consequences of test for patients with limited disease	
• True negatives - Patients undergo a less aggressive treatment which is the most effective in terms of benefit/risk trade-off.	8 (6-9)
• False positives - Patients proceed to unnecessary aggressive treatment with a high risk of serious adverse events and no higher gain in survival.	7 (4-9)

Table 4.7. "Natural frequencies": patients assessed for linfonodal and extra-nodal involvement*

		N of patients out of 100 submitted to the exam	
		According to FDG-PET	**According to CT**
Patients with extended disease (nodal / extra-nodal involvement)	True positives	36	32
	False negatives	3	7
Patients with limited disease	True negatives	60	57
	False positives	1	4
		100	100

* pre-test probability 39% (mean value between 35.4 and 42.4%)

Table 4.8. "Natural frequencies": patients assessed for bone marrow involvement*

		N of patients out of 100 submitted to the exam	
		According to FDG-PET	**According to MRI**
Patients with bone marrow involvement	True positives	9	9
	False negatives	1	1
Patients without bone marrow involvement	True negatives	81	68
	False positives	9	22
		100	100

* pre-test probability 10% (mean value between 5% and 15%)

4.3. Voting results

The panel agreed at the first voting round to judge the use of FDG-PET in staging of patients with Hodgkin's Lymphoma as appropriate, with a median score of 8 (range 6-9).

FINAL RATING FOR THE USE OF FDG-PET FOR STAGING OF HODGKIN'S LYMPHOMA:

APPROPRIATE

4.4. Conclusions

During the first meeting the panel reached an agreement in judging appropriate (median score 8) the use of FDG-PET for staging patients with Hodgkin's lymphoma, in order to distinguish n early, localised stage (I and II) from advanced, extended (stage III and IV) disease and direct patients to most appropriate treatment. The level of evidence for estimates of FDG-PET diagnostic accuracy was moderate, with FDG-PET performing better than comparator for detection of both linfonodal/extra-nodal involvement and bone marrow involvement.

All patients' important outcomes were considered by the panel to be critical (median scores 8 and 7).

5. Dose painting definition in radiation treatment of Hodgkin's lymphoma

Rationale

Standard treatment for patients with early stage Hodgkin's lymphoma consists in systemic chemotherapy followed by radiotherapy while in advanced-stage disease post chemotherapy involved-field radiotherapy (IF-RT) is usually indicated only in bulky disease (NCCN 2010).

During the last decade, radiation treatments delivered to patients with Hodgkin's lymphoma have markedly evolved in terms of radiation doses, fields and techniques (Kirby 2007, Hutchings 2007). The risk of late adverse effects of radiotherapy (RT), which include second malignancies and cardiac toxicity, is related to the radiation dose and the size of the irradiated volume. With the increasing use of chemotherapy to contain microscopic regional disease, it has been possible to reduce both RT field size and treatment dose (Kirby 2007). The IF-RT at reduced dose should decrease acute and late toxicity without reducing effectiveness of treatment. Clinical guidelines do not cite FDG-PET as a possible diagnostic tool in radiation treatment planning (ISH-ISEH 2009, AIOM 2009, ESMO 2010a, NCCN 2010)

Diagnostic role of PET

FDG-PET imaging could provide an additional parameter for dose painting in involved-field radiation treatment.

Treatment effectiveness

Standard treatment for initial, localized stage Hodgkin's lymphoma patients is systemic chemotherapy followed by involved-field radiotherapy that yields a complete remission in 97% of patients, a 12-year progression-free survival and overall survival of 94% (Bonadonna 2004). Advanced stage Hodgkin's lymphoma is usually treated with chemotherapy alone and radiotherapy is limited to patients having large residual masses after chemotherapy (ESMO 2010a).

Change in management

It is not possible to provide estimates as no studies have been retrieved.

Research question: FDG-PET in addition to conventional imaging

Does adding FDG-PET to conventional imaging improve IF-RT dose painting for patients treated for Hodgkin's lymphoma?

5.1. Systematic review of literature: results

Neither systematic reviews nor primary studies evaluating dose painting definition with FDG-PET were found.

Systematic reviews

None retrieved.

Primary studies

None retrieved.

Diagnostic accuracy estimate:

It is not possible to provide estimates.

LEVEL OF EVIDENCE: NONE

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 5.1*), and voted on the level of importance for each outcome. Main consequences related to accuracy of dose painting were voted important (median score of 5 and 4). No studies evaluating the impact of FDG-PET on clinical outcomes were found.

Table 5.1. Patient-important clinical outcomes and median scores of importance

Patient-important outcomes	**Median score (range)**
Consequences of test for patients undergoing involved-field radiation treatment	
• Accurate dose painting leading to best trade-off between benefits, in terms of survival and local control, and adverse effects due to toxicity	5 (3-8)
• Inaccurate dose painting with loss of optimization between expected benefits and adverse effects	4 (3-8)

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

5.3. Voting results

Due to the absence of studies, the panel classified the use of FDG-PET for IF-RT dose painting as indeterminate.

FINAL RATING FOR THE USE OF FDG-PET FOR IF-RT DOSE PAINTING DEFINITION IN HODGKIN'S LYMPHOMA:

INDETERMINATE

5.4. Conclusions

During the first meeting the panel discussed the potential diagnostic role of FDG-PET in radiation treatment planning and agreed to focus on dose painting definition, rather than on Target Volume definition. For the clinical question identified by the panel, the systematic review of the literature retrieved no studies and, during the second meeting, the panel judged this clinical indication as indeterminate due to lack of studies. Clinical consequences of accuracy of dose painting definition were voted important.

6. During treatment evaluation of early response to therapy in Hodgkin's lymphoma

Rationale

Early evaluation of response to therapy could differentiate patients who will have complete remission following standard conventional therapy alone (>80% of patients with Hodgkin's lymphoma), from those for whom alternative and more aggressive treatment strategies (second-line induction chemotherapy followed by high dose therapy/autologous stem cell transplantation) might be necessary. This would enable switching poor responders sooner to treatment regimens that would improve the likelihood and duration of remission (Kirby 2007). Conventional methods for monitoring response to treatment include clinical examination and contrast enhanced CT scan (Paolini 2007). Clinical guidelines indicate an FDG-PET or FDG-PET/CT scan as a potentially useful diagnostic tool to assess during treatment response of patients (AIOM 2009, NCCN 2010, ESMO 2010a).

Diagnostic role of FDG-PET

To distinguish early responders from early non-responders after first cycles of treatment in order to decide whether to continue standard treatment or direct non-responding patients to a more aggressive treatment.

Treatment effectiveness

Standard treatment for initial stage (I-II) of Hodgkin's lymphoma patients is systemic chemotherapy followed by involved-field radiotherapy; this therapeutic plan can yield a complete remission in up to 97% of patients and, at twelve years, a progression-free survival and an overall survival of up to 94% (Bonadonna 2004). In advanced-stage disease the standard treatment is systemic chemotherapy which yields a 5-year progression-free survival of 84% and a 5-year overall survival of 91%; post chemotherapy involved-field radiotherapy is usually indicated in bulky disease, where it allows a 5-year event-free and overall survival rates of 79% and 87%, respectively (Aleman 2003). However for patients who do not respond to first-line chemotherapy, change of chemotherapy, intensification of radiotherapy or autologous transplant can represent viable therapeutic options.

Pre-test probability and change in management

Data from primary studies suggest a median pre-test probability of non response (or incomplete response) of about 21% (Barnes 2011, Boisson 2007, Cerci 2010a, Dann 2010, Terasawa 2009, Zinzani 2012). Change in management due to midterm treatment FDG-PET/CT (consisting in change from standard to escalated chemotherapy) was reported by one study to be 9.4% (Dann 2010).

Research question: FDG-PET as replacement test

Is FDG-PET more accurate than conventional imaging in evaluating response during systemic chemotherapy of patients treated for Hodgkin's lymphoma?

6.1. Systematic review of literature: results

Results from update of systematic review of literature from January 2006

Five systematic reviews and seven additional primary studies on value of FDG-PET in evaluating early response during treatment were included.

Systematic reviews

Five systematic reviews were retrieved (AETSA 2007, Facey 2007, Kirby 2007, Terasawa 2009, Terasawa 2010). All reviews included studies evaluating FDG-PET accuracy in predicting response in patients undergoing a mid-term treatment evaluation. All reviews included studies on patients with Hodgkin's lymphoma, patients with non-Hodgkin's lymphoma and mixed populations. Two reviews selected studies including only advanced-stage Hodgkin's lymphoma patients (Terasawa 2009) or only patients evaluated at the end of high-dose chemotherapy and before autologous stem cell transplantation (Terasawa 2010).

Studies included in systematic reviews were of generally low quality. Many included studies were retrospective and used clinical follow up as reference standard for both patients with positive or negative FDG-PET scans. The review by Terasawa 2009 reports that all the included studies adopted standard guidelines on response assessment as reference standard, all sharing the limitation of unclear definition of follow up period or unclear situations where pathological confirmation was required.

Data on comparator were not available (only one study - included in AETSA 2007 - reported data on 67 Ga SPECT).

The inclusion of both prospective and retrospective studies and uncertainty about consecutive enrolment carries a high risk of spectrum bias. Moreover the lack of appropriate verification test for patients testing positive leads to a risk of overestimation of diagnostic accuracy.

The quality of the reviews was judged very low for Facey 2007, AETSA 2007 and Kirby 2007 (methods of review, criteria of studies' inclusion, quality appraisal of studies not fully described, poor results reporting) and high for Terasawa 2009 and Terasawa 2010.

All reviews conclude that, although FDG-PET might hold a prognostic value, given the methodological limitations in the primary studies, prospective studies with appropriate methodologies are needed to establish the clinical value of this information.

Table 6.1 reports estimates of diagnostic accuracy of FDG-PET for Hodgkin's lymphoma patients extracted from the systematic reviews.

Table 6.1. Results from systematic reviews on diagnostic accuracy of FDG-PET in evaluating during treatment response in Hodgkin's lymphoma patients

Reference	AETSA 2007	Facey 2007	Kirby 2007	Terasawa 2009	Terasawa 2010
Update to	August 2006	August 2005	September 2005	July 2007	July 2010
Number of studies	total number of studies: 10 7 on HL patients 2 on a mixed population (HL and NHL)	total number of studies: 9 1 on HL patients 4 on a mixed population (HL and NHL)	total number of studies: 15 2 on HL patients 6 on a mixed population (HL and NHL)	total number of studies: 13 6 on advanced stage HL patients (+1 on a mixed population - HL and NHL - excluded from pooled results)	total number of studies: 12 2 on pre-transplant HL patients 7 on a pre-transplant mixed population (HL and NHL)
Number of patients	631 with HL or NHL (range22-108) 496 with HL (range 3-108)	115 with HL or NHL (range: 16-46) 123 with HL (range: 10-85)	169 with HL or NHL (range: 30-54) 167 with HL (range: 3-85)	360 with HL (range: 22-108)	479 pre-transplant with HL or NHL (range: 15-101) pre-transplant HL patients: 187 (range: 24-68)
FDG-PET or FDG-PET/CT	<u>HL or NHL patients</u> sensitivity: 55.5-100% specificity: 50.0-100% <u>HL patients</u> sensitivity: 55.5-100% specificity: 50.0-100%	Narrative results only. "… midtherapy scans may be predictive of outcome midtherapy. However, there is no evidence of any associated changes in management (…) consequent upon this"	<u>HL or NHL patients</u> sensitivity: 42-100% specificity: 50-100% <u>HL patients</u> sensitivity: 67-80% specificity: 93-94%	<u>HL patients</u> sensitivity (pooled): 81% (95% CI 72-89%) specificity (pooled): 97% (95% CI 94-99%)	<u>HL or NHL patients</u> sensitivity 69% (95% CI 56-81%) specificity 81% (95% CI 73-87%) <u>HL patients</u> sensitivity (pooled): 79% (59-91%) specificity (pooled): 75% (58-86%)

(continues)

Reference	AETSA 2007	Facey 2007	Kirby 2007	Terasawa 2009	Terasawa 2010
Update to	August 2006	August 2005	September 2005	July 2007	July 2010
Comparator	67Ga SPECT (1 study) sensitivity: 40% specificity: 94%	none reported	none reported	none reported	none reported
Reference standard	follow up	follow up	unclear	standard guidelines on response assessment (possibly including follow up period or pathological confirmation)	follow up

Primary studies

Sixteen additional primary studies not included in the above-mentioned systematic reviews were retrieved (Advani 2007, Altamirano 2008, Avigdor 2010, Barnes 2011, Boisson 2007, Cerci 2010a, Dann 2010, Furth 2009, Jabbour 2007, Markova 2009, Le Roux 2011, Paolini 2007, Riad 2010, Schot 2007, Sher 2009, Zinzani 2012). Nine of these were excluded due to their prognostic aim - e.g. assessing the predictive accuracy of midterm treatment FDG-PET response in term of long term recurrence of disease (Advani 2007, Avigdor 2010, Furth 2009, Jabbour 2007, Markova 2009, Le Roux 2011, Paolini 2007, Schot 2007, Sher 2009).

Seven studies tested the diagnostic accuracy of midterm treatment FDG-PET response in predicting the status of disease (remission or progression) at the end of treatment. Five of them (Barnes 2011, Boisson 2007, Cerci 2010a, Dann 2010, Zinzani 2012) included only Hodgkin's lymphoma patients (total number 625), while other two (Altamirano 2008, Riad 2010) included both Hodgkin's and non-Hodgkin's lymphoma patients (total number 88, 52 of which with HL). Three studies (Barnes 2011, Riad 2010, Zinzani 2012) had a retrospective design and the others a prospective design. Three studies (Altamirano 2008, Cerci 2010a, Riad 2010) applied a valid reference standard - histopathology to confirm FDG-PET positive lesions and observation in negative patients according to validated criteria. Two studies incorporated FDG-PET results at the end of treatment in the reference standard leading to possible incorporation bias (Dann 2010, Zinzani 2012) and two studies applied an unclear reference standard (Barnes 2011, Boisson 2007). Two studies (Altamirano 2008, Riad 2010) compared diagnostic accuracy of FDG-PET with a comparator (CT or conventional imaging - CT, MRI, US).

Results from the seven primary studies (according to Hodgkin's lymphoma patients and mixed population studies) are reported in Table 6.2.

As the number of patient included in studies published after the systematic review of Terasawa 2009 added up to a greater number than that of patients included in the systematic review, estimates of all studies have been pooled and re-calculated (median with range) (*Table 6.3*).

Table 6.2. Results from primary studies on assessment of during treatment response to therapy in Hodgkin's lymphoma patients and mixed population studies

Reference	Barness 2011, Boisson 2007, Cerci 2010a, Dann 2010, Zinzani 2012	Altamirano 2008 and Riad 2010
Number of studies	5	2
Number of patients	625 (median 96, range 25-304)	79 (range 28-51), 52 with HL (range 7-45)
FDG-PET or FDG-PET/CT	sensitivity: range 55-80% specificity: range 74-93%	sensitivity: range 92.2-100% specificity: range 93.3-97.0%
Comparator	none	CT (1 study) sensitivity: 79.0% specificity: 50.0% conventional imaging (1 study) sensitivity: 83.0% specificity: 66.6%
Reference standard	histopathology and/or end of treatment follow up	histopathology and end of treatment follow up

Table 6.3. Overall results on assessment of during treatment FDG-PET response in Hodgkin's lymphoma patients

Diagnostic accuracy	
Number of studies	11
Number of patients	985 with HL (median 71; range: 10-304)
Pre-test probability of not response	21%
FDG-PET or FDG-PET/CT	FDG-PET sensitivity (median): 78% (range 55-100%) specificity (median): 95% (range 74-100%)
Comparator	Conventional imaging (1 study) sensitivity: 83.0% specificity: 66.6%
Reference standard	histopathology and/or end of treatment follow up
Reference	Primary study from Terasawa 2009, Barnes 2011, Boisson 2007, Cerci 2010a, Dann 2010, Zinzani 2012, Riad 2010 (comparator's data)

Comments of ASSR reviewer

A fairly large number of studies have been carried out, some of which were retrospective and used inappropriate reference standard. Data obtained pooling studies from a systematic review and subsequently published primary studies resulted in high specificity and low sensitivity with a wide range of value. Data on comparators are scarce.

Diagnostic accuracy estimates

FDG-PET	sensitivity (median): 78% (range 55-100%) specificity (median): 95% (range 74-100%)
Conventional imaging	sensitivity: (CT, MRI, US)*: 83% specificity: (CT, MRI, US)*: 66.6%

* data from only one study

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. Outcomes for patients correctly identified as non responders were judged most critical (median vote 8; range 6-9). All other consequences received a median vote of 7. No studies evaluating impact of FDG-PET on clinical outcomes were found.

The following matrix of natural frequencies was provided for patients undergoing during treatment FDG-PET (*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 non responders	
• True non responders (true positives) - Patients interrupt ineffective treatment and are directed to more aggressive treatments with a potential benefit on survival	8 (6-9)
• False responders (false negatives) - Patients complete ineffective treatment and do not proceed to alternative more aggressive treatments with a possible negative impact on survival	7 (4-9)
Consequences of test for responders	
• True responders (true negatives) - Patients complete effective treatment aimed at improving survival	7 (6-9)
• False non responders (false positives) - Patients interrupt effective treatment and are unnecessarily directed to more aggressive treatments with high risk of harm and no higher gain in survival	7 (6-9)

Table 6.5. Natural frequencies of patients assessed for response to midterm treatment*

		N of patients out of 100 submitted to the exam	
		According to FDG-PET	**According to conventional imaging**
Patients non responders	True non responders (FDG-PET true positive)	16	17
	False responders (FDG-PET false negative)	5	4
Patients responders	True responders (FDG-PET true negative)	75	53
	False non responders (FDG-PET false positive)	4	26
		100	100

* pre-test probability of residual mass: 21%

6.3. Voting results

After an initial slight disagreement, with votes ranging from uncertain to appropriate (median score 7; range 4-8) the panel agree, during the second round, in voting the use of FDG-PET for during treatment evaluation of patients' response to therapy as appropriate (median score 7, range 7-8).

FINAL RATING FOR THE USE OF FDG-PET FOR DURING TREATMENT EVALUATION OF EARLY RESPONSE TO THERAPY IN PATIENTS TREATED FOR HODGKIN'S LYMPHOMA:

APPROPRIATE

6.4. Conclusions

After an initial slight disagreement, with votes ranging from uncertain to appropriate (median score 7; range 4-8) the panel agree, during the second round, in voting the use of FDG-PET for during treatment evaluation of patients' response to therapy as appropriate (median score 7, range 7-8). The initial perplexity was due to the lack of evidence for impact on clinical outcomes following early switch of therapy. However, level of evidence for FDG-PET accuracy in predicting response to treatment resulted to be moderate, and all patients' important outcomes were voted critical.

7. End of treatment evaluation of response to therapy in Hodgkin's lymphoma

Rationale

Complete remission is the main objective of lymphoma's treatment and is usually associated with a longer progression-free survival, than partial remission. Patients with Hodgkin's lymphoma are usually treated with front-line therapy, with complete response (CR) rates ranging from 60 to 80% (Filmont 2007) although, after completion of conventional chemotherapy and/or radiotherapy, CT or MRI reveal residual masses in as many as 64% of treated patients, but only approximately 20% of these are reported to be positive for lymphoma on biopsy (Kirby 2007). These masses may contain residual disease, needing further treatment, or may represent fibrosis or necrotic tissue, which will remain stable or regress, in no need of additional treatment. Differentiation of residual active tumor from fibrosis or necrosis is crucial to decide on the need for further therapeutic interventions (Molnar 2010, Kirby 2007, NCCN 2010, NCCN 2011).

Clinical guidelines recommend an FDG-PET or FDG-PET/CT scan to assess response to treatment, to be performed not before two weeks after completing chemotherapy and not before 8-12 weeks after completing IF-RT (AIOM 2009, ISH-ISEH 2009, NCCN 2010, ESMO 2010a). Some guidelines (ESMO 2010a, NCCN 2010) recommend a confirmation biopsy in FDG-PET positive patients.

Diagnostic role of FDG-PET

To identify patients with residual disease who will benefit from further more aggressive treatment, in order to achieve a higher probability of cure.

Treatment effectiveness

Hodgkin's lymphoma's management has largely improved in the past few decades and the disease is now curable in at least 80% of patients (NCCN 2010). However patients who do not achieve complete response after first-line treatment have a poor prognosis and usually undergo individualised second-line treatment (AIOM 2009, NCCN 2010, ESMO 2010a).

Pre-test probability and change in management

Data from primary studies suggest a median pre-test probability of non response (or incomplete response) of about 21% (Terasawa 2009, Barnes 2011, Boisson 2007, Cerci 2010b, Dann 2010, Zinzani 2012).

Only one study (Kobe 2008) was found reporting data on change in management in patients candidate to consolidative radiotherapy. Patients with advanced and bulky disease and with residual mass at CT after 6-8 cycles of chemotherapy were evaluated with PET. About 79% of these (245/311) had a negative PET scan and did not undergo additional treatment, whilst the remaining 21% (66/311) with a positive FDG-PET scan received consolidating radiotherapy.

Research question: FDG-PET as add-on test

What is the diagnostic accuracy of FDG-PET in evaluating response to treatment in patients treated for Hodgkin's lymphoma and with residual mass at CT scan?

7.1. Systematic review of literature: results

Results from update of systematic review of literature from January 2006

Six systematic reviews and nine additional primary studies were included.

Systematic reviews

Six systematic reviews were retrieved (AETSA 2007, Zijlstra 2006, Facey 2007, Terasawa 2008, Kwee 2008). Two (AETSA 2007, Kirby 2007) included only studies evaluating FDG-PET accuracy in patients with residual masses, while the remaining 4 reviews included both studies comparing diagnostic accuracy of FDG-PET vs CT in all patients completing treatment and studies evaluating diagnostic accuracy of FDG-PET in patients with residual masses at CT scan. All reviews included studies on Hodgkin's and non-Hodgkin's lymphoma patients and mixed populations. Reviews have many studies in common.

Studies included in systematic reviews were of generally low quality. Many were retrospective and used clinical follow up as reference standard whether patients had positive or negative FDG-PET scans. The lack of appropriate verification test for patients testing positive carries a risk of overestimation of diagnostic accuracy. The inclusion of both prospective studies with unclear consecutive enrolment and retrospective studies carries a high risk of spectrum bias. Because majority of studies were retrospective, reported estimates of PPV and NPV have not been considered.

The quality of the reviews was judged very low for Facey 2007, AETSA 2007 and Kirby 2007 (methods of review, criteria of studies' inclusion and quality appraisal of studies not fully described, poor results reporting) and high for Zijlstra 2006, Kwee 2008 and Terasawa 2008.

All reviews conclude that, although FDG-PET might hold a prognostic value, the clinical value of this information is not clear.

Table 7.1 reports estimates of diagnostic accuracy of FDG-PET or FDG-PET/CT in all patients completing treatment or only in patients with residual masses at CT scan extracted from the systematic reviews.

Table 7.1. Results from systematic reviews on diagnostic accuracy of FDG-PET in evaluating end of treatment response in Hodgkin's lymphoma patients

Reference	AETSA 2007	Zijlstra 2006	Facey 2007	Kirby 2007	Terasawa 2008	Kwee 2008
Update to	2004	January 2004	August 2005	Jan 1997 - Sept 2005	July 2006	July 2007
Number of studies	3 on HL patients only	15 (5 on HL patients, 2 on NHL patient, 8 on a mixed population)	3 (2 on HL patients, 1 on a mixed population)	26 (all on patients with residual masses) (9 on HL patients, 4 on NHL patients, 13 on a mixed population)	19 (10 on HL patients, 3 on NHL patients, 6 on a mixed population)	19 (7 on HL patients, 2 on NHL patients, 10 on a mixed population)
Number of evaluable patients	89 with HL (median: 29, range: 28-32)	202 with HL (median: 37, range: 26-60) 418 with HL or NHL (median: 52, range: 32-88) 138 with NHL (median: 69, range: 45-93)	65 with HL (median: 32.5, range: 29-36) 58 with HL or NHL	360 with HL (median: 36, range: 26-63) 650 with HL or NHL (median: 40, range: 19-101) 270 with NHL (median: 66, range: 45-93)	474 with HL (median: 31, range: 5-71) 281 with NHL (median: 29.5, range: 5-73)	259 with HL (median: 32, range: 23-66) 123 with NHL (median 61.5, range: 45-78) 556 with HL or NHL (median: 45.5, range: 18-101)

(continues)

Reference	AETSA 2007	Zijlstra 2006	Facey 2007	Kirby 2007	Terasawa 2008	Kwee 2008
Update to	2004	January 2004	August 2005	Jan 1997 - Sept 2005	July 2006	July 2007
FDG-PET or FDG-PET/CT	<u>All patients</u> no data	<u>All patients</u> <u>HL patients (243 pts in total)</u> sensitivity: pooled 84% (95% CI 71-92%) specificity: pooled 90% (95% CI 84-94%) <u>NHL (201 pts in total)</u> sensitivity: pooled 72% (95% CI 61-82%) specificity: pooled 100% (95% CI 97-100%)	Narrative results only. PET shows similar sensitivity to CT but better specificity		<u>All patients</u> <u>HL (399 patients)</u> sensitivity: 50-100% specificity: 67-100% <u>NHL (281 patients)</u> sensitivity: 33-77% specificity: 82-100%	<u>All patients</u> **FDG-PET** <u>HL patients</u> sensitivity: 86.2-100% specificity: 57.1-100% <u>NHL</u> sensitivity: 60-87% specificity: 80-100% <u>HL or NHL</u> sensitivity: 71.4-100% specificity: 86.2-100% **FDG-PET/CT fusion** <u>HL patients</u> sensitivity: 100% (87.5-100) specificity: 90.7% (78.4-96.3%) <u>HL or NHL patients</u> sensitivity: 92.9-94.7% specificity: 90.6-100%

(continues)

Reference	AETSA 2007	Zijlstra 2006	Facey 2007	Kirby 2007	Terasawa 2008	Kwee 2008
Update to	2004	January 2004	August 2005	Jan 1997 - Sept 2005	July 2006	July 2007
	Patients with residual masses HL sensitivity: 80-100% specificity: 83.3-85%			Patients with residual masses HL sensitivity: median 95% (50-100%) specificity: median 86% (78-100%) NHL sensitivity: 60-87% specificity: 94-100% HL or NHL sensitivity: median 86% (43-100%) specificity: median 95% (73-100%)	Patients with residual mass HL (197 pts) sensitivity: 43-100% specificity: 67-100% NHL (78 pts) sensitivity: 33-87% specificity: 75-100%	
Comparator	HL patients with residual masses **CT** sensitivity: 25% specificity: 42% **67Ga-SPECT** sensitivity: 40% specificity: 96%	none reported	**CT** narrative results only	**CT** Mixed population sensitivity: median 78% (16-100%) specificity: not provided	None reported	**CT** HL patients only data on lesions Mixed population sensitivity: 25-100% specificity: 41.7-58.8%

(continues)

Reference	AETSA 2007	Zijlstra 2006	Facey 2007	Kirby 2007	Terasawa 2008	Kwee 2008
Update to	2004	January 2004	August 2005	Jan 1997 - Sept 2005	July 2006	July 2007
Reference standard	follow up	histology (only for a minority of patients), radiology and follow up (median >18 months)	unclear	follow up	follow up	follow up

Primary studies

Four additional primary studies on a mixed population of patients and five on Hodgkin's lymphoma patients only and not included in the above-mentioned systematic reviews were retrieved.

Four primary studies prospectively (Altamirano 2008, Talavera Rubio 2009) or retrospectively (Bucerius 2006, Riad 2010) evaluated end of treatment response with FDG-PET in a total of 187 patients with Hodgkin's lymphoma or non-Hodgkin's lymphoma (either indolent or aggressive). One study included only paediatric patients (Riad 2010). Data extracted from these primary studies are summarised in Table 7.2.

Table 7.2. Results from primary studies evaluating the role of FDG-PET in assessing end of treatment response in a mixed population of patients

Reference	Altamirano 2008, Bucerius 2006, Riad 2010, Talavera Rubio 2009
Number of patients	187
FDG-PET or FDG-PET/CT	FDG-PET (4 studies) sensitivity: 69-100% specificity: 90-98%
Comparator	Conventional imaging methods (CT, MRI, US) (1 study) sensitivity: 83% specificity: 67% CT (2 studies) sensitivity: 83-91% specificity: 38-63% Contrast-enhanced CT (1 study) sensitivity: 95% specificity: 95%
Reference standard	follow up and histology

Among the 5 studies on Hodgkin's lymphoma patients, two studies, Boisson 2007 and Mocikova 2010, compared FDG-PET/CT against CT in 25 and 113 Hodgkin's lymphoma patients respectively, using follow up as reference standard. One study (Furth 2009) compared FDG-PET with contrast-enhanced MRI in 29 paediatric HL patients and suspicion of relapse was confirmed by biopsy. When compared with CIM-MRI, FDG-PET seemed to perform better for both sensitivity and specificity while, when compared with CT, sensitivity of FDG-PET appeared lower and specificity higher than CT.

Results of these three studies are reported in Table 7.3.

Table 7.3. Results from primary studies assessing the role of FDG-PET or FDG-PET/CT in assessing end of treatment response in Hodgkin's lymphoma patients

Reference	Boisson 2007	Mocikova 2010	Furth 2009
Number of patients	25	113	29
FDG-PET or FDG-PET/CT	FDG-PET/CT sensitivity: 80% specificity: 100%	FDG-PET or FDG-PET/CT* sensitivity: 36% specificity: 86%	FDG-PET sensitivity: 100% specificity: 78%
Comparator	CT sensitivity: 80% specificity: 54.5%	CT* sensitivity: 64% specificity: 52%	Contrast-enhanced MRI sensitivity: 50% specificity: 11%
Reference standard	follow up (median: CT: 7 ± 4, FDG-PET/CT: 6.7 $\pm$ 4.2)	follow up	follow up (mean 46 months) and all imaging information

* estimates calculated by ASSR reviewer, authors only provided PPV and NPV

Finally two studies (Cerci 2010b, Molnar 2010) evaluated Hodgkin's lymphoma patients showing ambiguous residual mass at CT at the end of treatment. In the study by Cerci (Cerci 2010b) FDG-PET positive patients underwent histological confirmation and both FDG-PET-positive and FDG-PET-negative patients were followed-up for at least 18 months while, in the study by Molnar (Molnar 2010,) positive asymptomatic patients underwent biopsy, if the tumor was easily accessible, otherwise they were closely monitored. Both studies are well conducted and reported and used the appropriate reference standard to assess FDG-PET diagnostic accuracy.

Results from the two studies assessing FDG-PET as add-on test are reported in Table 7.4.

Table 7.4. Results from primary studies assessing the role of FDG-PET in investigating residual masses at CT performed at end of treatment in Hodgkin's lymphoma patients (as add-on test after CT)

Reference	Cerci 2010b	Molnar 2010
Number of patients	50	128
FDG-PET or FDG-PET/CT	FDG-PET sensitivity: 100% specificity: 92%	FDG-PET or FDG-PET/CT sensitivity: 82.9% specificity: 89.2%
Comparator	none	none
Reference standard	follow up and histology	follow up and histology

As 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, the pooled estimates from the only meta-analysis performed by Zijlstra et al (Zijlstra 2006) were chosen (*Table 7.5*) for diagnostic accuracy in all patients, while for estimates of diagnostic accuracy of FDG-PET as add-on test (scan performed only in patients with unconfirmed residual masses at conventional imaging), results from Terasawa et al (Terasawa 2008) were used.

Table 7.5. Results on diagnostic accuracy of FDG-PET in assessing end of treatment response in patients with Hodgkin's lymphoma

Diagnostic accuracy	All patients	Patients with residual masses at conventional imaging
Number of studies	7	9
Number of patients	243	197
Pre-test probability of relapse	median 31% (14-46%)	median: 20% (0-50%)
Results FDG-PET/ PET-CT	sensitivity: pooled 84% (95% CI 71-92%) specificity: pooled 90% (95% CI 84-94%)	sensitivity: 43-100% specificity: 67-100%
Results comparator	CT sensitivity: median 82% (64-91%) specificity: median 53% (38-63%) Conventional imaging methods (CT, MRI, US) sensitivity: range 50-83% specificity: range 11-67%	not applicable
Reference standard	histopathology on biopsies (minority of patients) or radiological and clinical follow up (majority of patients)	clinical follow up with or without histological confirmation
References	Altamirano 2008, Boisson 2007, Bucerius 2006, Furth 2009, Mocikova 2010, Riad 2010, Talavera Rubio 2009 (primary studies considered only for data on comparators), Zijlstra 2006	Terasawa 2008

Comments of ASSR reviewer

Many studies and several systematic reviews evaluated the diagnostic accuracy of FDG-PET in assessing end of treatment response in Hodgkin's lymphoma. FDG-PET seems to have a good overall accuracy in detecting residual disease in patients with Hodgkin's lymphoma, but data are flawed by several methodological limitations and authors of systematic reviews highlight the need for good quality studies to reliably assess the diagnostic accuracy of FDG-PET.

Two good quality primary studies addressed our research question (FDG-PET in add-on) and evaluated sensitivity and specificity of FDG-PET in assessing unconfirmed residual masses shown at CT scan.

Diagnostic accuracy estimates

All patients

FDG-PET sensitivity: pooled 84% (95% CI 71-92%)
specificity: pooled 90% (95% CI 84-94%)

CT sensitivity: median 82% (64-91%)
specificity: median 53% (38-63%)

Conventional imaging methods (CT, MRI, US)
sensitivity: range 50-83%
specificity: range 11-67%

Patients with unconfirmed residual masses at CT

FDG-PET sensitivity (range): 43-100%
specificity (range): 67-100%

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. All outcomes were considered critical with the highest score of 8 for consequences for non responding patients receiving more aggressive treatment.

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

Table 7.6. Patient-important clinical outcomes and median scores of importance

Patient-important outcomes	Median score (range)
Consequences of test for responders	
• True non responders (true positive) - patients undergo confirmatory biopsy and are directed to more aggressive treatment with potential benefit in survival	8 (6-9)
• False responders (false negatives) - patients do not receive necessary more aggressive treatment with a consequent negative impact on survival	7 (4-9)
Consequences of test for non responders	
• True responders (true negative) - patients are placed in follow up	7 (6-9)
• False non responders (false positive) - patients undergo unnecessary biopsy and anxiety before being placed in follow up	7 (4-9)

The following two matrices of "natural frequencies" were provided. The first one (*Table 7.7*) reports estimates from a head to head comparison between FDG-PET and CT for all patients assessed at the end of treatment, while the second one (*Table 7.8*) reports estimates only for patients found to have residual disease at CT: FDG-PET is compared against reference standard.

Table 7.7. "Natural frequencies": patients assessed for end of treatment response* (head to head comparison)

		N of patients out of 100 submitted to the exam	
		According to FDG-PET	**According to CT**
Patients with residual disease	True non responders	18	17
	False responders	3	4
Patients with complete remission	True responders	71	42
	False non responders	8	37
		100	100

* pre-test probability: 21%

Table 7.8. "Natural frequencies": patients with unconfirmed residual mass assessed for end of treatment response* (PET as add-on test after CT)

		N of patients out of 100 submitted to the exam	
		According to FDG-PET	**According to reference standard (biopsy)**
Patients with residual disease	True non responders	9-20	20
	False responders	0-11	0
Patients with complete remission	True responders	54-80	80
	False non responders	0-26	0
		100	100

* pre-test probability: 20%

7.3. Voting results

The panel agreed at the first meeting to judge appropriate the use of FDG-PET for the evaluation of patients' response to therapy at the end of treatment and the first round of voting registered a median score of 7 with votes ranging from 6 to 8.

FINAL RATING FOR THE USE OF FDG-PET FOR END OF TREATMENT EVALUATION OF RESPONSE TO THERAPY IN PATIENTS TREATED FOR HODGKIN'S LYMPHOMA:

APPROPRIATE

7.4. Conclusions

The panel reached an agreement during the first voting round in judging appropriate the use of FDG-PET for the evaluation of patients' response to therapy at the end of treatment for Hodgkin's lymphoma. The level of evidence for FDG-PET diagnostic accuracy was found to be moderate, with FDG-PET performing better than CT, especially in specificity.

All clinical outcomes were judged to be critical, with median votes equal to or higher than 7.

8. Follow up of patients treated for Hodgkin's lymphoma, with no suspicion of recurrence

Rationale

Hodgkin's lymphoma remains the main cause of patients' death during the first 10-15 years of follow up. Routine follow up is recommended to detect relapsed disease in order to start timely salvage therapy. The majority of relapses occur within the first 5 years from treatment and most follow up protocols include interim history and physical examination, blood tests every 2-4 months up to 2 years and then every 3-6 months for the next 3-5 years. A CT scan is usually performed every 6-12 months during the first 2-5 years of follow up. Chest X-ray is also useful in detecting recurrence of Hodgkin's lymphoma (5-23% of patients) (ACR 2010).

No guideline recommends FDG-PET in the follow up of patients with Hodgkin's lymphoma (AIOM 2009, ISH-ISEH 2009, NCCN 2010, ESMO 2010a).

Diagnostic role of PET

Earlier identification of relapse in asymptomatic patients could allow earlier institution of salvage therapy (Kirby 2007).

Treatment effectiveness

Patients with asymptomatic recurrence can be directed to second-line chemoradiotherapy or to salvage treatment (induction chemotherapy followed by high-dose chemotherapy and autologous stem cell transplantation) which is curative in around 60% of chemosensitive patients.

Pre-test probability and change in management

Estimate of pre-test probability of relapse is based on data from the only one study that reports six-monthly relapse data (El-Galay 2011) for a median follow up of 33 months. The median value resulted in 4% (range 0-10%).

Research question: FDG-PET as replacement test

Is FDG-PET more accurate than CT during follow up of asymptomatic patients treated for Hodgkin's lymphoma?

8.1. Systematic review of literature: results

Results from update of systematic review of literature from January 2006

One systematic review and five additional primary studies evaluating diagnostic accuracy were included.

Systematic reviews

The only retrieved review (Kirby 2007) included studies recruiting a mix of patients, like "clinically suspected", non "asymptomatic" patients, patients at completion of therapy. Only one of the included studies evaluated the role of FDG-PET in follow up of asymptomatic patients (Jerusalem 2003) and its results were extracted and summarized together with the other retrieved primary studies (see Table 8.1).

Primary studies

Nine primary studies were retrieved. Three of these were excluded because evaluated only efficiency and safety of FDG-PET (Petrausch 2010a), reported data accuracy based only on number of scan instead of number of patients (Lee 2010) or did not allow calculation of sensitivity and specificity (Zinzani 2009) as false negatives/positives results were not reported, but labelled as inconclusive.

Six studies were included: 3 studies applied FDG-PET (Jerusalem 2003, Meany 2007, Zinzani 2007), 2 FDG-PET/CT (Crocchiolo 2009, El-Galaly 2011a) and 1 both FDG-PET or FDG-PET/CT (Mocikova 2010). Around 62% of included patients were Ann Arbor clinical stage I or II and almost all had received chemotherapy and/or radiotherapy as first line treatment.

No clear follow up schemes were provided by Mocikova (2010), while in Meany (2007) follow up consisted in 4 FDG-PET scan for the first 2 years. Two to three FDG-PET scans accompanied by clinical visit in the first 2/3 years (yearly scan followed by visit) were applied in the remaining three studies. Three studies (Meany 2007, Zinzani 2007, El-Galaly 2011a) performed histological confirmation of positive FDG-PET; in Jerusalem (2003) PET positive findings not confirmed by conventional staging procedures and/or biopsy underwent a confirmatory PET study 4-6 weeks later, while in Crocchiolo (2009) confirmation was based on contrast-enhanced CT scans or magnetic resonance imaging (MRI) or bone marrow biopsy; method for PET positive confirmation is not reported in Mocikova (2010).

The studies suffer from major limitations: only in Meany (2007) there is a comparator; only Jerusalem (2003) is a prospective study; Mocikova (2010), Zinzani (2007) and El-Galaly (2011a) did not specify if the retrospective recruitment was consecutive or not; all studies suffer from absence or uncertainty of blinding during tests evaluation and possible verification bias. Data from single studies are reported in Table 8.1 while Table 8.2 reports overall results on diagnostic accuracy of FDG-PET.

Table 8.1. Results from primary studies on diagnostic accuracy of FDG-PET or FDG-PET/CT in the follow up of asymptomatic patients treated for Hodgkin's lymphoma

References	Jerusalem 2003	Meany 2007	Zinzani 2007	Crocchiolo 2009	Mocikova 2010	El-Galaly 2011a
Number of patients	17	23	57	27	67	101
FDG-PET/ PET-CT	sensitivity: 100% specificity: 79%	sensitivity: 100% specificity: 57%	sensitivity: 100% specificity: 77%	sensitivity: 100% specificity: 75%	sensitivity: 100% specificity: 80%	sensitivity: 100% specificity: 82%
Comparator	None	sensitivity: 100%* specificity: 71%*	none	none	none	none
Reference standard	PET positive finding not confirmed by conventional staging procedures and/or biopsy underwent a confirmatory PET study 4-6 weeks later	positive PET: histological confirmation follow up for PET negative	histological findings follow up for PET negative	PET/CT+: ceCT or MRI or bone marrow biopsy PET/CT-: follow up for PET negative	PET+: conclusions required additional examinations in order to confirm or to exclude a tumor PET-: follow up	PET/CT+: biopsy, repeated imaging or follow up PET/CT-: continuous follow up

ceCT: contrast-enhanced CT scans

MRI: magnetic resonance imaging

* CT was always simultaneously performed with FDG-PET. Even that, CT studies' results were not discussed when FDG-PET were negative; so, to calculate CT performances, assumptions on false negative (=0) have been done.

Table 8.2. Overall results for diagnostic accuracy of FDG-PET in follow up of Hodgkin's lymphoma patients

Diagnostic accuracy	
Number of studies	6
Number of patients	total 292; median 42 (range 17-101)
Pre-test probability	median: 14%; range: 9-26%
FDG-PET/PET-CT	sensitivity: 100% specificity: range 57-82%
Comparator	CT (only one study on 23 paediatric patients - Meany 2007) sensitivity: 100% specificity: 71%
Reference standard	follow up and/or histological findings and/or other imaging
References	Jerusalem 2003, Meany 2007, Zinzani 2007, Crocchiolo 2009, Mocikova 2010, El-Galaly 2011a

Comments of ASSR reviewer

Not so many data on the use of FDG-PET in follow up were found (six studies on less than 300 patients overall) and all the included studies suffer from some major limitations (absence of appropriate comparator, retrospective design, possible verification bias, absence of blinding during tests evaluation). All the studies reported a sensitivity of FDG-PET of 100% whilst the specificity ranged from 57 to 82%.

Diagnostic accuracy estimate

FDG-PET or FDG-PET/CT	sensitivity: 100% specificity: 57-82%
Comparator:	not possible to provide estimate (1 study on 23 patients)

LEVEL OF EVIDENCE: LOW

8.2. Clinical outcomes

To evaluate the balance between benefits and risks, the panel agreed to consider the presumed patient-important outcomes reported below (*Table 8.3*), and voted on the level of importance for each outcome. Median scores and ranges are reported for each outcome. Except for consequences for patients testing false negative which were considered critical (median score 7; range 3-8), all remaining patients' outcomes were voted important (median score 6; range 3-9). No studies investigating the impact of FDG-PET on clinical outcomes were found.

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

Patient-important outcomes	**Median score (range)**
Consequences of test for patients relapsing	
• True positives - patients undergo further test to confirm positive results and proceed to appropriate treatment	6 (3-9)
• False negatives - patients are falsely reassured, remain in follow up and delay treatment for recurrence	7 (3-8)
Consequences of test for patients not relapsing	
• True negatives - patients remain in follow up and are reassured	6 (3-9)
• False positives - patients undergo unnecessary further tests to prove negative and are exposed to unnecessary anxiety	5 (3-9)

A matrix of "natural frequencies" was provided (*Table 8.4*). It was not possible to compute estimates for the comparator as data were available from only one very small study.

Table 8.4. "Natural frequencies" of patients in follow up tested for recurrence*

		N of patients out of 100 submitted to the exam	
		According to FDG-PET	**According to CT**
Patients with asymptomatic recurrence	True positives	4	n.d.
	False negatives	0	n.d.
Patients without recurrence	True negatives	55-79	n.d.
	False positives	17-41	n.d.
		100	100

* pre-test probability: 4%

8.3. Voting results

The first voting round registered a strong disagreement among panellists with votes falling in the inappropriate, uncertain and appropriate regions (median score 4; range 2-7). The acquisition of a very recent study on a relative large number of patients (El-Galaly 2011a) influenced the discussion during the second meeting, in which the panel reached an agreement in judging inappropriate (median score 2; range 1-3) the use of FDG-PET in follow up.

FINAL RATING FOR THE USE OF FDG-PET FOR FOLLOW UP IN HODGKIN'S LYMPHOMA:

INAPPROPRIATE

8.4. Conclusions

At the first meeting the panellists strongly disagreed about the role of FDG-PET during follow up of patients treated for Hodgkin's lymphoma and with no suspicion of recurrence. In the first round votes fell in all three region of appropriateness (inappropriate, uncertain, appropriate) with a median score of 4 (range 2-7). Results from a recently acquired and included study, recruiting a much larger sample of patients than all previously published studies, influenced the discussion of the second meeting and the poor specificity of FDG-PET was determinant in bringing the panel to agree on the judgment of inappropriateness (median score 2; range 1-3). The level of evidence was considered low and all outcomes were voted important (median score 6; range 3-9), except for consequences for patients testing false negative, which were considered critical.

9. Staging of recurrence in patients treated for Hodgkin's lymphoma

Rationale

Hodgkin's lymphoma remains the main cause of patient death during the first 10-15 years of follow up. Usually relapses are discovered on the basis of the history and physical examination, with the most commonly reported symptom being a recurrence in early stage new lump, followed by constitutional symptoms (fever, night sweats, and weight loss) and pain (ACR 2010). Conventional workup in patients with suspect recurrence is a CT scan and a confirmation biopsy is usually requested (NCCN 2010).

When recurrence is confirmed restaging is useful to distinguish between patients with either localized or extended relapse (NCCN 2010, AIOM 2009), and additional imaging may prove necessary to guide confirmation biopsy. Patients with localized relapse can be treated with chemotherapy, with or without radiotherapy, while patients with extended relapse are candidate to high-dose chemotherapy followed by autologous stem cell transplantation (ESMO 2010a, AIOM 2010).

Among the retrieved clinical guidelines on Hodgkin's lymphoma the only one recommending a complete restaging, including an FDG-PET scan, in case of suspected relapse is the one published by NCCN (NCCN 2010).

Diagnostic role of FDG-PET

To restage patients with recurrence in order to distinguish between localized or extended relapse and establish appropriate therapeutic strategy.

Treatment effectiveness

Patients with a late relapse may be sensitive to conventional-dose chemotherapy, and re-treatment with initial chemotherapy may produce a second complete remission. In patients with early relapse (<12 months) or resistant to up-front therapy, the standard treatment consists in high-dose chemotherapy followed by autologous stem cell transplantation (high dose therapy/autologous stem cell transplantation) which yields a progression-free survival ranging from 45 to 77%, with an overall survival from 50 to 80%. Results are significantly better when a second remission or a minimal disease status is achieved before autologous stem cell transplantation (ISH-ISEH 2009). A subset of low-risk patients relapsing after primary treatment with two cycles of chemotherapy followed by radiotherapy can be successfully salvaged with a second, more intensive conventional chemotherapy (ESMO 2010a). If localized late relapse occurs, salvage radiotherapy alone can be considered (ESMO 2010a).

Pre-test probability and change in management

No data are available on pre-test probability of extended disease in patients with relapse.

The pre-test probability of any recurrence after suspicion, taken from two studies (Dittmann 2001, Pracchia 2007), ranges from 50 to 85.7%. Pre-test probability of bone marrow involvement in relapsing patients with Hodgkin's lymphoma ranges from 5 to 15% (Wu 2012).

No study was found reporting data on change in management.

Research question: FDG-PET as replacement test

Is FDG-PET more accurate than conventional imaging for diagnostic confirmation and staging of patients with a suspected recurrence of Hodgkin's lymphoma?

9.1. Systematic review of literature: results

Results from update of systematic review of literature from January 2006

Two systematic reviews and three additional primary studies were included.

Systematic reviews

Two systematic reviews (Kirby 2007, Wu 2012) - of low and moderate quality, respectively - have been retrieved including studies on the staging of patients with suspected recurrence of Hodgkin's lymphoma or mixed population of patients (Hodgkin's and non-Hodgkin's lymphoma).

The systematic review from Kirby (Kirby 2007) included only one study of 20 patients (Dittmann 2001) considering the staging of patients with suspected recurrence of Hodgkin's lymphoma. This study was added-up to the below reported primary studies published after the systematic reviews.

The systematic review from Wu (Wu 2012) evaluated the diagnostic accuracy of FDG-PET, FDG-PET/CT or MRI for detecting bone marrow involvement during the staging of patients with primary or relapsing lymphoma. Thirty-two studies - involving a total of 1826 patients, 392 with Hodgkin's lymphoma, 187 with non-Hodgkin's lymphoma and 1221 with Hodgkin's or non-Hodgkin's lymphoma - were included. A meta-analysis of data was performed showing higher, although heterogeneous, sensitivity and specificity of FDG-PET/CT compared to MRI (Wu 2012).

Table 9.1. Results from systematic reviews on Hodgkin's lymphoma staging with FDG-PET or FDG-PET/CT for detection of bone marrow involvement

Reference	Wu 2012
Update to	July 2010
Number of studies	total number of studies: 32 (8 on HL pts, 16 on a mixed population, 8 on aggressive NHL patients)
Number of patients	1 845 with HL or NHL (median: 45.5, range: 11-194) 690 with HL (median: 30, range: 6-88)
FDG-PET or FDG-PET/CT	Bone marrow involvement staging of primary disease and of recurrence **FDG-PET** HL+NHL sensitivity: mean 81.5% (95% CI 77.3-85.3%) specificity: mean 87.3% (95% CI 84.9-89.5%) **FDG-PET/CT** HL+NHL sensitivity: mean 91.6% (95% CI 85.1-95.9%) specificity: mean 90.3% (95% CI 85.9-93.7%)
Comparator	Bone marrow involvement, staging of primary disease and of recurrence **MRI** HL+NHL sensitivity: mean 90.3% (95% CI 82.4-95.5%) specificity: mean 75.9% (95% CI 69.8-81.2%)
Reference standard	histopathology and/or close clinical and imaging follow up of at least 6 months

Primary studies

Three studies - two (Bucerius 2006, Pracchia 2007) published after the above retrieved systematic reviews and one (Dittmann 2001) taken from the systematic review of Kirby (Kirby 2007) - evaluating the accuracy of FDG-PET in the diagnosis of relapse in patients with suspected recurrence of Hodgkin's lymphoma (Dittmann 2001, Pracchia 2007) or mixed population of Hodgkin's lymphoma and non-Hodgkin's lymphoma patients (Bucerius 2006) at any site were included. One additional, very recent study was retrieved but not included as it reported data on FDG-PET/CT scans instead of on patients (El-Galaly 2011a).

Included studies are limited by a possible incomplete verification of index test results (Dittmann 2001, Pracchia 2007), a retrospective design (Dittmann 2001), an uncertain blinding of lecture of tests (Pracchia 2007). Results are reported in Table 9.2.

Estimates of diagnostic accuracy of FDG-PET in diagnosis and staging of recurrence at any site are available only from three small primary studies for a total of 89 patients. Estimates of diagnostic accuracy of FDG-PET in staging of bone marrow recurrence are available from one systematic review (Wu 2012 - *Table 9.3*).

Table 9.2. Results from primary studies on diagnostic accuracy of FDG-PET for suspected recurrence of Hodgkin's lymphoma

References	Dittmann 2001, Bucerius 2006, Pracchia 2007	
Number of patients	89 (range 20-48) with HL or NHL	
FDG-PET/PET-CT	any recurrence	sensitivity: range 90-100% specificity: 0-80%
Comparator	CT (2 studies)	
	any recurrence	sensitivity: 100% specificity: 0-88%
Reference standard	biopsy and follow up	

Table 9.3. Diagnostic accuracy estimates of FDG-PET in detecting recurrence of Hodgkin's lymphoma at any site or at bone marrow

Diagnostic accuracy	any site	bone marrow involvement
Number of studies	3 (2 on HL pts, 1 on a mixed population)	32 (8 on HL pts, 16 on a mixed population, 8 on NHL patients)
Number of patients	89 (range 20- 48) with HL or NHL	1 845 with HL or NHL (median: 45.5, range: 11-194) 690 with HL (median: 30, range: 6-88)
Pre-test probability	range 50.0-85.7%	range 5-15%
FDG-PET or FDG-PET/CT	sensitivity: range 90-100% specificity: 0-80%	**FDG-PET/CT** HL+NHL sensitivity: mean 91.6% (95% CI 85.1-95.9%) specificity: mean 90.3% (95% CI 85.9-93.7%)
Comparator	**CT** (2 studies) any recurrence sensitivity: 100% specificity: 0-88%	**MRI** HL+NHL sensitivity: mean 90.3% (95% CI 82.4-95.5%) specificity: mean 75.9% (95% CI 69.8-81.2%)
Reference	Bucerius 2006, Dittmann 2001, Pracchia 2007	Wu 2012

Comments of ASSR reviewer

One systematic review - including mixed populations of patients (Hodgkin's and non-Hodgkin's lymphoma patients, staging of primary disease and recurrence) - addressing suspicion of bone marrow recurrence found that FDG-PET seems to have slightly higher diagnostic accuracy performance than that of comparator (MRI). These results are limited as in most studies the suspected additional lesions detected by FDG-PET didn't receive histological confirmation, leading to a possible verification bias.

For staging of patients with Hodgkin's lymphoma with suspected recurrence at any site only three small studies were found on a total of 89 patients and it is not possible to draw any conclusion.

Diagnostic accuracy estimates

Recurrence at any site

Due to sparse data it is not possible to provide estimates of diagnostic accuracy.

LEVEL OF EVIDENCE (RECURRENCE AT ANY SITE): VERY LOW

9.2. Clinical outcomes

To evaluate the balance between benefits and risks, the panel agreed to consider the presumed patient-important outcomes reported below (*Table 9.4*), and voted on the level of importance for each outcome. Consequences for patients with extended disease were voted critical (median score of 7 and 8), while consequences for patients with limited disease at relapse were voted important (median score of 6). No studies evaluating impact of FDG-PET on patients' important outcomes were found. No matrix of "natural frequencies" was provided due to the very low evidence of estimates on FDG-PET diagnostic accuracy for staging of recurrence.

Table 9.4. 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)

9.3. Voting results

The first voting round registered a slight disagreement among panellists with votes falling in the uncertain and appropriate regions (median score 7; range 5-8). This disagreement was resolved during the second discussion and the panel agreed in judging appropriate (median score 8; range 7-8) the use of FDG-PET in the diagnosis confirmation and staging of recurrence in patients treated for Hodgkin's lymphoma.

FINAL RATING FOR THE USE OF FDG-PET FOR DIAGNOSIS CONFIRMATION AND STAGING OF RECURRENCE IN PATIENTS TREATED FOR HODGKIN'S LYMPHOMA:

APPROPRIATE

9.4. Conclusions

The first voting round registered a slight disagreement among panellists with votes falling in the uncertain and appropriate regions (median score 7; range 5-8). Level of evidence for FDG-PET diagnostic accuracy was judged very low due to sparse data. However during the second meeting panellists agreed to judge the estimates for FDG-PET diagnostic accuracy for the initial staging of patients sufficiently reliable, although indirect, and applicable to staging of relapsing patients. The second voting round therefore registered an agreement on appropriateness (median score 8; range 7-8). Importance of staging was further highlighted by the critical importance assigned to clinical consequences of patients with extended disease, with a median score of 7 for detected extended disease and median score of 8 for undetected extended disease. Consequences for patients with limited disease were judged important (median score 6).

Aggressive non-Hodgkin's lymphoma

10. Staging of aggressive non-Hodgkin's lymphoma

Rationale

Non-Hodgkin's lymphomas (NHLs) are a heterogeneous group of lymphoproliferative disorders originating mostly (85% of cases) in B lymphocytes. Clinically, non-Hodgkin's lymphomas are classified as indolent (low grade), aggressive or highly aggressive (high grade), based on the morphology and the natural history of the disease (NCCN 2011).

The gold standard for the diagnosis is pathology from a sufficiently large surgical specimen or excisional lymph node biopsy to establish the histological subtype. When no superficial pathologic lymph nodes are detectable, CT/EUS guided biopsy with a large needle could be a valid option (AIOM 2009, NCCN 2011, Muslimani 2008).

After diagnosis of aggressive non-Hodgkin's lymphoma is placed, the stage of the disease is usually assessed by CT total body, to identify nodal and extra-nodal lesions, thus assessing the disease status. As bone marrow involvement occurs in approximately 20% to 40% patients with aggressive and highly aggressive non-Hodgkin's lymphoma, indicating a stage IV disease (Muslimani 2008, Wu 2012, Kwee 2008, NCCN 2011), a bone marrow biopsy is usually part of the staging assessment; however, being the bone marrow involvement usually patchy, false negatives results in BMB are not unusual (Muslimani 2008). Clinical guidelines recommend assessment with FDG-PET at baseline in addition to CT before treatment initiation in DLBC lymphoma patients (AIOM 2009, NCCN 2011, ESMO 2010b) to better assess the disease spread; for other, less common, types of aggressive lymphomas (such as mantle cell lymphoma or Burkitt lymphoma) recommendation is placed only for selected cases or under certain circumstances (NCCN 2011).

Diagnostic role of PET

To define disease extension and eventually to distinguish between early, localised stage (I and II) and advanced, extended (stage III and IV) disease, in order to decide between more and less aggressive treatment.

Treatment effectiveness

Effectiveness of treatment is extremely variable according to the lymphoma type, the disease stage and individual prognostic factors (AIOM 2009, NCCN 2011). Aggressive non-Hodgkin's lymphomas tend to develop more rapidly but have a higher likelihood of being cured than lower grade non-Hodgkin's lymphomas (Kirby 2007).

Early, localised diffuse large B-cell lymphoma (stage I-II) may be amenable to 3-4 cycles of immunochemotherapy followed by consolidative IF-RT whilst more advanced stages (stage III and IV) are usually treated with a longer immunochemotherapy treatment

(AIOM 2009, NCCN 2011). Prognosis is extremely good for patients with limited disease and no adverse risk factors (NCCN 2011) in which therapy yields a 5-yr progression-free survival rate of around 80% and a 5-yr OS of around 82% (Shenkier 2002). There is still no established standard of care for Mantle Cell Lymphoma (MCL): several chemotherapy regimens have shown significant activity in newly diagnosed MCL (overall response rate around 80% and a complete response rate of around 65%) but none of these regimens are curative in advanced disease (NCCN 2011).

Pre-test probability and change in management

Probability of extra-nodal involvement (indicating a stage III-IV of the disease) in aggressive non-Hodgkin's lymphomas is around 40% (Australian Cancer Network 2005).

Probability of bone marrow involvement, which indicates stage IV disease, in patients with aggressive non-Hodgkin's lymphomas ranges approximately from 20 to 40% (Muslimani 2008, Wu 2012, Kwee 2008, NCCN 2011).

Research question: FDG-PET associated with diagnostic CT

Does adding FDG-PET/CT lead to more accurate characterization of disease extension for patients with aggressive non-Hodgkin's lymphoma?

10.1. Systematic review of literature: results

Three systematic reviews and five further primary studies on diagnostic accuracy of FDG-PET or PET/CT were included.

Systematic reviews

Three systematic reviews evaluating diagnostic accuracy of FDG-PET or FDG-PET/CT in staging or restaging (Facey 2007, Kirby 2007, Kwee 2008, Wu 2012) including non-Hodgkin's lymphomas patients were retrieved. All the reviews included studies on Hodgkin's lymphomas patients, indolent and aggressive non-Hodgkin's lymphomas patients and mixed population and examined diagnostic accuracy both for staging and restaging. Kwee 2008 presented separate data for staging and restaging but reported diagnostic accuracy estimates using lesions as units of analysis and was therefore excluded. The review by Wu (Wu 2012) considered FDG-PET or FDG-PET CT only for detection of bone marrow involvement.

Studies included in the remaining systematic reviews (Facey 2007, Kirby 2007, Wu 2012) were of generally low quality: a large number was retrospective and use of consecutive enrolment of patients was uncertain for some of the prospective studies, leading to a possible spectrum bias. Only a limited number of studies used an appropriate reference standard test: additional sites identified on PET or indeed areas negative on PET but positive on conventional imaging (predominately CT) often didn't receive histological confirmation of presence or absence of disease. Lack of appropriate verification test

carries a risk of misinterpretation of diagnostic accuracy estimates. The only review where a meta-analysis of data was performed (Wu 2012) suggests a higher sensitivity for FDG-PET and FDG-PET/CT in comparison to MRI and a higher specificity of FDG-PET/CT if compared to the other two in detecting bone marrow involvement. However the authors of the review underline that sensitivity and specificity of FDG-PET and sensitivity of FDG-PET/CT appear to be highly heterogeneous, affecting their diagnostic value in the assessment of bone marrow involvement in malignant lymphoma (Wu 2012).

The quality of the reviews was judged very low for Facey 2007 and Kirby 2007 (methods of review, criteria of studies' inclusion and quality appraisal of studies not fully described, poor results reporting) and high for Wu 2012.

Results from systematic reviews on non-Hodgkin's lymphoma staging with FDG-PET or FDG-PET/CT are reported in Table 10.1.

Table 10.1. Results from systematic reviews on non-Hodgkin's lymphoma staging with FDG-PET or FDG-PET/CT

Reference	Facey 2007	Kirby 2007	Wu 2012
Update to	August 2005	September 2005	July 2010
Number of studies	total number of studies: 10 plus a systematic review (on 7 studies) (2 on NHL patients, 7 on a mixed population, 1 on HL patients)	total number of studies: 37 (2 on aggressive NHL, 17 on a mixed population, 11 on HL pts, 7 on indolent NHL)	total number of studies: 32 (8 on NHL pts, 16 on a mixed population, 8 on HL patients)
Number of patients	469 with HL or NHL (median: 42, range: 27-88) NHL patients: 279 (median: 29, range: 9-53)	1 465 with HL or NHL (median: 38, range: 4-91) 20 with aggressive NHL	1 845 with HL or NHL (median: 45.5, range: 11-194) 775 with aggressive NHL (median: 35, range: 11-112)
FDG-PET or FDG-PET/CT	Nodal and extra-nodal, staging and restaging, only narrative results: "Evidence from 1 SR reviewing 7 PSs, and 7 additional PSs shows that PET had specificity of at least 90% and sensitivity of 79-100% (or ≥90% in the new studies). PET consistently showed superior sensitivity to Ga scanning. Two older studies suggested PET was more accurate than CT for staging lymph node involvement, but one new study showed them to be comparable. There was evidence that all imaging methods may miss small disease foci."	Nodal and extra-nodal, staging and restaging **FDG-PET** NHL narrative results only HL+NHL sensitivity: median 93% (86-100%) specificity: median 99% (72-100%)	Bone marrow involvement, staging and restaging **FDG-PET** HL+NHL sensitivity: mean 81.5% (95% CI 77.3-85.3%) specificity: mean 87.3% (95% CI 84.9-89.5%) **FDG-PET/CT** HL+NHL sensitivity: mean 91.6% (95% CI 85.1-95.9) specificity: mean 90.3% (95% CI 85.9-93.7%)

(continues)

Reference	Facey 2007	Kirby 2007	Wu 2012
Update to	August 2005	September 2005	July 2010
Comparator	Nodal and extra-nodal, staging and restaging Only narrative results	Nodal and extra-nodal, staging and restaging **conventional imaging** **CT** HL+NHL sensitivity: median 81% specificity: median 93% **Ga scan** HL+NHL sensitivity: median 73% specificity: median 76%	Bone marrow involvement, staging and restaging **MRI** HL+NHL sensitivity: mean 90.3% (95% CI 82.4-95.5%) specificity: mean 75.9% (95% CI 69.8-81.2%)
Reference standard	concordance between FDG-PET and other imaging techniques, follow up	none, histopathological confirmation, CT, CT + follow up + histology, clinical information and follow up, gallium versus conventional imaging	histopathology and/or close clinical and imaging follow up of at least 6 months

* excluding NHL patients studied exclusively with MRI

Primary studies

Three primary studies (de Jong 2009, Kako 2007, Muslimani 2008) - for a total of 184 patients - assessed the accuracy of FDG-PET in the staging of patients with various type of aggressive non-Hodgkin's lymphomas (T/NK-cell lymphoma - Kako 2007, various histological types of aggressive non-Hodgkin's lymphomas - de Jong 2009 - or both aggressive or indolent non-Hodgkin's lymphomas - Muslimani 2008). Further 2 studies (Fuster 2006, Pinilla 2011) - for a total of 207 patients - assessed the accuracy of FDG-PET (both studies) or FDG-PET/CT (1 study) and considered a mixed population including Hodgkin's lymphomas patients together with non-Hodgkin's lymphomas patients and reported only aggregate results.

The accuracy of FDG-PET was assessed in detecting nodal or extra-nodal involvement (1 study: Pinilla 2011, *Table 10.2*), in detecting splenic involvement (1 study: de Jong 2009, *Table 10.3*), in detecting bone marrow involvement (4 studies: Fuster 2006, Kako 2007, Muslimani 2008, Pinilla 2011, *Table 10.4*).

All but one study had a retrospective design and an uncertain blinding of diagnostic imaging readers (Pinilla 2011); the study assessing the splenic involvement (de Jong 2009) had the incorporation of FDG-PET in the reference standard.

Table 10.2. Results from primary study on aggressive non-Hodgkin's lymphomas staging with FDG-PET assessing nodal and organ involvement

Reference	Pinilla 2011
Number of patients	101 (32 with HL, 69 with NHL)
FDG-PET/PET-CT	Nodal involvement FDG-PET sensitivity: 82% specificity: 81% Low dose FDG-PET/CT sensitivity: 97% specificity: 96% Full dose FDG-PET/CT sensitivity: 97% specificity: 97% Organ involvement FDG-PET sensitivity: 70% specificity: 76% Low dose FDG-PET/CT sensitivity: 92% specificity: 81% Full dose FDG-PET/CT sensitivity: 94% specificity: 81%
Comparator	Nodal involvement CT sensitivity: 90% specificity: 92% Organ involvement CT sensitivity: 87% specificity: 91%
Reference standard	clinical history; physical examination; laboratory work-up; iliac crest bone marrow biopsy; contrast-enhanced CT and other imaging findings (magnetic resonance imaging [MRI], Gallium scan); lumbar puncture; endoscopy; biopsies and surgery when clinically indicated; and follow up data

Table10.3. Results from primary study on aggressive non-Hodgkin's lymphomas staging with FDG-PET assessing splenic involvement

Reference	De Jong 2009
Number of patients	96 (all NHL patients)
FDG-PET/PET-CT	sensitivity: 77.3% specificity: 100%
Comparator	CT sensitivity: 91% specificity: 96%
Reference standard	coincidental findings of nodules positive for malignancy with at least 2 different imaging techniques (e.g. at both contrast-enhanced CT and FDG PET) or, when malignancy was found with only one imaging technique (e.g. at contrast-enhanced harmonic compound US), to have or not to have nodule size decrease (>50% in the greatest diameter) after chemotherapy

Table 10.4. Results from primary studies on aggressive non-Hodgkin's lymphomas staging with FDG-PET assessing bone marrow involvement

Reference	Kako 2007	Muslimani 2008	Fuster 2006	Pinilla 2011
Number of patients	41 (31 for initial staging)	57	106 (18 HL, 88 with NHL)	101 (32 with HL, 69 with NHL)
FDG-PET or FDG-PET/CT	FDG-PET sensitivity: 20% specificity: 96.7%	FDG-PET sensitivity: 87% specificity: 94.1%	FDG-PET sensitivity: 86% specificity: 99%	FDG-PET sensitivity: 29% specificity: 84% Low dose FDG-PET/CT sensitivity: 29% specificity: 90% Full dose FDG-PET/CT sensitivity: 29% specificity: 90%
Comparator	none	none	none	none
Reference standard	bone marrow examination and bone marrow biopsy (for bone marrow involvement)	bone marrow biopsy and follow up	bone marrow biopsy	clinical history; physical examination; laboratory work-up; iliac crest bone marrow biopsy; contrast-enhanced CT and other imaging findings (magnetic resonance imaging [MRI], Gallium scan); lumbar puncture; endoscopy; biopsies and surgery when clinically indicated; and follow up data

As the number of patient included in studies published after the systematic reviews added up to a smaller number than that of patients included in the systematic reviews, the latter's pooled estimates of FDG-PET accuracy in detecting nodal and extra-nodal extension (Kirby 2007) and bone marrow involvement (Wu 2012) were chosen and reported in Table 10.5.

Table 10.5. Diagnostic accuracy estimates of FDG-PET in detecting nodal and extra-nodal disease extension and bone marrow involvement

Diagnostic accuracy	Nodal and extra-nodal extension	Bone marrow involvement
Number of studies	37 (2 on NHL pts, 17 on a mixed population, 11 on HL patients, 7 on indolent NHL patients)	32 (8 on NHL pts, 16 on a mixed population, 8 on HL patients)
Number of patients	1 465 with HL or NHL (median: 38, range: 4-91) 20 patients with aggressive NHL	1 845 with HL or NHL (median: 45.5, range: 11-194) 775 with aggressive NHL (median: 35, range: 11-112)
Pre-test probability	not available	bone marrow involvement 5-15%
FDG-PET or FDG-PET/CT	**FDG-PET** HL+NHL sensitivity: median 93% (range 86-100%) specificity: median 99% (range 72-100%)	**FDG-PET/CT** HL+NHL sensitivity: mean 91.6% (95% CI 85.1-95.9) specificity: mean 90.3% (95% CI 85.9-93.7%)
Comparator	**CT** HL+NHL sensitivity: median 81% (range not provided) specificity: median 93% (range not provided) **Ga scan** HL+NHL sensitivity: median 73% (range not provided) specificity: median 76% (range not provided)	**MRI** HL+NHL sensitivity: mean 90.3% (95% CI 82.4-95.5%) specificity: mean 75.9% (95% CI 69.8-81.2%)
Reference	Kirby 2007	Wu 2012

Comments of ASSR reviewer

Many publications have been retrieved on FDG-PET use for staging of patients with aggressive non-Hodgkin's lymphoma. Most of them included patients with Hodgkin's lymphoma and patients with non-Hodgkin's lymphoma and didn't provide estimates for single populations. Many studies are affected by some important limitations. Nevertheless FDG-PET seems to have slightly higher diagnostic accuracy performance than that of comparators (CT, MRI). The results of studies published after the systematic reviews do not modify these conclusions.

Diagnostic accuracy estimates

Nodal and extra-nodal disease extension

FDG-PET	sensitivity: median 93% (range 86-100%) specificity: median 99% (range 72-100%)
Comparator: CT	sensitivity: median 81% (range not provided) specificity: median 93% (range not provided)

Bone marrow involvement

FDG-PET/CT	sensitivity: mean 91.6% (95% CI 85.1-95.9) specificity: mean 90.3% (95% CI 85.9-93.7%)
Comparator: MRI	sensitivity: mean 90.3% (95% CI 82.4-95.5%) specificity: mean 75.9% (95% CI 69.8-81.2%)

LEVEL OF EVIDENCE: MODERATE

10.2. Clinical outcomes

To evaluate the balance between benefits and risks, the panel agreed to consider the presumed patient-important outcomes reported below (*Table 10.6*), and voted on the level of importance for each outcome. All patients' important outcomes were judged critical with a median score of 7 and ranges between 3 and 9. No studies evaluating impact of FDG-PET on clinical outcomes were found.

Two matrices of "natural frequencies" were provided for assessment of nodal/extra-nodal extension (*Table 10.7*) and for bone marrow involvement (*Table 10.8*).

Table 10.6. Patient-important clinical outcomes and median scores of importance

Patient-important outcomes	Median score (range)
Consequences of test for patients with extended disease	
• True positives - patients receive a more aggressive treatment that improves survival, but increases risks of adverse effects.	7 (4-8)
• False negatives - patients do not receive necessary aggressive treatment with possible negative impact on survival	7 (3-9)
Consequences of test for patients with limited disease	
• True negatives - patients undergo a less aggressive treatment that is the most effective in terms of benefit/risk trade-off	7 (4-8)
• False positives - patients proceed to unnecessary more aggressive treatment with a high risk of serious adverse events and no higher gain on survival	7 (3-9)

Table 10.7. Natural frequencies": patients assessed for nodal and extra-nodal disease extension*

		N of patients out of 100 submitted to the exam	
		According to FDG-PET/CT	**According to CT**
Patients with extended disease (extra-nodal involvement)	True positives	37	32
	False negatives	3	8
Patients with localized disease	True negatives	59	56
	False positives	1	4
		100	100

* pre-test probability: 40%

Table 10.8. "Natural frequencies": patients assessed for bone marrow involvement*

		N of patients out of 100 submitted to the exam	
		According to FDG-PET/CT	**According to MRI**
Patients with extended disease (bone marrow involvement)	True positives	27	27
	False negatives	3	3
Patients with localized disease	True negatives	63	53
	False positives	7	17
		100	100

* pre-test probability: 30% (mean value between 20 and 40%)

10.3. Voting results

The panel agreed at the first voting round to judge appropriate the use of FDG-PET in staging of patients diagnosed with aggressive non-Hodgkin's lymphoma (median score 8; range 7-9).

FINAL RATING FOR THE USE OF FDG-PET FOR STAGING OF PATIENTS DIAGNOSED WITH AGGRESSIVE NON-HODGKIN'S LYMPHOMA:

APPROPRIATE

10.4. Conclusions

During the first meeting the panel reached an agreement in judging appropriate (median score 8; range 7-9) the use of FDG-PET for staging patients with aggressive non-Hodgkin's lymphoma, in order to distinguish early, localised stage (I and II) from advanced, extended (stage III and IV) disease and direct patients to most appropriate treatment. The level of evidence for estimates of FDG-PET diagnostic accuracy was moderate, with FDG-PET performing better than comparators for detection of both linfonodal/extra-nodal involvement and bone marrow involvement. Nevertheless the panel agreed not to propose FDG-PET in replacement of CT, which is often performed at diagnosis and provides a useful basis for monitoring response to therapy during treatment.

All patients' important outcomes were considered by the panel to be critical (median scores 7).

11. Dose painting definition of radiation treatment of aggressive non-Hodgkin's lymphoma

Rationale

Most common aggressive non-Hodgkin's lymphomas (diffuse large B-cell lymphoma and mantle cell lymphomas) are treated with different regimens of chemotherapy and radiotherapy is generally used after chemotherapy only in patients with localized (I, II) stage diffuse large B-cell lymphoma, as consolidation treatment (NCCN 2011). Among the retrieved guidelines (AIOM 2009, ESMO 2010b, NCCN 2010), no one addresses the use of FDG-PET in radiotherapy planning for patients with aggressive non-Hodgkin's lymphoma.

Diagnostic role of PET

FDG-PET imaging could provide an additional parameter for dose painting in involved-field radiation treatment.

Treatment effectiveness

Patients affected by diffuse large B-cell lymphoma without adverse risk factors have a very good prognosis. For patients with limited disease and a good prognosis, standard of care is a short (3-4 cycles) course of systemic immunochemotherapy followed by radiotherapy that yields a PROGRESSION-FREE SURVIVAL at two years of 94% (NCCN 2011). Patients with advanced disease and/or a poor prognosis are treated with a longer course of immunochemotherapy (6-8 cycles) followed or not by radiotherapy (AIOM 2009, NCCN 2011).

Change in management

It is not possible to provide estimates as no studies have been retrieved.

Research question: FDG-PET in addition to conventional imaging

Does adding FDG-PET to conventional imaging improve IF-RT dose painting for patients treated for non-Hodgkin's lymphoma

11.1. Systematic review of literature: results

Results from update of systematic review of literature from January 2006

Neither systematic reviews nor primary studies evaluating dose painting definition with FDG-PET were found.

Systematic reviews

None retrieved.

Primary studies

None retrieved.

Diagnostic accuracy estimate

It was not possible to provide estimates due to the fact that no studies were retrieved.

LEVEL OF EVIDENCE: NONE

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 11.1*), and voted on the level of importance for each outcome. Main consequences related to accuracy of dose painting were voted not important (median score of 3; ranges 1-6 and 1-7). No studies evaluating the impact of FDG-PET on clinical outcomes were found.

Table 11.1. Patient-important clinical outcomes and median scores of importance

Patient-important outcomes	Median score (range)
Consequences of test for patients undergoing involved-field radiation treatment	
• Accurate dose painting leading to best trade-off between benefits, in terms of survival and local control, and adverse effects due to toxicity	3 (1-6)
• Inaccurate dose painting with loss of optimization between expected benefits and adverse effects	3 (1-7)

11.3. Voting results

Due to the absence of studies, the panel classified the use of FDG-PET for IF-RT dose painting as indeterminate.

FINAL RATING FOR THE USE OF FDG-PET FOR IF-RT DOSE PAINTING DEFINITION IN PATIENTS TREATED FOR AGGRESSIVE NON-HODGKIN'S LINFOMA:

INDETERMINATE

11.4. Conclusions

During the first meeting the panel discussed the potential diagnostic role of FDG-PET in radiation treatment planning and agreed to focus on dose painting definition, rather than on target volume definition. For the clinical question identified by panel the systematic review of the literature retrieved no studies and, during the second meeting, the panel judged this clinical indication as indeterminate due to lack of studies. Clinical consequences of accuracy of dose painting definition were, however, voted not important.

12. During treatment evaluation of early response to therapy in patients treated for aggressive non-Hodgkin's lymphoma

Rationale

Early evaluation of response to therapy could potentially differentiate those patients who will have complete remission after standard conventional therapy alone (<50% aggressive non-Hodgkin's lymphomas) from those for whom more aggressive treatment strategies might be needed. This would enable good responders to be treated minimally, without additional risks, and poor responders to be switched to more aggressive regimens that could improve the likelihood and duration of remission (Kirby 2007).

Clinical guidelines do not share similar recommendations on the use of FDG-PET scan to assess during treatment response in diffuse large B-cell lymphoma patients: only guidelines by AIOM (AIOM 2009) and NCCN (NCCN 2011) recommend FDG-PET in patients with stage I-II at the end of chemotherapy and before radiotherapy. However, in case of positivity, they advise for a confirmation biopsy.

Diagnostic role of FDG-PET

To distinguish early responders from early non responders after first cycles of treatment in order to decide whether to continue standard treatment or direct non responders to more aggressive treatment.

Treatment effectiveness

Early, localised diffuse large B-cell lymphoma (stage I-II) may be amenable to 3-4 cycles of immunochemotherapy followed by consolidative IF-RT whilst more advanced stages (stage III and IV) are usually treated with a longer immunochemotherapy treatment (AIOM 2009, NCCN 2011). For patients who do not respond to first-line chemotherapy, change of chemotherapy, intensification of radiotherapy with or without autologous transplant represent viable therapeutic options.

A standard of care for mantle cell lymphoma is still lacking.

Pre-test probability and change in management

Pre-test probability of malignant residual mass after treatment ranges from 6 to 12% (Kirby 2007).

Change in management due to midterm treatment FDG-PET/CT, reported by two studies (Strobel 2007, Cahu 2011), ranged from 10 to 13.6%. The change consisted in switching from a chemotherapy treatment to another or from chemotherapy to radiotherapy.

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

What is the diagnostic accuracy of FDG-PET in during treatment evaluation of response to systemic chemotherapy in patients treated for aggressive non-Hodgkin's lymphoma?

12.1. Systematic review of literature: results

Results from update of systematic review of literature from January 2006

Five systematic reviews and three additional primary studies on diagnostic accuracy of FDG-PET or FDG-PET/CT were included. Two primary studies on the impact of FDG-PET on clinical outcomes were included.

Systematic reviews

Five systematic reviews were retrieved (AETSA 2007, Facey 2007, Kirby 2007, Terasawa 2009, Terasawa 2010). All the reviews included studies evaluating FDG-PET accuracy in predicting response in patients undergoing a mid-term treatment evaluation for aggressive non-Hodgkin's lymphoma. Two reviews selected studies including only DLBCL patients (Terasawa 2009) or only patients evaluated at the end of high-dose chemotherapy and before autologous stem cell transplantation (Terasawa 2010).

All reviews included studies on Hodgkin's lymphoma patients, non-Hodgkin's lymphoma patients and mixed populations.

Studies included in systematic reviews were of generally low quality and highly heterogeneous regarding the risk of treatment failure and the different therapeutic approaches. Most of the included studies were retrospective and used clinical follow up as reference standard for patients both with positive and negative FDG-PET scans. The review by Terasawa (Terasawa 2009) reports that all the included studies adopted standard guidelines on response assessment as reference standard, shared the limitation of unclear definition of follow up period and/or unclear situations where pathological confirmation was required. In general, the frequent lack of appropriate verification test for patients testing positive - histological confirmation - carries a risk of overestimation of FDG-PET diagnostic accuracy.

Data on comparator were not available (only one study - included in AETSA 2007 - reported data on 67-Ga SPECT).

The inclusion of both prospective, with unclear consecutive enrolment of patients, and retrospective studies brings a high risk of spectrum bias. Because of the large number of retrospective studies, reported estimates of PPV and NPV have not been considered.

The quality of the reviews was judged very low for Facey 2007, AETSA 2007 and Kirby 2007 (due to methods of review and criteria of studies' inclusion, quality appraisal of studies not fully described, poor results reporting) and high for Terasawa 2009 and Terasawa 2010.

All the reviews conclude that, although FDG-PET might hold a prognostic value, given the methodological limitations of the primary studies, good quality prospective studies are needed to assess the clinical value of this information.

Table 12.1 reports estimates of diagnostic accuracy of FDG-PET for non-Hodgkin's lymphoma patients extracted from the systematic reviews.

Table 12.1. Results from systematic reviews on diagnostic accuracy of FDG-PET in evaluating during treatment response in aggressive non-Hodgkin's lymphoma patients

Reference	AETSA 2007	Facey 2007	Kirby 2007	Terasawa 2009	Terasawa 2010
Update to	August 2006	August 2005	September 2005	July 2007	July 2010
Number of studies	10 7 on HL patients, 1 on NHL patients, 2 on a mixed population (HL and NHL)	9 1 on HL patients, 4 on NHL patients, 4 on a mixed population (HL and NHL)	15 2 on HL patients, 6 on NHL patients, 7 on a mixed population (HL and NHL)	13 6 on advanced HL patients, 6 on advanced NHL patients (+1 on a mixed population - HL and NHL - excluded from pooled results)	12 2 on pre-transplant HL patients, 3 on pre-transplant NHL patients, 7 on a pre-transplant mixed population (HL and NHL)
Number of patients	631 with HL or NHL (range: 2-210) 149 with NHL (range 20-90)	301 with NHL (range: 24-90) 115 with NHL or HL (range: 16-46)	514 with NHL (range: 10-121) 169 with HL or NHL (range: 30-54)	311 with NHL (range: 21-83)	pre-transplant NHL patients: 307 (range: 24-83)
FDG-PET or FDG-PET/CT	<u>HL or NHL patients</u> sensitivity: 55.5-100% specificity: 50.0-100% <u>NHL patients</u> sensitivity: 76.2% (70.3-75.1%) specificity: 71.0% (69.8-71.4%)	Narrative results only "… midtherapy scans may be predictive of outcome midtherapy. However, there is no evidence of any associated changes in management (…) consequent upon this"	<u>NHL patients</u> sensitivity: 42-100% specificity: 70-100% <u>NHL or HL patients</u> sensitivity: 42-100% specificity: 48-100%	<u>NHL patients</u> sensitivity (pooled): 78% (95% CI 64-87%) specificity (pooled): 87% (95% CI 75-93%)	<u>NHL patients</u> sensitivity (pooled): 77% (95% CI 54-90%) specificity (pooled): 77% (95% CI 63-88%) <u>HL or NHL patients</u> sensitivity 69% (95% CI 56-81%) specificity 81% (95% CI 73-87%)
Comparator	none reported	none reported	none reported	none reported	none reported
Reference standard	follow up	follow up	unclear	follow up	follow up

Primary studies

Twelve additional primary studies, not included in the above-mentioned systematic reviews, were retrieved (Altamirano 2008, Cashen 2011, Dickinson 2010, Han 2009, Itti 2009, Itti 2010, Just 2008, Moskowitz 2010, Qiao 2010, Riad 2010, Yoo 2011, Zinzani 2011) but nine of them (Cashen 2011, Dickinson 2010, Han 2009, Itti 2009, Itti 2010, Just 2008, Qiao 2010, Yoo 2011, Zinzani 2011) had a prognostic aim (i.e. tested the predictive accuracy of any kind of midterm treatment FDG-PET response in term of long term recurrence of disease) and were therefore excluded from further analyses.

The three remaining studies tested the diagnostic accuracy of midterm treatment FDG-PET response in predicting the status of disease (remission or progression) at the end of treatment. One of them (Moskovitz 2010) included only non-Hodgkin's lymphoma patients (total number 97), while other two (Altamirano 2008 and Riad 2010) included both Hodgkin's lymphoma and non-Hodgkin's lymphoma patients (total number 79, 27 with non-Hodgkin's lymphoma). All but one study (Riad 2010) had a prospective design and all three applied a valid reference standard - histopathology to confirm FDG-PET positive lesions and follow up in negative patients according to validated criteria.

Two studies (Altamirano 2008, Riad 2010) compared diagnostic accuracy of FDG-PET with a comparator (CT or conventional imaging - CT, MRI, US).

Results from these three studies are reported in Table 12.2.

As the number of patient included in studies published after the systematic reviews added up to a smaller number than that of patients included in the high quality systematic review of Terasawa 2009, the latter's pooled estimates of FDG-PET accuracy in assessing during treatment response in patients with aggressive non-Hodgkin's lymphoma are reported in Table 12.3.

Table 12.2. Results from primary studies on assessment of during treatment response to therapy in aggressive non-Hodgkin's lymphoma and mixed population of patients (non-Hodgkin's lymphoma or Hodgkin's lymphoma)

Reference	Altamirano 2008, Riad 2010	Moskowitz 2010
Number of patients	79 (range: 28-51), 27 NHL patients (range: 6-21)	97 (with aggressive NHL)
FDG-PET or FDG-PET/CT	sensitivity: range 92.2-100% specificity: range 93.3-97.7.0%	sensitivity: 62.5% specificity: 60.7%
Comparator	CT (1 study) sensitivity: 79.0% specificity: 50.0% Conventional imaging (1 study) sensitivity: 83.0% specificity: 66.6%	none
Reference standard	histopathology and follow up	histopathology and follow up

Table 12.3. Overall results on assessment of during treatment FDG-PET response in aggressive non-Hodgkin's lymphoma patients

Diagnostic accuracy	
Number of studies	6
Number of patients	311 with aggressive NHL (diffuse large B-cell lymphoma) (range: 21-83)
Pre-test probability of not response	6-12%
FDG-PET or FDG-PET/CT	sensitivity (pooled): 78% (95% CI 64-87%) specificity (pooled): 87% (95% CI 75-93%)
Comparator	Conventional imaging (1 study) sensitivity: 83.0% specificity: 66.6%
Reference standard	follow up and histology
Reference	Terasawa 2009, Kirby 2007 (pre-test probability data), Riad 2010 (comparator's data)

Comments of ASSR reviewer

A fairly large number of studies have been carried out, mostly with prognostic objective. Some were retrospective and used inappropriate reference standard. Data from a systematic review reported pooled diagnostic accuracy estimates for FDG-PET with high specificity but lower sensitivity. Data on comparators are scarce.

Diagnostic accuracy estimates

FDG-PET	sensitivity: 78% (95% CI 64-87%) specificity: 87% (95% CI 75-93%)
Conventional imaging	sensitivity*: 83% specificity*: 66.6%

* data only from one study

LEVEL OF EVIDENCE: MODERATE

Impact of FDG-PET on clinical outcomes

Systematic reviews

None retrieved.

Primary studies

Two non randomized controlled studies (Kasamon 2009, Moskowitz 2010) were retrieved evaluating clinical outcomes of patients with aggressive non-Hodgkin's lymphoma (diffuse large B cell, follicular grade 3, peripheral T cell lymphomas) selected for a change of therapy regimen - intensification of chemotherapy and possible autologous transplant - on the basis of mid-term FDG-PET response results (with biopsy verification in Moskowitz 2010).

The primary outcome was disease free survival (Kasamon 2009, Moskowitz 2010) and adverse events (Kasamon 2009). Only one study (Moskowitz 2010) tested the statistical difference of survival between transplanted patients resulting PET-negative or PET-positive and biopsy-negative, finding no difference ($p = 0.275$). All studies are burdened by lack of control for confounding factors.

Synthesis of results are reported in Table 12.4.

Table 12.4. Results from studies on impact on clinical outcomes of FDG-PET during treatment

References	Kasamon 2009	Moskowitz 2010
Number of patients	59	98
Follow up	median 34.1 months	median 44 months
Event free survival	2-year FDG-PET negative patients (26): 89% FDG-PET positive patients (33): 75% 3-year FDG-PET negative patients (26): 82% FDG-PET positive patients (33): 65%	FDG-PET negative patients (59): 86.4% FDG-PET positive AND negative biopsy patients (33): 78.8% FDG-PET positive AND positive biopsy patients (5): 60.0% FDG-PET negative vs FDG-PET positive/biopsy negative p = 0.275
Adverse events	FDG-PET positive patients (33): 1 died of hepatic veno-occlusive disease, another developed self-limited veno-occlusive disease; 1 died from multiple strokes and pneumonia; 1 developed myelodysplastic syndrome and died after non-myeloablative allogeneic transplantation FDG-PET negative patients (26): 1 patient died of leukaemia	not considered

Comments of ASSR reviewer

Two non randomized controlled trials explored the impact on clinical outcomes of FDG-PET midterm treatment response in selecting patients with aggressive non-Hodgkin's lymphoma for a change of therapy regimen (intensification of chemotherapy with or without autologous transplant). Results are difficult to interpret as studies were not designed to control for confounding factors. One study disclosed no difference on event-free survival between FDG-PET positive/biopsy negative and FDG-PET negative patients. Due to the scarcity of data no conclusion can be drawn.

LEVEL OF EVIDENCE: VERY LOW

12.2. Clinical outcomes

To evaluate the balance between benefits and risks, the panel agreed to consider the presumed patient-important outcomes reported below (*Table 12.5*), and voted on the level of importance for each outcome. Patients' important outcomes were rated critical (median score 7; ranges 2-9) for true non responders, false non responders and false responders. Outcomes for true responders were voted important (median 5; range 2-9). Data on clinical outcomes reported from two non randomized controlled studies were judged inconclusive.

A matrix of "natural frequencies" was provided for assessment of early response to therapy during treatment (*Table 12.6*).

Table 12.5. Patient-important clinical outcomes and median scores of importance

Patient-important outcomes	Median score (range)
Consequences of test for early non responders	
• True non responders (true positives) - patients interrupt ineffective treatment and are switched to a more aggressive treatment with potential benefit for survival	7 (2-8)
• False responders (false negatives) - patients complete ineffective treatment and do not proceed to alternative more aggressive treatment with a possible negative impact on survival	7 (2-9)
Consequences of test for early responders	
• True responders (true negatives) - patients complete effective treatment with a potential benefit for survival	5 (2-9)
• False non responders (false positives) - patients interrupt effective treatment and are unnecessarily directed to more aggressive treatment with high risk of serious adverse events and no higher gain in survival	7 (2-9)

Table 12.6. "Natural frequencies": patients assessed for early response to therapy*

		N of patients out of 100 submitted to the exam	
		According to FDG-PET	**According to conventional imaging (TC, MRI, US)**
Patients non responders	True non responders	7	7
	False responders	2	2
Patients responders	True responders	79	61
	False non responders	12	30
		100	100

* pre-test probability: 9% (mean value between 6 and 12%)

12.3. Voting results

During the first meeting the voting results showed a slight disagreement, with votes ranging from inappropriate to uncertain (median score 4; range 1-8). The second voting round found panellists in agreement in judging inappropriate the use of FDG-PET for the evaluation of patients' early response to therapy during treatment (median score 3; ranges 2-3).

FINAL RATING FOR THE USE OF FDG-PET FOR EVALUATION OF EARLY RESPONSE TO THERAPY OF PATIENTS TREATED FOR AGGRESSIVE NON-HODGKIN'S LYMPHOMA:

INAPPROPRIATE

12.4. Conclusions

During the first meeting the voting results showed a slight disagreement, with votes ranging from inappropriate to uncertain (median score 4; range 1-8). During the second meeting disagreement was resolved through discussion, as it was clarified that response during treatment is better assessed in terms of mass reduction using CT scan. The second voting round found panellists in agreement in judging inappropriate the use of FDG-PET for the evaluation of patients' early response to therapy during treatment (median score 3; ranges 2-3). Level of evidence for diagnostic accuracy was judged moderate and clinical outcomes were rated critical (median score 7; ranges 2-9) for true non responders, false non responders and false responders. Outcomes for true responders were voted important (median 5; range 2-9).

13. End of treatment evaluation of response to therapy in aggressive non-Hodgkin's lymphoma

Rationale

Patients with aggressive non-Hodgkin's lymphoma (NHL) usually are treated with front-line therapy, with complete remission rates ranging from 60 to 80% (Filmont 2007). However, following completion of conventional chemotherapy and/or radiotherapy, in 30-60% of patients treated for aggressive non-Hodgkin's lymphoma, CT or MRI can reveal tiny remnants of what was originally a large mass or normal-sized (i.e. up to 10 mm) lymph nodes where there was previous obvious pathological lymphadenopathy. This can lead to uncertainty - on radiological grounds - as to whether there is still active disease. Such masses are observed more frequently in patients with aggressive non-Hodgkin's lymphoma than in patients with indolent non-Hodgkin's lymphoma. Only a maximum of 20% of these residual masses at completion of treatment are reported to be positive for lymphoma on biopsy and patients will eventually relapse. Distinguishing responding patients from those who do not respond to therapy could have a major impact on clinical management and, ultimately, on clinical outcomes (Kirby 2007, NCCN 2011).

Clinical guidelines recommend FDG-PET to assess the response at the end of treatment but with a bioptic confirmation in case of positivity (AIOM 2009, ESMO 2010b, NCCN 2011).

Diagnostic role of FDG-PET

To identify patients with residual disease at the end of treatment in order to direct them to the most appropriate treatment and achieve higher probability of cure.

Treatment effectiveness

In patients affected by diffuse large B-cell lymphoma, with limited disease and without adverse risk factors, standard of care (a short course of systemic immunochemotherapy followed by radiotherapy) (AIOM 2010, NCCN 2011) usually yields a 5-year progression-free survival rate of around 80% and a 5-year OS of around 82% (Shenkier 2002). Patients with advanced disease and/or a poor prognosis are usually treated with a longer course of immunochemotherapy (6-8 cycles) (AIOM 2009, NCCN 2011). Patients not responding to first-line therapy are usually directed to induction chemotherapy and, in case of partial or complete response, to high dose chemotherapy and autologous stem

cell transplantation; for patients who are not candidate to transplant, possible options include second-line therapy or observation (NCCN 2011).

Mantle cell lymphoma is mostly incurable with conventional chemotherapy and a standard of care is still lacking. Relapsing or not-responding patients may be directed to second-line or experimental treatments (NCCN 2011).

Pre-test probability and change in management

Tiny remnant of what was originally a large mass or normal-sized (i.e. up to 10mm) lymph nodes where there was previous obvious pathological lymphadenopathy is present in as many as 30-60% of aggressive non-Hodgkin's lymphoma patients but only approximately 20% of these are reported to be positive for lymphoma on biopsy giving a pre-test probability of malignant residual mass after treatment ranging from 6 to 12% (Kirby 2007).

Research question: FDG-PET as add-on test

What is the diagnostic accuracy of FDG-PET in evaluating response to treatment of patients treated for aggressive non-Hodgkin's lymphoma and with residual mass at CT?

13.1. Systematic review of literature: results

Results from update of systematic review of literature from January 2006

Five systematic reviews and four primary additional studies were included.

Systematic reviews

Five systematic review were retrieved (Zijlstra 2006, Facey 2007, Kirby 2007, Terasawa 2008, Kwee 2008) for a total of 41 studies and 2012 patients on the use of FDG-PET in the evaluation of the end of treatment response. One (Kirby 2007) included only studies evaluating FDG-PET accuracy in patients with residual masses, while the remaining 4 reviews included both studies comparing diagnostic accuracy of FDG-PET versus CT in all patients completing treatment and studies evaluating diagnostic accuracy of FDG-PET in patients with residual masses at CT scan.

All the reviews included studies on Hodgkin's lymphoma patients, non-Hodgkin's lymphoma patients and mixed populations; Zijlstra 2006 and Terasawa 2008 included only non-Hodgkin's lymphoma patients with aggressive disease. Reviews have many studies in common.

Studies included in systematic reviews were of generally low quality. Many were retrospective and used clinical follow up as reference standard whether patients had positive or negative FDG-PET scans. The lack of appropriate verification test for patients testing positive leads to a risk of overestimation of diagnostic accuracy. The inclusion of

both prospective studies with unclear consecutive enrolment and retrospective studies carries a high risk of spectrum bias. Because of the large number of retrospective studies, reported estimates of PPV and NPV have not been considered.

The quality of the reviews was judged very low for Facey 2007 and Kirby 2007 (methods of review, criteria of studies' inclusion and quality appraisal of studies not fully described, poor results reporting) and high for Zijlstra 2006, Kwee 2008 and Terasawa 2008.

All reviews conclude that, although FDG-PET might hold a prognostic value, the clinical value of this information is not clear.

Table 13.1 reports estimates of diagnostic accuracy of FDG-PET or FDG-PET/CT for aggressive non-Hodgkin's lymphoma patients both in all patients completing treatment or only in patients with residual mass at CT scan and extracted from the systematic reviews.

Table 13.1. Results from systematic reviews on diagnostic accuracy of FDG-PET in evaluating end of treatment response in aggressive non-Hodgkin's lymphoma patients

Reference	Zijlstra 2006	Facey 2007	Kirby 2007	Terasawa 2008	Kwee 2008
Update to	January 2004	August 2005	January 1997 - September 2005	July 2006	July 2007
Number of studies	15 (2 on NHL patient, 5 on HL patients, 8 on a mixed population)	3 (1 on a mixed population, 2 on HL patients)	26 (all on patients with residual masses) (4 on NHL patients, 9 on HL patients, 13 on a mixed population)	19 (3 on NHL patients, 10 on HL, 6 on a mixed population)	19 (2 on NHL patients, 7 on HL patients, 10 on a mixed population)
Number of evaluable patients	138 with NHL (median: 69; range: 45-93) 418 with HL or NHL (median: 52; range: 32-88) 202 with HL (median: 37, range: 26-60)	58 with HL or NHL 65 with HL (median: 32.5, range: 29-36)	270 with NHL (median: 66; range: 45-93) 20 with HL or NHL (median: 40; range: 19-101) 360 with HL (median: 36, range: 26-63)	281 with NHL (median: 29.5,range: 5-73) 474 with HL (median: 31; range: 5-71)	123 with NHL (median 61.5; range: 45-78) 556 with HL or NHL (median: 45.5; range: 18-101) 259 with HL (median: 32, range: 23-66)

(continues)

Reference	Zijlstra 2006	Facey 2007	Kirby 2007	Terasawa 2008	Kwee 2008
Update to	January 2004	August 2005	January 1997 - September 2005	July 2006	July 2007
FDG-PET or FDG-PET/CT	All patients NHL (201 patients in total) sensitivity: pooled 72% (95% CI 61-82%) specificity: pooled 100% (95% CI 97-100%) HL patients (243 pts in total) sensitivity: pooled 84% (95% CI 71-92%) specificity: pooled 90% (95% CI 84-94%)	Narrative results only. PET shows similar sensitivity to CT but better specificity	Patients with residual mass NHL sensitivity: 60-87% specificity: 94-100% HL or NHL sensitivity: median 86% (43-100%) specificity: median 95% (73-100%) HL sensitivity: median 95% (50-100%) specificity: median 86% (78-100%)	All patients NHL (281 patients) sensitivity: 33-77% specificity: 82-100% HL (399 patients) sensitivity: 50-100% specificity: 67-100% Patients with residual mass NHL (78 patients) sensitivity: 33-87% specificity: 75-100% HL (197 patients) sensitivity: 43-100% specificity: 67-100%	All patients **FDG-PET** NHL sensitivity: 60-87% specificity: 80-100% HL or NHL sensitivity: 60-100% specificity: 57.1-100% HL patients sensitivity: 86.2-100% specificity: 57.1-100% **FDG-PET/CT fusion** HL or NHL patients sensitivity: 92.9-100% specificity: 90.7-100% HL patients (1 study) sensitivity: 100% (87.5-100) specificity: 90.7% (78.4-96.3%)

(continues)

Reference	Zijlstra 2006	Facey 2007	Kirby 2007	Terasawa 2008	Kwee 2008
Update to	January 2004	August 2005	January 1997 - September 2005	July 2006	July 2007
Comparator	none reported	**CT** narrative results only	**CT** <u>mixed population</u> sensitivity: median 78% (16-100%) specificity: not provided	None reported	**CT** <u>mixed population</u> sensitivity: 25-100% specificity: 41.7-58.8% <u>HL patients</u> only data on lesions
Reference standard	histology (only for a minority of patients), radiology and follow up (median >18 months)	unclear	follow up	follow up	follow up

Primary studies

Nine additional primary studies not included in the above-mentioned systematic reviews were retrieved, four on a mixed population of patients and five on aggressive non-Hodgkin's lymphoma patients only.

Four primary studies evaluated prospectively (Altamirano 2008, Talavera Rubio 2009) or retrospectively (Bucerius 2006, Riad 2010) end of treatment response with FDG-PET in a total of 206 patients with Hodgkin's or non-Hodgkin's lymphoma (either indolent or aggressive). One study included only paediatric patients (Riad 2010). Data extracted from these primary studies are summarised in Table 13.2.

Table 13.2. Results from primary studies evaluating the role of FDG-PET in assessing end of treatment response in mixed populations of patients

Reference	Altamirano 2008, Bucerius 2006, Riad 2010, Talavera Rubio 2009
Number of patients	187
FDG-PET or FDG-PET/CT	FDG-PET (4 studies) sensitivity: 69-100% specificity: 90-98%
Comparator	Conventional imaging methods (CT, MRI, US) (1 study) sensitivity: 83% specificity: 67% CT (2 studies) sensitivity: 83-91% specificity: 38-63% Contrast-enhanced CT (1 study) sensitivity: 95% specificity: 95%
Reference standard	follow up and histology

Among the five studies on aggressive non-Hodgkin's lymphoma patients only, two (Karantanis 2007, Karantanis 2010) reported data only on lesions and were therefore excluded. The remaining three studies (Bodet-Millin 2010, Cahu 2011, Cashen 2011) were also excluded as they reported only prognostic performance of FDG-PET.

As 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, the pooled estimates from the only meta-analysis performed by Zijlstra et al (Zijlstra 2006) were chosen (*Table 13.3*) for diagnostic accuracy of FDG-PET in all patients, while for estimates of diagnostic accuracy of FDG-PET as add-on test

(scan performed only in patients with unconfirmed residual masses at conventional imaging), results from Terasawa et al (Terasawa 2008) were used. Both the systematic reviews included also studies on aggressive non-Hodgkin's lymphoma patients only.

Table 13.3. Results on diagnostic accuracy of FDG-PET in assessing end of treatment response in patients with aggressive non-Hodgkin's lymphoma

Diagnostic accuracy	All NHL patients	NHL patients with residual masses at conventional imaging
Number of studies	2 on NHL patients and 8 on HL/NHL patients	3 on NHL patients only
Number of NHL evaluable patients	201	281
Pre-test probability of relapse	14-46%	0-50%
Results FDG-PET/PET-CT	sensitivity: pooled 72% (95% CI 61-82%) specificity: pooled 100% (95% CI 97-100%)	sensitivity: range 33-87% specificity: range 75-100%
Results comparator	Conventional imaging methods (CT, MRI, US) (1 study) sensitivity: 83% specificity: 67% CT (2 studies) sensitivity: 83-91% specificity: 38-63% Contrast-enhanced CT (1 study) sensitivity: 95% specificity: 95%	not applicable
Reference standard	histopathology on biopsies (minority of patients) or radiological and clinical follow up (majority of patients)	clinical follow up with or without histological confirmation
References	Altamirano 2008, Bucerius 2006, Riad 2010, Talavera Rubio 2009 (primary studies considered only for data on comparators), Zijlstra 2006	Terasawa 2008

Comments of ASSR reviewer

Many studies and several systematic reviews evaluated the diagnostic accuracy of FDG-PET in assessing end of treatment response in aggressive non-Hodgkin's lymphoma data are flawed by methodological limitations and authors of systematic reviews highlight the need of good quality studies. From the presently available data FDG-PET seems to have a high specificity but a lower and more heterogeneous sensitivity in both detecting residual disease in patients with aggressive non-Hodgkin's lymphoma and in assessing the nature of unconfirmed residual masses shown at CT scan.

Diagnostic accuracy estimates

All patients

FDG-PET sensitivity: pooled 72% (95% CI 61-82%)
specificity: pooled 100% (95% CI 97-100%)

CT sensitivity: 83-91% (2 studies)
specificity: 38-63% (2 studies)

Conventional imaging methods (CT, MRI, US)
sensitivity: 83% (1 study)
specificity: 67% (1 study)

Patients with unconfirmed residual masses at CT

FDG-PET sensitivity: range 33-87%
specificity: range 75-100%

LEVEL OF EVIDENCE: MODERATE

13.2. Clinical outcomes

To evaluate the balance between benefits and risks, the panel agreed to consider the presumed patient-important outcomes reported below (*Table 13.4*), and voted on the level of importance for each outcome. Clinical outcomes were judged to be critical (median score of 7) except for consequences for patients testing false non responders which were voted important (median score 4; range 3-8). No studies evaluating FDG-PET impact on clinical outcomes were found.

The following two matrices of "natural frequencies" were provided. The first one (*Table13.5)* reports estimates from a head to head comparison between FDG-PET and CT for all patients assessed at the end of treatment, while the second one (*Table 13.6*) reports estimates only for patients found to have residual disease at CT and FDG-PET is compared against reference standard.

Table13.4. Patient-important clinical outcomes and median scores of importance

Patient-important outcomes	**Median score (range)**
Consequences of test for patients with residual disease	
• True non responders (true positives) - patients undergo confirmatory biopsy, when possible, and are directed to more aggressive treatments with potential benefit for survival	7 (6-8)
• False responders (false negatives) - patients do not proceed to necessary more aggressive treatment with a possible negative impact on survival	7 (4-9)
Consequences of test for patients with complete remission	
• True responders (true negatives) - patients do not proceed to further treatment and are placed in follow up	7 (4-8)
• False non responders (false positives) - patients undergo unnecessary biopsy and anxiety before being placed if follow up	4 (3-8)

Table 13.5. "Natural frequencies" of patients assessed for end of treatment response* (head to head comparison)

		N of patients out of 100 submitted to the exam	
		According to FDG-PET	**According to CT**
Patients with residual disease	True non responders	6	7-8
	False responders	3	1-2
Patients with complete remission	True responders	91	35-57
	False non responders	0	34-56
		100	100

* pre-test probability 9% (mean value between 6 and 12%)

Table 13.6. Natural frequencies": Patients with unconfirmed residual mass assessed for end of treatment response* (PET in add-on to CT)

		N of patients out of 100 submitted to the exam	
		According to FDG-PET	**Reference standard (biopsy)**
Patients with residual disease	True non responders	7-17	20
	False responders	3-13	0
Patients without residual disease	True responders	60-80	80
	False non responders	0-20	0
		100	100

* pre-test probability 20%

13.3. Voting results

During the first meeting the panel agreed to judge appropriate the use of FDG-PET in the evaluation of patients' response to therapy at the end of treatment. Votes resulted in a median score of 7 with a range between 5 and 8.

FINAL RATING FOR THE USE OF FDG-PET FOR EVALUATION OF EARLY RESPONSE TO THERAPY OF PATIENTS TREATED FOR NON-HODGKIN'S LYMPHOMA:

APPROPRIATE

13.4. Conclusions

The panel reached an agreement during the first voting round in judging appropriate the use of FDG-PET for the evaluation of patients' response to therapy at the end of treatment for Hodgkin's lymphoma (median score 7; range 5-8). The level of evidence for FDG-PET diagnostic accuracy was found to be moderate, with FDG-PET showing a higher specificity than CT. Clinical outcomes were judged to be critical (median score of 7) except for consequences for patients testing false non responders which were voted important (median score 4; range 3-8).

14. Follow up in patients treated for aggressive non-Hodgkin's lymphoma, with no suspicion of recurrence

Rationale

Follow up of patients with a complete response to therapy includes laboratory exams and physical examination every 3 months for the first 2 years, then every 6 months for the following 3 years. A CT scan can be performed after 6, 12, 24 months after the completion of treatment (Kirby 2007, AIOM 2009). Thereafter, follow up is based upon symptoms, clinical examination and laboratory investigations (Kirby 2007).

Among the retrieved guidelines (AIOM 2009, ESMO 2010b, NCCN 2010), no one recommends FDG-PET in the follow up of patients with no suspicion of recurrence.

Diagnostic role of PET

Earlier identification of asymptomatic relapsing patients could allow earlier institution of salvage therapy (Kirby 2007).

Treatment effectiveness

In relapsing patients treatment of choice is second line (salvage) chemotherapy followed by - in patients with complete or partial response - a consolidation therapy with high dose chemotherapy and autologous stem cell transplantation, which yields a significantly higher five years event-free survival and overall survival than second line treatment (EFS: 46% VS 12%; OS: 53% VS 32%) (Philip 1995).

Pre-test probability and change in management

Overall, >30% of diffuse large B-cell lymphoma will ultimately relapse (ESMO 2010b). This rate could be considered the hypothetical cumulative maximum extent of change in management in this clinical scenario.

Research question: FDG-PET as replacement test

Is FDG-PET more accurate than CT during follow up of asymptomatic patients treated for aggressive non-Hodgkin's lymphoma?

14.1. Systematic review of literature: results

Results from update of systematic review of literature from January 2006

Only three primary studies evaluating diagnostic accuracy were included.

Systematic reviews

The only one retrieved systematic review (Kirby 2007) was excluded after full-text evaluation as none of the included studies met our inclusion/exclusion criteria, in fact: Jerusalem (2003) and Dittman (2001) recruited only Hodgkin's lymphoma patients; Van Den Boosche (2002) included only nine non-Hodgkin lymphoma patients; Castellucci (2005) recruited a mixed population of patients at completion of therapy, suspected recurrence or during follow up; Hart (2005) investigated the use FDG-PET to monitor response to allogeneic transplantation.

Primary studies

Seven primary studies were retrieved but only three satisfied our inclusion criteria (El-Galaly 2011b, Petrausch 2010b, Zinzani 2007): 1 study applied FDG-PET and 2 FDG-PET/CT. Around 71% of included patients were Ann Arbor clinical stage I or II and all patients have been received (multi-agent) chemotherapy with or without radiotherapy as first line treatment. Follow up scheme was not reported in one study (Petrausch 2010b) while in the other two follow up contemplated 1 to 2 FDG-PET scans in the first two years, a yearly scan for the next three years (only Zinzani 2007), a physical examination with a haematological and chemical survey every 3-4 months for the first 2 years and then every 6 months for the next 3 years (only Zinzani 2007). Confirmation of positive FDG-PET studies were provided by histology/biopsy (El-Galaly 2011b, Petrausch 2010b, Zinzani 2007) and/or follow up (El-Galaly 2011b, Petrausch 2010b) and/or other imaging technique (El-Galaly 2011b).

All these studies were limited by absence of comparator, retrospective design, possible verification bias, absence or uncertainty of blinding during tests evaluation. Results of the three primary studies are reported in Table 14.1, while overall results are reported in Table 14.2.

Table 14.1. Results from studies on diagnostic accuracy of FDG-PET (aggressive non-Hodgkin's lymphoma, follow up of asymptomatic patients).

References	El-Galaly 2011b	Petrausch 2010b	Zinzani 2007
Number of patients	52	35	94
FDG-PET/ PET-CT	sensitivity: 100% specificity: 81%*	sensitivity: 100% specificity: 97%	sensitivity: 100% specificity: 98%
Comparator	none	none	none
Reference standard	follow up, biopsy or radiological findings	biopsy (suspected recurrence) and follow up	histological findings

* Data recalculated on number of patients (authors reported specificity based on number of scans - 89%)

Table 14.2. Overall results for diagnostic accuracy of FDG-PET in follow up of aggressive non-Hodgkin's lymphoma patients

Diagnostic accuracy	
Number of studies	3
Number of patients	181; median 52 (range 35-94)
Pre-test probability	median: 7.7%; range: 7.4-8.6%
Results	
FDG-PET/PET-CT	sensitivity: 100% specificity: range 81-98%
Comparator	none
Reference standard	follow up and/or histological findings and/or other imaging
References	El-Galaly 2011b, Petrausch 2010b, Zinzani 2007

Comments of ASSR reviewer

Three studies with an overall number of 181 patients studied were retrieved and included. All of them suffer of some degree of mayor limitation (absence of appropriate comparator, retrospective design, possible verification bias, absence of blinding during tests evaluation). Diagnostic accuracy estimates are of very low evidence due to sparse data and data on comparators are not available.

Diagnostic accuracy estimate

Due to sparse data it is not possible to provide estimates of diagnostic accuracy.

LEVEL OF EVIDENCE: VERY LOW

14.2. Clinical outcomes

To evaluate the balance between benefits and risks, the panel agreed to consider the presumed patient-important outcomes reported below (*Table 14.3*), and voted on the level of importance for each outcome. Patients' important outcomes were voted not important for patients testing false positive (median score 2; range 3-8) and important for true relapsing patients (median score of 5; range 3-8), for patients in remission and for false negative patients (median score of 4). No studies investigating the impact of FDG-PET on the above clinical outcomes were found. No "natural frequencies" were provided due to the very low level of evidence for FDG-PET diagnostic accuracy.

Table 14.3. Patient-important clinical outcomes and median scores of importance

Patient-important outcomes	Median score (range)
Consequences of test for patients relapsing	
• True positives - patients undergo further test to confirm positive results and proceed to appropriate treatment	5 (3-8)
• False negatives - patients are falsely reassured remain in follow up and delay treatment for recurrence	4 (2-8)
Consequences of test for patients not relapsing	
• True negatives - patients, remain in follow up and are reassured	4 (2-9)
• False positives - patients undergo unnecessary further tests to prove negative and are exposed to unnecessary anxiety	3 (3-8)

14.3. Voting results

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

FINAL RATING FOR THE USE OF FDG-PET IN FOLLOW UP OF PATIENTS TREATED FOR AGGRESSIVE NON-HODGKIN'S LYMPHOMA AND WITH NO SUSPISCION OF RECURRENCE:

INAPPROPRIATE

14.4. Conclusions

Level of evidence for FDG-PET diagnostic accuracy in identifying relapse in patients in follow up and with no suspicion of recurrence was found to be very low. The first voting round registered a slight disagreement between inappropriate and uncertain ratings (median score 3; range 2-4), but during the second meeting disagreement was resolved through discussion and the second voting round registered an agreement on inappropriate (median score 3; range 1-3).

Patients' important outcomes were judged important (median score 4 and 5), except for patients testing false positives which were considered not important (median score 3).

15. Staging of recurrence in patients treated for aggressive non-Hodgkin's lymphoma

Rationale

Overall, >30% of diffuse large B-cell lymphoma will ultimately relapse. If a recurrence is suspected, histological verification should be obtained whenever possible, and is mandatory in relapses >12 months after the initial diagnosis (ESMO 2010b).

Patients with relapsed diffuse large B-cell lymphoma are usually treated with a second-line chemotherapy regimen which, in case of partial or complete response, is followed by high-dose chemotherapy and autologous stem cell transplantation (high dose therapy/autologous stem cell transplantation) (ESMO 2010b). Mantle cell lymphoma patients initially responding to combination chemotherapy typically relapse within 1 year of therapy. The median survival in patients from the time of the initial diagnosis is approximately 3 years, and 1 year following relapse (Khouri 2003).

Clinical guidelines (ESMO 2010, NCCN 2011) recommend to repeat a complete staging in patients suspected for recurrence thus including FDG-PET examination among recommended imaging examinations.

Diagnostic role of PET

To distinguish between localized and extended recurrence in order to decide between less aggressive or more aggressive treatment.

Treatment effectiveness

Patients with relapsed diffuse large B-cell lymphoma are usually treated with a second-line chemotherapy regimen which, in case of partial or complete response, is followed by high-dose chemotherapy and autologous stem cell transplantation (high dose therapy/autologous stem cell transplantation). Patients that achieve a complete response to second-line chemotherapy (before high dose therapy/autologous stem cell transplantation) have a superior overall survival to that of patients that achieve only a partial response (NCCN 2011). Patients not suitable for high-dose therapy and/or transplantation may be treated with the second-line chemotherapy regimen which may be combined with involved-field radiotherapy (ESMO 2010b).

The optimal therapeutic approach to recurrent mantle cell lymphoma remains to be defined (NCCN 2011).

Pre-test probability and change in management

No data are available on pre-test probability of extended disease in patients with relapse of aggressive non-Hodgkin's lymphoma.

Taken from one study (Mohile 2008) the pre-test probability of any recurrence after suspicion is 27.3%. Pre-test probability of bone marrow involvement in relapsing patients with non-Hodgkin's lymphoma ranges from 20 to 40% (Wu 2012).

15.1. Systematic review of literature: results

Results from update of systematic review of literature from January 2006

One systematic review and two primary studies were included.

Systematic reviews

Two systematic reviews (Kirby 2007, Wu 2012) - of low and moderate quality respectively - have been retrieved potentially including studies on the staging of patients with suspected recurrence of aggressive non-Hodgkin's lymphoma or mixed population of patients (Hodgkin's lymphoma and non-Hodgkin's lymphoma patients).

The systematic review from Kirby (Kirby 2007) was excluded as it did not include any study or data on staging of patients with suspected recurrence of non-Hodgkin's lymphoma or mixed population (aggressive non-Hodgkin's lymphoma and Hodgkin's lymphoma patients).

The systematic review from Wu (Wu 2012) evaluated the diagnostic accuracy of FDG-PET, FDG-PET/CT or MRI for detecting bone marrow involvement during the staging of patients with primary or relapsing lymphoma. Thirty-two studies - involving 1845 patients with Hodgkin's lymphoma (392), non-Hodgkin's lymphomas (187) or both (1221) - were included. A meta-analysis of data was performed and a higher sensitivity for FDG-PET and FDG-PET/CT was found in comparison to MRI and a higher specificity of FDG-PET/CT if compared to the other two in detecting bone marrow involvement. But, on the other hand, the sensitivity and specificity of FDG-PET studies and the sensitivity of FDG-PET/CT appear to be highly heterogeneous, affecting their diagnostic value in the assessment of bone marrow involvement in malignant lymphoma (Wu 2012).

Table 15.1. Results from systematic reviews on aggressive non-Hodgkin's lymphoma staging with FDG-PET or FDG-PET/CT for bone marrow involvement

Reference	Wu 2012
Update to	July 2010
Number of studies	total number of studies: 32 8 on NHL pts, 16 on a mixed population, 16 on HL patients
Number of patients	1 845 total (median 45.5 range 18-194) 339 with NHL (median: 39, range: 18-194)
FDG-PET or FDG-PET/CT	Bone marrow involvement, staging and restaging **FDG-PET** HL+NHL sensitivity: mean 81.5% (95% CI 77.3-85.3%) specificity: mean 87.3% (95% CI 84.9-89.5%) **FDG-PET/CT** HL+NHL sensitivity: mean 91.6% (95% CI 85.1-95.9) specificity: mean 90.3% (95% CI 85.9-93.7%)
Comparator	Bone marrow involvement, staging and restaging **MRI** HL+NHL sensitivity: mean 90.3% (CI I5%: 82.4-95.5%) specificity: mean 75.9% (95% CI 69.8-81.2%)
Reference standard	histopathology and/or close clinical and imaging follow up of at least 6 months

Primary studies

Two studies (Bucerius 2006, Mohile 2008) published after the above retrieved systematic review (Wu 2012) evaluating the accuracy of FDG-PET in the restaging of patients with suspected recurrence at any site of patients with primary central nervous system lymphoma (Mohile 2008) or mixed population of Hodgkin's lymphoma and non-Hodgkin's lymphoma patients (Bucerius 2006) were included. One study (Mohile 2008) is limited by the retrospective design and the uncertain blinding of lecture of tests. Results are reported in Table 15.2.

Estimates of diagnostic accuracy of FDG-PET in staging of bone marrow recurrence are available only from one systematic review (Wu 2012 - *Table 15.3*). Estimates of diagnostic accuracy of FDG-PET in staging of recurrence at any site are available only from two primary studies (*Table 15.3*).

Table 15.2. Results from primary studies on diagnostic accuracy of FDG-PET in non-Hodgkin's lymphoma patients with suspected recurrence at any site

References	Bucerius 2006	Mohile 2008
Number of studies	1	1
Number of patients	48 with NHL or HL	11 with primary central nervous system lymphoma
FDG-PET/PET-CT	sensitivity: 98% specificity: 75%	sensitivity: 100% specificity: 87.5%
Comparator	CT sensitivity: 100% specificity: 88%	None
Reference standard	biopsy and follow up	biopsy and follow up

Table 15.3. Diagnostic accuracy estimates of FDG-PET in detecting recurrence of non-Hodgkin's lymphoma at any site or at bone marrow

Diagnostic accuracy	Any site	Bone marrow involvement
Number of studies	2 1 on NHL pts, 1 on a mixed population	32 8 on NHL pts, 16 on a mixed population, 8 on HL patients
Number of patients	59 (range 11-48)	1845 patients 339 with NHL (median: 39, range: 18-194)
Pre-test probability	range 27.3%	range 5-15%
FDG-PET or FDG-PET/CT	**FDG-PET** HL+NHL or NHL sensitivity: range 98-100% specificity: 75-87.5%	**FDG-PET** HL+NHL sensitivity: mean 81.5% (95% CI 77.3-85.3%) specificity: mean 87.3% (95% CI 84.9-89.5%) **FDG-PET/CT** HL+NHL sensitivity: mean 91.6% (95% CI 85.1-95.9) specificity: mean 90.3% (95% CI 85.9-93.7%)
Comparator	CT (1 study) sensitivity: 100% specificity: 88%	**MRI** HL+NHL sensitivity: mean 90.3% (95% CI 82.4-95.5%) specificity: mean 75.9% (95% CI 69.8-81.2%)
Reference	Bucerius 2006, Mohile 2008	Wu 2012

Comments of ASSR reviewer

One systematic review - including mixed populations of patients (Hodgkin's lymphoma and non-Hodgkin's lymphoma patients, staging and restaging) - evaluated FDG-PET for detection of bone marrow.

For staging of patients with Hodgkin's lymphoma with suspected recurrence at any site only two small studies were found on a total of 59 patients and no conclusions can be drawn.

Diagnostic accuracy estimates

Recurrence at any site

Due to sparse data no estimates of diagnostic accuracy can be provided.

LEVEL OF EVIDENCE (RECURRENCE AT ANY SITE): VERY LOW

15.2. Clinical outcomes

To evaluate the balance between benefits and risks, the panel agreed to consider the presumed patient-important outcomes reported below (*Table 15.4*), and voted on the level of importance for each outcome. Clinical consequences for patients with extended recurrence were voted critical with a median score of 7, while consequences for patients with localized recurrence were voted important (median scores of 6 and 5). No studies investigating the impact of FDG-PET on clinical outcomes were found and no matrix of "natural frequencies" was provided due to the very low level of evidence found for FDG-PET diagnostic accuracy in staging patients with recurrence. No studies investigating the impact of FDG-PET on the clinical outcomes were found.

Table 15.4. Patient-important clinical outcomes and median scores of importance

Patient-important outcomes	Median score (range)
Consequences of test for patients with any extended recurrence	
• True positives - patients undergo confirmatory biopsy, when possible, and proceed to aggressive treatment in order to prolong survival	7 (4-8)
• False negatives - patients are wrongly understaged and treated with a less intensive therapy, with a possible negative impact on their survival	7 (3-8)
Consequences of test for patients with a localized recurrence	
• True negatives - patients are treated with a less intensive therapy in order to prolong survival	6 (4-8)
• False positives - patients are wrongly upstaged, undergo unnecessary biopsy - that proves negative - and anxiety and are treated with a less aggressive treatment	5 (2-8)

15.3. Voting results

After an initial disagreement between panellists, with ratings falling in the uncertain and appropriate regions (median score 7; range 5-8), the panel agreed during the second meeting to judge appropriate the use of FDG-PET in staging of recurrence (median score 7; range 6-8).

FINAL RATING FOR THE USE OF FDG-PET IN STAGING OF RECURRENCE IN PATIENTS TREATED FOR AGGRESSIVE NON-HODGKIN'S LYMPHOMA: APPROPRIATE

15.4. Conclusions

The first voting round registered a slight disagreement among panellists with votes falling in the uncertain and appropriate regions (median score 7; range 5-8). Level of evidence for FDG-PET diagnostic accuracy was judged very low due to sparse data. However during the second meeting panellists agreed to judge the estimates for FDG-PET diagnostic accuracy for the initial staging of patients sufficiently reliable, although indirect, and applicable to staging of relapsing patients. The second voting round therefore registered an agreement on appropriateness (median score 7; range 6-8). Importance of staging was further highlighted by the critical importance assigned to clinical consequences for patients with extended disease, with a median score of 7 for detected extended disease and median score of 8 for undetected extended disease. Consequences for patients with limited disease were judged important (median scores of 6 and 5).

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Peer review reports

Reviewer 1

I am attaching a few comments. The major concern is in the variability in the studies on which the conclusions are based regarding how scans were performed and, more importantly, how they were interpreted. I would be glad to elaborate on any of my comments if there is a need for me to do so.

Thank you for the opportunity to review this important document.

Overall, this document represents a thoughtful analysis of the complexities involved in the use of FDG-PET in the management of patients with HL and aggressive NHL.

However, a number of issues that are not adequately addressed.

1. All studies suffer from variability in technique. This issue is particular relevant for the interim scans where the positive predictive value is extremely low. There are also significant differences in how scans were interpreted. Until recently, there was no standardized assessment for interim scans, for example.
2. It appears that multiple histologic types of aggressive NHL are being mixed. The discussion should be restricted to DLBCL; MCL and T-NHL should be excluded and the discussion clear in the histologic types included.
3. The role of PET replacing BM should be dealt with in greater depth: it appears quite possible that BM can be excluded in HL, but not in NHL because of the possibility of a discordant histology.
4. The authors should include the reference by Straus et al (Blood 2012) on limited stage HL.
5. It is likely important in HL to distinguish early vs late stage with interim scans.
6. In DLBCL it is critical to distinguish rituximab studies from non-rituximab studies because of the high rate of false positives with the antibody.
7. The statement that early stage HL is treated with chemotherapy and RT is not necessarily true: RT is being used in fewer patients.
8. The issue of the preference for interim vs end of treatment scans is neglected as is the potential variable of number of cycles prior to interim PET.
9. Methodologic issues may be a problem: the use of CECT, PET vs PET-CT. The case for interim PET in NHL is overstated. Need to consider the differences between the early vs later studies and the role of rituximab.
10. The level of evidence for PET in the staging of recurrence is described as very low for HL and NHL, yet it is considered "appropriate". I do not understand that logic. In HL, localized RT can be used to successfully manage limited recurrence, but that is usually not the case with aggressive DLBCL.

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Reviewer 2

I have read the sections on follow up (and some others) from your comprehensive report on the use of PET in the management of lymphoma. Very impressive work. I only have a few comments, mainly grammar.

Congratulation on you work.

Page 23: 1st line - suggest change to "the role of routine FDG-PET"
3rd line - suggest change "region" to "categories"
7th line - suggest change "was determinant in bringing" to "made", erase "to"
8th line - suggest change of "inappropriateness" to "inappropriate"
two last lines - must be very few patients that are tested false negative - if any?

Page 25 final section - suggest change of "level of evidence…" to "The diagnostic accuracy of routine PET for identifying…"

Page 26 5th line - suggest change to "patient outcomes were judged important"

Page 85 2nd section, line two: suggest adding "and" instead of "," after non "asymptomatic" patients. What is non asymptomatic patients - the same as symptomatic?
3rd section, line one - "they" is missing after because

Page 86 7th column - repeted should be changed to "repeated"
Please state that the data from our study was specifically provided for this report (because it is not found in our paper) in the table

Page 87 suggest change of "not so many" to "sparse"

Page 88 1st line - suggest to erase "presumed"

Page 89 suggest to write "routine" PET in last of line of section one and first line of section two. Clinically indicated PET has a role in follow up as it effectively disproves relapse

Page 133 1st section, line six - suggest writing "None of the retrieved guidelines recommend routine PET in the follow up …"
3rd section, line one - suggest "*in relapse patients the treat*ment of choice is salvage … This *approach* yields… than second line therapy *alone*"

Page 134 section three: suggest change of contemplated to included

Page 135 Why is the Zinzani study included here, when not in the HL section
section two - "mayor" should be changed to "major" and "suffer of" to "suffer from"
Suggest "diagnostic accuracy estimates are based on very limited evidence"

Best regards

Tarec Christoffer El-Galaly
Department of Haematology
Aalborg Hospital, Aarhus University Hospital, Denmark

Reviewer 3

Please find here attached my (preliminary) review to the dossier. Would you like me to deepen and document the statements of my observations, I will do it. Let me express my thankfulness for having involved me in this task: I have been engaged in specific prograqms to implement PET center networks for clinical trials in several foreign countires and it is a honour to have contribute also in my homeland.

STADIAZIONE DEL LINFOMA DI HODGKIN - APPROPRIATO

Durante la prima riunione il panel ha concordato nel giudicare appropriato (voto mediano 8; range 6-9) l'uso della FDG-PET per la stadiazione dei pazienti con linfoma di Hodgkin, al fine di distinguere la malattia precoce e localizzata (stadi I e II) da quella avanzata ed estesa (stadi III e IV) e avviare i pazienti al trattamento più appropriato. Il livello di evidenza per le stime di accuratezza diagnostica della FDG-PET è stato giudicato moderato, con la FDG-PET che mostra una migliore accuratezza rispetto al comparatore nell'individuazione del coinvolgimento a livello sia nodale che extranodale. Tutti gli esiti clinici riguardanti i pazienti sono stati considerati critici dal panel (voti mediani: 8 e 7).

Osservazioni

La stadiazione con PET al baseline ha comportato un cambio di trattamento in circa l'11% dei pazienti (trattamento più aggressivo). Inoltre, la valutazione della malattia al baseline mediante PET viene giudicata dagli esperti appropriata come strumento indispensabile per valutare la risposta precoce durante la chemioterapia (Interim pet). Quest'ultima dovrebbe essere sempre interpretata mediante raffronto - stazione linfonodale per stazione linfonodale - con la PET baseline.

DEFINIZIONE DEL "DOSE PAINTING" NEL TRATTAMENTO RADIOTERAPICO "INVOLVED-FIELD" DEI PAZIENTI CON LINFOMA DI HODGKIN - INDETERMINATO

Durante la prima riunione il panel ha discusso il potenziale ruolo diagnostico della FDG-PET nella pianificazione del trattamento radioterapico e ha concordato di focalizzare l'analisi sull'impiego della FDG-PET nella definizione del "dose painting" anziché del target volume. Relativamente al quesito clinico individuato dal panel la revisione sistematica della letteratura non ha reperito alcuno studio e, durante il secondo incontro, il panel ha giudicato il quesito clinico indeterminato per la mancanza di studi. Le conseguenze cliniche dell'accuratezza della FDG-PET nella definizione del "dose painting" sono state giudicate importanti.

Osservazioni

Nessun commento.

VALUTAZIONE, DURANTE IL TRATTAMENTO, DELLA RISPOSTA PRECOCE ALLA TERAPIA DEL LINFOMA DI HODGKIN - APPROPRIATO

Dopo un lieve disaccordo iniziale, con voti che variavano dall'incerto all'appropriato (voto mediano: 7; range 4-8), durante il secondo incontro il panel ha concordato nel votare appropriato l'uso della FDG-PET nella valutazione, durante il trattamento, della risposta precoce alla terapia del linfoma di Hodgkin (voto mediano: 7, range 7-8). La perplessità iniziale era dovuta alla mancanza di evidenze riguardo l'impatto che un cambio precoce di terapia potrebbe avere sugli esiti clinici. Tuttavia, il livello di evidenza relativo all'accuratezza della FDG-PET nel prevedere la risposta alla terapia è risultato moderato e tutti gli esiti clinici dei pazienti sono stati votati critici.

Osservazioni

Concordo sia sulle perplessità che sulle conclusioni finali del panel. Mentre risulta ormai fuori dubbio il ruolo prognostico della PET effettuata precocemente durante il trattamento standard di prima linea, la evidenza che la modulazione della terapia (intensificazione o de-intensificazione) sulla base dei risultati della interim PET deriva solo da studi retrospettivi o prospettici non randomizzato. Pertanto il livello di evidenza (level of evidence: LOE) è compreso tra III e IV. Inoltre, non esistono criteri standard attualmente accettati dalla comunità internazionale per la valutazione della interim PET e pertanto gli esperti raccomandano che la interim PET venga effettuata, nel linfoma di Hodgkin, solo nell'ambito di protocolli clinici ben disegnati. Esiste una sola segnalazione sulla utilità di questa metodica nel predire l'outcome della terapia di salvataggio di seconda linea (LOE V) e pertanto non vi è sufficiente evidenza per consigliare la interim PET nella terapia di seconda linea.

VALUTAZIONE DELLA RISPOSTA ALLA FINE DEL TRATTAMENTO DEL LINFOMA DI HODGKIN - APPROPRIATO

Durante la prima riunione, il panel ha concordato nel giudicare appropriato l'uso della FDG-PET nella valutazione della risposta dei pazienti alla terapia alla fine del trattamento per il linfoma di Hodgkin. Il livello di evidenza relativo all'accuratezza diagnostica della FDG-PET è risultato moderato, con una performance diagnostica della FDG-PET migliore di quella della CT, soprattutto relativamente alla specificità. Tutti gli esiti clinici sono stati giudicati critici, con voti mediani uguali o maggiori di 7.

Osservazioni

Occorre, a mio parere, distinguere i casi in cui la PET viene effettuata al termine della terapia, senza altre indicazioni, e quando viene effettuata in presenza di una massa singola residua (Terasawa JCO 2008). Infatti, nel caso di massa singola residua visibile con metodica competitor, la PET dimostra una specificità e un PPV più bassi che nella valutazione standard al termine della terapia per la presenza di falsi positivi. Pertanto, nel primo caso, il messaggio dovrebbe essere che in presenza di una massa singola residua captante FDG è richiesta una metodica di conferma (inclusa la biopsia). Un ruolo del tutto nuovo al fine del trattamento è quello della PET nel programmare la sede di radioterapia

nel casi di singole masse residue FDG-avide nel linfoma di Hodgkin in stadio avanzato: in questo caso la PET consente di trattare in tutta sicurezza con radioterapia le masse residue visibili alla TC che siano FDG-avide (Engert 2011) (LOE III).

FOLLOW UP DEI PAZIENTI TRATTATI PER LINFOMA DI HODGKIN, SENZA SOSPETTO DI RICADUTA - INAPPROPRIATO

Durante il primo incontro, i membri del panel erano fortemente in disaccordo sul ruolo della FDG-PET durante il follow up dei pazienti trattati per linfoma di Hodgkin e senza sospetto di ricaduta. Durante la prima votazione i voti espressi sono ricaduti in tutte e tre le regioni dell'appropriatezza (inappropriato, incerto e appropriato) con un valore mediano di 4 (range 2-7). I risultati ricavati da un recente studio che include la popolazione più ampia di tutti gli studi precedentemente pubblicati hanno influenzato la discussione durante il secondo incontro e la scarsa specificità della FDG-PET è stata determinante nel condurre il panel al giudizio di inappropriatezza (voto mediano: 2; range 1-3). Il livello di evidenza è stato giudicato basso e tutti gli esiti clinici sono stati giudicati importanti (voto mediano: 6; range 3-9), tranne che per i pazienti con un test falso negativo per i quali l'esito è stato considerato critico.

Osservazioni

La probabilità che ha un test di dimostrare una recidiva di malattia in un paziente asintomatico dipende dalla probabilità che la malattia recidivi dopo una data terapia e l'accuratezza globale del test in quel tipo di pazienti trattati con quella terapia (Armitage 2006). Poiché l'85% dei pazienti con linfoma di Hodgkin che hanno una recidiva sono sintomatici, e poiché la probabilità che la malattia ricada dopo terapia con ABVD non è oltre il 20%, l'esecuzione di una "surveillance PET" in un paziente asintomatico in RC dopo trattamento standard in linfoma di Hodgkin è considerata inappropriata. Potrebbe esservi una eccezione nei pazienti con più alta probabilità di ricadere (pazienti con interim PET positiva), ma questo non è mai stato dimostrato da alcun trial. Infine, non vi è alcuna dimostrazione che anticipare la terapia di 6-8 mesi (quanto in media anticipato da una PET positiva) costituisca un vantaggio per l'outcome del trattamento.

STADIAZIONE DELLA RICADUTA NEI PAZIENTI TRATTATI PER LINFOMA DI HODGKIN - APPROPRIATO

Durante la prima votazione si è verificato un lieve disaccordo tra i componenti del panel con voti nella regione dell'incerto e dell'appropriato (voto mediano: 7; range 5-8). Il livello di evidenza per l'accuratezza diagnostica della FDG-PET è stato giudicato molto basso a causa di sparse data. Tuttavia, durante la seconda riunione, i membri del panel hanno giudicato le stime di accuratezza diagnostica della FDG-PET nella stadiazione iniziale del linfoma di Hodgkin sufficientemente attendibili, anche se indirette, ed applicabili alla stadiazione di pazienti con ricaduta. Durante la seconda votazione si è quindi raggiunto un accordo nel giudicare appropriato l'impiego della FDG-PET per la conferma diagnostica e la stadiazione della ricaduta nei pazienti trattati per linfoma di

Hodgkin (voto mediano 8; range 7-8). L'importanza della stadiazione è stata ulteriormente evidenziata dall'importanza degli esiti clinici per i pazienti con malattia estesa che è stata giudicata critica (con un voto mediano di 7 per i pazienti con malattia estesa individuata dal test e di 8 per i pazienti con malattia estesa che il test non è in grado di individuare). Le conseguenze per i pazienti con malattia limitata sono state giudicate importanti (voto mediano: 6).

Osservazioni

Esiste uno score prognostico per valutare la prognosi dei pazienti ricaduti che comprende il tempo della ricaduta dall'ultima terapia (maggiore o minore di 12 mesi), il valore di emoglobina e lo stadio alla ricaduta (III-IV verso I-II) (Josting A. J Clin Oncol 2001). Pertanto la stadiazione alla ricaduta deve essere accurata (LOE III-IV). La PET risulta inoltre adeguata per poter programmare una biopsia per conferma istologica della ricadute (SOR: strength of recommendation A).

STADIAZIONE DEL LINFOMA NON-HODGKIN AGGRESSIVO- APPROPRIATO

Durante la prima riunione il panel ha unanimemente giudicato appropriato l'impiego della FDG-PET per la stadiazione dei pazienti con linfoma non-Hodgkin (voto mediano: 8; range 7-9) per distinguere la malattia precoce e localizzata (stadi I e II) da quella avanzata ed estesa (stadi III e IV) ed avviare i pazienti al trattamento più appropriato. Il livello di evidenza per le stime di accuratezza diagnostica della FDG-PET è stato giudicato moderato con la FDG-PET che mostra una migliore accuratezza rispetto al comparatore nell'individuare il coinvolgimento sia nodale ed extranodale sia del midollo osseo. Tuttavia il panel è stato d'accordo sul non proporre la FDG-PET in sostituzione alla TC che è spesso eseguita alla diagnosi e che fornisce uno strumento utile per il monitoraggio della risposta durante il trattamento. Tutti gli esiti clinici riguardanti i pazienti sono stati considerati critici dal panel (voto mediano: 7).

Osservazioni

Esistono osservazioni derivanti da studi ben condotti che l'accuratezza globale della PET nel definire lo stadio alla diagnosi è superiore a quella del comparatore, e che nel 5% dei casi la stadiazione effettuata mediante PET comporti una variazione (intensificazione) di terapia (LOE III). Inoltre, in alcuni sottotipi di linfomi (follicolare, mantellare) esistono studi che dimostrano come l'attività metabolica del tumore sia valutabile con misurazione del SUV (Standardized Uptake Value) (level of evidence V).

DEFINIZIONE DEL "DOSE PAINTING" NELLA RADIOTERAPIA INVOLVED-FIELD NEL LINFOMA NON-HODGKIN AGGRESSIVO - INDETERMINATO

Durante la prima riunione il panel ha discusso il potenziale ruolo diagnostico della FDG-PET nella pianificazione del trattamento radioterapico e ha concordato di focalizzare l'analisi sull'analisi dell'impiego della FDG-PET nella definizione del "dose painting" piuttosto che in quella del target volume. Relativamente al quesito clinico individuato dal panel la revisione sistematica della letteratura non ha reperito alcuno studio e, durante

il secondo incontro, il panel ha giudicato il quesito clinico indeterminato per mancanza di studi. Le conseguenze cliniche dell'accuratezza della FDG-PET nella definizione del dosepainting sono state comunque giudicate non importanti.

Osservazioni

Nessun commento.

VALUTAZIONE, DURANTE IL TRATTAMENTO, DELLA RISPOSTA PRECOCE ALLA TERAPIA DELLINFOMA NON-HODGKIN AGGRESSIVO - INAPPROPRIATO

Durante la prima riunione il risultato della votazione ha mostrato un lieve disaccordo con voti che variavano dall'inappropriato all'incerto (voto mediano: 4; range 1-8). Durante il secondo incontro, il disaccordo iniziale è stato risolto attraverso la discussione ed è stato chiarito che la risposta durante il trattamento viene meglio valutata attraverso la riduzione della massa tumorale con l'esame TC. Pertanto, durante la seconda votazione, vi è stato accordo nel giudicare inappropriato l'utilizzo della FDG-PET per la valutazione, effettuata durante il trattamento, della risposta precoce alla terapia (voto mediano: 3, range 2-3). Il livello di evidenza relativo all'accuratezza diagnostica è stato giudicato moderato e gli esiti clinici sono stati considerati critici (voto mediano: 7, range 2-9) per i pazienti veri non responders, falsi non responders e falsi responders alla terapia. Gli esiti per i veri responders alla terapia sono stati votati importanti (voto mediano: 5, range 2- 9).

Osservazioni

Non è vero che la riduzione della massa tumorale valutata mediante TC correli meglio dell'imaging funzionale nel predire la risposta al trattamento nei linfomi aggressivi a grandi cellule B. Non esistono studi di raffronto prospettico tra le due metodiche. Per quanto riguarda il potere predittivo della interim PET, la maggior parte degli studi (retrospettivi) finora pubblicati dimostra l'utilità prognostica di tale strumento. Tuttavia concordo con il panel nel considerare inappropriata tale metodica nella valutazione interim della chemiosensibilità per le seguenti ragioni: (a) la maggioranza degli studi pubblicati sono retrospettivi; (b) in una buona parte di questi, veniva effettuato un cambiamento di terapia sulla base dei risultati della interim PET; (c) non esistono criteri consolidati per l'interpretazione degli esami PET; (d) il criterio di interpretazione più efficace risulta quello quantitativo (SUV) ma tale misura non risulta correttamente utilizzabile in studi retrospettivi.

VALUTAZIONE DELLA RISPOSTA ALLA FINE DEL TRATTAMENTO DEL LINFOMA NON-HODGKIN AGGRESSIVO - APPROPRIATO

Durante la prima riunione, il panel ha concordato nel giudicare appropriato l'uso della FDG-PET nella valutazione della risposta dei pazienti alla terapia alla fine del trattamento per il linfoma non-Hodgkin (voto mediano: 7; range 5-8). Il livello di evidenza relativo all'accuratezza diagnostica della FDG-PET è risultato moderato, con la FDG-PET che

mostra una migliore specificità della TC. Gli esiti clinici sono stati giudicati critici (voto mediano di 7) tranne nel caso delle conseguenze per i pazienti falsi non responders che sono state giudicate importanti (voto mediano: 4; range 3-8).

Osservazioni

Concordo con il panel. Esiste tuttavia un problema di sensibilità e di risultati falsi negativi. Infatti la sensibilità è compresa tra 50 e 100% a seconda dei diversi studi e il potere predittivo negativo non è altissimo, a differenza di quanto osservato nel linfoma di Hodgkin (LOE II). Concordo anche sulla specificità non ottimale, in particolare in casi risultati falsi positivi in presenza di un singolo spot FDG-avido. Un ruolo del tutto nuovo è esercitato dalla PET al termine del trattamento per programmare la radioterapia sulle masse residue FDG-avide: ma a differenza del linfoma di Hodgkin non esistono studi pubblicati, ma solo segnalazioni a congressi.

FOLLOW UP DEI PAZIENTI TRATTATI PER LINFOMA NON-HODGKIN AGGRESSIVO, SENZA SOSPETTO DI RICADUTA - INAPPROPRIATO

Il livello di evidenza relativo all'accuratezza diagnostica della FDG-PET nell'identificare la ricaduta nei pazienti in follow up e senza sospetto di ricaduta è risultato molto basso. La prima votazione ha registrato un lieve disaccordo tra l'inappropriato e l'incerto (voto mediano: 3; range 2-4) ma durante il secondo incontro il disaccordo è stato risolto attraverso la discussione e con la seconda votazione si è raggiunto un accordo sull'inappropriatezza (voto mediano: 3; range 1-3). Tutti gli esiti clinici dei pazienti sono stati giudicati importanti (voti mediani 4 e 5), tranne quelli dei pazienti che dovessero risultare falsamente positivi che sono stati giudicati non importanti (voto mediano: 3).

Osservazioni

Per quanto riguarda i pazienti asintomatici che effettuato una PET di sorveglianza valgono le considerazioni fatte per il linfoma di Hodgkin e concordo perfettamente con il panel. Analogamente alle osservazioni fatte nel linfoma di Hodgkin esiste tuttavia un gruppo di pazienti ad altro rischio (aaIPI ≥2), in cui potrebbe essere indicata l'esecuzione di una PET ogni sei mesi dopo il raggiungimento della RC (remissione completa) (LOE IV).

STADIAZIONE DELLA RICADUTA NEI PAZIENTI TRATTATI PER LINFOMA NON-HODGKIN AGGRESSIVO - APPROPRIATO

Durante la prima votazione si è verificato un lieve disaccordo tra i componenti del panel con voti nella regione dell'incerto e dell'appropriato (voto mediano: 7; range 5-8). Il livello di evidenza per l'accuratezza diagnostica della FDG-PET è stato giudicato molto basso a causa di sparse data. Tuttavia durante la seconda riunione, i membri del panel hanno giudicato le stime di accuratezza diagnostica della FDG-PET nella stadiazione iniziale sufficientemente attendibili, anche se indirette, e applicabili alla stadiazione di pazienti con ricaduta. Durante la seconda votazione si è pertanto registrato un accordo sull'appropriatezza (voto mediano: 7; range 6-8). L'importanza della stadiazione è stata ulteriormente evidenziata dall'importanza degli esiti clinici per i pazienti con malattia

estesa che è stata giudicata critica con un voto mediano di 7 per i pazienti con malattia estesa individuata dal test e di 8 per i pazienti con malattia estesa che il test non è in grado di individuare (pazienti falsi negativi per malattia estesa). Le conseguenze per i pazienti con malattia limitata sono state giudicate importanti (voti mediani 6 e 5).

Osservazioni

Il linfoma a grandi cellule B aggressivo recidiva nelle sedi iniziali solo nel 60% dei casi (diversamente da quanto succede per il linfoma di Hodgkin dove le recidive sono nell'80% dei casi nelle stesse sedi riscontrate al baseline) (LOE IV). Pertanto risulta indicato avere una valutazione puntuale delle sedi di recidiva per poter programmare una biopsia per conferma istologica e una terapia proporzionatamente efficace e appropriata in caso di recidiva in sede extranodale (LOE IV). Pertanto, a mio parere, la PET in fase di recidiva del linfoma è appropriata.

Best regards,

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Appendices

Appendix 1.
Voting forms

ORI
Osservatorio Regionale per l'Innovazione

CRITERIA FOR APPROPRIATE USE OF POSITRON EMISSION TOMOGRAPHY IN ONCOLOGY

2010-2012

HODGKIN'S AND AGGRESSIVE NON-HODGKIN'S LYMPHOMA

VOTING FORMS

NAME

_____

Agenzia sanitaria e sociale regionale

RegioneEmilia-Romagna

HODGKIN'S LYMPHOMA

CLINICAL QUESTION

Role of FDG-PET in the staging of Hodgkin's lymphoma

Rationale

Accurate staging of dissemination with CT total body is still a mainstay of the initial evaluation of patients diagnosed with lymphoma. (Namberger 2007). However CT can fail to identify a considerable number of sites (especially abdominal ones, Hutchings 2006) leading to a possible underestimation of clinical stage. Staging of lymphomas usually includes a bone marrow biopsy to judge bone marrow involvement (Namberger 2007, Kwee 2008, NCCN 2010). Clinical guidelines recommend an FDG-PET/CT scan for the appropriate staging of HL patients, before commencing treatment (AIOM 2009, ISH-ISEH 2009, ESMO 2010a, NCCN 2010).

Diagnostic role of FDG-PET

To define disease extension and to distinguish between early, localised stage (I and II) and advanced, extended (stage III and IV) disease, in order to direct patients to most appropriate treatment.

Treatment effectiveness

Hodgkin's lymphoma is now curable in at least 80% of patients (NCCN 2010) with different therapeutic approaches according to the disease stage: patients in early stage (I and II) are usually treated with chemotherapy followed by radiation (involved-field radiation therapy, IFRT). Patients with advanced stage disease (III and IV) are usually treated with a longer course of chemotherapy, radiotherapy being limited to patients with bulky disease and with large residual masses after chemotherapy (AIOM 2009, NCCN 2010, ESMO 2010a).

Pre-test probability and change in management

Probability at diagnosis of stage I-II disease ranges approximately from 48 to 64.6%, and from 35.4 to 52% for stage III-IV (Boisson 2007, Hutchings 2006, Cerci 2011).

Bone marrow involvement, that indicates stage IV disease, is usually present in 5-15% of patients (Wu 2012).

Research question: FDG-PET/CT as replacement test

Is FDG-PET/CT more accurate than CT in characterizing disease extension?

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

Nodal and extra-nodal disease extension

FDG-PET	sensitivity: median 93% (range 86-100%) specificity: median 99% (range 72-100%)
Comparator: CT	sensitivity: median 81% (no range provided) specificity: median 93% (no range provided)

Bone marrow involvement

FDG-PET/CT	sensitivity: mean 91.6% (95% CI 85.1-95.9%) specificity: mean 90.3% (95% CI 85.9-93.7%)
Comparator MRI	sensitivity: mean 90.3% (95% CI 82.4-95.5%) specificity. mean 75.9% (95% CI 69.8-81.2%)

Patient-important clinical outcomes	**Level of importance* (1-9)**
Consequences of test for patients with extended disease	
True positives - patients receive a more aggressive treatment that improves survival but increases adverse effects	
False negatives - patients do not receive necessary aggressive treatment which could improve chance of cure, with possible negative impact on survival	
Consequences of test for patients with limited disease	
True negatives - patients undergo a less aggressive treatment which is the most effective in terms of benefit/risk trade-off	
False positives - patients proceed to unnecessary aggressive treatment with a high risk of serious adverse events and no higher gain in survival	

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

Matrix of natural frequencies:
patients assessed for linfonodal and extra-nodal involvement

		N of patients out of 100 submitted to the exam	
		According to FDG-PET	**According to CT**
Patients with extended disease (nodal / extra-nodal involvement)	True positives	36	32
	False negatives	3	7
Patients with limited disease	True negatives	60	57
	False positives	1	4
		100	100

* pre-test probability 39% (mean value between 35.4% and 42.4%)

Matrix of natural frequencies:
patients assessed for bone marrow involvement*

		N of patients out of 100 submitted to the exam	
		According to FDG-PET/CT	**According to MRI**
Patients with bone marrow involvement	True positives	9	9
	False negatives	1	1
Patients without bone marrow involvement	True negatives	81	68
	False positives	9	22
		100	100

* pre-test probability 10% (mean value between 5% and 15%)

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 (due to lack of studies)									

CLINICAL QUESTION

Role of FDG-PET in dose painting definition in radiation treatment of Hodgkin's lymphoma

Rationale

The risk of late adverse effects of RT, which include second malignancies and cardiac toxicity, is related to the radiation dose and the size of the irradiated volume The IF-RT at reduced dose aims to decrease acute and late toxicity without reducing effectiveness of treatment. Clinical guidelines do not cite FDG-PET as a possible diagnostic tool in radiation treatment planning (ISH-ISEH 2009, AIOM 2009, ESMO 2010a, NCCN 2010).

Diagnostic role of FDG-PET

FDG-PET imaging could provide an additional parameter for dose painting in involve-field radiation treatment.

Treatment effectiveness

Standard treatment for initial, localized stage HL patients is systemic chemotherapy followed by involved-field radiotherapy. Advanced stage HL is usually treated with chemotherapy alone and radiotherapy is limited to patients having large residual masses after chemotherapy (AIOM 2009, NCCN 2010, ESMO 2010a).

Change in management

It is not possible to provide estimates as no studies have been retrieved.

Research question: FDG-PET in addition to conventional imaging

Does adding FDG-PET to conventional imaging improve IF-RT dose painting for patients treated for Hodgkin's lymphoma?

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

No studies retrieved.

Patient-important outcomes	**Level of importance* (1-9)**
Consequences of test for patients undergoing involved-field radiation treatment	
Accurate dose painting leading to best trade-off between benefits, in terms of survival and local control, and adverse effects due to toxicity	
Inaccurate dose painting with loss of optimization between expected benefits and 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 (due to lack of studies)									

CLINICAL QUESTION

Role of FDG-PET in during treatment evaluation of early response to therapy in Hodgkin's lymphoma

Rationale

Early evaluation of response to therapy could differentiate patients who will have complete remission following standard conventional therapy alone (>80% HL) from those for whom alternative, more aggressive treatment strategies (second-line induction chemotherapy followed by high dose therapy/autologous stem cell transplantation) might be necessary. This would enable switching poor responders sooner to treatment regimens that would improve the likelihood and duration of remission (Kirby 2007). Conventional methods for monitoring response to treatment include clinical examination and contrast enhanced CT scan (Paolini 2007). Clinical guidelines indicate an FDG-PET or FDG-PET/CT scan as a potentially useful diagnostic tool to assess during treatment response of patients (AIOM 2009, NCCN 2010, ESMO 2010a).

Diagnostic role of FDG-PET

To distinguish early responders from early non responders after first cycles of treatment in order to decide whether to continue standard treatment or direct non responders to more aggressive treatment.

Treatment effectiveness

Standard treatment for initial stage (I-II) of Hodgkin's lymphoma patients (systemic chemotherapy followed by involved-field radiotherapy) can yield a complete remission in up to 97% of patients and, at twelve years, a progression-free survival and an overall survival of up to 94% (Bonadonna 2004). In advanced-stage disease a longer course of systemic chemotherapy is required, which yields a 5-year progression-free survival of 84% and a 5-year overall survival of 91%; post chemotherapy involved-field radiotherapy is usually indicated in bulky disease, where it allows a 5-year event-free and overall survival rates of 79% and 87%, respectively (Aleman 2003). However for patients who do not respond to first-line chemotherapy, change of chemotherapy, intensification of radiotherapy or autologous transplant can represent viable therapeutic options.

Pre-test probability and change in management

Data from primary studies suggest a median pre-test probability of non response (or incomplete response) of about 21% (Terasawa 2009, Barness 2011, Boisson 2007, Cerci 2010, Dann 2010, Zinzani 2012). Change in management due to midterm treatment FDG-PET/CT (consisting in change from standard to escalated chemotherapy) was reported by one study to be 9.4% (Dann 2010).

Research question: FDG-PET as replacement test

Is FDG-PET more accurate than conventional imaging in evaluating response during systemic chemotherapy of patients treated for Hodgkin's lymphoma?

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

FDG-PET

sensitivity: median 78%

specificity: median 95%

Conventional imaging (CT, MRI, US)*

sensitivity: 83%

specificity: 66.6%

* data from only one study

Patient-important outcomes	**Level of importance* (1-9)**
Consequences of test for non responders	
True non responders (true positives) - patients interrupt ineffective treatment and are directed to more aggressive treatments with a potential benefit on survival	
False responders (false negatives) - patients complete ineffective treatment and do not proceed to alternative more aggressive treatments with a possible negative impact on survival	
Consequences of test for responders	
True responders (true negatives) - patients complete effective treatment aimed at improving survival	
False non responders (false positives) - patients interrupt effective treatment and are unnecessarily directed to more aggressive treatments with high risk of harm and no higher gain in survival	

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

Matrix of natural frequencies:
patients assessed for bone marrow involvement*

		N of patients out of 100 submitted to the exam	
		According to FDG-PET	**According to conventional imaging**
Patients non responders	True non responders (true positives)	16	17
	False responders (false negatives)	5	4
Patients responders	True responders (true negatives)	75	53
	False non responders (false positives)	4	26
		100	100

* pre-test probability of residual mass: 21%

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 (due to lack of studies)									

CLINICAL QUESTION

Role of FDG-PET in the end of treatment evaluation of response to therapy in Hodgkin's lymphoma

Rationale

After completion of conventional chemotherapy and/or radiotherapy, differentiation of residual active tumor from fibrosis or necrosis, visible at CT, is crucial to decide on the need for further therapeutic interventions (Molnar 2010, Kirby 2007, NCCN 2010, NCCN 2011). Clinical guidelines recommend an FDG-PET or FDG-PET/CT scan to assess response to treatment (AIOM2009, ISH-ISEH 2009, NCCN 2010, ESMO 2010a) Some guidelines (ESMO 2010a, NCCN 2010) recommend a confirmation biopsy in PET positive patients.

Diagnostic role of FDG-PET

To identify patients with residual disease which will benefit from further more aggressive treatment, in order to achieve a higher probability of cure.

Treatment effectiveness

Patients who do not achieve CR after first-line treatment usually undergo individualised second-line treatment (AIOM 2009, NCCN 2010, ESMO 2010a).

Pre-test probability and change in management

Data from primary studies suggest a median pre-test probability of non response (or incomplete response) of about 21% (Terasawa 2009, Barness 2011, Boisson 2007, Cerci 2010b, Dann 2010, Zinzani 2012).

One study (Kobe 2008) on 311 patients with advanced and bulky disease reported a change in management in 21% (66/311) of patients according to FDG-PET results.

Research question: FDG-PET as add-on test

What is the diagnostic accuracy of FDG-PET in evaluating response to treatment in patients treated for Hodgkin's lymphoma and with residual mass at CT scan?

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

All patients

FDG-PET sensitivity: pooled 84% (95% CI 71-92%)
specificity: pooled 90% (95% CI 84-94%)

CT sensitivity: median 82% (64-91%)
specificity: median 53% (38-63%)

Conventional imaging methods (CT, MRI, US)
sensitivity: range 50-83%
specificity: range 11-67%

Patients with unconfirmed residual masses at CT

FDG-PET sensitivity (range): 43-100%
specificity (range): 67-100%

Patient-important outcomes	**Level of importance* (1-9)**
Consequences of test for patients with residual disease	
True non responders (true positive) - patients undergo confirmatory biopsy and are directed to more aggressive treatment with potential benefit in survival	
False responders (false negatives) - patients do not receive necessary more aggressive treatment with a consequent negative impact on survival	
Consequences of test for patients with complete remission	
True responders (true negatives) - patients are placed in follow up	
False non responders (false positive) - patients undergo unnecessary biopsy and anxiety before being placed in follow up	

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

Matrix of "natural frequencies":
patients assessed for end of treatment response * (head to head comparison)

		N of patients out of 100 submitted to the exam	
		According to FDG-PET	**According to CT**
Patients with residual disease	True non responders	18	17
	False responders	3	4
Patients with complete remission	True responders	71	42
	False non responders	8	37
		100	100

* pre-test probability: 21%

Matrix of "natural frequencies":
patients with unconfirmed residual mass assessed for end of treatment response* (PET in add-on to CT)

		N of patients out of 100 submitted to the exam	
		According to FDG-PET	**According to reference standard (biopsy)**
Patients with residual disease	True non responders	9-20	20
	False responders	0-11	0
Patients with complete remission	True responders	54-80	80
	False non responders	0-26	0
		100	100

* pre-test probability: 20%

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 (due to lack of studies)									

CLINICAL QUESTION

Role of FDG-PET in the follow up of patients treated for Hodgkin's lymphoma, with no suspicion of recurrence

Rationale

Hodgkin's lymphoma remains the main cause of patients' death during the first 10-15 years of follow up.

Routine follow up is recommended and, as the majority of relapses occur within the first 5 years from treatment, most follow up protocols include: interim history and physical examination, blood tests every 2-4 months up to 2 years and then every 3-6 months for the next 3-5 years, CT scan every 6-12 months during the first 2-5 years (AIOM 2009, NCCN 2010); a chest x-ray is also useful in detecting recurrence of Hodgkin's lymphoma (5-23% of patients) (ACR 2010).

No guideline recommends FDG-PET in the follow up of patients with Hodgkin's lymphoma (AIOM 2009, ISH-ISEH 2009, NCCN 2010, ESMO 2010a).

Diagnostic role of PET

Earlier identification of relapse in asymptomatic patients could allow earlier institution of salvage therapy (Kirby 2007).

Treatment effectiveness

Patients with asymptomatic recurrence can be directed to second-line chemoradiotherapy or to salvage treatment (induction chemotherapy followed by high-dose chemotherapy and autologous stem cell transplantation) which is curative in around 60% of chemosensitive patients.

Pre-test probability and change in management

Estimate of pre-test probability of relapse is based on data from the only one study that reports six-monthly relapse data (El-Galay 2012) for a median follow up of 33 months. The median value resulted in 4% (range 0-10%)

Research question: FDG-PET as replacement test

Is FDG-PET more accurate than CT during follow up of asymptomatic patients treated for Hodgkin's lymphoma?

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

FDG-PET/CT-PET

sensitivity 100%

specificity: 57-82%

Patient-important outcomes	**Level of importance* (1-9)**
Consequences of test for relapsing patients	
True positives - patients undergo further test to confirm positive results and proceed to necessary treatment	
False negatives - patients are falsely reassured, remain in follow up and delay treatment for recurrence	
Consequences of test for not relapsing patients	
True negatives - patients remain in follow up and are reassured.	
False positives - patients undergo unnecessary further tests to prove negative and are exposed to unnecessary anxiety	

* not important (score 1-3)

important (4-6)

critical (7-9)

to a decision

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 (due to lack of studies)									

CLINICAL QUESTION

Role of FDG-PET in the diagnosis confirmation and staging of recurrence in patients treated for Hodgkin's lymphoma

Rationale

Conventional workup in patients with suspect recurrence is a CT scan and confirmation biopsy (NCCN 2010). When recurrence is confirmed restaging is useful to distinguish between patients with either localized or extended relapse (NCCN 2010, AIOM 2009), and additional imaging may prove necessary to guide confirmation biopsy.

Among the retrieved clinical guidelines on Hodgkin's lymphoma, the only one recommending a complete restaging including an FDG-PET scan is the one published by NCCN (NCCN 2010).

Diagnostic role of FDG-PET

To guide biopsy and to restage patients with recurrence in order to distinguish between localized or extended relapse and establish appropriate therapeutic strategy.

Treatment effectiveness

Patients with a late relapse may be sensitive to conventional-dose chemotherapy, and re-treatment with initial chemotherapy may produce a second complete remission. In patients with early (<12 months) relapse or resistant to up-front therapy, the standard treatment consists in high-dose chemotherapy followed by autologous stem cell transplantation (high dose therapy/autologous stem cell transplantation), which yields a progression-free survival ranging from 45 to 77%, with an overall survival from 50 to 80%. A subset of low-risk patients relapsing after primary treatment can be successfully salvaged with a second, more intensive conventional chemotherapy (ESMO 2010a). If localized late relapse occurs, salvage radiotherapy alone can be considered (ESMO 2010a).

Pre-test probability and change in management

No data are available on pre-test probability of extended disease in patients with relapse.

The pre-test probability of any recurrence after suspicion, taken from two studies (Dittmann 2001, Pracchia 2007), ranges from 50 to 85.7%. Pre-test probability for bone marrow involvement in relapsing patients ranges from 5 to 15% (Wu 2012).

Research question: FDG-PET as replacement test

Is FDG-PET more accurate than conventional imaging for diagnostic confirmation and staging of patients with a suspected recurrence of Hodgkin lymphoma?

Diagnostic accuracy estimates

Recurrence at any site **Level of evidence: very low**

Due to sparse data it is not possible to provide estimates of diagnostic accuracy

Patient-important outcomes	**Level of importance* (1-9)**
Consequences of test for patients with any extended recurrence	
True positives - patients undergo confirmatory biopsy and proceed to aggressive treatment (high dose therapy/autologous stem cell transplantation) in order to prolong survival	
False negatives - patients are wrongly understaged and treated with a less intensive therapy, with a possible negative impact on their survival	
Consequences of test for patients without an extended recurrence	
True negatives - patients are treated with a less aggressive treatment	
False positives - patients are wrongly upstaged, undergo an unnecessary biopsy - that proves negative - and anxiety, and are treated with a less aggressive treatment	

* 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 (due to lack of studies)									

AGGRESSIVE NON-HODGKIN'S LYMPHOMA

CLINICAL QUESTION

Role of FDG-PET in the staging of aggressive non-Hodgkin's lymphoma

Rationale

After diagnosis of aggressive non-Hodgkin's lymphoma is placed, the stage of the disease is usually assessed by CT total.

A bone marrow biopsy is usually part of the staging assessment even if false negatives results in BMB are not unusual (Muslimani 2008). Clinical guidelines recommend assessment with FDG-PET at baseline in addition to CT in DLBC lymphoma patients (AIOM 2009, NCCN 2011, ESMO 2010b); for other, less common, types of aggressive lymphomas (such as mantle cell lymphoma or Burkitt lymphoma) recommendation is placed only for selected cases or under specific circumstances (NCCN 2011).

Diagnostic role of PET

To define disease extension and to distinguish between early, localised stage (I and II) and advanced, extended (stage III and IV) disease, in order to decide between more and less aggressive treatment.

Treatment effectiveness

Prognosis is good for patients with limited disease and no adverse risk factors (NCCN 2011) in which therapy (3-4 cycles of immunochemotherapy followed by consolidative IF-RT) yields a 5-yr progression-free survival of around 80% and 5-yr OS of around 82% (Shenkier 2002). More advanced stages (stage III and IV) are usually treated with a longer immunochemotherapy treatment (AIOM 2009, NCCN 2011). There is still no established standard of care for Mantle Cell Lymphoma (MCL): several chemotherapy regimens have shown significant activity in newly diagnosed MCL but none of these regimens are curative in advanced disease (NCCN 2011).

Pre-test probability and change in management

Probability of extra-nodal involvement (indicating a stage III-IV of the disease) in aggressive non-Hodgkin's lymphoma is around 40% (Australian Cancer Network 2005).

Probability of bone marrow involvement, which indicates stage IV disease, in patients with aggressive NHL ranges approximately from 20 to 40% (Muslimani 2008, Wu 2012, Kwee 2008, NCCN 2011).

Research question: FDG-PET associated with diagnostic CT

Does adding FDG-PET/CT lead to more accurate characterization of disease extension for patients with aggressive non-Hodgkin lymphoma?

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

Nodal and extra-nodal disease extension

FDG-PET	sensitivity: median 93% (range 86-100%) specificity: median 99% (range 72-100%)
Comparator-CT	sensitivity: median 81% (range not provided) specificity: median 93% (range not provided)

Bone marrow involvement

FDG-PET/CT	sensitivity: mean 91.6% (95% CI 85.1-95.9%) specificity: mean 90.3% (95% CI 85.9-93.7%)
Comparator-MRI	sensitivity: mean 90.3% (95% CI 82.4-95.5%) specificity: mean 75.9% (95% CI 69.8-81.2%)

Patient-important outcomes	**Level of importance* (1-9)**
Consequences of test for patients with extended disease	
True positives - patients receive a more aggressive that improves survival, but increases risks of adverse effects.	
False negatives - patients do not receive necessary aggressive treatment with possible negative impact on survival	
Consequences of test for patients with limited disease	
True negatives - patients undergo a less aggressive treatment that is the most effective in terms of benefit/risk trade-off	
False positives - patients proceed to unnecessary aggressive treatment with a high risk of serious adverse events and no higher gain in survival	

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

Matrix of "natural frequencies": nodal and extra-nodal disease extension*

		N of patients out of 100 submitted to the exam	
		According to FDG-PET/CT	**According to CT**
Patients with extended disease (extra-nodal involvement)	True positives	37	32
	False negatives	3	8
Patients with localized disease	True negatives	59	56
	False positives	1	4
		100	100

* pre-test probability: 40%

Matrix of "natural frequencies": bone marrow involvement*

		N of patients out of 100 submitted to the exam	
		According to FDG-PET/CT	**According to MRI**
Patients with extended disease (bone marrow involvement)	True positives	27	27
	False negatives	3	3
Patients with localized disease	True negatives	63	53
	False positives	7	17
		100	100

* pre-test probability: 30% (mean value between 20 and 40%)

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 (due to lack of studies)									

CLINICAL QUESTION

Role of FDG-PET in dose painting definition of radiation treatment for patients with aggressive non-Hodgkin's lymphoma

Rationale

Most common aggressive non-Hodgkin's lymphomas (DLBC and Mantle cell lymphomas) are treated with different regimens of chemotherapy; radiotherapy is generally used after chemotherapy only in patients with localized (I, II) stage diffuse large B-cell lymphoma, as a consolidation treatment (NCCN 2011). Among the retrieved guidelines (AIOM 2009, ESMO 2010b, NCCN 2010), no one addresses the use of FDG-PET in radiotherapy planning for patients with aggressive non-Hodgkin's lymphoma.

Diagnostic role of PET

FDG-PET imaging could provide an additional parameter for dose painting in involved-field radiation treatment.

Treatment effectiveness

For diffuse large B-cell lymphoma patients with limited disease and a good prognosis, standard of care is a short (3-4 cycles) course of systemic immunochemotherapy followed by radiotherapy, which yields a PROGRESSION-FREE SURVIVAL at two years if 94% (NCCN 2011). Patients with advanced disease and/or a poor prognosis are treated with a longer course of immunochemotherapy (6-8 cycles) followed or not by radiotherapy (AIOM 2009, NCCN 2011).

Change in management

It is not possible to provide estimates as no studies have been retrieved.

Research question: FDG-PET in addition to conventional imaging

Does adding FDG-PET to conventional imaging improve IF-RT dose painting for patients treated for non-Hodgkin's lymphoma?

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

No studies retrieved.

Patient-important outcomes	**Level of importance* (1-9)**
Consequences of test for patients undergoing involved-field radiation treatment	
Accurate dose painting leading to best trade-off between benefits, in terms of survival and local control, and adverse effects due to toxicity	
Inaccurate dose painting with loss of optimization between expected benefits and 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 (due to lack of studies)									

CLINICAL QUESTION

Role of FDG-PET in during treatment evaluation of response to therapy in patients treated for aggressive non-Hodgkin's lymphomas

Rationale

Early evaluation of response to therapy could potentially discriminate good responders who can be treated minimally, without additional risks, from poor responders who can be switched to more aggressive regimens that could improve the likelihood and duration of remission (Kirby 2007).

Clinical guidelines do not share similar recommendations on the use of FDG-PET scan to assess during treatment response in diffuse large B-cell lymphoma patients: only guidelines by AIOM (AIOM 2009) and NCCN (NCCN 2011) recommend FDG-PET in patients with stage I-II at the end of chemotherapy and before radiotherapy. However, in case of positivity, they advise for a confirmation biopsy.

Diagnostic role of FDG-PET

To distinguish early responders from early non responders after first cycles of treatment in order to decide whether to continue standard treatment or direct non responders to more aggressive treatment.

Treatment effectiveness

For patients who do not respond to first-line chemotherapy, change of chemotherapy, intensification of radiotherapy with or without autologous transplant represent viable therapeutic options. A standard of care for mantle cell lymphoma is still lacking.

Pre-test probability and change in management

Pre-test probability of malignant residual mass after treatment ranges from 6 to 12% (Kirby 2007).

Change in management due to midterm treatment FDG-PET/CT (consisting in switching from a chemotherapy treatment to another or from chemotherapy to radiotherapy), reported by two studies (Strobel 2007, Cahu 2011), ranged from 10 to 13.6%.

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

What is the diagnostic accuracy of FDG-PET in during treatment evaluation of response to systemic chemotherapy in patients treated for aggressive non-Hodgkin's lymphoma?

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

FDG-PET

sensitivity: 78% (95% CI 64-87%)

specificity: 87% (95% CI 75-93%)

Conventional imaging (TC, MRI, US)*

sensitivity: 83%

specificity*: 66.6%

* data from only one study

Patient-important outcomes	**Level of importance* (1-9)**
Consequences of test for early non responders	
True non responders (true positives) - patients interrupt ineffective treatment and are switched to a more aggressive treatment with potential benefit for survival	
False responders (false negatives) - patients complete ineffective treatment and do not proceed to alternative more aggressive treatment with a possible negative impact on survival	
Consequences of test for early responders	
True responders (true negatives) - patients complete effective treatment with a potential benefit for survival	
False non responders (false positives) - patients interrupt effective treatment and are unnecessarily directed to more aggressive treatment with high risk of serious adverse events and no higher gain in survival	

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

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

Two non randomized controlled trial explored the impact on clinical outcomes of FDG-PET midterm treatment response in selecting patients with aggressive non-Hodgkin's lymphoma for a change of therapy regimen (intensification of chemotherapy with or without autologous transplant) but results are difficult to interpret due to methodological flaws and no conclusion can be drawn. Due to the very low level of evidence it was not possible to provide any estimate for impact on clinical outcomes.

Matrix of "natural frequencies": early response to treatment*

		N of patients out of 100 submitted to the exam	
		According to FDG-PET	**According to conventional imaging (TC, MRI, US)**
Patients non responders	True non responders	7	7
	False responders	2	2
Patients responders	True responders	79	61
	False non responders	12	30
		100	100

* pre-test probability: 9% (mean value between 6 and 12%)

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 (due to lack of studies)									

CLINICAL QUESTION

Role of FDG-PET in the end of treatment evaluation of response to therapy in aggressive non-Hodgkin's lymphoma

Rationale

Patients with aggressive non-Hodgkin lymphoma (NHL) usually are treated with front-line therapy, with complete remission (CR) rates ranging from 60 to 80% (Filmont 2007).

Distinguishing patients with residual masses at the end of treatment from those with residual disease has a major impact on clinical management and, ultimately, on clinical outcomes (Kirby 2007, NCCN 2011).

Clinical guidelines recommend FDG-PET to assess the response at the end of treatment but with a bioptic confirmation in case of positivity (AIOM 2009, ESMO 2010b, NCCN 2011).

Diagnostic role of FDG-PET

To identify patients with residual disease at the end of treatment in order to direct them to the most appropriate treatment and achieve higher probability of cure.

Treatment effectiveness

Patients not responding to first-line therapy are usually directed to induction chemotherapy and possibly to high dose therapy and autologous stem cell transplantation; for patients who are not candidate to transplant, possible options include second-line therapy (NCCN 2011). Mantle cell lymphoma (MCL) is mostly incurable with conventional chemotherapy and a standard of care is still lacking. Relapsing or not-responding patients may be directed to second-line or experimental treatments (NCCN 2011).

Pre-test probability and change in management

Residual masses are present in 30-60% of patients with aggressive non-Hodgkin's lymphoma at the end of treatment but only approximately 20% of these are reported to be positive for lymphoma on biopsy giving a pre-test probability of malignant residual mass ranging from 6 to 12% (Kirby 2007).

Research question: FDG-PET as add-on test

What is the diagnostic accuracy of FDG-PET in evaluating response to treatment of patients treated for aggressive non-Hodgkin's lymphoma and with residual mass at CT?

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

All patients

FDG-PET sensitivity: pooled 72% (95% CI 61-82%)
specificity: pooled 100% (95% CI 97-100%)

CT sensitivity: 83-91%
specificity: 38-63% (2 studies)

Conventional imaging methods (CT, MRI, US)
sensitivity: 83%
specificity: 67% (1 study)

Patients with unconfirmed residual masses at CT

FDG-PET sensitivity: range 33-87%
specificity: range 75-100%

Patient-important outcomes	**Level of importance* (1-9)**
Consequences of test for patients with residual disease	
True non responders (true positives) - patients undergo confirmatory biopsy, when possible, and are directed to more aggressive treatments with potential benefit for survival	
False responders (false negatives) - patients do not proceed to necessary more aggressive treatment with a possible negative impact on survival	
Consequences of test for patients with complete remission	
True responders (true negatives) - patients do not proceed to further treatment and are placed in follow up	
False non responders (false positives) - patients undergo unnecessary biopsy and anxiety before being placed if follow up	

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

Matrix of "natural frequencies": end of treatment response
All patients* (head to head comparison)

		N of patients out of 100 submitted to the exam	
		According to FDG-PET	**According to CT**
Patients with residual disease	True non responders	6	7-8
	False responders	3	1-2
Patients with complete remission	True responders	91	35-57
	False non responders	0	34-56
		100	100

* pre-test probability 9% (mean value between 6 and 12%)

Matrix of "natural frequencies": end of treatment response
Patients with unconfirmed residual mass* (PET in add-on to CT)

		N of patients out of 100 submitted to the exam	
		According to FDG-PET	**Reference standard (biopsy)**
Patients with residual disease	True non responders	7-17	20
	False responders	3-13	0
Patients without residual disease	True responders	60-80	80
	False non responders	0-20	0
		100	100

* pre-test probability: 20%

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 (due to lack of studies)									

CLINICAL QUESTION

Role of FDG-PET in follow up in patients with aggressive non-Hodgkin's lymphoma and no suspicion of recurrence

Rationale

Follow up of patients with a complete response to therapy includes laboratory exams and physical examination every 3 months for the first 2 years, then every 6 months for the following 3 years. A CT scan can be performed after 6, 12, 24 months after the completion of treatment (Kirby 2007, AIOM 2009). Thereafter, follow up is based upon symptoms, clinical examination and laboratory investigations (Kirby 2007). If a recurrence is suspected, histological verification should be obtained whenever possible, and is mandatory in relapses >12 months after the initial diagnosis (ESMO 2010b).

Among the retrieved guidelines (AIOM 2009, ESMO 2010b, NCCN 2010), no one recommends FDG-PET in the follow up of patients with no suspicion of recurrence.

Diagnostic role of PET

Earlier identification of asymptomatic relapsing patients could allow earlier institution of salvage therapy (Kirby 2007).

Treatment Effectiveness

In relapsing patients treatment of choice is second line (salvage) chemotherapy followed by - in patients with complete or partial response - a consolidation therapy with high dose therapy and autologous stem cell transplantation, which yields a significantly higher 5-year event-free survival and overall survival than second line treatment (EFS: 46% vs 12%; OS: 53% vs 32%) (Philip 1995).

Pre-test probability and change in management

Overall, >30% of diffuse large B-cell lymphoma will ultimately relapse (ESMO 2010b).

Research question: FDG-PET as replacement test

Is FDG-PET more accurate than CT during follow up of asymptomatic patients treated for aggressive non-Hodgkin's lymphoma?

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

Due to sparse data it is not possible to provide estimates of diagnostic accuracy.

Patient-important outcomes	**Level of importance* (1-9)**
Consequences of test for relapsing patients	
True positives - patients undergo further test to confirm positive results and proceed to appropriate treatment	
False negatives - patients are falsely reassured remain in follow up and delay treatment for recurrence	
Consequences of test for not relapsing patients	
True negatives - patients, remain in follow up and are reassured	
False positives - patients undergo unnecessary further tests to prove negative and are exposed to unnecessary anxiety	

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

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 (due to lack of studies)									

CLINICAL QUESTION

Role of FDG-PET in the staging of recurrence in patients treated for aggressive non-Hodgkin's lymphoma

Rationale

Overall, >30% of diffuse large B-cell lymphoma will ultimately relapse. Mantle Cell Lymphoma patients initially responding to combination chemotherapy typically relapse within 1 year of therapy. The median survival in patients from the time of the initial diagnosis is approximately 3 years, and 1 year following relapse (Khouri 2003).

Some clinical guidelines (ESMO 2010, NCCN 2011) recommend to repeat a complete staging in patients suspected for recurrence thus including FDG-PET examination.

Diagnostic role of PET

To distinguish between localized and extended recurrence in order to decide between less aggressive or more aggressive treatment.

Treatment effectiveness

Patients with relapsed diffuse large B-cell lymphoma are usually treated with a second-line chemotherapy regimen which, in case of partial or complete response, is followed by high-dose chemotherapy and autologous stem cell transplantation (high dose therapy/autologous stem cell transplantation). Patients that achieve a complete response to second-line chemotherapy (before high dose therapy/autologous stem cell transplantation) have a superior overall survival to that of patients that achieve only a partial response (NCCN 2011). Patients not suitable for high-dose therapy and or transplantation may be treated with the second-line chemotherapy regimen which may be combined with involved-field radiotherapy (ESMO 2010b).

The optimal therapeutic approach to recurrent Mantle Cell Lymphoma remains to be defined (NCCN 2011).

Pre-test probability and change in management

No data are available on pre-test probability of extended disease in patients with relapse of aggressive non-Hodgkin's lymphoma. Taken from one study (Mohile 2008) the pre-test probability of any recurrence after suspicion is 27.3%. Pre-test probability for bone marrow involvement in relapsing patients ranges from 20 to 40% (Wu 2012).

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

Recurrence at any site

Due to sparse data no estimates of diagnostic accuracy can be provided.

Patient-important outcomes	**Level of importance* (1-9)**
Consequences of test for patients with any extended recurrence	
True positives - patients undergo confirmatory biopsy, when possible, and proceed to aggressive treatment in order to prolong survival	
False negatives - patients are wrongly understaged and treated with a less intensive therapy, with a possible negative impact on their survival	
Consequences of test for patients without an extended recurrence	
True negatives - patients are treated with a less intensive therapy in order to prolong survival	
False positives - patients are wrongly upstaged, undergo unnecessary biopsy - that proves negative - and anxiety and are treated with a less aggressive treatment	

* 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 (due to lack of studies)									

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

ORI
Osservatorio Regionale per l'Innovazione

HODGKIN'S LYMPHOMA

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 February 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
7. fdg NEAR/2 18: ti,ab,kw
8. **1/7 OR**
9. "Lymphoma"/exp
10. **8 AND 9**

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. "Lymphoma"[Mesh:noexp]
26. "Hodgkin Disease"[Mesh]
27. "Lymphoma, Non-Hodgkin"[Mesh]
28. "lymphomas"[Title/Abstract]
29. "lymphoma"[Title/Abstract]
30. "hodgkin's"[Title/Abstract]
31. "hodgkins"[Title/Abstract]
32. "hodgkin"[Title/Abstract]
33. "hodgkin s"[Title/Abstract]
34. "lymphogranuloma"[Title/Abstract]
35. "non hodgkin"[Title/Abstract]
36. "non hodgkin s b"[Title/Abstract]
37. "non hodgkin's"[Title/Abstract]
38. "reticulum cell sarcoma"[Title/Abstract]
39. "reticulum cell sarcomas"[Title/Abstract]
40. "reticulosarcoma"[Title/Abstract]
41. "reticulosarcomas"[Title/Abstract]
42. "lymphosarcoma"[Title/Abstract]
43. "lymphosarcomas"[Title/Abstract]
44. "lymphatic sarcoma"[Title/Abstract]
45. "lymphatic sarcomas"[Title/Abstract]
46. "burkitt's"[Title/Abstract]
47. "burkitt"[Title/Abstract]
48. "burkitt s"[Title/Abstract]
49. "lymphocytic leukemia"[Title/Abstract]
50. "lymphocytic leukemias"[Title/Abstract]
51. "lymphomatoid granulomatoses"[Title/Abstract]
52. "lymphomatoid granulomatosis"[Title/Abstract]
53. "brill symmers disease"[Title/Abstract]
54. "immunoblastoma"[Title/Abstract]
55. "immunoblastomas"[Title/Abstract]
56. "immunoblastosarcoma"[Title/Abstract]
57. "immunoblastosarcomas"[Title/Abstract]
58. "immunoblastic sarcoma"[Title/Abstract]
59. "immunoblastic sarcomas"[Title/Abstract]

60. "granulomatous slack skin"[Title/Abstract]
61. "lymphomatoid papulosis"[Title/Abstract]
62. "mycosis fungoides"[Title/Abstract]
63. "pagetoid reticulosis"[Title/Abstract]
64. "woringer kolopp disease"[Title/Abstract]
65. "ketron goodman disease"[Title/Abstract]
66. "sezary lymphoma"[Title/Abstract]
67. "sezary's syndrome"[Title/Abstract]
68. "sezary syndrome"[Title/Abstract]
69. **25/68 OR**
70. **69 AND 24**
71. "editorial"[Publication Type]
72. "comment"[Publication Type]
73. "letter"[Publication Type]
74. **71/73 OR**
75. **70 NOT 74**

Limit: humans

EMBASE search strategy

1. "positron emission tomography"/syn
2. "fluorodeoxyglucose f 18"/exp
3. "fluorodeoxyglucose f 18"/syn
4. "computer assisted emission tomography"/exp
5. "computer assisted emission tomography" OR
6. pet
7. "pet scans"
8. "pet scanner"
9. "pet scan"
10. "pet/ct scan"
11. "pet/ct scans"
12. "pet/ct"
13. "positron emission tomography/computed tomography"
14. pet NEAR/4 scan*
15. pet NEAR/4 ct
16. **1/23 OR**
17. "lymphoma"/de
18. "hodgkin disease"/exp
19. "classical hodgkin lymphoma"/exp
20. "nonhodgkin lymphoma"/exp
21. "intestine lymphoma"/de
22. "skin lymphoma"/exp
23. "reed sternberg cell"/de
24. "cutaneous t cell lymphoma"/exp
25. "histiocytic lymphoma"/exp
26. "marginal zone lymphoma"/exp
27. "t cell lymphoma"/exp
28. **17/27 OR**
29. **16 AND 28**

Limits: humans

Publication type: article; article in press; erratum; short survey

CHAPTER 4
Staging of Hodgkin's lymphoma

Diagnostic accuracy

Systematic reviews

Author, year	Facey 2007
Technology	FDG-PET or FDG-PET/CT
Disease	malignant (Hodgkin's, non-Hodgkin's) lymphoma
Objective	to assess: ▪ primary diagnosis ▪ **X** staging (before treatment) ▪ response to treatment (during treatment) ▪ restaging (after treatment) (residual disease) ▪ follow up in asymptomatic patients ▪ diagnosis of suspected recurrence ▪ recurrence ▪ impact on management ▪ impact of clinical outcomes
Inclusion criteria	P patients with malignant lymphoma I FDG-PET or FDG-PET/CT C conventional workup (CWU), Ga scanning, bone marrow biopsy (BMB) R suitable O diagnostic accuracy S prospective, at least 12 (primary studies) or 6 (treatment response planning) patients
Years covered by the search	2000-2005
Study selection data extraction, quality assessment performed by two authors independently	yes
Comprehensive bibliographic search: at least two databases searched	yes
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	yes
Searched also unpublished studies	no
Language restriction	yes (only studies in English, French, German, Spanish or Italian)

Overall number of references retrieved and n of included studies reported	yes
n. and references of excluded studies reported, reason given	no
Characteristics of included studies clearly reported in tables	yes
Methodological quality of primary studies assessed; criteria reported	no
Results of quality assessment used to formulate results and conclusions	yes
Meta-analysis performed with appropriate statistic methods	no, only narrative results
Publication bias assessed	no
N. of included studies study design	total number of studies: 10 plus a systematic review (on 7 studies) 1 on HL patients, 7 on a mixed population, 3 on NHL patients
N. of included patients	469 with HL or NHL (median: 42, range: 27-88) 188 with HL (median: 18; range: 4-88)
Reference standard	concordance between FDG-PET and other imaging techniques, follow up
Comparator	conventional workup (CWU), Ga scanning, bone marrow biopsy (BMB)
Performance results	Only narrative results. Data mixed for staging and restaging (after treatment or suspected recurrence) "Evidence from one SR reviewing seven PSs, and seven additional PSs shows that PET had specificity of at least 90% and sensitivity of 79-100% (or > 90% in the new studies). PET consistently showed superior sensitivity to Ga scanning. Two older studies suggested PET was more accurate than CT for staging lymph node involvement, but one new study showed them to be comparable. There was evidence that all imaging methods may miss small disease foci."
Impact on management	"There is some evidence of management/staging changes in 10-20% of patients from diagnostic accuracy studies, but the changes are not well documented."
Impact on clinical outcome	not assessed

Recommendations and conclusions	Evidence from one SR reviewing seven PSs, and seven additional PSs shows that PET had specificity of at least 90% and sensitivity of 79-100% (or >90% in the new studies). PET consistently showed superior sensitivity to Ga scanning. Two older studies suggested PET was more accurate than CT for staging lymph node involvement, but one new study showed them to be comparable. There was evidence that all imaging methods may miss small disease foci. There is some evidence of management/staging changes in 10-20% of patients from diagnostic accuracy studies, but the changes are not well documented.
Notes	

Author, year	**Kirby 2007**
Technology	FDG-PET
Disease	malignant lymphoma
Objective	to assess: ▪ primary diagnosis ▪ X staging (before treatment) ▪ response to treatment (during treatment) ▪ restaging (after treatment) (residual disease) ▪ follow up in asymptomatic patients ▪ diagnosis of suspected recurrence ▪ recurrence ▪ impact on management ▪ impact of clinical outcomes
Inclusion criteria	P patients with malignant lymphoma I FDG-PET C not specified R not specified O diagnostic accuracy, change in management S case reports were excluded where more substantial series exist. Studies using gamma camera PET scanners were also excluded
Years covered by the search	January 1997 and September 2005
Study selection data extraction, quality assessment performed by two authors independently	not specified
Comprehensive bibliographic search: at least two databases searched	yes
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	yes
Searched also unpublished studies	no
Language restriction	yes (only studies in English)
Overall number of references retrieved and n of included studies reported	no
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	unclear; unclear
Results of quality assessment used to formulate results and conclusions	yes
Meta-analysis performed with appropriate statistic methods	no
Publication bias assessed	no
N. of included studies study design	total number of studies: 37 11 on HL pts, 17 on a mixed population, 9 on NHL pts retrospective (27/36), prospective (9/36)
N. of included patients	1 465 with HL or NHL (median: 38, range: 4-91) 681 with HL (median: 26, range: 4-88)
Reference standard	CT and clinical follow up (4), CT and bone marrow biopsy (2), clinical follow up (2), conventional staging and clinical follow up (2), Ga, CT and clinical follow up (3), pathology or clinical follow up (1), histopathological confirmation (5), histology and follow up (1), CT, follow up and histology (5)
Comparator	CT only (4), CT and/or Ga scanning (2), conventional staging incl CT/endoscopy (1), none (3)
Performance results	Nodal and extra-nodal, staging and restaging HL **FDG-PET** sensitivity: median 94% (range: 87-100%) specificity: "too rarely reported to be meaningfully summarized" ("false negatives cases occurred in 0-12% of patients") **Conventional imaging** sensitivity: median 77% (20-93%) specificity: not reported HL+NHL patients **FDG-PET** sensitivity: median 93% specificity: median 99% **CT** sensitivity: median 81% specificity: median 93% **Ga scanning** sensitivity: median 73% specificity: median 76%

Impact on management	HL patients (no pooled estimates) **FDG-PET** upstaging: 14.5% (11-55%) downstaging: 7% (0-28%) change in management: median 14% (range: 0-25%) HL+NHL patients **FDG-PET** change in management: median 10.5% (range: 10-62%)
Impact on clinical outcome	not reported
Recommendations and conclusions	The general impression from these studies is that PET has a higher sensitivity than conventional imaging for peripheral and thoracic lymph nodes as well as for the detection of extra-nodal disease. It consistently influences the staging of Hodgkin's lymphoma and in a smaller percentage of cases alters management such that it can reasonably be proposed as an important additional staging investigation to conventional staging procedures. However, false negatives do occur (0-12%) such that PET should not replace other imaging modalities and should also be cautiously applied for changing a CT-based staging downwards.
Notes	

Author, year	**Wu 2012**
Technology	FDG-PET or FDG-PET/CT
Disease	HL and aggressive NHL, bone marrow involvement detection
Objective	to assess: ▪ primary diagnosis ▪ **X** staging (before treatment) ▪ response to treatment (during treatment) ▪ restaging (after treatment) (residual disease) ▪ follow up in asymptomatic patients ▪ diagnosis of suspected recurrence ▪ **X** recurrence ▪ impact on management ▪ impact of clinical outcomes
Inclusion criteria	P patients with primary malignant lymphoma or recurrent malignant lymphoma after complete remission I FDG-PET or FDG-PET/CT (only combined, not sequential) C MRI R histopathology and/or close clinical and imaging follow up of at least 6 months O diagnostic accuracy S articles of 10 or more patients included, raw data available to calculate true positives and false negatives values
Years covered by the search	January 1995 - July 2010
Study selection data extraction, quality assessment performed by two authors independently	yes
Comprehensive bibliographic search: at least two databases searched	yes
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	not clear
Searched also unpublished studies	no
Language restriction	yes (only studies in English and Chinese)
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

Results of quality assessment used to formulate results and conclusions	no
Meta-analysis performed with appropriate statistic methods	yes
Publication bias assessed	yes
N. of included studies study design	32 (5 on PET/CT, 20 on PET and 8 on MRI) 8/32 on aggressive NHL patients only, 16/32 on a mixed population, 8/32 HL patients only; retrospective (14/32), prospective (11/32), ND (7/32); blinded (3/32), not blinded/unclear blinding (29/32); consecutive recruitment (16/32)
N. of included patients	1 845 (690 with HL, 775 with aggressive NHL, 380 with HL or NHL)
Reference standard	histopathology and/or close clinical and imaging follow up of at least 6 months
Comparator	MRI
Performance results	Bone marrow involvement, staging and restaging <u>HL+ aggressive NHL</u> **FDG-PET** sensitivity: mean 81.5% (95% CI 77.3-85.3%) (highly heterogeneous, heterogeneity chi-squared = 187.03) specificity: mean 87.3% (95% CI 84.9-89.5%) (highly heterogeneous, heterogeneity chi-squared = 270.59) **FDG-PET/CT** sensitivity: mean 91.6% (95% CI 85.1-95.9) (highly heterogeneous, heterogeneity chi-squared = 45.63) specificity: mean 90.3% (95% CI 85.9-93.7%) (heterogeneity chi-squared = 10.18) **MRI** sensitivity: mean 90.3% (95% CI 82.4-95.5%) (heterogeneity chi-squared = 25.83) specificity: mean 75.9% (95% CI 69.8-81.2%) (heterogeneity chi-squared = 21.12)
Impact on management	not assessed
Impact on clinical outcome	not assessed
Recommendations and conclusions	PET/CT was a highly sensitive and specific modality in diagnosing patients with bone marrow involvement in lymphoma. Compared with MRI and PET alone, PET/CT can play much more important roles in staging of lymphoma.
Notes	

Synoptic table of primary studies on staging in patients with Hodgkin's lymphoma

Author, year	Design	N. of patients (with HL)	Reference test	Pre-test probability of extended disease	Disease extension	Test	Sensitivity	Specificity
Boisson 2007	retrospective	37 (37)	BMB+MRI (in discordant cases between BMB and PET)	not available	extra-nodal, BM involvement	FDG-PET	80%	86%
						no comparator		
Cerci 2011	prospective	210 (210)	TP: concordant positive findings of clinical evaluation, CT, PET, BMB TN: concordant positive findings of clinical evaluation, CT, PET, BMB FP: lesions that spontaneously resolved in FU; FN: not defined	52%	nodal, extra-nodal, BM involvement	FDG-PET total body	98%	95%
						CT total body	87%	97%
					bone marrow	FDG-PET	94%	98%
						BMB	71%	100%
de Jong 2009	retrospective	111 (15)	FU with PET/CT	67% (HL patients)	spleen	FDG-PET (splenic)	70%	80%
						CT	91%	96%
Furth 2006	prospective	33 (33)	all clinical and imaging information; biopsy in only 4/33 (only a part of patients in which FDG-PET and CIM were discordant)	48%	nodal and extra-nodal	FDG-PET	94%	94%
						CIM (CT+MRI)	75%	94%
						FDG-PET+CIM (side by side)	88%	100%
						FDG-PET+CIM (image fusion)	100%	100%
Fuster 2006	retrospective consecutive	106 (18)	bone marrow biopsy	26%	bone marrow	FDG-PET	86%	99%
						biopsy	57%	100%

Author, year	Design	N. of patients (with HL)	Reference test	Pre-test probability of extended disease	Disease extension	Test	Sensitivity	Specificity
Picardi 2009	prospective cross sectional	100 (100)	coincidental findings of malignant nodules with at least 2 imaging techniques or nodule size decrease (>50%) after chemotherapy	not available	extra-nodal (splenic)	FDG-PET	43%	100%
						CT	43%	96%
Pinilla 2011	prospective cross sectional	101 (32)	combined (biopsy, follow up, other exams)	not available	nodal	FDG-PET	82%	81%
						LD_FDG-PET/CT	97%	96%
						FD_FDG-PET/CT	97%	97%
						CT	90%	92%
					organ	FDG-PET	70%	76%
						LD_FDG-PET/CT	92%	81%
						FD_FDG-PET/CT	94%	81%
						CT	87%	91%
					bone marrow	FDG-PET	29%	84%
						LD_FDG-PET/CT	29%	90%
						FD_FDG-PET/CT	29%	90%
					all	FDG-PET	73%	80%
						LD_FDG-PET/CT	89%	89%
						FD_FDG-PET/CT	90%	89%

Primary studies

Author, year	Boisson 2007
Technology	FDG-PET
Disease	Hodgkin's lymphoma
Objective	to evaluate the standardized uptake value (SUV) according to different parameters of HL and to evaluate the impact of PET on the initial staging and on the follow uo at the Centre of Nuclear Medicine Jean-Perrin
Patients characteristics	37 patients with histologically confirmed Hodgkin's lymphoma
Index test	FDG-PET/CT
Comparator	CT
Reference standard	bone marrow biopsy + MRI
Country	France
Outcomes considered	diagnostic accuracy, change in management
Study design	retrospective study
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	yes
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	yes
Withdrawals from the study explained	yes
Pre-test probability	2.7% (for bone marrow involvement)

Results	Disease extension (nodal and extra-nodal involvement) FDG-PET/CT no data on diagnostic accuracy CT no data available bone marrow involvement FDG-PET/CT sensitivity: 80% specificity: 86% accuracy: 85% CT no data available Change in management: 10 patients were diagnosed with an extensive instead of limited disease with a subsequent change on therapeutic management.
Authors' recommendations and conclusions	Indications of PET in lymphoma tourned out to be quite broad. We discovered that the maximum SUV was significantly higher for mixed cellularity HL than nodular sclerosis HL. Our study confirms the utility of PET in the assessment and follow uo of HL. Thanks to its excellent performance it will allow a personalised adaptation of therapeutic management of patients even if some aspects regarding the execution of the test are still to be defined.
Notes	

Author, year	**Cerci 2011**
Technology	FDG-PET
Disease	Hodgkin's lymphoma
Objective	to analyze the combined data from our prospective studies to evaluate the cost-effectiveness of FDG-PET in initial staging of patients with HL
Patients characteristics	210 newly diagnosed Hodgkin's lymphoma patients (median age: 33.7±14.9)
Index test	FDG-PET
Comparator	CT (for nodal and extra-nodal disease extension) and BMB (for bone involvement)
Reference standard	Positive concordant findings at whole-body PET, CT, or BMB were interpreted as true positives Concordant negative findings of clinical evaluation, CT, and PET were regarded as true absence of disease In cases of discordance between PET and CT, response to treatment and follow up data were used to assess the overall accuracy of the patient's disease status. Lesions were considered true positive if abnormalities either persisted on a follow up PET or CT scan with no interval treatment or resolved on a follow up scan in patients who had received interval treatment. Conversely, lesions that resolved on follow up scanning without interval treatment were not lymphoma and were considered false positive. In particular, concordance between CCS and MS was rated if both procedures provided the same disease stage. In contrast, discordance was established when CCS stage identified with conventional diagnostic procedures was different from MS identified with PET. They were then investigated with further techniques (magnetic resonance imaging [MRI] for bone marrow evaluation) or evaluated by clinical follow up, comparing PET and CT scans acquired at staging and at the end of treatment. A final consensus was achieved in all discordant cases
Country	Italy and Brazil
Outcomes considered	diagnostic accuracy
Study design	prospective cross-sectional study
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes

Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	yes
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	not specified
Withdrawals from the study explained	not applicable
Pre-test probability	of extended disease: 52%
Results	<u>Nodal and extra-nodal disease extension</u> FDG-PET sensitivity: 97.9% (95-98%) specificity: 95.3% (91-97%) CT sensitivity: 87.3% (84-89%) specificity: 96.8% (93-98%) <u>Bone marrow involvement</u> FDG-PET sensitivity: 94.2% (79-99%) specificity: 98.2% (94-99%) BMB sensitivity: 71.4% (53-84%) specificity: 100% (97-100%)
Authors' recommendations and conclusions	FDG-PET is more accurate than CT and BMB in HL staging. Given observed probabilities, FDG-PET is highly cost-effective in the public health care program in Brazil.
Notes	

Author, year	**de Jong 2006**
Country	The Netherlands
Technology	FDG-PET
Disease	Hodgkin's lymphoma and non-Hodgkin's lymphoma
Objective	the sensitivity and specificity of PET, CT, and PET/CT for initial splenic involvement were determined
Patients characteristics	111 subjects with a mean age of 56.1±16.7 (SD) years (range, 17.3-86.1 years). The histologic diagnoses were non-Hodgkin's lymphoma in 96 (86% - 40 with diffuse large B-cell lymphoma) and Hodgkin's disease in 15 (14%) patients. According to the Ann Arbor system, the patients were found to have disease in stage 4 (n=35, 32%), stage 3 (n=19, 17%), stage 2 (n=30, 27%), and stage 1 (n=27, 24%)
Index test	FDG-PET
Comparator	CT
Reference standard	Initial splenic involvement can be confirmed with follow up PET/CT. A reference standard strongly suggestive of initial splenic involvement in lymphoma is reversal of progression of splenic size and the finding of splenic nodules or splenic uptake on follow up PET and CT in relation to other disease sites. This strategy has been used in previous studies
Outcomes considered	diagnostic accuracy
Study design	retrospective cross-sectional study
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	no
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	not clear

Independent and blind interpretation of index test and reference standard results	no
Withdrawals from the study explained	not applicable
Pre-test probability	32 patients (29%) were determined to have true splenic involvement, and 79 to have no splenic involvement. HL patients: 10 out of 15 (66.7%) with splenic involvement NHL patients: 22 out 96 (22.9%) with splenic involvement NHL (diffuse large B-cell lymphoma): 9 out of 40 (22.5%) with splenic involvement NHL (other lymphomas): 13 out of 56 (23.2%) with splenic involvement
Results	Splenic involvement (HL + NHL) FDG-PET sensitivity: 75% specificity: 98.7% CT sensitivity: 91% specificity: 96% Splenic involvement (HL) FDG-PET sensitivity: 70% specificity: 80% CT sensitivity: 90% specificity: 100% Splenic involvement (all NHL) FDG-PET sensitivity: 77.3% specificity: 100% CT sensitivity: 90.9% specificity: 95.9% Splenic involvement (NHL - diffuse large B-cell lymphoma) FDG-PET sensitivity: 67% specificity: 100% CT sensitivity: 100% specificity: 90.0% *(continues)*

	Splenic involvement (NHL - other lymphomas) FDG-PET sensitivity: 85% specificity: 100% CT sensitivity: 85% specificity: 100%
Authors' recommendations and conclusions	For the initial staging of splenic involvement in the patients with malignant lymphoma in this study, the stepwise findings of, first, splenic greater than hepatic FDG uptake at PET, second, the presence of low-attenuation nodules at CT, and, third, an enlarged CT splenic index greater than 725 cm^3 have 100% sensitivity and 95% specificity for the presence of splenic involvement. This approach can be tested prospectively and used for future determination of which change in CT splenic index corresponds to partial remission and which to complete remission.

Author, year	**Furth 2006**
Technology	FDG-PET
Disease	pediatric Hodgkin's lymphoma
Objective	to investigate the value of retrospective image fusion of PET with CT and MRI data in initial staging of paediatric HD compared with separate and side-by-side image interpretation regarding the diagnostic accuracy and confidence as well as the impact on individual therapy group assignment
Patients characteristics	33 patients (17 female 17, 16 male; range of age: 4 to 18 years, mean 14.2) with histologically proven HD
Index test	FDG-PET
Comparator	conventional imaging modalities (CIM = CT and MRI)
Reference standard	all available clinical and imaging information: a region was judged as involved or not involved by HD if the findings in CIM and FDG-PET as well as the clinical status were concordantly positive or negative. In case of discrepant findings in CIM and PET or a discordant clinical status (including US), biopsies were obtained from lesions relevant for the therapy decision whenever an agreement of patients and parents was given and this was possible in only 4 cases. Additionally, a minimum follow up of 12 months was mandatory
Country	Germany
Outcomes considered	diagnostic accuracy, change in management
Study design	prospective cross-sectional study
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	no (biopsy only for a minority of patients)
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	no (only patients with discordant findings between FDG-PET and CIM were candidates to biopsy)

Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	yes
Withdrawals from the study explained	not applicable
Pre-test probability	of limited disease (stage I-II): 17/33 (52%) of patients
Results	Disease extension (nodal and extra-nodal) FDG-PET sensitivity: 94% specificity: 94% Conventional imaging modalities (CT+MRI) sensitivity: 75% specificity: 94% Side-by-side analysis of FDG-PET, CT, MRI sensitivity: 87.5% specificity: 100% Fused images of FDG-PET, CT, MRI analysis sensitivity: 100% specificity: 100% Disease extension (nodal and extra-nodal) region-based analysis FDG-PET sensitivity: 84% specificity: 95% Conventional imaging modalities (CT+MRI) sensitivity: 74% specificity: 96% Side-by-side analysis of FDG-PET, CT, MRI sensitivity: 96% specificity: 96% Fused images of FDG-PET, CT, MRI analysis sensitivity: 95% specificity: 99%
Authors' recommendations and conclusions	Correlative image analysis of CIM and FDG-PET is superior to CIM alone and FDG-PET alone. Thus, performing FDG-PET and correlation to CIM in HD of the childhood and adolescence is desirable for accurate initial staging and therapy decision making. Employing a sophisticated registration tool for image fusion, staging accuracy, and reviewers' confidence can be further improved.
Notes	All the results for the patient-based analysis were calculated by raw data provided by authors.

Author, year	**Fuster 2006**
Country	Spain
Technology	FDG-PET
Disease	Hodgkin's lymphoma and non-Hodgkin's lymphoma
Objective	to assess the usefulness of [18F]fluorodeoxyglucose positron emission tomography in the detection of bone marrow involvement in malignant lymphoma, and its impact in clinical management
Patients characteristics	106 consecutive patients (54 female, 52 male) with a mean age of 53±15 years and a confirmed diagnosis of lymphoid neoplasm by the World Health Organization criteria, who were referred for staging (n=81) or restaging (n=25) of known Hodgkin's lymphoma (n=18) or NHL (n=88) by means of [18F]FDG-PET imaging. The categories of NHL found in this series were diffuse large B-cell (n=37), follicular (n = 21), peripheral T-cell (n=7), mantle cell (n=7), marginal zone (n=5) and other cell types (n=11)
Index test	FDG-PET
Comparator	none
Reference standard	bone marrow biopsy
Outcomes considered	diagnostic accuracy
Study design	prospective cross-sectional study
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	no
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	yes
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	no

Independent and blind interpretation of index test and reference standard results	not clear
Withdrawals from the study explained	not applicable
Pre-test probability	24 patients (26.4%) with bone marrow involvement
Results	**Bone marrow involvement** FDG-PET sensitivity: 85.7% specificity: 98.9%
Authors' recommendations and conclusions	Positron emission tomography and bone marrow biopsy are complementary in assessing the presence of bone marrow involvement in patients with malignant lymphoma. In our series, positron emission tomography was more sensitive than bone marrow biopsy in Hodgkin's and non-Hodgkin's lymphoma, except in follicular lymphoma.

Author, year	**Picardi 2009**
Technology	FDG-PET
Disease	Hodgkin's lymphoma
Objective	to prospectively compare contrast-enhanced harmonic compound ultrasonography, CT, and FDG-PET in detecting nodular infiltration in the spleen of patients with newly diagnosed Hodgkin's lymphoma
Patients characteristics	100 patients with Hodgkin's lymphoma (median age: 30, range 18-74)
Index test	FDG-PET
Comparator	CT, contrast-enhanced harmonic compound US
Reference standard	coincidental findings of nodules positive for malignancy with at least 2 different imaging techniques (e.g. at both contrast-enhanced CT and FDG-PET) or, when malignancy was found with only one imaging technique (e.g. at contrast-enhanced harmonic compound US), to have or not to have nodule size decrease (≥50% in the greatest diameter) after chemotherapy
Country	Italy
Outcomes considered	diagnostic accuracy
Study design	prospective cross-sectional study
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	yes
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	yes

Withdrawals from the study explained	yes
Pre-test probability	13%
Results	Extra-nodal (splenic) involvement FDG-PET sensitivity: 43.3% (95% CI 0.26-0.62%) specificity: 100% (calculated by ASSR reviewer) CT sensitivity: 43.3% (95% CI 0.26-0.62%) specificity: 95.7% (calculated by ASSR reviewer) Contrast-enhanced US sensitivity: 100% specificity: 100%
Authors' recommendations and conclusions	US with tissue harmonic compound technology and intravenous microbubble-based microvasculature study as part of the diagnostic workup to staging patients with Hodgkin's lymphoma allows for a more correct assessment of the spleen status thus avoiding the risk of understaging, which may lead to under-treatment.

Author, year	**Pinilla 2011**
Country	Spain
Technology	FDG-PET, FDG-PET/CT
Disease	Hodgkin's lymphoma and non-Hodgkin's lymphoma
Objective	to compare the accuracy of contrast-enhanced CT and PET alone and of hybrid PET/CT, performed with either low-dose unenhanced CT (LD-PET/CT) or full-dose enhanced CT (FD-PET/CT) in detecting nodal and extra-nodal lesions in the initial staging of an unselected population of patients with lymphoma
Patients characteristics	101 patients (59 female and 42 male, mean age 50 years, range 15-83 years) with histopathologically proven and untreated lymphoma were enrolled in this prospective study for initial staging; 32 patients with HL
Index test	FDG-PET
Comparator	CT, low dose FDG-PET/CT, full dose FDG-PET/CT
Reference standard	reference standard as the sum of many factors: clinical history; physical examination; laboratory workup; iliac crest bone marrow biopsy; contrast-enhanced CT and other imaging findings (magnetic resonance imaging [MRI], Gallium scan); lumbar puncture; endoscopy; biopsies and surgery when clinically indicated; and follow up data
Outcomes considered	diagnostic accuracy
Study design	prospective cross-sectional study (unclear if consecutive recruitment)
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	no
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not applicable
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes

Execution of the reference standard described	no
Independent and blind interpretation of index test and reference standard results	yes
Withdrawals from the study explained	not applicable
Pre-test probability	not available
Results	**Nodal assessment** CT sensitivity 90% (95% CI 86-94%) specificity 92% (95% CI 86-97%) PET sensitivity 82% (95% CI 77-87%) specificity 81% (95% CI 73-88%) Low dose PET/CT sensitivity 97% (95% CI 95-99%) specificity 96% (95% CI 93-99%) Full dose PET/CT sensitivity 97% (95% CI 95-99%) specificity 97% (95% CI 94-100%) **Organ evaluation** CT sensitivity 87% (95% CI 78-96%) specificity 91% (95% CI 83-99%) PET sensitivity 70% (95% CI 58-82%) specificity 76% (95% CI 64-88%) Low dose PET/CT sensitivity 92% (95% CI 83-99%) specificity 81% (95% CI 69-92%) Full dose PET/CT sensitivity 94% (95% CI 86-100%) specificity 81% (95% CI 69-92%) **Bone marrow involvement** PET sensitivity 29% (95% CI 13-45%) specificity 84% (95% CI 76-93%) Low dose PET/CT sensitivity 29% (95% CI 13-45%) specificity 90% (95% CI 83-97%) Full dose PET/CT sensitivity 29% (95% CI 13-45%) specificity 90% (95% CI 83-97%) *(continues)*

	Overall diagnostic accuracy PET sensitivity 73% (95% CI 68-78%) specificity 80% (95% CI 75-84%) Low dose PET/CT sensitivity 89% (95% CI 85-92%) specificity 89% (95% CI 85-92%) Full dose PET/CT sensitivity 90% (95% CI 85-93%) specificity 89% (95% CI 85-93%)
Authors' recommendations and conclusions	PET/CT is an accurate technique for the initial staging of lymphomas without significant differences between Low Dose-PET/CT and Full Dose-PET/CT. Full Dose-PET/CT detects relevant incidental findings that are missed on Low Dose-PET/CT

CHAPTER 5
Dose painting definition in radiation of Hodgkin's lymphoma

Diagnostic accuracy

Systematic reviews

None retrieved.

Primary studies

None retrieved.

CHAPTER 6
During treatment evaluation of early response to therapy in Hodgkin's lymphoma

Diagnostic accuracy

Systematic reviews

Author, year	**HTA AETSA 2007**
Technology	FDG-PET or FDG-PET/CT
Disease	HL
Objective	to assess: ▪ primary diagnosis ▪ staging (before treatment) ▪ **X** response to treatment (during treatment) ▪ restaging (after treatment) (residual disease) ▪ follow up in asymptomatic patients ▪ diagnosis of suspected recurrence ▪ recurrence ▪ impact on management ▪ impact of clinical outcomes
Inclusion criteria	P patients with HL or NHL I FDG-PET or FDG-PET/CT C CT, MRI R histology or follow up >12 months O diagnostic accuracy, efficacy and change in management S RCT, systematic review, HTA, prospective cohorts, number of patients >10, with histological confirmation, follow up ≥12 months, comparison with other imaging techniques; studies reporting results on sensitivity, specificity, PPV, NPV, efficacy, effectiveness, data on change in management
Years covered by the search	2004-2006
Study selection data abstraction, quality assessment performed by two authors independently	yes

Comprehensive bibliographic search: at least two databases searched	yes
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	yes
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
Results of quality assessment used to formulate results and conclusions	unclear
Meta-analysis performed with appropriate statistic methods	no, meta-analysis not performed due to heterogeneity
Publication bias assessed	yes
N. of included studies study design	total number of studies included in the review: 10 (7 in HL, 2 in HL+NHL, 1 in aggressive NHL) + 1 systematic review; 10/10 prospective studies 7 on during-treatment response in HL (of which 2 including both patients with HL and patients with NHL); 7/7 prospective
N. of included patients	total number of patients (with HL or NHL): 631 (22-108) number of HL patients: 496 (3-108)
Reference standard	follow up
Comparator	67Ga SPECT (1 study)

Performance results	FDG-PET HL or NHL patients sensitivity: 55.5-100% specificity: 50-100% HL patients sensitivity: 55.5-100% specificity: 50-100% 67Ga SPECT (1 study) sensitivity: 40% specificity: 94% PPV: 80% NPV: 94%
Impact on management	not assessed
Impact on clinical outcome	not assessed
Recommendations and conclusions	In patients with Hodgkin's lymphoma FDF-PET positive predictive value after 2-3 chemotherapy cycles fluctuated between 93,4% (95% IC 92.6-94.3) and 100% (95% IC 99.3-100%). At the end of treatment FDF-PET positive predictive value fluctuated between 94.3% (95% IC 92.8-95.7) and 100% (95% IC 97.1-100). In patients with negative FDG-PET, both during and at the end of treatment, the percentage of patients in period of remission during follow uo was higher than in patients with positive FDG-PET.

Author, year	**Facey 2007**
Technology	FDG-PET
Disease	HL
Objective	to assess: ▪ primary diagnosis ▪ staging (before treatment) ▪ **X** response to treatment (during treatment) ▪ restaging (after treatment) (residual disease) ▪ follow up in asymptomatic patients ▪ diagnosis of suspected Recurrence ▪ recurrence ▪ impact on management ▪ impact of clinical outcomes
Inclusion criteria	P patients with malignant lymphoma I FDG-PET C conventional workup (CWU), Ga scanning, bone marrow biopsy (BMB) R not specified O diagnostic accuracy S prospective, at least 12 (primary studies) or 6 (treatment response planning) patients
Years covered by the search	2000-2005
Study selection data abstraction, quality assessment performed by two authors independently	yes
Comprehensive bibliographic search: at least two databases searched	yes
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	yes
Searched also unpublished studies	no
Language restriction	yes (only studies in English, French, German, Spanish or Italian)
Overall number of references retrieved and n of included studies reported	yes
n. and references of excluded studies reported, reason given	no
Characteristics of included studies clearly reported in tables	yes

Methodological quality of primary studies assessed; criteria reported	no
Results of quality assessment used to formulate results and conclusions	yes
Meta-analysis performed with appropriate statistic methods	no, only narrative results
Publication bias assessed	no
N. of included studies study design	total number of studies 9 1 including only HL patients 4 including only NHL patients 4 including HL or NHL patients unclear
N. of included patients	total number of patients: 397 number of patients with HL: 123 (range 10-85) number of patients with HL or NHL: 115 (range 16-46)
Reference standard	clinical follow up
Comparator	CT, BMB
Performance results	Narrative results only. "… midtherapy scans may be predictive of outcome midtherapy. However, there is no evidence of any associated changes in management (…) consequent upon this"
Impact on management	not assessed
Impact on clinical outcome	not assessed
Recommendations and conclusions	There is evidence from nine PSs that midtherapy scans may be predictive of outcome midtherapy. As yet, however, there is no evidence of any associated changes in management (such as intensification or switch in therapy) consequent upon this.

Author, year	**Kirby 2007**
Technology	FDG-PET
Disease	HL
Objective	to assess: ▪ primary diagnosis ▪ staging (before treatment) ▪ **X** response to treatment (during treatment) ▪ restaging (after treatment) (residual disease) ▪ follow up in asymptomatic patients ▪ diagnosis of suspected recurrence ▪ recurrence ▪ impact on management ▪ impact of clinical outcomes
Inclusion criteria	P patients with malignant lymphoma I FDG-PET C not specified R not specified O diagnostic accuracy, change in management S case reports were excluded where more substantial series exist. Studies using gamma camera PET scanners were also excluded
Years covered by the search	from January 1997 to September 2005
Study selection data abstraction, quality assessment performed by two authors independently	not specified
Comprehensive bibliographic search: at least two databases searched	yes
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	yes
Searched also unpublished studies	no
Language restriction	yes (only studies in English)
Overall number of references retrieved and n of included studies reported	no
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; no

Results of quality assessment used to formulate results and conclusions	unclear
Meta-analysis performed with appropriate statistic methods	no
Publication bias assessed	no
N. of included studies study design	total number of studies 15 8 evaluating during-treatment response in HL (of which only 2 including only patients with HL and 4 on post HDC prior to ASCT) unclear
N. of included patients	total number of patients: 681 (16-121) patients with HL: 167 (3-85) patients with HL OR NHL: 169 (range: 30-54)
Reference standard	unclear
Comparator	none
Performance results	FDG-PET (data from the only 2 studies exclusively on HL patients) sensitivity: 67-80% specificity: 93-94% PPV: 62-94% NPV: 80-94% accuracy: 89-91% FDG-PET (data from all the 8 studies, thus including also NHL patients and studies on post HDC prior to ASCT) sensitivity: 42-100% specificity: 50-100% PPV: 62-91% NPV: 50-100% accuracy: 65-91% FDG-PET (data from the 5 studies on post HDC prior to ASCT) sensitivity: 58-100% specificity: 48-88% PPV: 65-87% NPV: 67-100% accuracy: 68-90%
Impact on management	not assessed
Impact on clinical outcome	not assessed

Recommendations and conclusions	In summary, interim PET offers a reliable method for early prediction of long-term remission and PFS in Hodgkin’s lymphoma. Interim PET, in combination with stage, is able to identify patients at high risk of relapse who are potential candidates for more intensive treatment. The use of interim PET to stratify risk, predict prognosis and modify treatment should be tested in prospective randomized controlled trials such as the current UK early Hodgkin’s lymphoma trial testing the omission of involved-field radiotherapy for patients achieving PET negativity after chemotherapy.

Author, year	**Terasawa 2009**
Technology	FDG-PET or FDG-PET/CT
Disease	advanced-stage HL
Objective	to assess: ▪ primary diagnosis ▪ staging (before treatment) ▪ **X** response to treatment (during treatment) ▪ restaging (after treatment) (residual disease) ▪ follow up in asymptomatic patients ▪ diagnosis of suspected recurrence ▪ recurrence ▪ impact on management ▪ impact of clinical outcomes
Inclusion criteria	P patients with DLBCL or advanced-stage HL I FDG-PET performed between the first and the fourth cycle of first-line chemotherapy C not specified R follow up with or without pathologic confirmation O sensitivity and specificity S prospective and retrospective studies, that evaluated at least 10 patients and included at least five patients who progressed during chemotherapy or relapsed through clinical follow up
Years covered by the search	Ovid MEDLINE and EMBASE from 1966 through July 2006 PubMed from August 2006 through July 2007
Study selection data abstraction, quality assessment performed by two authors independently	yes
Comprehensive bibliographic search: at least two databases searched	yes
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	yes
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
Results of quality assessment used to formulate results and conclusions	yes
Meta-analysis performed with appropriate statistic methods	yes
Publication bias assessed	yes
N. of included studies study design	total 13 7 (6 on HL patients only, 1 including HL and NHL patients) 5/7 prospective
N. of included patients	total number of patients: 671 number of patient with advanced HL: 360
Reference standard	follow up with or without pathologic confirmation
Comparator	
Performance results	FDG-PET or FDG-PET/CT (pooled estimates) HL patients sensitivity: 0.81 (95% CI 0.72-0.89) specificity: 0.97 (95% CI 0.94-0.99) positive LR: 28.4 (95% CI 14.2-56.7) negative LR: 0.19 (95% CI 0.12-0.30)
Impact on management	not assessed
Impact on clinical outcome	not assessed
Recommendations and conclusions	For low- to intermediate-risk advanced-stage HL, FDG-PET performed after a few cycles of standard chemotherapy seems to be a reliable prognostic test to identify poor responders, warranting prospective studies to assess PET-based treatment strategies.

Author, year	**Terasawa 2010**
Technology	FDG-PET or FDG-PET/CT
Disease	HL, aggressive NHL (DLBCL and others), indolent NHL
Objective	to assess: ▪ primary diagnosis ▪ staging (before treatment) ▪ **X** response to treatment (during treatment) ▪ restaging (after treatment) (residual disease) ▪ follow up in asymptomatic patients ▪ diagnosis of suspected recurrence ▪ recurrence ▪ impact on management ▪ impact of clinical outcomes
Inclusion criteria	P patients with HL, aggressive NHL (DLBCL and others), indolent NHL I FDG-PET performed during or after induction chemotherapy and before high-dose chemotherapy followed by autologous stem cell transplantation C conventional restaging (computed tomography [CT] or magnetic resonance imaging, and bone marrow biopsy) R follow up with or without pathologic confirmation O sensitivity and specificity S prospective and retrospective studies, that evaluated at least 10 patients and included at least five patients who progressed during chemotherapy or relapsed through clinical follow up
Years covered by the search	PubMed up to July 2010
Study selection data abstraction, quality assessment performed by two authors independently	yes
Comprehensive bibliographic search: at least two databases searched	no
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 (QUADAS)
Results of quality assessment used to formulate results and conclusions	yes (only results)
Meta-analysis performed with appropriate statistic methods	yes (not reported heterogeneity)
Publication bias assessed	no
N. of included studies study design	12 (7 including HL and NHL patients; 2 only HL patients; 3 only aggressive NHL patients) 3/12 prospective design
N. of included patients	total number of patients: 630 pre-transplant HL patients: 187 (range 24-68) 479 pre-transplant with HL or NHL (range: 15-101)
Reference standard	follow up with or without pathologic confirmation
Comparator	conventional restaging (computed tomography [CT] or magnetic resonance imaging, and bone marrow biopsy
Performance results	FDG-PET or FDG-PET/CT (pooled estimates patients with aggressive HL only) <u>HL patients</u> sensitivity 79% (59-91%) specificity 75% (58-86%) <u>HL or NHL patients</u> sensitivity 69% (95% CI 56-81%) specificity 81% (95% CI 73-87%)
Impact on management	not assessed
Impact on clinical outcome	not assessed
Recommendations and conclusions	18F-FDG-PET performed after salvage therapy appears to be an appropriate test to predict treatment failure in patients with refractory or relapsed lymphoma who receive high-dose chemotherapy. Some evidence suggests PET is superior to conventional restaging for this purpose. Given the methodological limitations in the primary studies, prospective studies with standardized methodologies are needed to confirm and refine these promising results.

Synoptic table of primary studies on during treatment evaluation with FDG-PET of response to therapy in patients treated for Hodgkin's lymphoma: recurrent disease as endpoint

Author, year	Technology	Patient number	Study design	Reference standard	Endpoint	Pre-test probability	Sensitivity	Specificity
Altamirano 2008	F-FDG-PET	28 (HL and NHL)	prospective	biopsy; follow up; guidelines established by the International response evaluation criteria in solid tumors Group (RECIST)	response to treatment	not assessed	92%	93%
	CT						79%	50%
Barnes 2011	FDG-PET	96	retrospective	not clear	treatment failure	14%	62%	89%
Boisson 2007	FDG-PET	25	retrospective	follow up	response to treatment (not clearly defined)	not assessed	80%	74%
Cerci 2010	FDG-PET	104	prospective	follow up and histological confirmation of PET positive lesions	treatment failure	21%	72.2%	82.9%
Dann 2010	FDG-PET/CT	96	prospective	follow up	treatment failure	6.3%	55.0%	78%
Riad 2010	F-FDG-PET/CT	51 (HL and NHL)	retrospective	histopathological exam and clinical follow up	response to treatment	not assessed	100%	97.7%
Zinzani 2012	FDG-PET	304	retrospective	restaging according to the revised response criteria for malignant lymphoma of the International harmonization project at end of treatment (including both a PET scan and a CT scan)	treatment failure	15%	72%	93%

Primary studies

Author, year	Altamirano 2008
Country	Mexico
Technology	18F-FDG-PET
Disease	Hodgkin's lymphoma and non-Hodgkin's lymphoma
Objective	to determine the diagnostic accuracy of 18FDG after three cycles and at the end of chemotherapy in non-Hodgkin's lymphoma (NHL) or Hodgkin's lymphoma (HL)
Patients characteristics	40 patients but only 28 patients where studied 15 patients were female (53.6%) and 13 were male (46.4%) with a mean age of 43 years (range: 15-74 years) 7 patients corresponded to HL diagnosis (25%) and 21 to NHL (75%)
Index test	18F-FDG-PET
Comparator	CT
Reference standard	follow up (median 18 months, range: 6-24 months; Guidelines established by the International response evaluation criteria in solid tumors Group (RECIST)
Outcomes considered	sensitivity, specificity, diagnostic accuracy, PPV, NPV
Study design	prospective cross-sectional study
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not clear
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	no
Execution of the reference standard described	no
Independent and blind interpretation of index test and reference standard results	yes

Withdrawals from the study explained	not applicable
Pre-test probability	
Results	18F-FDG-PET sensitivity: 92% specificity: 93% accuracy: 93% PPV: 92% NPV: 93% CT sensitivity: 79% specificity: 50% accuracy: 64% PPV: 61% NPV: 70%
Authors' recommendations and conclusions	18FDG had greater prognostic values than CT after the third and last cycle of chemotherapy. PET after three cycles of chemotherapy is predictive of 18-month outcome in patients with intermediate and aggressive NHL and HL and may help in the identification of patients who would benefit from more intensive treatment or from a change in chemotherapy.

Author, year	**Barnes 2011**
Technology	FDG-PET
Disease	Hodgkin's lymphoma
Objective	to assess the "value of both interim and end-of-treatment PET scans in patients with nonbulky limited-stage HL treated with a combination of Adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD), with or without radiation"
Patients characteristics	96 patients with limited-stage non bulky Hodgkin's lymphoma (defined as mass <10 cm or less than one-third of the intrathoracic diameter for mediastinal disease), with cHL histology, who have received Adriamycin, bleomycin, vinblastine, and dacarbazine, with or without radiation. The median age was 34 (range 18-77 years). The majority of patients had Ann Arbor stage II disease (88%). Seventy-two (75%) patients had nodular sclerosis cHL, with 9 (9%) having mixed cellularity and 15 (16%) having cHL not otherwise specified
Index test	FDG-PET interim PET imaging after two to four cycles of treatment and end-of-treatment PET imaging
Comparator	none
Reference standard	not clear
Country	USA
Outcomes considered	diagnostic accuracy
Study design	retrospective study
Spectrum of patients representative of the individuals who will receive the test in practice	no
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not applicable
Execution of the index and comparator tests adequately described	no
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	yes
Pre-test probability	14% (non responders)
Results	interim FDG-PET (non responders) sensitivity: 62% specificity: 89%
Authors' recommendations and conclusions	Interim PET scans were not predictive of outcome, compared with scans carried out at completion of therapy. End-of-treatment PET was highly predictive of PFS and OS, regardless of interim PET result. In this low-risk patient population, even patients with interim positive PET scans show a favourable prognosis.

Author, year	**Boisson 2007**
Technology	FDG-PET
Disease	Hodgkin's lymphoma
Objective	to evaluate the standardized uptake value (SUV) according to different parameters of HL and to evaluate the impact of PET on the initial staging and on the follow uo at the Centre of Nuclear Medicine Jean-Perrin
Patients characteristics	25 patients with histologically confirmed Hodgkin's lymphoma
Index test	FDG-PET "PET evaluation was carried out visually and according to the criteria adopted by our centre: a patient is considered with complete response (CR) if a pathological signal is not detected, with a partial response if a pathological signal above the mediastinal background for above-diaphragm lesions and above hepatic background for under-diaphram lesions is detected, in progression if more lesions are detected or if no response is detected for lesions identified during the disease staging"
Comparator	
Reference standard	follow up
Country	France
Outcomes considered	diagnostic accuracy on response to treatment (not clearly defined)
Study design	retrospective study
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	yes
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes

Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	yes
Withdrawals from the study explained	yes
Pre-test probability	not assessable (data lacking)
Results	FDG-PET (response to treatment) sensitivity: 80% specificity: 74% PPV: 44% NPV: 93% diagnostic accuracy: 75%
Authors' recommendations and conclusions	Indications of PET in lymphoma tourned out to be quite broad. We discovered that the maximum SUV was significantly higher for mixed cellularity HL than nodular sclerosis HL. Our study confirms the utility of PET in the assessment and follow uo of HL. Thanks to its excellent performance it will allow a personalised adaptation of therapeutic management of patients even if some aspects regarding the execution of the test are still to be defined.

Author, year	**Cerci 2010**
Technology	FDG-PET
Disease	Hodgkin's lymphoma
Objective	to assess the prognostic value of 18F-FDG-PET performed after 2 cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) standard-dose therapy in HL
Patients characteristics	104 histologically confirmed HD undergoing ABVD standard dose therapy (stage I-II: 4 cycles, stage III: 6 cycles, stage IV: 8 cycles; RT given to stage I-II patients after chemotherapy or to patients with bulky disease); 34/43 patients (79.1%) with early-stage disease underwent combined therapy, 27/61 (44.3%) patients with advanced disease underwent combined therapy; median age: 28 years
Index test	FDG-PET (after 2 cycles of chemotherapy) PET negative: no pathologic 18F-FDG uptake at any site, including all sites of previously increased pathologic uptake PET positive: the presence of focal 18F-FDG uptake that could not be attributed to physiologic biodistribution PET minimal residual uptake (MRU): low-grade 18F-FDG uptake with avidity less than, equal to, or only slightly higher than the uptake in mediastinal blood pool structures, according to the definition of Gallamini et al.
Comparator	
Reference standard	follow up and histological confirmation of PET positive lesions
Country	Brazil
Outcomes considered	diagnostic accuracy on treatment failure
Study design	prospective study, consecutive enrollment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	yes
Execution of the index and comparator tests adequately described	yes

Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	unclear
Withdrawals from the study explained	yes
Pre-test probability	22/104 (21%)
Results	FDG-PET (detection of treatment failures, important: minimal residual uptake considered as negative scan) sensitivity: 72.2% (49-88%) specificity: 82.9% (72-90%) PPV: 53.3% (34-71%) NPV: 91.8% (82-96%)
Authors' recommendations and conclusions	PET2 (e.g. after two cycles of chemotherapy) appears to be the most important prognostic factor in HL and provides valuable prognostic information in patients with HL treated with ABVD, with 3-y EFS rates of 53.4% for patients with a PET2-positive scan and 90.5% for patients with a PET2-negative scan. A negative interim 18FFDG-PET scan is highly predictive of treatment success in HL patients overall and in subgroups with early- or advanced-stage disease, independent of the risk according to IPS. However, clinical trials are needed to define the best way to use this important new prognostic factor in designing response-adapted therapies.

Author, year	**Dann 2010**
Technology	FDG-PET/CT
Disease	HL
Objective	to assess the prognostic performance of interim FDG-PET/CT in HL patients treated with various chemotherapy protocols, using four different scores to define response on FDGPET/CT. A static visual binary score was initially used prospectively for response evaluation on interim FDG-PET/CT. FDG-PET/CT studies were then retrospectively reviewed and compared using a dynamic visual score and two additional static visual scores with either mediastinal or liver blood pool uptake as a comparator
Patients characteristics	96 patients with classic HL (median age: 30 years, range: 17-57 years) treated with initially standard (if international prognostic score, IPS, ≤2, 41 patients) or escalated (if IPS ≥3, 22 patients) BEACOPP or ABVD (33 patients) chemotherapy regimen
Index test	FDG-PET/CT after 1 (15 patients) or 2 (81 patients) cycles of chemotherapy FDG-PET/CT results interpreted according to a visual binary score: ▪ positive: presence of any focus of increased uptake that could not be related to physiologic biodistribution of the tracer or to a known benign process; a decreased but residual uptake was also interpreted as positive ▪ negative: no foci of increased uptake unrelated to physiologic or benign tracer uptake
Comparator	
Reference standard	follow up for at least 1 year (median 59 months, range: 11-71 months) or until disease progression
Country	Israel
Outcomes considered	diagnostic accuracy (according to a "static" visual binary score and to a dynamic visual score and two additional static visual scores with either mediastinal or liver blood pool uptake as a comparator) change in management 5-year PFS and OS
Study design	cross-sectional prospective study (static visual binary score) and retrospective analysis (dynamic visual score and the 2 additional static visual scores)
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes

Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	yes
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	no
Execution of the reference standard described	no
Independent and blind interpretation of index test and reference standard results	unclear
Withdrawals from the study explained	not applicable
Pre-test probability	recurrence at follow up: 6/96 (7%)
Results	FDG-PET/CT interpreted by static visual score (prospective evaluation) Diagnostic accuracy sensitivity: 55% (95% CI 23-88%) specificity: 78% (95% CI 69-87%) PPV: 21% (95% CI 5-37%) NPV: 94% (95% CI 88-99%) accuracy: 76% (95% CI 67-84%) Change in management according to interim (during-treatment) FDG-PET/CT results 9/96 (9.4%) patients 5-year progression-free survival interim FDG-PET/CT negative patients: 94% (95% CI 89-99%) interim FDG-PET/CT positive patients: 79% (95% CI 71-87%) Overall survival interim FDG-PET/CT negative patients: 99% (95% CI 97-100%) interim FDG-PET/CT positive patients: 87% (95% CI 80-94%) *(continues)*

	FDG-PET/CT interpreted by a dynamic visual 5-point score, score 0-2: negative, 3-4: positive (retrospective evaluation) sensitivity: 33% (95% CI 2-64%) specificity: 96% (95% CI 93-100%) PPV: 50% (95% CI 10-90%) NPV: 93% (95% CI 88-98%) accuracy: 91% (95% CI 85-96%) <u>5-year progression-free survival</u> interim FDG-PET/CT negative patients: 93% (95% CI: 88-98%) interim FDG-PET/CT positive patients: 50% (95% CI: 40-60%) <u>Overall survival</u> interim FDG-PET/CT negative patients: 98% (95% CI 95-100%) interim FDG-PET/CT positive patients: 67% (95% CI 58-76%) FDG-PET/CT interpreted by the static score by Consensus of imaging Subcommittee (CIS), using mediastinal blood pool uptake as a comparator (retrospective evaluation) sensitivity: 44% (95% CI 12-76%) specificity: 80% (95% CI 72-88%) PPV: 19% (95% CI 2-36%) NPV: 93% (95% CI 87-99%) accuracy: 77% (95% CI 68-85%) <u>5-year progression-free survival</u> interim FDG-PET/CT negative patients: 93% (95% CI 88-98%) interim FDG-PET/CT positive patients: 81% (95% CI 73-89%) FDG-PET/CT interpreted by a static score using liver blood pool uptake as a comparator (retrospective evaluation) sensitivity: 33% (95% CI 2-64%) specificity: 85% (95% CI 77-92%) PPV: 19% (95% CI 0-38%) NPV: 92% (95% CI 86-98%) accuracy: 80% (95% CI 72-88%) <u>5-year progression-free survival</u> interim FDG-PET/CT negative patients: 92% (95% CI 87-97%) interim FDG-PET/CT positive patients: 81% (95% CI 73-88%)

Authors' recommendations and conclusions	In conclusion, the current study confirms the value of interim FDG-PET/CT for predicting treatment failure in HL in a cohort of patients followed for a longer time than previously reported. FDG-PET/CT demonstrated a consistently similar performance, with a high NPV in patients treated with three different chemotherapy protocols. The data also suggest that for practical purposes patients with an interim FDG-PET score of 0 or 1 should be managed as having a negative study and reduction of therapy from escalated BEACOPP to the standard regimen should be considered for such individuals. On the other hand, patients with an interim FDG-PET score of 3 or 4 are at high risk of disease progression. Importantly, while the limitations of studying a relatively small number of subjects is recognized, the findings of the present investigation nevertheless suggest that a dynamic visual scoring system improves the PPV and specificity of interim FDG-PET/CT as compared to a static FDG-PET/CT scoring at a single time point during therapy. Larger studies and further incorporation of a dynamic scoring system into prospective studies relying on interim FDG-PET/CT monitoring are needed to validate and confirm these findings.

Author, year	**Riad 2010**
Country	Egypt
Technology	18F-FDG-PET/CT
Disease	Hodgkin's lymphoma and non-Hodgkin's lymphoma
Objective	to evaluate the performance of 18F-FDG-PET/CT and to compare diagnostic accuracy of 18F-FDG-PET/CT with conventional imaging modalities(CIM) in the evaluation of early treatment response in Hodgkin's and non-Hodgkin's lymphoma
Patients characteristics	152 total patients (35 female and 117 male) with histologically proven malignant lymphoma 8 117 HD, 35, NHL) range age 3-18 years they were divided into 4 groups: Group I: 41 patients for initial staging Group II: 51 patients (45 HD, 6 NHL) for evaluating early treatment response after two to three cycles of chemotherapy. Five patients were stage I, 20 were stage II, 18 were stage III and 8 were stage IV Group III: 42 patients for evaluating treatment response 4-8 weeks after the end of their treatment Group IV: 18 patients evaluated for long-term follow up
Index test	18F-FDG-PET
Comparator	conventional imaging modalities (CIM - CT, MRI, US, physical examination, bone marrow biopsy when available)
Reference standard	histopathological exam and clinical follow up
Outcomes considered	sensitivity, specificity, diagnostic accuracy, PPV, NPV
Study design	retrospective cross-sectional study
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 clear
Execution of the index and comparator tests adequately described	yes

Did patients receive the same reference standard regardless of the index test result	no
Execution of the reference standard described	no
Independent and blind interpretation of index test and reference standard results	not clear
Withdrawals from the study explained	not applicable
Pre-test probability	
Results	18F-FDG-PET/CT sensitivity: 100% specificity: 97.7% accuracy: 98% PPV: 85.7% NPV: 100% CIM sensitivity: 83% specificity: 66.6% accuracy: 68.6% PPV: 25% NPV: 96.7%
Authors' recommendations and conclusions	PET/CT in paediatric lymphoma is more accurate than CIM. We recommend that it should be the first modality for all purposes in initial staging, evaluating treatment response and follow up.

Author, year	**Zinzani 2012**
Technology	FDG-PET
Disease	Hodgkin's lymphoma
Objective	to assess the early prognostic value of PET after two cycles of treatment, evaluating visual data
Patients characteristics	304 patients; male/female 150/154; median age 32 (13-78); stage I A/B 11 (3.6%), II A 136 (44.7%), II B 57 (18.8%), III A/B 62 (20.4%), IV A/B 38 (12.5%), B-symptoms 124 (40.8%); bulky disease: mediastinum 86 (28.3%), nodal 11 (3.6%); bone marrow involvement 9 (3.0%). First-line therapy: ABVD 214; ABVD + radiotherapy 90
Index test	Interim PET (PET+2) evaluation was performed after completion of the second cycle of therapy, immediately before the third cycle. A study was considered PET+2-negative if no pathological FDG uptake was seen at any site, including all sites of previously increased pathological uptake. A study was considered PET+2-positive if a focal FDG uptake was seen that could not be attributed to physiological biodistribution, benign uptake or normal anatomy, with clearly increased activity relative to the background. Minimal residual uptake on the PET+2 scan was defined as low-grade FDG uptake with avidity less than, equal to or only slightly higher than the uptake in the mediastinal blood pool structures, according to the definition of Gallamini et al. Patients with minimal residual uptake on the PET+2 scan were considered PET negative for the analysis, without estimating the proportion of patients with minimal residual uptake or focusing on them as a distinct category. On the basis of these criteria, PET scans were scored as negative or positive
Comparator	none
Reference standard	after first-line treatment all patients were restaged according to the revised response criteria for malignant lymphoma of the international harmonization project. complete restaging, with both a PET scan and a CT scan, was performed at least 1 month after the first-line treatment was completed, or after 3 months after the completion of radiotherapy. Responses assessed at this time point were then compared to the best response obtained so far, according to the interim PET analysis
Country	Italy
Outcomes considered	diagnostic accuracy
Study design	retrospective study

Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	no
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not applicable
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	no
Withdrawals from the study explained	yes
Pre-test probability	15% (non responders)
Results	interim FDG-PET (non responders) sensitivity: 72% specificity: 93%
Authors' recommendations and conclusions	Our results demonstrate the role of an early PET scan as a significant step forward in the management of patients with early-stage or advanced-stage HL.

CHAPTER 7
End of treatment evaluation of response to therapy in Hodgkin's lymphoma

Diagnostic accuracy

Systematic reviews

Author, year	HTA AETSA 2007
Technology	FDG-PET or FDG-PET/CT
Disease	malignant lymphoma
Objective	to assess: ▪ primary diagnosis ▪ staging (before treatment) ▪ response to treatment (during treatment) ▪ **X** restaging (after treatment) (residual disease) ▪ follow up in asymptomatic patients ▪ diagnosis of suspected recurrence ▪ recurrence ▪ impact on management ▪ impact of clinical outcomes
Inclusion criteria	P patients with HL or NHL I FDG-PET or FDG-PET/CT C R histology or follow up >12 months O CT, MRI S RCT, systematic review, HTA, prospective cohorts, number of patients >10, with histological confirmation, follow up ≥12 months, comparison with other imaging techniques; studies reporting results on sensitivity, specificity, PPV, NPV, efficacy, effectiveness, data on change in management
Years covered by the search	2004-2006
Study selection data abstraction, quality assessment performed by two authors independently	yes
Comprehensive bibliographic search: at least two databases searched	yes
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	yes

Searched also unpublished studies Language restriction	no 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
Results of quality assessment used to formulate results and conclusions	unclear
Meta-analysis performed with appropriate statistic methods	not possible to perform a meta-analysis, only descriptive results
Publication bias assessed	yes
N. of included studies study design	10 3/10 on HL patients (3/3 prospective, 3/3 consecutive recruitment) in total: 10 studies (7 in HL, 2 in HL+NHL, 1 in aggressive NHL); 7/10 on during treatment response, 3/10 on end of treatment response; 10/10 prospective studies, 7/10 with consecutive recruitment
N. of included patients	89 pts with HL (range: 28-32) in total 574 (439 pts with HL, 135 with NHL)
Reference standard	follow up >12 months
Comparator	67Ga-SPECT (1 study), CT (1 study)
Performance results	FDG-PET (range) sensitivity: 80-100% specificity: 83-85% PPV: 50-75% NPV: 96-100% CT (1 study) sensitivity: 25% specificity: 42% PPV: 7% NPV: 77% 67Ga-SPECT (1 study) sensitivity: 40% specificity: 96% PPV: 65% NPV: 90%
Impact on management	not assessed
Impact on clinical outcome	not assessed

Recommendations and conclusions	Therefore, in patients with HL, negative FDG-PET scan at the end of treatment is a good prognostic factor, while a positive scan is associated to high recurrence risk, so patients with positive FDG-PET need more intensive follow uo. FDG-PET is better than CT and 67-Ga SPECT in detecting chemotherapy response in patients with Hodgkin's lymphoma. FDG-PET has to be used in addition to conventional imaging in end of treatment evaluation in patients with HL and DLBCL, particularly in patients with residual masses.
Notes	

Author, year	**Facey 2007**
Technology	FDG-PET
Disease	malignant lymphoma
Objective	to assess: ▪ primary diagnosis ▪ staging (before treatment) ▪ response to treatment (during treatment) ▪ **X** restaging (after treatment) (residual disease) ▪ follow up in asymptomatic patients ▪ diagnosis of suspected recurrence ▪ recurrence ▪ impact on management ▪ impact of clinical outcomes
Inclusion criteria	P patients with malignant lymphoma I FDG-PET C erythrocyte sedimentation rate (ESR), Ga scanning, CT R follow up O diagnostic accuracy S prospective, at least 12 (primary studies) or 6 (treatment response planning) patients
Years covered by the search	2000-2005
Study selection data abstraction, quality assessment performed by two authors independently	yes
Comprehensive bibliographic search: at least two databases searched	yes
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	yes
Searched also unpublished studies	no
Language restriction	yes (only studies in English, French, German, Spanish or Italian)
Overall number of references retrieved and n of included studies reported	yes
n. and references of excluded studies reported, reason given	no
Characteristics of included studies clearly reported in tables	yes
Methodological quality of primary studies assessed; criteria reported	no

Results of quality assessment used to formulate results and conclusions	yes
Meta-analysis performed with appropriate statistic methods	no, only narrative results
Publication bias assessed	no
N. of included studies study design	total 8 5 to predict prognosis, of which 2 and 1 on HL and NHL patients only, respectively and 2 on a mixed population of patients 3 studies on the investigation of residual mass (2 on HL patients and 1 on a mixed population of patients) unclear
N. of included patients	total: 339 208 with HL (median: 32, range: 16-43) to investigate residual mass: 65 with HL (median: 32.5, range: 29-36) 58 with HL or NHL
Reference standard	follow up
Comparator	Ga scanning, erythrocyte sedimentation rate (ESR), CT
Performance results	narrative results only: PET shows similar sensitivity to CT but a better specificity
Impact on management	not assessed
Impact on clinical outcome	not assessed
Recommendations and conclusions	Five new PSs showed that PET was a better predictor of relapse after therapy than CT. There is no evidence that this information has been used to inform subsequent treatment. There is evidence (one SR reviewing eight PSs of PET, and three additional PSs) that post-therapy PET had similar sensitivity and better specificity than Ga scanning and CT scanning to evaluate residual masses. An economic evaluation in advanced HL showed that PET was highly cost-effective (£ 5 000 per life-year) and predicted large savings in unnecessary consolidation RT when used instead of CT, or after CT-positive scans.
Notes	

Author, year	**Kirby 2007**
Technology	FDG-PET
Disease	Hodgkin's disease and non-Hodgkin's lymphoma
Objective	to assess: ▪ primary diagnosis ▪ staging (before treatment) ▪ response to treatment (during treatment) ▪ **X** response to treatment (end of treatment) ▪ follow up in asymptomatic patients ▪ diagnosis of suspected recurrence ▪ recurrence ▪ impact on management ▪ impact of clinical outcomes
Inclusion criteria	P patients with Hodgkin's disease or non-Hodgkin's lymphoma I FDG-PET C: CT, conventional imaging studies (CIS) R histology, follow up, other imaging techniques O diagnostic accuracy (sensitivity, specificity, PPV, NPV) S retrospective or prospective studies, evaluating post-treatment patients
Years covered by the search	January 1997 to July 2005
Study selection data abstraction, quality assessment performed by two authors independently	unclear
Comprehensive bibliographic search: at least two databases searched	yes
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 studies)
Overall number of references retrieved and n of included studies reported	no
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	unclear; no

Results of quality assessment used to formulate results and conclusions	yes
Meta-analysis performed with appropriate statistic methods	no
Publication bias assessed	no
N. of included studies study design	total: 26 9/26 only including HL patients; 13/26 including HL and NHL patients as well; 4/26 only on NHL patients unclear
N. of included patients	360 with HL (median: 36, range: 26-63) 270 with NHL (median: 66; range: 45-93) 650 with HL or NHL (median: 40; range: 19-101)
Reference standard	unclear
Comparator	CT, conventional imaging studies
Performance results	FDG-PET, studies on HL patients only (9/26 studies) sensitivity: median 95% (50-100%) specificity: median 86% (78-100%) NPV: 96% (84-100%) PPV: 77 (60-100%) median PFS in PET positive pts: 14% (0-40%) (median follow up: 6-31 months) median PFS in PET negative pts: 93% (91-100%) (median follow up: 6-31 months) FDG-PET, studies on a mixed population (13/26 studies) sensitivity: median 86% (43-100%) specificity: median 95% (73-100%) NPV: 93% (83-100%) PPV: 88% (56-100%) accuracy: 91% (80-97%) median PFS at 1-3 years in PET positive pts: 11% (0-31%) median PFS at 1-3 years in PET negative pts: 91% (81-100%)
Impact on management	not assessed
Impact on clinical outcome	not assessed
Recommendations and conclusions	none
Notes	

Author, year	**Kwee 2008**
Technology	FDG-PET or FDG-PET/CT
Disease	malignant lymphoma
Objective	to assess: ▪ primary diagnosis ▪ staging (before treatment) ▪ response to treatment (during treatment) ▪ **X** restaging (after treatment) (residual disease) ▪ follow up in asymptomatic patients ▪ diagnosis of suspected recurrence ▪ recurrence ▪ impact on management ▪ impact of clinical outcomes
Inclusion criteria	P patients with malignant lymphoma I FDG-PET or FDG-PET/CT (CT and WB-MRI) C other imaging techniques R pathology confirmation or follow up of at least 6 months O diagnostic accuracy S comparative trials, at least 6-month follow up, giving separate results for staging and restaging; excluded studies investigating only bone marrow involvement, with a number of patients <10, not providing absolute numbers of diagnostic performances (necessary to provide confidence intervals)
Years covered by the search	until 25th July 2007
Study selection data abstraction, quality assessment performed by two authors independently	yes
Comprehensive bibliographic search: at least two databases searched	yes
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	unclear
Searched also unpublished studies	no
Language restriction	yes (only English, German, French studies)
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
Results of quality assessment used to formulate results and conclusions	yes
Meta-analysis performed with appropriate statistic methods	not possible due to different scoring systems used
Publication bias assessed	no
N. of included studies study design	total of 19 (4/19 prospective) 7 on HL patients, 10 on a mixed population, 2 on NHL patients 3 investigating CT, 17 investigating FDG-PET, 4 investigating FDG-PET/CT 4/19 prospective
N. of included patients	259 with HL (median: 32, range: 23-66) 123 with NHL (median 61.5; range: 45-78) 556 with HL or NHL (median: 45.5; range: 18-101)
Reference standard	histology or follow up ≥6 months
Comparator	not specified
Performance results	FDG-PET <u>HL patients (9 studies)</u> sensitivity: 86.2-100% specificity: 57.1-100% <u>Mixed population (6 studies)</u> sensitivity: 71.4-100% specificity: 86.2-100% FDG-PET/CT fusion <u>HL patients (1 study)</u> sensitivity: 100% (87.5-100%) specificity: 90.7% (78.4-96.3%) <u>HL or NHL patients</u> sensitivity: 92.9-94.7% specificity: 90.6-100% CT <u>HL patients (1 study)</u> only data on lesions <u>Mixed population (2 studies)</u> sensitivity: 25-100% specificity: 41.7-58.8%
Impact on management	not assessed
Impact on clinical outcome	not assessed

Recommendations and conclusions	In conclusion, the studies included in this systematic review were of moderate methodological quality and used different scoring systems to stage malignant lymphoma. CT remains the standard imaging modality for initial staging of malignant lymphoma, while FDG-PET has an essential role in restaging. Early results suggest that FDG-PET/CT fusion outperforms both CT alone and FDG-PET alone. Data on the diagnostic performance of WB-MRI are lacking. Future well-designed studies, expressing their results according to the Ann Arbor staging system, are needed to determine which imaging modality is most accurate and cost-effective in staging malignant lymphoma.
Notes	

Author, year	**Terasawa 2008**
Technology	FDG-PET
Disease	HL and aggressive NHL
Objective	to assess: ▪ primary diagnosis ▪ staging (before treatment) ▪ response to treatment (during treatment) ▪ **X** response to treatment (end of treatment)/restaging (residual disease) ▪ follow up in asymptomatic patients ▪ diagnosis of suspected recurrence ▪ recurrence ▪ impact on management ▪ impact of clinical outcomes
Inclusion criteria	P patients with Hodgkin's lymphoma or aggressive NHL I FDG-PET C other imaging techniques (CT, MRI, ultrasonography) R histological confirmation and/or follow up O diagnostic accuracy S on at least 10 patients that completed first-line chemotherapy or radiotherapy or chemo-radiotherapy followed by clinical follow up with or without pathological confirmation, with data available on individual patients (units of analysis instead of lesions/organs)
Years covered by the search	from January 1966 to July 2006
Study selection, data abstraction, quality assessment performed by two authors independently	unclear
Comprehensive bibliographic search: at least two databases searched	yes
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	yes
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; yes
Results of quality assessment used to formulate results and conclusions	yes
Meta-analysis performed with appropriate statistic methods	meta-analysis not performed: too few data points to reliably estimate the summary ROC curves and confidence regions for summary sensitivity and specificity
Publication bias assessed	yes
N. of included studies study design	total 19 (10 on HL patients only, 6 on HL and aggressive NHL as well, 3 on aggressive NHL only) 14/19 retrospective; only 1 assessing FDG-PET/CT accuracy; age: 2-85; median time from therapy completion to PET: 1-5.2 months; median follow up: 9.3-62 months
N. of included patients	474 with HL (median: 31; range: 5-71) 254 with NHL (median: 29.5; range: 5-73)
Reference standard	clinical follow up with or without histological confirmation
Comparator	none indicated
Performance results	FDG-PET, HL patients, post-therapy evaluation sensitivity: 50-100% specificity: 67-100% FDG-PET, HL patients, evaluation of residual masses at conventional imaging sensitivity: 43-100% specificity: 67-100% the area under the curve for the summary ROC curve was 0.94 for post-therapy evaluations and 0.93 for residual mass evaluations, and the Q* statistic was 0.88 for post-therapy evaluations and 0.86 for residual mass evaluations
Impact on management	not assessed
Impact on clinical outcome	not assessed
Recommendations and conclusions	The currently available data show that 18F-FDG-PET has good overall accuracy in detecting residual disease in patients with HD who have completed first-line therapy. The current literature has methodological weaknesses that may overestimate accuracy. Because data from original studies are limited, our review could not find robust evidence to answer the question of whether clinicians should routinely use PET to assess the post-therapeutic response, suggesting that they should be cautious about making clinical decisions based solely on a PET result.
Notes	

Author, year	**Zijlstra 2006**
Technology	FDG-PET
Disease	Hodgkin's disease and (aggressive) non-Hodgkin's lymphoma
Objective	to assess: ▪ primary diagnosis ▪ staging (before treatment) ▪ response to treatment (during treatment) ▪ **X** response to treatment (end of treatment) ▪ follow up in asymptomatic patients ▪ diagnosis of suspected recurrence ▪ recurrence ▪ impact on management ▪ impact of clinical outcomes
Inclusion criteria	P histologically proven Hodgkin's disease and (aggressive) non-Hodgkin's lymphoma I dedicated FDG-PET C not specified R histology or follow up of at least 12 months O diagnostic accuracy (sensitivity, specificity, PPV, NPV) S retrospective or prospective studies of at least 10 patients in which evaluation of post-treatment patients following first-line therapy
Years covered by the search	until January 2004
Study selection data abstraction, quality assessment performed by two authors independently	yes
Comprehensive bibliographic search: at least two databases searched	yes
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	only reference list of retrieved articles
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; yes ("The studies included were of moderate methodological quality, with a 40% score for internal validity, and a 64% score for external validity)
Results of quality assessment used to formulate results and conclusions	yes
Meta-analysis performed with appropriate statistic methods	yes
Publication bias assessed	no
N. of included studies study design	15, 5/15 only including HL patients, 8/15 including HL as well NHL patients; 2/15 only on NHL prospective (6/15), retrospective (9/15); consecutive enrolment in 2/15 studies prospective + retrospective (1/15)
N. of included patients	202 with HL (median: 37, range: 26-60) 138 with NHL (median: 69; range: 45-93) 418 with HL or NHL (median: 52; range: 32-88)
Reference standard	histology (only for a minority of patients), radiology and follow up (median >18 months)
Comparatorr	
Performance results	FDG-PET HL patients sensitivity: 84% (95% CI 71-92%) specificity: 90% (95% CI 84-94%) LR-: 0.26 (95% CI 0.12-0.58) LR+: 5.6 (95% CI 3.46-9.13) NHL sensitivity: 72% (95% CI 61-82%) specificity: 100% (95% CI 94-100%)
Impact on management	not assessed
Impact on clinical outcome	Impossible to assess due to the "variability of the applied endpoints (overall survival, progression-free survival, relapse-free survival, disease-free survival) […] and the lack of specified data for Hodgkin's and non-Hodgkin's lymphoma as separate entities. There was no apparent inverse relation between sensitivity and specificity for either HD or NHL (Spearman -0.4 and -0.3, respectively)."

Recommendations and conclusions	The presently available evidence on the diagnostic performance of FDG-PET in evaluating the response to first-line therapy for HD and NHL is useful. Standardization of procedures is required before implementation in clinical practice. FDG-PET appears to be the most helpful non invasive modality for differentiating tumor recurrence from fibrosis when CT scanning shows a residual mass. If abnormal FDG uptake is seen, further investigation is mandatory. In the case of a negative PET-scan, no further investigations at that particular time point are necessary, but minimal residual disease and the risk of a late relapse cannot be completely excluded.

Synoptic table of primary studies on end of treatment evaluation of response to therapy in patients treated for Hodgkin's lymphoma

Author, year	Disease	Patient number	Tech-nology	Reference test	FDG-PET sensitivity	FDG-PET specificity	FDG-PET PPV	FDG-PET NPV	FDG-PET accuracy	Comparator	Comp. sensit.	Comp. specif.	Comp. PPV	Comp. NPV	Comp. accur.
Altamirano 2008	HL or NHL	28 (7 HL, 21 aggr NHL)	FDG-PET	follow up (median 18 months, range: 6-24 months)	100%	95%				CT	83%	63%			
Boisson 2007	HL	25	FDG-PET/CT	follow up (median: CT: 7+4, FDG-PET/CT: 6.7+4.2)	80%	100%	100%	95%	96%	CT	80%	55%	45%	86%	63%
Bucerius 2006	HL or NHL	79 (30 HL, 49 aggr NHL)	FDG-PET	histopathology and/or follow up	69%	90%				CT	91%	38%			
Cerci 2010b	HL	50	FDG-PET	PET+: histology PET -: follow up (mean 34± 12 months)	100%	92%	93%	100%	96%	CT	87%	74%			

Author, year	Disease	Patient number	Tech-nology	Reference test	FDG-PET sensitivity	FDG-PET specificity	FDG-PET PPV	FDG-PET NPV	FDG-PET accuracy	Comparator	Comp. sensit.	Comp. specif.	Comp. PPV	Comp. NPV	Comp. accur.
Furth 2009	HL (pediatric)	29	FDG-PET	follow up (mean 42 months)	100%	78%	25%	100%	79%	conventional imaging methods (CT, MRI, US)	50%	11%	4%	75%	14%
Mocikova 2010	HL	113	FDG-PET or FDG-PET/CT	PET+: biopsy PET -: follow up (mean 34± 12 months)	36%	86%	26%	90%	79%	CT	64%	52%	16%	9120%	53%
Molnar 2010	HL	128	FDG-PET	PET+: histology or clinical signs PET-: follow up (mean 75,5 months)	83%	89%	74%	93%	88%						
Riad 2010	HL or NHL	51 (45 HL, 6 aggr NHL)	FDG-PET/CT	histopathology and/or follow up	100%	98%				conventional imaging methods (CT, MRI, US)	83%	67%			
Talavera Rubio 2009	HL or NHL	29	FDG-PET/CT	biopsy (2 pts), or clinical FU (mean: 14,5 months)	96%	98%				contrast-enhanced CT	95%	95%			

Primary studies

Author, year	Altamirano 2008
Country	Mexico
Technology	18F-FDG-PET
Disease	Hodgkin's lymphoma and non-Hodgkin's lymphoma
Objective	to determine the diagnostic accuracy of 18FDG after three cycles and at the end of chemotherapy in non-Hodgkin's lymphoma (NHL) or Hodgkin's lymphoma (HL)
Patients characteristics	40 patients but only 28 patients where studied 15 patients were female (53.6%) and 13 were male (46.4%) with a mean age of 43 years (range: 15-74 years) 7 patients corresponded to HL diagnosis (25%) and 21 to NHL (75%)
Index test	18F-FDG-PET
Comparator	CT
Reference standard	follow up (median 18 months, range: 6-24 months; Guidelines established by the International response evaluation criteria in solid tumors Group (RECIST)
Outcomes considered	sensitivity, specificity, diagnostic accuracy, PPV, NPV
Study design	prospective cross-sectional study
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not clear
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	no
Independent and blind interpretation of index test and reference standard results	yes

Withdrawals from the study explained	not applicable
Pre-test probability	
Results	18F-FDG-PET sensitivity: 100% specificity: 95% accuracy:96% PPV:90% NPV:100% CT sensitivity: 83% specificity: 63% accuracy: 68% PPV: 41% NPV: 92%
Authors' recommendations and conclusions	18FDG had greater prognostic values than CT after the third and last cycle of chemotherapy. PET after three cycles of chemotherapy is predictive of 18-month outcome in patients with intermediate and aggressive NHL and HL and may help in the identification of patients who would benefit from more intensive treatment or from a change in chemotherapy.

Author, year	**Boisson 2007**
Technology	FDG-PET/CT
Disease	Hodgkin's lymphoma
Objective	io evaluate the standardized uptake value (SUV) according to different parameters of HL and to evaluate the impact of PET on the initial staging and on the follow uo at the Centre of Nuclear Medicine Jean-Perrin
Patients characteristics	25 patients with histologically confirmed Hodgkin's lymphoma
Index test	FDG-PET/CT
Comparator	CT
Reference standard	follow up (median: CT: 7±4, FDG-PET/CT: 6.7+4.2)
Country	France
Outcomes considered	diagnostic accuracy
Study design	retrospective study
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	yes
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	yes
Withdrawals from the study explained	yes
Pre-test probability	not applicable

Results	FDG-PET/CT (response to treatment) sensitivity: 80% specificity: 100% PPV: 100% NPV: 95% diagnostic accuracy: 96% CT (response to treatment) sensitivity: 80% specificity: 54.5% PPV: 44.5% NPV: 85.5% diagnostic accuracy: 62.5%
Authors' recommendations and conclusions	Indications of PET in lymphoma tourned out to be quite broad. We discovered that the maximum SUV was significantly higher for mixed cellularity HL than nodular sclerosis HL. Our study confirms the utility of PET in the assessment and follow uo of HL. Thanks to its excellent performance it will allow a personalised adaptation of therapeutic management of patients even if some aspects regarding the execution of the test are still to be defined.
Notes	

Author, year	**Bucerius 2006**
Country	Germany
Technology	FDG-PET
Disease	Hodgkin's lymphoma and non-Hodgkin's lymphoma
Objective	to compare the performance of FDG-PET and conventional imaging (CI) at three different time points during the course of the disease including diagnosis of recurrence
Patients characteristics	169 patients (59 female, 110 male: aged 45.9±4,8 years; range 15-80 years) with histologically proven HD (69-41%) or NHL (100-59%); staging at baseline (42 patients), monitoring response to treatment (79 patients), diagnosis of recurrence (48 patients)
Index test	FDG-PET
Comparator	CT
Reference standard	histological examination and/or clinical follow up
Outcomes considered	sensitivity, specificity, diagnostic accuracy, PPV, NPV
Study design	retrospective cross-sectional study
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	yes
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	no
Execution of the reference standard described	no
Independent and blind interpretation of index test and reference standard results	yes
Withdrawals from the study explained	not applicable
Pre-test probability	

Results	FDG-PET sensitivity: 69% specificity: 90% accuracy: 83% PPV: 77% NPV: 85% CT sensitivity: 91% specificity: 38% accuracy: 55% PPV: 42% NPV: 90%
Authors' recommendations and conclusions	FDG-PET appears to be superior to CI for monitoring response to treatment.

Author, year	**Cerci 2010b**
Technology	FDG-PET (in add-on to CT in patients with CRu at CT)
Disease	newly diagnosed HL
Objective	to assess the cost/effectiveness of fluorine-18-fluorodeoxyglucose positron emission tomography (FDG-PET) in patients with Hodgkin's lymphoma (HL) with unconfirmed complete remission (CRu) or partial remission (PR) after first-line treatment
Patients characteristics	50 patients being in unconfirmed complete response (CRu) or partial response (PR) at conventional imaging after first-line chemotherapy (4-8 cycles according to stage) followed or not by consolidation radiotherapy (after 4 cycles of chemotherapy for stage I-II or in case of bulky disease regardless of clinical stage)
Index test	FDG-PET (after at least 1 month at completion of chemotherapy or at least 3 months after radiotherapy)
Comparator	
Reference standard	histology in PET-positive patients and follow up in PET-negative patients
Country	Brazil
Outcomes considered	diagnostic accuracy
Study design	prospective cross-sectional study
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	yes
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	no (histology for PET-positive and follow up for PET-negative patients)
Execution of the reference standard described	yes

Independent and blind interpretation of index test and reference standard results	unclear
Withdrawals from the study explained	yes
Pre-test probability	of residual disease: 25/50 (50%) of patients with Cru/PR after fist-line treatment
Results	**FDG-PET**, diagnostic accuracy **in add-on** on patients with Cru/PR at conventional imaging sensitivity: 100% specificity: 92% PPV: 92.3% NPV: 100% accuracy: 95.9% **CT**, diagnostic accuracy, **in all patients** (CR/Cru/PR) after first-line treatment sensitivity: 87% specificity: 73.6% PPV: 51.9% NPV: 94.5% accuracy: 77.7%
Authors' recommendations and conclusions	The results of our study indicate that FDG-PET has a high negative predictive value. PET has been able to confirm all patients with absence of HL after first-line therapy. However, FDG-avid lesions need biopsy confirmation because false-positive results may occur in 4% of patients, usually as a result of comorbid inflammatory/infectious diseases. Optimal stratification of post-therapy response should include FDG-PET combined with pathology assessment. For patients with HL presenting in CRu/PR with suspicious residual masses after first-line therapy, restaging FDG-PET is highly cost effective, providing 19% cost savings to the local restaging program and 1% cost savings to the total public HL health care program.
Notes	

Author, year	**Furth 2009**
Technology	FDG-PET (as replacement test)
Disease	advanced-stage Hodgkin's lymphoma (pediatric)
Objective	to deliver prospective data on the potential of FDG-PET for response assessment in paediatric HL early and late response assessment by FDG-PET was performed in order to identify the optimal time point for reliable response assessment. In addition, mere visual and quantitative analysis of FDG-PET were compared with regard to identification of patients with an increased risk for relapse
Patients characteristics	29 paediatric patients with advanced-stage histologically confirmed HD undergoing chemotherapy (from 4 to 6 cycles according to the risk group)
Index test	FDG-PET (14-17 days after completion of chemotherapy)
Comparator	CIM (conventional imaging methods, i.e. CT, MRI, ultrasound)
Reference standard	follow up (mean 46 months) and all imaging information (biopsy only in case of suspicion of relapse)
Country	Germany
Outcomes considered	diagnostic accuracy
Study design	multicentre prospective study, consecutive enrollment
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	yes
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes

Independent and blind interpretation of index test and reference standard results	yes
Withdrawals from the study explained	yes
Pre-test probability	2/40 (5%)
Results	**FDG-PET** (detection of residual disease) sensitivity: 100% specificity: 78% PPV: 25% NPV: 100% accuracy: 79% **CIMs** (detection of residual disease) sensitivity: 50% specificity: 11% PPV: 4% NPV: 75% accuracy: 14%
Authors' recommendations and conclusions	In conclusion, early and late therapy response assessment by FDG-PET helps to identify pediatric HL patients with an excellent prognosis, which might benefit from de-escalation of antineoplastic therapy. If omission of radiotherapy without reduction of cure rates is possible in these patients is part of the investigations within the current European therapy optimization study.
Notes	

Author, year	**Mocikova 2010**
Technology	FDG-PET or FDG-PET/CT
Disease	HL
Objective	to analyze routine use of PET after therapy, during the follow up and in suspected relapse outside the clinical trial
Patients characteristics	113 HL patients (median age: 32, 17-78) after first-line treatment and during follow up since 1999 till 2008. Median follow up of the group since the end of therapy was 34 (range 3-109) months
Index test	FDG-PET or FDG-PET/CT after chemotherapy (median: 17 days, range: 7-26) or radiotherapy (median: 41 days, range: 24-287)
Comparator	CT
Reference standard	follow up, histology
Country	Czech Republic
Outcomes considered	diagnostic accuracy
Study design	retrospective
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	no
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	unclear
Withdrawals from the study explained	yes
Pre-test probability	of relapse: 14/113 (12.4%) patients

Results	Diagnostic accuracy FDG-PET or FDG-PET/CT PPV: 26% NPV: 90.4% CT PPV: 16% NPV: 91.2%
Authors' recommendations and conclusions	Our analysis showed that there is no need for regular follow up with CT and PET examinations in PET-negative patients at the end of therapy with low ratio of true-positive PET scans (3.9%). Positive PET at the end of therapy and during follow up should be evaluated with caution. Based on our experience, PET should be carried out during the follow up in clinically suspected relapse: negative PET scan can exclude tumor, none of our PET-negative patients relapsed, and in all cases of tumor, PET was positive.
Notes	

Author, year	**Molnar 2010**
Technology	FDG-PET
Disease	HL
Objective	to assess the value of FDG-PET for prediction of remission of relapse in HL in a rather large cohort of patients after a long follow up
Patients characteristics	128 HL patients
Index test	FDG-PET
Comparator	
Reference standard	PET positive: clinical examination/biopsy PET negative: follow up (mean: 75.5 months; range: 20-156)
Country	Hungary
Outcomes considered	diagnostic accuracy
Study design	retrospective consecutive cohort
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	yes
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	unclear
Withdrawals from the study explained	yes
Pre-test probability	of relapse: 35/128 (27.3%) of patients

Results	Diagnostic accuracy **FDG-PET** sensitivity: 82.9% specificity: 89.2% PPV: 74.4% NPV: 93.3% accuracy: 87.5%
Authors' recommendations and conclusions	PET examinations help to plan individual, risk-adopted treatment modalities, which improves both the curability and he long-term quality of life in young people with Hodgkin's lymphoma.
Notes	

Author, year	**Riad 2010**
Country	Egypt
Technology	18F-FDG-PET/CT
Disease	Hodgkin's lymphoma and non-Hodgkin's lymphoma
Objective	to evaluate the performance of 18F-FDG-PET/CT and to compare diagnostic accuracy of 18F-FDG-PET/CT with conventional imaging modalities(CIM) in the evaluation of early treatment response in Hodgkin's and non-Hodgkin's lymphoma
Patients characteristics	152 total patients (35 females and 117 males) with histologically proven malignant lymphoma 8 117 HD, 35, NHL) range age 3-18 years they were divided into four groups: Group I: 41 patients for initial staging Group II: 51 patients (45 HD, 6 NHL) for evaluating early treatment response after 2 to 3 cycles of chemotherapy. Five patients were stage I, 20 were stage II, 18 were stage III and 8 were stage IV Group III: 42 patients for evaluating treatment response 4-8 weeks after the end of their treatment Group IV: 18 patients evaluated for long-term follow up
Index test	18F-FDG-PET
Comparator	conventional imaging modalities (CIM - CT, MRI, US, physical examination, bone marrow biopsy when available)
Reference standard	histopathological exam and clinical follow up
Outcomes considered	sensitivity, specificity, diagnostic accuracy, PPV, NPV
Study design	retrospective cross-sectional study
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 clear
Execution of the index and comparator tests adequately described	yes

Did patients receive the same reference standard regardless of the index test result	no
Execution of the reference standard described	no
Independent and blind interpretation of index test and reference standard results	not clear
Withdrawals from the study explained	not applicable
Pre-test probability	
Results	18F-FDG-PET/CT sensitivity: 100% specificity: 90.9% accuracy: 92.8% PPV: 75% NPV: 100% CIM sensitivity: 55.5% specificity: 57.5% accuracy: 57.1% PPV: 26.3% NPV: 82.6%
Authors' recommendations and conclusions	PET/CT in paediatric lymphoma is more accurate than CIM. We recommend that it should be the first modality for all purposes in initial staging, evaluating treatment response and follow up

Author, year	**Talavera Rubio 2009**
Country	Spain
Technology	18F-FDG-PET/CT
Disease	Hodgkin's lymphoma and non-Hodgkin's lymphoma
Objective	to define the utility of intravenous contrast administration in the PET-CT (PET-CTc) in patients with lymphoma in order to determine its possible indications
Patients characteristics	142 patients with malignant lymphoma but only those with a final diagnosis established (78, 47 males and 31) were included 15 patients were female (53.6%) and 13 were male (46.4%) with a mean age of 43 years (range: 15-74 years) 7 patients corresponded to HL diagnosis (25%) and 21 to NHL (75%)
Index test	18F-FDG-PET
Comparator	CT
Reference standard	clinical and radiological follow up: every 6 months median follow up: 18 months (range 6-24 months)
Outcomes considered	sensitivity, specificity, diagnostic accuracy, PPV, NPV
Study design	prospective cross-sectional study
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not clear
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	no
Independent and blind interpretation of index test and reference standard results	not clear

Withdrawals from the study explained	not applicable
Pre-test probability	
Results	18F-FDG-PET/CT sensitivity: 100% specificity: 95% accuracy: 96% PPV: 90% NPV: 100% CT sensitivity: 83% specificity: 63% accuracy: 68% PPV: 41% NPV: 92%
Authors' recommendations and conclusions	18FDG had greater prognostic values than CT after the third and last cycle of chemotherapy. PET after three cycles of chemotherapy is predictive of 18-month outcome in patients with intermediate and aggressive NHL and HL and may help in the identification of patients who would benefit from more intensive treatment or from a change in chemotherapy.

CHAPTER 8
Follow up of patients treated for Hodgkin's lymphoma, with no suspicion of recurrence

Diagnostic accuracy

Systematic reviews

Author, year	**Kirby 2007**
Technology	FDG-PET
Disease	NHL + HL
Objective	to assess: ▪ primary diagnosis ▪ staging (before treatment) ▪ response to treatment (during treatment) ▪ restaging (after treatment) (residual disease) ▪ **X** follow up in asymptomatic patients ▪ diagnosis of suspected recurrence ▪ recurrence ▪ impact on management ▪ impact of clinical outcomes
Inclusion criteria	P patients with malignant lymphoma I FDG-PET C CT R not specified O diagnostic accuracy, change in management S case reports were excluded where more substantial series exist. Studies using gamma camera PET scanners were also excluded
Years covered by the search	January 1997 - September 2005
Study selection, data extraction, quality assessment performed by two authors independently	unknown
Comprehensive bibliographic search: at least two databases searched	yes, PubMed and Medline
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	partly: hand search on reference list of retrieved studies was performed

Searched also unpublished studies Language restriction	no English
Overall number of references retrieved and n of included studies reported	no
N. and references of excluded studies reported, reason given	no
Characteristics of included studies clearly reported in tables	not applicable
Methodological quality of primary studies assessed; criteria reported	yes
Results of quality assessment used to formulate results and conclusions	yes
Meta-analysis performed with appropriate statistic methods	not applicable
Publication bias assessed	not applicable
N. of included studies study design	1; 4 not reported
N. of included patients	21; 36+16+NR+15
Reference standard	none
Comparator	CT
Performance results	Dittman et al. (The only study that clearly delineates between early post-treatment assessment of a residual mass, and late assessment of patients clinically suspected to have relapsed): ▪ 21 cases were imaged using CT and PET scanning at a median of 760 days (61-2 797) post-treatment ▪ a suspected relapse of Hodgkin's lymphoma was correctly diagnosed by CT and by PET imaging in 18 cases (86%) ▪ in 3 patients (14%), both CT and PET imaging resulted in a false positive finding ▪ in 1 patient, histology showed chronic lymphadenitis ▪ in 2 others, clinical follow up found them to be progression-free at 29 and 33 months (both of these patients declined biopsy) ▪ sensitivity of both CT and PET in the diagnosis of relapse was 100%, and PPV was 85.7% ▪ the quantification of FDG uptake did not improve the accuracy of PET for the diagnosis of relapse *(continues)*

Jerusalem et al.
(investigated 36 patients with histologically verified Hodgkin's lymphoma with PET scanning performed prospectively at 1 month after the end of treatment and then every 4-6 months for 2-3 years after the completion of therapy. A confirmatory scan was performed 4-6 weeks later in any patient with abnormal FDG uptake):

- CT imaging at the end of treatment showed 17 patients to be in CR:
  - 11 of these had a negative FDG-PET scan, none of whom relapsed
  - 6 had a positive PET scan of whom 50% relapsed
- 19 patients had residual masses on CT at the end of treatment:
  - 14 of these had a negative PET scan and have not relapsed
  - 5 had a positive PET scan, of whom two relapsed
- in total, 11 patients had a positive PET scan at some point after completion of primary therapy:
  - only 5 were confirmed to have relapsed
  - the 6 left (55%) with falsely positive PET scans but in each case the confirmatory PET scan was negative
  - all 5 relapses were correctly identified by PET before clinical symptoms or signs, laboratory results or CT imaging suggested relapse. Confirmation of relapsed disease was obtained by biopsy in four patients at a median of 4 months (range, 1-9) after PET scanning, and by unequivocal clinical symptoms and CT in the remaining patient 3 months after PET
- these data suggest a role for PET in detecting preclinical relapse, enabling patients to receive salvage chemotherapy with minimal disease rather than overt relapse. However, despite the high positive predictive value, histological or other evidence of disease recurrence should be sought prior to commencement of salvage chemotherapy because of the high rate of false positives. It remains to be determined how detecting preclinical relapse ultimately impacts upon treatment and outcome.

(continues)

	Castellucci et al. (evaluated the significance of increased uptake of FDG on PET scans performed in lymphoma patients at completion of therapy, suspected recurrence or during follow up. Overall, 354 scans were reported as showing increased uptake (244 in NHL patients and 110 in HL patients). Minimum follow up was 8 months (median 10 months, and range 8-14 months): ▪ in 286 cases, uptake was reported to be indicative of malignant lymphoma: - on clinical follow up, 274 (96%) of these were found to be true positives - thus, the false positive rate was 4%. ▪ malignant lymphoma was excluded in all patients whose FDG uptake was reported to be non-pathological; i.e. there were no false negatives Hart et al. (reported on the use of PET in guiding donor lymphocyte infusions post-allogeneic transplantation. At least one PET scan was performed in 15 patients at a median of 343 days post-transplantation): ▪ the first PET scan was informative in 11 out of 15 patients and influenced the administration of donor lymphocyte infusions in 9 of these (earlier administration in 2, earlier dose escalation in 1, withholding of DLI in 5 and dose reduction in 1) ▪ such data form the basis for further prospective study of the role of PET in these patients Van den Bossche et al. (level 3 study looking retrospectively at PET versus high-dose 67Ga scintigraphy for the follow up of lymphoma patients and comparing this with a "gold standard" of conventional imaging, bone marrow examination and clinical follow up - Sixteen patients were included (10 NHL and six HL) and there were 18 imaging episodes): ▪ in 11 episodes, the results obtained by both gallium and PET imaging were in agreement with the conventional staging in regard to the presence or absence of disease, although the abnormalities found on PET were always more extensive ▪ in 2 episodes, PET showed normalization of uptake over a longer period than gallium scanning ▪ in 4 episodes, gallium scanning was negative whilst PET visualized non-tumour-related pathology (including lung infection, rib fracture and dense thymic tissue)

Impact on management	no
Impact on clinical outcome	no
Recommendations and conclusions	none
Notes	

Synoptic table of primary studies on follow up of asymptomatic patients treated for Hodgkin's lymphoma

Author, year	Disease	N. of patients	Mean/ median age	Mean/ median follow up (months)	Range follow up	Pre-test probabil.	Index test	Reference test	Compar.	Sens index	Spec index	PPV index	NPV index	Sens* comp	Spec* comp	PPV* comp	NPV* comp
Crocchiolo 2009	HL	27	35	34	4-71	25.9%	FDG-PET/CT	PET/CT+: ceCT, MRI or BM biopsy PET/CT-: follow up	not specified	100%	75%	58%	100%	not specified	not specified	not specified	not specified
El-Galaly 2011	HL	101	36	33	2-91	4% (median)	FDG-PET/CT	PET/CT+: biopsy, repeated imaging or follow up PET/CT-: continuous follow up	not specified	100%	82%	not specified	not specified	not specified	not specified	not specified	not specified
Jerusalem 2003	HL	17	28	30	not specified	17.6%	FDG-PET	not specified	not specified	100%	79%	50%	100%	not specified	not specified	not specified	not specified
Meany 2007	HL	23	14.2	not specified	1-42	8.7%	FDG-PET	PET+: histological confirmation	CT*	100%	57%	18%	100%	100%	71%	25%	100%
Mocikova 2010	HL	67	32	34	not specified	9%	FDG-PET/CT	PET+: biopsy, follow up PET-: none	not specified	100%	80%	33%	100%	not specified	not specified	not specified	not specified
Zinzani 2007	HL	57	26	60	not specified	17.5%	FDG-PET	PET+: histological findings	not specified	100%	77%	48%	100%	not specified	not specified	not specified	not specified

* CT was always simultaneously performed with FDG-PET. Even that, CT studies' results were not discussed when FDG-PET were negative; so, to calculate CT performances, assumption on false negative (=0) have been done.

Primary studies

Author, year	Crocchiolo 2009
Technology	FDG-PET/CT
Disease	HL
Objective	to evaluate the role of 18FDG-PET/CT in identifying relapse during follow up of Hodgkin's lymphoma (HL) patients in complete remission after upfront or salvage treatment
Patients characteristics	27 consecutive patients (a total of 165 18FDG-PET/CT scans during the follow up period - median per patient 5, range 2-15): ▪ median age was 35 years old (range 17-83) ▪ median follow up duration was 34 months (range 4-71) ▪ HL was diagnosed at: - stage I in 1 patient (4%) - stage II in 12 (44%) - stage III in 9 (33%) - stage IV in 5 (19%) pts ▪ 20 patients were in: - first complete remission after ABVD chemotherapy - 6 patients were in second complete remission after HDS and ASCT - 1 patient received allogeneic stem cell transplantation - 9 patients received also consolidation radiotherapy
Index test	FDG-PET/CT
Comparator	
Reference standard	for PET/CT+: contrast-enhanced CT scans or magnetic resonance imaging (MRI) or bone marrow biopsy for PET/CT-: follow up
Country	Italy
Outcomes considered	recurrence
Study design	retrospective
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	no
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	no
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	no
Withdrawals from the study explained	unclear
Pre-test probability	25.92% (7/27)
Results	HL pts: 27, n. of PET scans: 165 rel/PET+: 7/13 PPV: 54% FP rate: 46% specificity: 70% sensitivity: 100% NPV: 100%
Authors' recommendations and conclusions	18FDG-PET/ CT represents a sensitive test during post-remission follow up of HL patients after completion of therapy Balancing overall costs and potential benefits, we would recommend: ▪ the performance of a routine PET/CT scan during follow up of those patients who are at high risk of relapse, especially in the first and second year after the end of treatment; ▪ however, due to the high rate of false positive findings, caution must be adopted when interpreting PET/CT results: - when at least two among multiple, subdiaphragmatic, and previously involved sites show abnormal FDG uptake, a confirmatory biopsy is suggested to start timely salvage therapy; - in the other cases, further follow up is advisable, always taking into account patient's medical history, symptoms, and other imaging information.
Notes	

Author, year	**El-Galaly 2011**
Technology	FDG-PET/CT
Disease	Hodgkin's lymphoma
Objective	the aim of this retrospective study was to investigate the value of PET/CT surveillance during the follow up of HL patients in first remission
Patients characteristics	161 patients with HL at first remission (median age: 36, 15-80), stage I-II: 50%, stage III-IV: 50%; first-line therapy: chemotherapy alone (48%), radiotherapy alone (3%), chemio + radiotherapy: 49
Index test	FDG-PET/CT
Comparator	
Reference standard	biopsy, clinical follow up (median: 33 months, range 2-91 months), repeated imaging TP biopsy-verified HL relapse FP FDG-PET positive but disproved by biopsy or repeated imaging TN continuous remission 2 months after negative FDG-PET FN relapse within 2 months after a negative FDG-PET
Country	Denmark
Outcomes considered	diagnostic accuracy for relapse in patients without (follow up) or with (recurrence) suspected relapse
Study design	retrospective study
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	yes
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	no (FDG-PET positive: biopsy, repeated imaging, clinical course; FDG-PET negative: clinical follow up)
Execution of the reference standard described	yes

Independent and blind interpretation of index test and reference standard results	not specified
Withdrawals from the study explained	not applicable
Pre-test probability	median 4% (0-10%)
Results	FDG-PET/CT sensitivity: 100% specificity: 82%
Authors' recommendations and conclusions	A negative PET/CT reliably rules out a relapse. The high false positive rate, however, is an important limitation and a confirmatory biopsy is mandatory for the diagnosis of a relapse. With no proven survival benefit for patients with a pre-clinically diagnosed relapse, the high costs and low positive predictive value make PET/CT unfit for routine surveillance of Hodgkin's lymphoma patients.

Author, year	**Jerusalem 2003**
Technology	FDG-PET
Disease	HL
Objective	to examine the value of whole-body positron emission tomography (PET) for the detection of preclinical relapse
Patients characteristics	n. of cases: 36 (17 patients in complete remission) median age (years): 28 (range 13-71) sex: male: 13 female: 23 disease status: initial presentation: 26 first relapse: 8 second relapse: 2 histology: nodular sclerosis: 31 mixed cellularity: 4 lymphocyte depletion: 1 Ann Arbor clinical stage: I: 6 II: 19 III: 6 IV: 5 B symptoms: yes: 10 no: 26 lactate dehydrogenase greater than normal: yes: 8 no: 28 treatment: chemotherapy alone: 25 chemotherapy and radiotherapy: 6 radiotherapy alone: 5
Index test	FDG-PET
Comparator	none
Reference standard	PET positive finding not confirmed by conventional staging procedures and/or biopsy undergone a confirmatory PET study 4-6 weeks later
Country	Belgium
Outcomes considered	data accuracy
Study design	prospective
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	yes
Execution of the index and comparator tests adequately described	yes (index)
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	unclear
Withdrawals from the study explained	no withdrawals
Pre-test probability	overall: 5/36 (13.9%); residual mass: 2/19 (10.5%); complete remission: 3/17 (17.6%)
Results	overall: TP: 5 FN: 0 FP: 6 TN: 26 residual mass: TP: 2 FN: 0 FP: 3 TN: 14 no residual mass: TP: 3 FN: 0 FP: 3 TN: 11

Authors' recommendations and conclusions	Our data suggest the potential of 18F-FDG-PET to detect preclinical relapse in patients with HD: this could help identify patients requiring salvage chemotherapy at the time of minimal disease rather than at the time of clinically overt relapse. Further studies are warranted to determine the impact of PET on treatment management and outcome: the aim of follow up procedures is not only to detect preclinical relapse but mainly to obtain better results by starting salvage treatment earlier. A cost-benefit analysis will also be necessary before 18F-FDG-PET can be used routinely in the follow up of patients with HD.
Notes	

Author, year	**Meany 2007**
Technology	FDG-PET/CT
Disease	HL
Objective	the primary objective: to determine the number of scans that gave true negative, true positive, false negative and false positive results in a pediatric HL patient population. secondary objectives: calculating the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV)
Patients characteristics	23 (of 25 consecutive patients) were eligible for review age: range 5-19, mean 14.2, median 15 gender: males: 10 (43.5%) females: 13 (56.5%) stages: IA (1 patient), IB (1 patient), IIA (7 patients), IIB (4 patients), IIIA (2 patients), IIIB (2 patients), IVA (3 patients), IVB (3 patients) histological classification: nodular sclerosis HL in 16 patients, mixed cellularity in 5 patients lymphocyte predominant in 2 patients (one lymphocyte rich classical HL and the other nodular lymphocyte predominant HL) treatment: chemotherapy and external beam radiation: 20 chemotherapy: 3
Index test	FDG-PET
Comparator	CT
Reference standard	positive PET: histological confirmation;
Country	USA
Outcomes considered	TP, TN, FP, FN, sensitivity, specificity, PPV and NPV
Study design	retrospective
Spectrum of patients representative of the individuals who will receive the test in practice	unclear
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	unclear
Execution of the index and comparator tests adequately described	unclear
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	no
Withdrawals from the study explained	yes
Pre-test probability	8.69% (2/23)
Results	FDG-PET TP: 2 TN: 12 FP: 9 FN: 0 sensitivity: 100% specificity: 57.1% PPV: 18.2% NPV: 100% CT TP: 2 TN: 15 FP: 6 FN: 0 sensitivity: 100% specificity: 71.4% PPV: 25.2% NPV: 100%
Authors' recommendations and conclusions	We do not recommend treatment decisions be based solely on PET scan results.
Notes	* CT was always simultaneously performed with FDG-PET. Even that, CT studies' results were not discussed when FDG-PET were negative; so, to calculate CT performances, assumptions on false negative (= 0) have been done

Author, year	**Mocikova 2010**
Technology	FDG-PET, FDG-PET/CT
Disease	HL
Objective	to analyze the clinical impact of routine PET examination during the follow up for relapse detection in PET-negative HL patients at the end of therapy
Patients characteristics	number of patients: 113 (follow up 94) gender: male/female 58/55 median age (years): 32; range: 17-78 histology: nodular sclerosis: 73 mixed cellularity: 30 lymphocyte depletion: 3 lymphocyte-predominant HL: 3 not defined: 4 Ann Arbor clinical stage: I: 7 II: 52 III: 27 IV: 27 first-line treatment: chemotherapy: 47 chemotherapy and radiotherapy: 65 radiotherapy: 1
Index test	FDG-PET, FDG-PET/CT
Comparator	
Reference standard	positive PET: conclusions required additional examinations in order to confirm or to exclude a tumor negative PET: no further examinations were carried out
Country	Czech Republic
Outcomes considered	diagnostic accuracy
Study design	retrospective
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	unclear
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	unclear

Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	no
Execution of the reference standard described	no
Independent and blind interpretation of index test and reference standard results	no
Withdrawals from the study explained	no withdrawals
Pre-test probability	overall: 11.7% (11/94); regular follow up: 8.95% (6/67); suspected relapse follow up: 18.51% (5/27).
Results	follow up (94 patients - 182 PET scans): regular follow up (67 patients - 155 PET scans): PET negative: 49 patients, 137 scans PET positive:18 patients, 18 scans - TP: 6 patients, 6 scans - FP: 12 patients, 12 scans suspected relapse follow up (27 patients - 27 PET scans): PET negative: 16 patients, 16s cans PET positive:11 patients, 11 scans - TP: 5 patients, 5 scans - FP: 6 patients, 6 scans
Authors' recommendations and conclusions	Our analysis showed that there is no need for regular follow up with PET scans in PET-negative patients at the end of therapy: the ratio of true-positive PET scans during the follow up is low (3.9%). Positive PET at the end of therapy and during follow up should be evaluated with caution.
Notes	

Author, year	**Zinzani 2007**	
Technology	FDG-PET	
Disease	mediastinal lymphoma	
Objective	to verify the reliability of positive PET scans of the mediastinum in following up patients with mediastinal lymphoma	
Patients characteristics		HD / aggressive NHL
	n. of patients	57 / 94
	age (years)	
	median	26 / 52
	range	16-42 / 28-65
	sex	
	male	30 / 54
	female	27 / 40
	histology	
	DLBCL	84
	PMLBCL	10
	stage	
	I-II	52 / 85
	III-IV	5 / 9
	bulky disease	25 / 52
Index test	FDG-PET	
Comparator		
Reference standard	histological findings	
Country	Italy	
Outcomes considered	diagnostic accuracy	
Study design	retrospective	
Spectrum of patients representative of the individuals who will receive the test in practice	unclear	
Patients selection criteria clearly described	yes	
Verification by reference standard of all subjects	yes	
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	yes	
Execution of the index and comparator tests adequately described	yes	

Did patients receive the same reference standard regardless of the index test result	yes (different biopsy technique based on index test results)
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	no
Withdrawals from the study explained	no withdrawals
Pre-test probability	HD: 17.54% (10/57); [all: 11.26% (17/151)]
Results	true positive PET/positive PET all (30 patients) 57% - 17/30 HD (21 patients) 47.62% - 10/21 calculated PET accuracy parameters for HD: sensitivity: 100% specificity: 77% PPV: 48% NPV: 100%
Authors' recommendations and conclusions	A positive PET scan of the mediastinum of a patient being followed up for a mediastinal lymphoma should not be considered sufficient for diagnostic purposes in view of its lack of discrimination. Histological confirmation can safely be carried out with various biopsy techniques, the choice of which should be made on the basis of the findings of the clinical and imaging studies of the individual case.
Notes	

CHAPTER 9
Staging of recurrence of patients treated for Hodgkin's lymphoma

Diagnostic accuracy

Systematic reviews

Author, year	Wu 2012
Technology	FDG-PET or FDG-PET/CT
Disease	malignant lymphoma
Objective	to assess: ▪ primary diagnosis ▪ **X** staging (before treatment) ▪ response to treatment (during treatment) ▪ restaging (after treatment) (residual disease) ▪ follow up in asymptomatic patients ▪ diagnosis of suspected recurrence ▪ recurrence ▪ impact on management ▪ impact of clinical outcomes
Inclusion criteria	P patients with malignant lymphoma I FDG-PET or FDG-PET/CT or MRI C not specified R histopathology and/or close clinical and imaging follow up of at least 6 months O diagnostic accuracy S articles of ten or more patients included, raw data available (excluded reviews, case reports, letters etc)
Years covered by the search	January 1995 - July 2010
Study selection data abstraction, quality assessment performed by two authors independently	yes
Comprehensive bibliographic search: at least two databases searched	yes
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	no
Searched also unpublished studies	no
Language restriction	yes (only studies in English and Chinese)

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
Results of quality assessment used to formulate results and conclusions	no
Meta-analysis performed with appropriate statistic methods	yes
Publication bias assessed	yes
N. of included studies study design	32 (5 on PET/CT, 20 on PET and 8 on MRI) retrospective (14/32), prospective (11/32), ND (7/32)
N. of included patients	1 845 with HL or NHL (median: 45.5, range: 11-194) 690 with HL (median: 30, range: 6-88)
Reference standard	histopathology and/or close clinical and imaging follow up of at least 6 months
Comparator	MRI
Performance results	bone marrow involvement detection PET/CT sensitivity: mean 91.6% (95% CI: 85.1-95.9) (highly heterogeneous, heterogeneity chi-squared = 45.63) specificity: mean 90.3% (95% CI: 85.9-93.7%) (heterogeneity chi-squared = 10.18) PET sensitivity: mean 81.5% (95% CI: 77.3-85.3%) (highly heterogeneous, heterogeneity chi-squared = 187.03) specificity: mean 87.3% (95% CI: 84.9-89.5%) (highly heterogeneous, heterogeneity chi-squared = 270.59) MRI sensitivity: mean 90.3% (95% CI: 82.4-95.5%) (heterogeneity chi-squared = 25.83) specificity: mean 75.9% (95% CI: 69.8-81.2%) (heterogeneity chi-squared = 21.12)
Impact on management	not assessed
Impact on clinical outcome	not assessed

Recommendations and conclusions	PET/CT was a highly sensitive and specific modality in diagnosing patients with bone marrow involvement in lymphoma, compared with MRI and PET alone, PET/CT can play much more important roles in staging of lymphoma.
Notes	

Synoptic table of studies on the staging of the recurrence in patients treated for Hodgkin's lymphoma

Author, year	Disease	N. of patients	Pre-test probability	Index test	Reference test	Comp	Sens index	Spec index	PPV index	NPV index	Sens* comp	Spec* comp	PPV* comp	NPV* comp
Bucerius 2006	HL or NHL	48		FDG-PET	histological examination and/or clinical follow up	CT	98%	75%	95%	86%	100%	88%	98&	100%
Dittmann 2001	HL	21	85.7% (18/21 patients with relapse)	FDG-PET	biopsy of the new or progressive mass or by follow up over at least 6 months	CT	100%	0%			100%	0%		
Pracchia 2007	HL	20	50%	FDG-PET	for FDG-PET+: positive scan and lesions confirmed by biopsy or clinical progression for FDG-PET-: negative scan and no evidence of clinical progression during follow up	none	90%	80%						

Primary studies

Author, year	Bucerius 2006
Country	Germany
Technology	FDG-PET
Disease	Hodgkin's lymphoma and non-Hodgkin's lymphoma
Objective	to compare the performance of FDG-PET and conventional imaging (CI) at three different time points during the course of the disease including diagnosis of recurrence
Patients characteristics	169 patients (59 female, 110 male: aged 45.9±14,8 years; range 15-80 years) with histologically proven HD (69) or NHL (100); staging at baseline (42 patients), monitoring response to treatment (79 patients), diagnosis of recurrence (48 patients)
Index test	FDG-PET
Comparator	CT
Reference standard	histological examination and/or clinical follow up
Outcomes considered	sensitivity, specificity, diagnostic accuracy, PPV, NPV
Study design	retrospective cross-sectional study
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	yes
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	no
Execution of the reference standard described	no
Independent and blind interpretation of index test and reference standard results	yes
Withdrawals from the study explained	not applicable
Pre-test probability	

Results	FDG-PET sensitivity: 98% specificity: 75% accuracy: 94% PPV: 95% NPV: 86% CT sensitivity: 100% specificity: 88% accuracy: 98% PPV: 98% NPV: 100%
Authors' recommendations and conclusions	The extent of disease could be more reliably assessed by FDG-PET than by CT for staging at baseline and monitoring response treatment but not for diagnosis of recurrence.

Author, year	**Dittmann 2001**
Technology	FDG-PET
Disease	Hodgkin's lymphoma
Objective	to investigate the role of FDG-PET in comparison to radiological criteria derived from CT-scans in the post-treatment evaluation of residual masses in patients with Hodgkin's disease and in cases of suspected recurrent disease during follow up
Patients characteristics	24 patients with residual tumors and 21 patients with suspected relapse patients with relapsed disease received either standard dose salvage chemotherapy after first-line irradiation alone or salvage chemotherapy consisting mostly of 2 cycles of induction VIP(E) (etoposide, ifosfamide, cisplatin, (epirubicin) chemotherapy followed by high-dose BEAM chemotherapy (BCNU, etoposide, adriamycin, methotrexate) with autologous stem cell support according to institutional practice
Index test	FDG-PET
Comparator	CT
Reference standard	biopsy of the new or progressive mass or by follow up over at least 6 months
Country	Germany
Outcomes considered	diagnostic accuracy of any recurrence
Study design	retrospective study, uncertain if 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
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	blinding of index and comparator tests
Withdrawals from the study explained	not applicable
Pre-test probability	85.7% (18/21 patients with relapse)
Results	FDG-PET sensitivity: 100% (18/18) specificity: 0% (0/3) CT sensitivity: 100% (18/18) specificity: 0% (0/3)
Authors' recommendations and conclusions	In patients with suspected relapse, sensitivity and positive predictive value for the diagnosis of the relapse were 100% and 86%, respectively, yielding the same results for both methods. FDG-PET performed in HD patients with residual masses appears to offer important additional information regarding the presence of viable HD in these residual lesions. In patients with suspected relapse of HD, FDG-PET seems not to offer any information over CT scans. Using SUVs is not superior to visual assessment of PET alone.

Author, year	**Pracchia 2007**
Technology	FDG-PET
Disease	Hodgkin's lymphoma
Objective	to investigate the role of the metabolic test with FDG, CGC-PET with FDG, in staging and in the evaluation of HL patients with residual masses or new suspicious lesions
Patients characteristics	20 patients evaluated with FDG scanning due to the presence of residual masses or a new lesion found on CT or physical examination; (25%) had a suspicious lesion on the cervical region, 13 (65%) in the thoracic region, and 2 (10%) in the abdominal region
Index test	CGC-PET with FDG
Comparator	none
Reference standard	true positives = those with a positive scan and with lesions confirmed by biopsy or clinical progression of disease true negatives = those with a negative scan and no evidence of clinical progression during follow up
Country	Brazil
Outcomes considered	diagnostic accuracy of any recurrence
Study design	prospective study
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not applicable
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	not reported

Withdrawals from the study explained	no
Pre-test probability	50%
Results	FDG-PET sensitivity: 90% specificity: 80%
Authors' recommendations and conclusions	The metabolic test comprising CGC-PET with fluorodeoxyglucose had a higher diagnostic accuracy than conventional methods in the staging of Hodgkin's lymphoma and thus is a valuable non invasive tool for the diagnosis of suspicious lesions.

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AGGRESSIVE NON-HODGKIN'S LYMPHOMA

TABLES OF EVIDENCE

Agenzia sanitaria e sociale regionale

RegioneEmilia-Romagna

CHAPTER 10
Staging of aggressive non-Hodgkin's lymphoma

Diagnostic accuracy

Systematic reviews

Author, year	Facey 2007
Technology	FDG-PET or FDG-PET/CT
Disease	malignant lymphoma
Objective	to assess: ▪ primary diagnosis ▪ **X** staging (before treatment) ▪ response to treatment (during treatment) ▪ restaging (after treatment) (residual disease) ▪ follow up in asymptomatic patients ▪ diagnosis of suspected recurrence ▪ recurrence ▪ impact on management ▪ impact of clinical outcomes
Inclusion criteria	P patients with malignant lymphoma I FDG-PET or FDG-PET/CT C conventional workup (CWU), Ga scanning, bone marrow biopsy (BMB) R suitable O diagnostic accuracy S prospective, at least 12 (primary studies) or 6 (treatment response planning) patients
Years covered by the search	2000-2005
Study selection data extraction, quality assessment performed by two authors independently	yes
Comprehensive bibliographic search: at least two databases searched	yes
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	yes
Searched also unpublished studies	no
Language restriction	yes (only studies in English, French, German, Spanish or Italian)
Overall number of references retrieved and n of included studies reported	yes

N. and references of excluded studies reported, reason given	no
Characteristics of included studies clearly reported in tables	yes
Methodological quality of primary studies assessed; criteria reported	no
Results of quality assessment used to formulate results and conclusions	yes
Meta-analysis performed with appropriate statistic methods	no, only narrative results
Publication bias assessed	no
N. of included studies study design	total number of studies: 10 (plus a systematic review on 7 studies), 2 on NHL patients, 7 on a mixed population unclear
N. of included patients	279 with NHL (median: 29, range: 9-53)
Reference standard	concordance between FDG-PET and other imaging techniques, follow up
Comparator	conventional workup (CWU), Ga scanning, bone marrow biopsy (BMB)
Performance results	nodal and extra-nodal staging and restaging: only narrative results "Evidence from one SR reviewing seven PSs, and seven additional PSs shows that PET had specificity of at least 90% and sensitivity of 79-100% (or >90% in the new studies). PET consistently showed superior sensitivity to Ga scanning. Two older studies suggested PET was more accurate than CT for staging lymph node involvement, but one new study showed them to be comparable. There was evidence that all imaging methods may miss small disease foci. There is some evidence of management/staging changes in 10-20% of patients from diagnostic accuracy studies, but the changes are not well documented". Three retrospective PSs in mixed populations suggest that PET/CT was more accurate than CT. The accuracy of PET was fairly high in these studies, but PET/CT appears to add value in a few patients, with changes in PET staging in three out of 71 and three out of 27 patients in two studies
Impact on management	"There is some evidence of management/staging changes in 10-20% of patients from diagnostic accuracy studies, but the changes are not well documented"
Impact on clinical outcome	not assessed

Recommendations and conclusions	Evidence from one SR reviewing seven PSs, and seven additional PSs shows that PET had specificity of at least 90% and sensitivity of 79-100% (or >90% in the new studies). PET consistently showed superior sensitivity to Ga scanning. Two older studies suggested PET was more accurate than CT for staging lymph node involvement, but one new study showed them to be comparable. There was evidence that all imaging methods may miss small disease foci. There is some evidence of management/staging changes in 10-20% of patients from diagnostic accuracy studies, but the changes are not well documented.
Notes	

Author, year	**Kirby 2007**
Technology	FDG-PET
Disease	Hodgkin's disease and non-Hodgkin's lymphoma
Objective	to assess: ▪ primary diagnosis ▪ **X** staging (before treatment) ▪ response to treatment (during treatment) ▪ response to treatment (end of treatment) ▪ follow up in asymptomatic patients ▪ diagnosis of suspected recurrence ▪ recurrence ▪ impact on management ▪ impact of clinical outcomes
Inclusion criteria	P patients with Hodgkin's disease or non-Hodgkin's lymphoma I FDG-PET C CT, conventional imaging studies (CIS) R histology, follow up, other imaging techniques O diagnostic accuracy (sensitivity, specificity, PPV, NPV) S retrospective or prospective studies, evaluating post-treatment patients
Years covered by the search	January 1997 - July 2005
Study selection data abstraction, quality assessment performed by two authors independently	unclear
Comprehensive bibliographic search: at least two databases searched	yes
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 studies)
Overall number of references retrieved and n of included studies reported	no
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	unclear; no

Results of quality assessment used to formulate results and conclusions	yes
Meta-analysis performed with appropriate statistic methods	no
Publication bias assessed	no
N. of included studies study design	2 on aggressive NHL, 17 on a mixed population, 11 on HL pts, 7 on indolent NHL unclear
n. of included patients	1 465 total 20 with aggressive NHL
Reference standard	unclear
comparator	CT, conventional imaging studies
Performance results	FDG-PET NHL narrative results only HL+NHL sensitivity: median 93% (86-100%) specificity: median 99% (72-100%)
Impact on management	not assessed
Impact on clinical outcome	CT HL+NHL sensitivity: median 81% specificity: median 93% Ga scan HL+NHL sensitivity: median 73% specificity: median 76%
Recommendations and conclusions	none

Author, year	**Wu 2012**
Technology	FDG-PET or FDG-PET/CT
Disease	malignant (non-Hodgkin's and Hodgkin's) lymphoma, bone marrow involvement detection
Objective	to assess: ▪ primary diagnosis ▪ **X** staging (before treatment) ▪ response to treatment (during treatment) ▪ restaging (after treatment) (residual disease) ▪ follow up in asymptomatic patients ▪ diagnosis of suspected recurrence ▪ **X** recurrence ▪ impact on management ▪ impact of clinical outcomes
Inclusion criteria	P patients with primary malignant lymphoma or recurrent malignant lymphoma after complete remission I FDG-PET or FDG-PET/CT (only combined, not sequential) C MRI R histopathology and/or close clinical and imaging follow up of at least 6 months O diagnostic accuracy S articles of ten or more patients included, raw data available to calculate true positives and false negatives values
Years covered by the search	January 1995 to July 2010
Study selection data extraction, quality assessment performed by two authors independently	yes
Comprehensive bibliographic search: at least two databases searched	yes
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	not clear
Searched also unpublished studies	no
Language restriction	yes (only studies in English and Chinese)
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
Results of quality assessment used to formulate results and conclusions	no
Meta-analysis performed with appropriate statistic methods	yes
Publication bias assessed	yes
N. of included studies study design	32 (5 on PET/CT, 20 on PET and 8 on MRI) 8/32 on NHL patients only, 16/32 on a mixed population, 8/32 HL patients only; retrospective (14/32), prospective (11/32), ND (7/32); blinded (3/32), not blinded/unclear blinding (29/32); consecutive recruitment (16/32)
N. of included patients	1 845 (775 with NHL, 690 with HL, 380 with HL or NHL)
Reference standard	histopathology and/or close clinical and imaging follow up of at least 6 months
Comparator	MRI
Performance results	Bone marrow involvement detection, staging and restaging <u>Mixed population</u> FDG-PET sensitivity: mean 81.5% (95% CI 77.3-85.3%) (heterogeneity chi-squared = 187.03, P = 0.000) specificity: mean 87.3% (95% CI 84.9-89.5%) (heterogeneity chi-squared = 270.59, P = 0.000) FDG-PET/CT sensitivity: mean 91.6% (95% CI 85.1-95.9) (heterogeneity chi-squared = 45.63, P = 0.000) specificity: mean 90.3% (95% CI 85.9-93.7%) (heterogeneity chi-squared = 10.18, P = 0.037) MRI sensitivity: mean 90.3% (95% CI 82.4-95.5%) (heterogeneity chi-squared = 25.83 P = 0.001) specificity: mean 75.9% (95% CI 69.8-81.2%) (heterogeneity chi-squared = 21.12 P = 0.004)
Impact on management	not assessed
Impact on clinical outcome	not assessed
Recommendations and conclusions	PET/CT was a highly sensitive and specific modality in diagnosing patients with bone marrow involvement in lymphoma. Compared with MRI and PET alone, PET/CT can play much more important roles in staging of lymphoma.
Notes	

Synoptic table of primary studies on diagnosis confirmation and staging in patients with aggressive non-Hodgkin's lymphoma

Author, year	Design	N. of patients (pts with NHL)	reference test	pre-test probability of extended disease	Disease extension	test	sensitivity	specificity
de Jong 2009	retrospective	111 (15)	FU with PET/CT	23% (NHL pts)	spleen (all NHL)	FDG-PET	77.3%	100%
						CT	90.9%	95.9%
					spleen (DLBCL pts)	FDG-PET	67%	100%
						CT	100%	90%
Fuster 2006	retrospective consecutive	106 (88)	bone marrow biopsy	26%	bone marrow	FDG-PET	86%	99%
						biopsy	57%	100%
						CT	43%	96%
Kako 2007	retrospective	41	clinical examination, CT or bone marrow examination (nodal and cutaneous lesions) and BM biopsy (for bone marrow involvement)	14.3% (for bone marrow involvement)	bone marrow	FDG-PET	20%	96.7%
Muslimani 2008	retrospective	57 (with aggressive NHL)	bone marrow biopsy	40.0% (aggr. NHL, bone marrow involvement)	bone marrow (aggr. NHL, calculated by ASSR reviewer)	FDG-PET	87%	94.1%

Author, year	Design	N. of patients (pts with NHL)	reference test	pre-test probability of extended disease	Disease extension	test	sensitivity	specificity
Pinilla 2011	prospective cross-sectional	101 (69)	combined (biopsy, FU, other exams)	not available	nodal	FDG-PET	82%	81%
						LD_FDG-PET/CT	97%	96%
						FD_FDG-PET/CT	97%	97%
						CT	90%	92%
					extra-nodal	FDG-PET	70%	76%
						LD_FDG-PET/CT	92%	81%
						FD_FDG-PET/CT	94%	81%
						CT	87%	91%
					bone marrow	FDG-PET	29%	84%
						LD_FDG-PET/CT	29%	90%
						FD_FDG-PET/CT	29%	90%
					all	FDG-PET	73%	80%
						LD_FDG-PET/CT	89%	89%
						FD_FDG-PET/CT	90%	89%

Primary studies

Author, year	de Jong 2006
Country	The Netherlands
Technology	FDG-PET
Disease	Hodgkin's lymphoma and non-Hodgkin's lymphoma
Objective	the sensitivity and specificity of PET, CT, and PET/CT for initial splenic involvement were determined
Patients characteristics	111 subjects with a mean age of 56.1±16.7 (SD) years (range 17.3-86.1 years). The histologic diagnoses were non-Hodgkin's lymphoma in 96 (86% - 40 with diffuse large B-cell lymphoma) and Hodgkin's disease in 15 (14%) patients. According to the Ann Arbor system, the patients were found to have disease in stage 4 (n=35, 32%), stage 3 (n=19, 17%), stage 2 (n=30, 27%), and stage 1 (n=27, 24%)
Index test	FDG-PET
Comparator	CT
Reference standard	initial splenic involvement can be confirmed with follow up PET/CT. A reference standard strongly suggestive of initial splenic involvement in lymphoma is reversal of progression of splenic size and the finding of splenic nodules or splenic uptake on follow up PET and CT in relation to other disease sites. This strategy has been used in previous studies
Outcomes considered	diagnostic accuracy
Study design	retrospective cross-sectional study
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	no
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes

Execution of the reference standard described	not clear
Independent and blind interpretation of index test and reference standard results	no
Withdrawals from the study explained	not applicable
Pre-test probability	32 patients (29%) were determined to have true splenic involvement, and 79 to have no splenic involvement HL patients: 10 out of 15 (66.7%) with splenic involvement NHL patients: 22 out 96 (22.9%) with splenic involvement NHL (diffuse large B-cell lymphoma): 9 out of 40 (22.5%) with splenic involvement NHL (other lymphomas): 13 out of 56 (23.2%) with splenic involvement
Results	Splenic involvement (HL + NHL) FDG-PET sensitivity: 75% specificity: 98.7% CT sensitivity: 91% specificity: 96% Splenic involvement (HL) FDG-PET sensitivity: 70% specificity: 80% CT sensitivity: 90% specificity: 100% Splenic involvement (all NHL) FDG-PET sensitivity: 77.3% specificity: 100% CT sensitivity: 90.9% specificity: 95.9% *(continues)*

	Splenic involvement (NHL - diffuse large B-cell lymphoma) FDG-PET sensitivity: 67% specificity: 100% CT sensitivity: 100% specificity: 90% Splenic involvement (NHL - other lymphomas) FDG-PET sensitivity: 85% specificity: 100% CT sensitivity: 85% specificity: 100%
Authors' recommendations and conclusions	For the initial staging of splenic involvement in the patients with malignant lymphoma in this study, the stepwise findings of, first, splenic greater than hepatic FDG uptake at PET, second, the presence of low-attenuation nodules at CT, and, third, an enlarged CT splenic index greater than 725 cm3 have 100% sensitivity and 95% specificity for the presence of splenic involvement. This approach can be tested prospectively and used for future determination of which change in CT splenic index corresponds to partial remission and which to complete remission.

Author, year	**Fuster 2006**
Country	Spain
Technology	FDG-PET
Disease	Hodgkin's lymphoma and non-Hodgkin's lymphoma
Objective	to assess the usefulness of [18F]fluorodeoxyglucose positron emission tomography in the detection of bone marrow involvement in malignant lymphoma, and its impact in clinical management
Patients characteristics	106 consecutive patients (54 female, 52 male) with a mean age of 53±15 years and a confirmed diagnosis of lymphoid neoplasm by the World Health Organization criteria, who were referred for staging (81) or restaging (25) of known Hodgkin's lymphoma (n=18) or NHL (n=88) by means of [18F]FDG-PET imaging. The categories of NHL found in this series were diffuse large B-cell (n=37), follicular (n=21), peripheral T-cell (n=7), mantle cell (n=7), marginal zone (n=5) and other cell types (n=11)
Index test	FDG-PET
Comparator	none
Reference standard	bone marrow biopsy
Outcomes considered	diagnostic accuracy
Study design	prospective cross-sectional study
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	no
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	yes
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	no

Independent and blind interpretation of index test and reference standard results	not clear
Withdrawals from the study explained	not applicable
Pre-test probability	24 patients (26.4%) with bone marrow involvement
Results	Bone marrow involvement FDG-PET sensitivity: 85.7% specificity: 98.9%
Authors' recommendations and conclusions	Positron emission tomography and bone marrow biopsy are complementary in assessing the presence of bone marrow involvement in patients with malignant lymphoma. In our series, positron emission tomography was more sensitive than bone marrow biopsy in Hodgkin's and non-Hodgkin's lymphoma, except in follicular lymphoma.

Author, year	**Kako 2007**
Technology	FDG-PET
Disease	aggressive T-CL
Objective	to retrospectively review the results of FDG-PET in patients with T/NK-cell neoplasms diagnosed according to the World Health Organization (WHO) classification, and examine the positive rate of pre-treatment FDG-PET
Patients characteristics	41 patients with a pathological diagnosis of T/NK-cell neoplasm that underwent FDG-PET scanning at initial diagnosis (31 patients) and at relapse or progression (10 pts); median age 57 years. Only 35 patients considered for bone marrow involvement (available BMB)
Index test	FDG-PET
Comparator	
Reference standard	clinical examination, CT or bone marrow examination (nodal and cutaneous lesions) and BM biopsy (for bone marrow involvement)
Country	Japan
Outcomes considered	diagnostic accuracy
Study design	retrospective study
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	unclear
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	no
Independent and blind interpretation of index test and reference standard results	no
Withdrawals from the study explained	not applicable

Pre-test probability	for bone marrow involvement (initial staging or restaging): 5/35 (14.3%) of patients
Results	Bone marrow involvement (initial diagnosis and recurrence) FDG-PET sensitivity: 20% specificity: 96.7%
Authors' recommendations and conclusions	In conclusion, our study showed that T/NK-cell neoplasms were generally FDG-avid as B-cell neoplasms. Although a careful interpretation should be carried out for each patient, this result could support further evaluation of clinical significance of FDG-PET in T/NK-cell neoplasms. However, the ability of FDG-PET to detect cutaneous lesions, except for tumoros ones, and BM involvement may not be reliable.

Author, year	**Muslimani 2008**
Technology	FDG-PET
Disease	aggressive NHL
Objective	to assess the ability of 18F-FDG-PET scan to ascertain the presence of BM involvement in the absence of a positive BMB in NHL and as a function of the tumors aggressiveness
Patients characteristics	57 with aggressive NHL +40 with indolent NHL, total of 97 patients 42 males, 54 females age range 42-81 years; mean age 68 years all 97 patients were examined by 18F-FDG-PET scan for initial staging before starting any radio- or chemotherapy, and all had unilateral posterior iliac crest BM aspiration and BMB which was analyzed after standard procedures and the final diagnosis was graded as positive or negative for involvement
Index test	FDG-PET
Comparator	
Reference standard	bone marrow biopsy (initial BMB and CT-guided biopsy in case of FDG-PET positive in selected iliac crest BMB negative patients)
Country	USA
Outcomes considered	diagnostic accuracy
Study design	retrospective study
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	yes
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	no
Execution of the reference standard described	yes

Independent and blind interpretation of index test and reference standard results	unclear
Withdrawals from the study explained	no
Pre-test probability	pre-test probability of bone marrow involvement in aggressive NHL: 23/57 (40%) patients
Results	<u>Bone marrow involvement, FDG-PET accuracy</u> for aggressive NHL (calculated by ASSR reviewer) sensitivity: 87% specificity: 94.1% overall (indolent and aggressive NHL together) (calculated by ASSR reviewer) sensitivity: 79% specificity: 91% PPV: 86% NPV: 87%
Authors' recommendations and conclusions	With an overall sensitivity of 79% and specificity of 91%, 18F-FDG-PET scan shows potential to detect BM involvement in NHL (which would otherwise be missed by iliac crest BMB) with no significant difference in the ability of the18F-FDG-PET scan to detect this involvement between the indolent-NHL and the aggressive/highly aggressive-NHL groups. Furthermore, 18F-FDG-PET can be used to direct the site of the biopsy, and image-guided repeat BMB should be considered in patients with negative initial iliac crest BMB, whose PET demonstrates BM involvement in a different site.

Author, year	**Pinilla 2011**
Country	Spain
Technology	FDG-PET, FDG-PET/CT
Disease	Hodgkin's lymphoma and non-Hodgkin's lymphoma
Objective	to compare the accuracy of contrast-enhanced CT and PET alone and of hybrid PET/CT, performed with either low-dose unenhanced CT (LD-PET/CT) or full-dose enhanced CT (FD-PET/CT) in detecting nodal and extra-nodal lesions in the initial staging of an unselected population of patients with lymphoma
Patients characteristics	101 patients (59 female and 42 male, mean age 50 years, range 15-83 years) with histopathologically proven and untreated lymphoma were enrolled in this prospective study for initial staging; 69 patients with NHL
Index test	FDG-PET
Comparator	CT, low dose FDG-PET/CT, full dose FDG-PET/CT
Reference standard	reference standard as the sum of many factors: clinical history; physical examination; laboratory workup; iliac crest bone marrow biopsy; contrast-enhanced CT and other imaging findings (magnetic resonance imaging [MRI], Gallium scan); lumbar puncture; endoscopy; biopsies and surgery when clinically indicated; and follow up data
Outcomes considered	diagnostic accuracy
Study design	prospective cross-sectional study (unclear if consecutive recruitment)
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	no
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not applicable
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes

Execution of the reference standard described	no
Independent and blind interpretation of index test and reference standard results	yes
Withdrawals from the study explained	not applicable
Pre-test probability	not available
Results	Nodal involvement PET sensitivity 82% (95% CI 77-87%) specificity 81% (95% CI 73-88%) Low dose PET/CT sensitivity 97% (95% CI 95-99%) specificity 96% (95% CI 93-99%) Full dose PET/CT sensitivity 97% (95% CI 95-99%) specificity 97% (95% CI 94-100%) CT sensitivity 90% (95% CI 86-94%) specificity 92% (95% CI 86-97%) Extra-nodal involvement PET sensitivity 70% (95% CI 58-82%) specificity 76% (95% CI 64-88%) Low dose PET/CT sensitivity 92% (95% CI 83-99%) specificity 81% (95% CI 69-92%) Full dose PET/CT sensitivity 94% (95% CI 86-100%) specificity 81% (95% CI 69-92%) CT sensitivity 87% (95% CI 78-96%) specificity 91% (95% CI 83-99%) Bone marrow involvement PET sensitivity 29% (95% CI 13-45%) specificity 84% (95% CI 76-93%) Low dose PET/CT sensitivity 29% (95% CI 13-45%) specificity 90% (95% CI 83-97%) Full dose PET/CT sensitivity 29% (95% CI 13-45%) specificity 90% (95% CI 83-97%) *(continues)*

	Overall diagnostic accuracy PET sensitivity 73% (95% CI 68-78%) specificity 80% (95% CI 75-84%) Low dose PET/CT sensitivity 89% (95% CI 85-92%) specificity 89% (95% CI 85-92%) Full dose PET/CT sensitivity 90% (95% CI 85-93%) specificity 89% (95% CI 85-93%)
Authors' recommendations and conclusions	PET/CT is an accurate technique for the initial staging of lymphomas without significant differences between Low Dose-PET/CT and Full Dose-PET/CT. Full Dose-PET/CT detects relevant incidental findings that are missed on Low Dose-PET/CT

CHAPTER 11
Dose painting definition in radiation treatment of aggressive non-Hodgkin's lymphoma

Diagnostic accuracy

Systematic reviews

None retrieved.

Primary studies

None retrieved.

CHAPTER 12
During treatment evaluation of early response to therapy in aggressive non-Hodgkin's lymphoma

Diagnostic accuracy

Systematic reviews

Author, year	HTA AETSA 2007
Technology	FDG-PET or FDG-PET/CT
Disease	aggressive NHL
Objective	to assess: ▪ primary diagnosis ▪ staging (before treatment) ▪ **X** response to treatment (during treatment) ▪ restaging (after treatment) (residual disease) ▪ follow up in asymptomatic patients ▪ diagnosis of suspected recurrence ▪ recurrence ▪ impact on management ▪ impact of clinical outcomes
Inclusion criteria	P patients with HL or NHL I FDG-PET or FDG-PET/CT C CT, MRI R histology or follow up >12 months O diagnostic accuracy, efficacy and change in management S RCT, systematic review, HTA, prospective cohorts, number of patients >10, with histological confirmation, follow up ≥12 months, comparison with other imaging techniques; studies reporting results on sensitivity, specificity, PPV, NPV, efficacy, effectiveness, data on change in management
Years covered by the search	2004-2006
Study selection data abstraction, quality assessment performed by two authors independently	yes
Comprehensive bibliographic search: at least two databases searched	yes
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	yes

Searched also unpublished studies Language restriction	no 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
Results of quality assessment used to formulate results and conclusions	unclear
Meta-analysis performed with appropriate statistic methods	no, meta-analysis not performed due to heterogeneity
Publication bias assessed	yes
N. of included studies study design	3 on during treatment response including NHL patients (1 including only NHL patients); 3/3 prospective total number of studies included in the review: 10 (7 in HL, 2 in HL+NHL, 1 in aggressive NHL) + 1 systematic review; 10/10 prospective studies
N. of included patients	631 with HL or NHL (range: 2-2 108) 149 with NHL (range 20-90)
Reference standard	follow up
Comparator	
Performance results	FDG-PET (only NHL patients) sensitivity: 76.2 (70.3-75.1%) specificity: 71.0 (69.8-71.4%) FDG-PET (NHL and HL patients) sensitivity: 55.5-100% specificity: 50.0-100%
Impact on management	not assessed
Impact on clinical outcome	not assessed
Recommendations and conclusions	In lymphoma patients with positive pre-treatment FDG-PET, during treatment scan should be provided to evaluate chemotherapy response and prognosis, even if relation between outcomes and change in management has not been demonstrated.

Author, year	**Facey 2007**
Technology	FDG-PET
Disease	NHL
Objective	to assess: ▪ primary diagnosis ▪ staging (before treatment) ▪ **X** response to treatment (during treatment) ▪ restaging (after treatment) (residual disease) ▪ follow up in asymptomatic patients ▪ diagnosis of suspected recurrence ▪ recurrence ▪ impact on management ▪ impact of clinical outcomes
Inclusion criteria	P patients with malignant lymphoma I FDG-PET C conventional workup (CWU), Ga scanning, bone marrow biopsy (BMB) R not specified O diagnostic accuracy S prospective, at least 12 (primary studies) or 6 (treatment response planning) patients
Years covered by the search	2000-2005
Study selection data abstraction, quality assessment performed by two authors independently	yes
Comprehensive bibliographic search: at least two databases searched	yes
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	yes
Searched also unpublished studies	no
Language restriction	yes (only studies in English, French, German, Spanish or Italian)
Overall number of references retrieved and n of included studies reported	yes
N. and references of excluded studies reported, reason given	no
Characteristics of included studies clearly reported in tables	yes

Methodological quality of primary studies assessed; criteria reported	no
Results of quality assessment used to formulate results and conclusions	yes
Meta-analysis performed with appropriate statistic methods	no, only narrative results
Publication bias assessed	no
N. of included studies study design	8 (4/8 including only NHL patients) unclear
N. of included patients	301 with NHL (range: 24-90) 115 with NHL or HL (range: 16-46)
Reference standard	clinical follow up
Comparator	CT, bone marrow biopsy, MRI, Ga scan
Performance results	data needed to assess diagnostic accuracy available only for 3 out of 9 studies; pooled estimates not available
Impact on management	not assessed
Impact on clinical outcome	not assessed
Recommendations and conclusions	There is evidence from nine PSs that midtherapy scans may be predictive of outcome midtherapy. As yet, however, there is no evidence of any associated changes in management (such as intensification or switch in therapy) consequent upon this.

Author, year	**Kirby 2007**
Technology	FDG-PET
Disease	NHL
Objective	to assess: ▪ primary diagnosis ▪ staging (before treatment) ▪ **X** response to treatment (during treatment) ▪ restaging (after treatment) (residual disease) ▪ follow up in asymptomatic patients ▪ diagnosis of suspected recurrence ▪ recurrence ▪ impact on management ▪ impact of clinical outcomes
Inclusion criteria	P patients with malignant lymphoma I FDG-PET C not specified R not specified O diagnostic accuracy, change in management S case reports were excluded where more substantial series exist. Studies using gamma camera PET scanners were also excluded
Years covered by the search	January 1997 and September 2005
Study selection data abstraction, quality assessment performed by two authors independently	N.D.
Comprehensive bibliographic search: at least two databases searched	yes
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	yes
Searched also unpublished studies	no
Language restriction	yes (only studies in English)
Overall number of references retrieved and n of included studies reported	no
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; no

Results of quality assessment used to formulate results and conclusions	unclear
Meta-analysis performed with appropriate statistic methods	no
Publication bias assessed	no
N. of included studies study design	13 evaluating during-treatment response in NHL (of which 6 including only patients with NHL and 5 on post HDC prior to ASCT) unclear
N. of included patients	514 NHL patients (range 10-121) 169 with HL or NHL (range: 30-54)
Reference standard	unclear
Comparator	none
Performance results	FDG-PET (data from the 6 studies exclusively on NHL patients) sensitivity: 42-100% specificity: 70-100% PPV: 44-100% NPV: 64-100% accuracy: 69-96% FDG-PET (data from all the 13 studies, thus including also HL patients and studies on post HDC prior to ASCT) sensitivity: 42-100% specificity: 48-100% PPV: 44-100% NPV: 50-100% accuracy: 65-96%
Impact on management	not assessed
Impact on clinical outcome	not assessed
Recommendations and conclusions	[…] it appears that persistent PET positivity after a few cycles of chemotherapy is associated with a much higher probability of relapse (positive predictive value (PPV), 44-100%). Progression-free survival ranges from 10 to 50% at 1 year for PET positive patients, and from 79 to 100% at 1 year for PET negative patients. The high relapse rate seen in PET positive patients is reported to be consistent in both early and advanced stages.[…] Aside from prognostic value, however, the clinical utility of this information is yet to be evaluated and there is no firm evidence to date to suggest that early change in therapy in poorly responding patients improves survival.

Author, year	**Terasawa 2009**
Technology	FDG-PET or FDG-PET/CT
Disease	aggressive NHL (DLBCL)
Objective	to assess: ▪ primary diagnosis ▪ staging (before treatment) ▪ **X** response to treatment (during treatment) ▪ restaging (after treatment) (residual disease) ▪ follow up in asymptomatic patients ▪ diagnosis of suspected recurrence ▪ recurrence ▪ impact on management ▪ impact of clinical outcomes
Inclusion criteria	P patients with DLBCL or advanced-stage HL I FDG-PET performed between the first and the fourth cycle of first-line chemotherapy C not specified R follow up with or without pathologic confirmation O sensitivity and specificity S prospective and retrospective studies, that evaluated at least 10 patients and included at least five patients who progressed during chemotherapy or relapsed through clinical follow up
Years covered by the search	Ovid MEDLINE and EMBASE from 1966 through July 2006 PubMed from August 2006 through July 2007
Study selection data abstraction, quality assessment performed by two authors independently	yes
Comprehensive bibliographic search: at least two databases searched	yes
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	yes
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	yes

clearly reported in tables	
Methodological quality of primary studies assessed; criteria reported	yes
Results of quality assessment used to formulate results and conclusions	yes
Meta-analysis performed with appropriate statistic methods	yes
Publication bias assessed	yes
N. of included studies study design	7 (1 including HL and NHL patients) 3/7 prospective
N. of included patients	total number of patients: 671 patients with aggressive NHL (DLBCL): 311
Reference standard	follow up with or without pathologic confirmation
comparator	
Performance results	FDG-PET or FDG-PET/CT (pooled estimates) sensitivity: 0.78 (95% CI 0.64-0.87) specificity: 0.87 (95% CI 0.75-0.93) positive LR: 5.9 (95% CI 2.8-12.3) negative LR: 0.26 (95% CI 0.15-0.46) Q* statistic for the summary ROC curve: 0.82
Impact on management	not assessed
Impact on clinical outcome	not assessed
Recommendations and conclusions	For DLBCL, no reliable conclusions can be drawn due to heterogeneity. Interim PET remains an unproven test for routine clinical practice. Its use should be reserved for research settings where treatment regimens and imaging conditions are standardized.

Author, year	**Terasawa 2010**
Technology	FDG-PET or FDG-PET/CT
Disease	HL, aggressive NHL (DLBCL and others)
Objective	to assess: ▪ primary diagnosis ▪ staging (before treatment) ▪ **X** response to treatment (during treatment) ▪ restaging (after treatment) (residual disease) ▪ follow up in asymptomatic patients ▪ diagnosis of suspected recurrence ▪ recurrence ▪ impact on management ▪ impact of clinical outcomes
Inclusion criteria	P patients with HL, aggressive NHL (DLBCL and others), indolent NHL I FDG-PET performed during or after induction chemotherapy and before high-dose chemotherapy followed by autologous stem cell transplantation C conventional restaging (computed tomography [CT] or magnetic resonance imaging, and bone marrow biopsy) R follow up with or without pathologic confirmation O sensitivity and specificity S prospective and retrospective studies, that evaluated at least 10 patients and included at least five patients who progressed during chemotherapy or relapsed through clinical follow up
Years covered by the search	PubMed up to July 2010
Study selection data abstraction, quality assessment performed by two authors independently	yes
Comprehensive bibliographic search: at least two databases searched	no
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 (QUADAS)
Results of quality assessment used to formulate results and conclusions	yes (only results)
Meta-analysis performed with appropriate statistic methods	yes (not reported heterogeneity)
Publication bias assessed	no
N. of included studies study design	12 (7 including HL and NHL patients; 2 only HL patients; 3 only aggressive NHL patients) 3/12 prospective design
N. of included patients	total number of patients: 630 patients with aggressive HL: 187 patients with aggressive NHL (DLBCL or other types): 307 patients with indolent NHL: 66
Reference standard	follow up with or without pathologic confirmation
Comparator	conventional restaging (computed tomography [CT] or magnetic resonance imaging, and bone marrow biopsy)
Performance results	FDG-PET or FDG-PET/CT (pooled estimates patients with aggressive NHL only) predictive accuracy of survival sensitivity (pooled): 77% (95% CI 54-90%) specificity (pooled): 77% (95% CI 63-88%)
Impact on management	not assessed
Impact on clinical outcome	not assessed
Recommendations and conclusions	18F-FDG-PET performed after salvage therapy appears to be an appropriate test to predict treatment failure in patients with refractory or relapsed lymphoma who receive high-dose chemotherapy. Some evidence suggests PET is superior to conventional restaging for this purpose. Given the methodological limitations in the primary studies, prospective studies with standardized methodologies are needed to confirm and refine these promising results.
Notes	high quality

Synoptic table of primary studies on diagnostic accuracy of FDG-PET in during treatment evaluation of response to therapy in patients treated for aggressive non-Hodgkin's lymphoma

Author, year	Technology	Patient number	Treatment regimen	Study design	Reference standard	End-point	Pre-test probability	Sensitivity	Specificity
Altamirano 2008	18F-FDG-PET	28	chemotherapy	prospective	biopsy; follow up; guidelines established by the International response evaluation criteria in solid tumors Group (RECIST)	response to treatment	n.a.	92.2%	93.3%
	CT							79%	50%
Moskowitz 2010	FDG-PET/CT before transplant	98	high-dose therapy/autologous stem-cell rescue (HDT/ASCR)	prospective	biopsy on FDG-PET positive patients and follow up on FDG-PET negative patients	response to treatment (high-dose therapy)	13.4%	62.5%	60.7%
Riad 2010	18F-FDG-PET/CT	51	chemotherapy	retrospective	histopathological exam and clinical follow up	response to treatment	n.a.	100%	97.7%

Primary studies

Author, year	Altamirano 2008
Country	Mexico
Technology	18F-FDG-PET
Disease	Hodgkin's lymphoma and non-Hodgkin's lymphoma
Objective	to determine the diagnostic accuracy of 18FDG after three cycles and at the end of chemotherapy in non-Hodgkin's lymphoma (NHL) or Hodgkin's lymphoma (HL)
Patients characteristics	40 patients but only 28 patients where studied 15 patients were female (53.6%) and 13 were male (46.4%) with a mean age of 43 years (range: 15-74 years) 7 patients corresponded to HL diagnosis (25%) and 21 to NHL (75%)
Index test	18F-FDG-PET
Comparator	CT
Reference standard	follow up (median 18 months, range: 6-24 months; guidelines established by the International response evaluation criteria in solid tumors Group (RECIST)
Outcomes considered	sensitivity, specificity, diagnostic accuracy, PPV, NPV
Study design	prospective cross-sectional study
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not clear
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	no
Execution of the reference standard described	no
Independent and blind interpretation of index test and reference standard results	yes

Withdrawals from the study explained	not applicable
Pre-test probability	
Results	18F-FDG-PET sensitivity: 92.2% specificity: 93.3% accuracy: 93% PPV: 92% NPV: 93% CT sensitivity: 79.0% specificity: 50.0% accuracy: 64% PPV: 61% NPV: 70%
Authors' recommendations and conclusions	18FDG had greater prognostic values than CT after the third and last cycle of chemotherapy. PET after three cycles of chemotherapy is predictive of 18-month outcome in patients with intermediate and aggressive NHL and HL and may help in the identification of patients who would benefit from more intensive treatment or from a change in chemotherapy.

Author, year	**Moskowitz 2010**
Country	USA
Technology	FDG-PET/CT
Disease	CD20+ DLBCL or primary mediastinal DLBCL (PMBL)
Objective	to determine whether interim FDG-PET scans could identify patients who might benefit from high-dose therapy/ autologous stem-cell rescue (HDT/ASCR) as part of initial treatment and to determine whether HDT/ASCR could be avoided in patients with multiple IPI risk factors but normal interim restaging (defined as a negative interim FDG-PET scan and/or a negative biopsy of FDG-positive disease), using our strategy of dose-dense sequential therapy
Index test	FDG-PET/CT before autologous stem cell transplant
Patients characteristics	98 newly diagnosed, DLBCL patients who were eligible for transplantation. Median age was 47 years; 16 patients (16%) were between age 60 and 65 years. One patient progressed on therapy, and 97 patients received all of the planned therapy induction chemotherapy consisted of four doses of accelerated R-CHOP (R-CHOPac) administered within a 14-day cycle. One additional dose of rituximab preceded cycle 1 on day -2
Reference standard	biopsy on FDG-PET positive patients and follow up on FDG-PET negative patients
Outcomes considered	diagnostic accuracy
Study design	prospective, single-centre
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	yes
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes

Execution of the reference standard described	no
Independent and blind interpretation of index test and reference standard results	partial
Withdrawals from the study explained	yes
Pre-test probability	not response to therapy 13/97 (13.4%)
Results	diagnostic accuracy of FDG-PET response before autologous stem cell transplant (calculation by ASSR reviewers) sensitivity: 5/8 = 62.5% specificity: 51/84 = 60.7%
Authors' recommendations and conclusions	This study demonstrates a highly effective strategy for the treatment of advanced-stage DLBCL, one that cured approximately 80%of patients. However, an interim FDG-PET scan did not identify those patients at high risk for a poor outcome. At present, suspected residual active DLBCL on interim restaging FDG-PET scans should be confirmed by biopsy before initiating a change in therapy.

Author, year	**Riad 2010**
Country	Egypt
Technology	18F-FDG-PET/CT
Disease	Hodgkin's lymphoma and non-Hodgkin's lymphoma
Objective	to evaluate the performance of 18F-FDG-PET/CT and to compare diagnostic accuracy of 18F-FDG-PET/CT with conventional imaging modalities(CIM) in the evaluation of early treatment response in Hodgkin's and non-Hodgkin's lymphoma
Patients characteristics	152 total patients (35 females and 117 males) with histologically proven malignant lymphoma 8 117 HD, 35, NHL) Range age 3-18 years They were divided into four groups: Group I: 41 patients for initial staging Group II: 51 patients (45 HD, 6 NHL) for evaluating early treatment response after two to three cycles of chemotherapy. Five patients were stage I, 20 were stage II, 18 were stage III and 8 were stage IV Group III: 42 patients for evaluating treatment response 4-8 weeks after the end of their treatment Group IV: 18 patients evaluated for long-term follow up
Index test	18F-FDG-PET
Comparator	conventional imaging modalities (CIM - CT, MRI, US, physical examination, bone marrow biopsy when available)
Reference standard	histopathological exam and clinical follow up
Outcomes considered	sensitivity, specificity, diagnostic accuracy, PPV, NPV
Study design	retrospective cross-sectional study
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 clear
Execution of the index and comparator tests adequately described	yes

Did patients receive the same reference standard regardless of the index test result	no
Execution of the reference standard described	no
Independent and blind interpretation of index test and reference standard results	not clear
Withdrawals from the study explained	not applicable
Pre-test probability	
Results	18F-FDG-PET/CT sensitivity: 100% specificity: 97.7% accuracy: 98% PPV: 85.7% NPV: 100% CIM sensitivity: 83% specificity: 66.6% accuracy: 68.6% PPV: 25% NPV: 96.7%
Authors' recommendations and conclusions	PET/CT in paediatric lymphoma is more accurate than CIM. We recommend that it should be the first modality for all purposes in initial staging, evaluating treatment response and follow up.

Impact on clinical outcomes

Systematic reviews

None retrieved.

Primary studies

Author, year	Kasamon 2009
Country	USA
Technology	FDG-PET/CT
Disease	aggressive non-Hodgkin's lymphoma
Objective	to test the risk-adapted therapy - based on early PET - for aggressive NHL (early intensification with platinum-based chemotherapy then ASCT in PET-positive patients)
Patients characteristics	59 patients aged >18 years with measurable, aggressive NHL (diffuse large B cell, follicular grade 3, and peripheral T cell lymphomas) who had received no more than 3 cycles of standard first-line chemotherapy Ninety-five percent of patients had large B cell lymphoma, and 97% of patients received ®CHOP-21 with the remaining 3% receiving R-CHOP-14. Twenty-six of 59 patients (44%) were interpreted as having negative mid-treatment PET and 33 (56%) as having positive mid-treatment PET. The median follow up for all patients is 33.6 months (range: 1.3-54.5 months) and 37.2 months for surviving patients. The estimated 2-year EFS of the entire cohort is 77% and 2-year OS is 82%
Test	all who joined had mid-treatment PET/CT in addition to conventional restaging. A baseline PET scan was not required, but when available was used for comparison. Mid-treatment PET/CT was performed between days 11 and 20 of cycle 2 or 3 The PET was interpreted qualitatively and the result dichotomized as "negative" (no evidence of malignant disease) or "positive" (focal or diffuse uptake in an area suspicious for a residual or new focus of malignancy). Within this designation, tumor FDG uptake relative to mediastinal blood pool structures was graded on a 5-point scale: 0, no tumor activity (cold); 1, minimal (less than background); 2, equivocal (equal to background); 3, moderate (greater than background); 4, intense (much greater than background). Scores of 3 or 4 were considered positive
Intervention	patients with negative mid-treatment PET completed the remaining standard therapy, without early ASCT

Comparator	in the absence of progression, those with positive mid-treatment PET received 2 cycles of ESHAP (etoposide, methylprednisolone, high-dose cytarabine, cisplatin) or ICE (ifosfamide, carboplatin, etoposide) with rituximab added for B cell tumors, then stem cell collection during the second cycle followed by high-dose therapy and ASCT. Two patients with positive mid-treatment PET received an extra cycle of R-CHOP for logistic reasons before changing therapies. Biopsies of abnormally FDG avid areas were not performed. Radiation therapy after ASCT was permissible
Verification test	none
Outcomes considered	event-free survival adverse events
Results	patients with positive mid-treatment PET 33 28 (85%) received ASCT. Two PET-positive patients withdrew consent and were censored on the mid-treatment PET date. Three were ineligible because of disease progression prior to planned ASCT. The median follow up after ASCT is 34.1 months overall (range: 1.3-49.7 months) and 36.0 months for surviving patients. 2-year event-free survival after ASCT 75% 3-year event-free survival after ASCT 65% In the 28 transplanted PET-positive patients, 1 died at 1.4 months of hepatic veno-occlusive disease, and another developed self-limited veno-occlusive disease; 1 died at 9.9 months from multiple strokes and pneumonia, with negative evaluations for lymphoma; and 1 developed MDS and died after nonmyeloablative allogeneic transplantation. PET-negative patients 26. In the absence of events, all completed full-course therapy, with none receiving more than 6 chemotherapy cycles. 4 (15%) have had documented relapse or progression to date 2-year event-free survival 89% 3-year event-free survival 82% In the PET-negative group, 1 died of leukaemia Formal comparison between the PET-positive and PET-negative cohorts is not intended because of the differences in therapy
Study design	prospective series
Representativeness of the exposed cohort	truly representative of the average / somewhat representative of the average **X** / selected group of users / no description
Selection of the non exposed cohort	from the same community as the exposed cohort **X** / from a different source / no description
Ascertainment of exposure	secure record **X** / structured interview / written self report / no description

Demonstration that outcome of interest was not present at start of study	yes **X** / no
Comparability of cohorts on the basis of the design or analysis	**no control of some important factors** / study controls for some important factors / study controls for any additional factor
Assessment of outcome	independent blind assessment / record linkage / self report / no description **X**
Was follow up long enough for outcomes to occur	yes **X** / no
Adequacy of follow up of cohorts	complete follow up - all subjects accounted for / subjects lost to follow up unlikely to introduce bias - small number lost **X** follow up rate <…% (select an adequate %) and no description of those lost / no statement
Authors' recommendations and conclusions	Our results suggest that mid-treatment PET scanning is useful in guiding therapy, and that such individualized therapy is feasible. The relative contribution of ASCT compared with a platinum- and etoposide containing salvage regimen, and to what degree early ASCT affects survival in mid-treatment PET-positive patients, are ultimately phase III questions. Further investigations of individualized, risk-adapted strategies based on early metabolic imaging are warranted.

Author, year	**Moskowitz 2010**
Country	USA
Technology	FDG-PET/CT
Disease	CD20+ DLBCL or primary mediastinal DLBCL (PMBL)
Objective	to determine whether interim FDG-PET scans could identify patients who might benefit from high-dose therapy/autologous stem-cell rescue (HDT/ASCR) as part of initial treatment and to determine whether HDT/ASCR could be avoided in patients with multiple IPI risk factors but normal interim restaging (defined as a negative interim FDG-PET scan and/or a negative biopsy of FDG-positive disease), using our strategy of dose-dense sequential therapy
Patients characteristics	98 newly diagnosed, DLBCL patients who were eligible for transplantation median age was 47 years; 16 patients (16%) were between age 60 and 65 years 1 patient progressed on therapy, and 97 patients received all of the planned therapy induction chemotherapy consisted of four doses of accelerated R-CHOP (R-CHOPac) administered within a 14-day cycle. One additional dose of rituximab preceded cycle 1 on day -2
Test	computed tomography (CT) and FDG-PET scans were repeated 10 to 14 days after the start of the fourth cycle of R-CHOPac
Intervention	patients who had resolution of all FDG-positive sites of disease (without development of new sites) proceeded to consolidation A (three cycles of ICE [ifosfamide, carboplatin, etoposide] chemotherapy)
Comparator	patients with residual FDG-positive disease that correlated with CT findings underwent repeat biopsy. If the biopsy was negative, the patient received consolidation A therapy; if the biopsy was positive, the patient received consolidation B (two cycles of ICE and then one cycle of RICE [rituximab+ICE]) followed by HDT and autologous stem-cell transplantation). Those patients whose bone marrow was initially positive and remained positive after induction received consolidation B
Verification test	biopsy on FDG-PET positive patients and follow up on FDG-PET negative patients
Outcomes considered	progression-free survival

Results	At a median follow up of 44 months, the Kaplan-Meier estimates of patients alive and progression free were 90% (95% CI 83% to 98%) and 79% (95% CI 69% to 89%), respectively. patients with negative interim FDG-PET scan and receiving consolidation A: 59 progression free: 51 patients with positive interim FDG-PET: 38 5/38 had a positive biopsy and received consolidative transplantation (consolidation B) 3/5 are alive and progression free. 33/38 had a negative biopsy received consolidation A 26 of those patients remain alive without evidence of DLBCL progression free survival PET negative vs PET positive/biopsy negative P = 0.275
Study design	prospective series
Representativeness of the exposed cohort	truly representative of the average / somewhat representative of the average **X** / selected group of users / no description
Selection of the non exposed cohort	from the same community as the exposed cohort **X** / from a different source / no description
Ascertainment of exposure	secure record **X** / structured interview / written self report / no description
Demonstration that outcome of interest was not present at start of study	yes **X** / no
Comparability of cohorts on the basis of the design or analysis	**no control of some important factors** / study controls for some important factors / study controls for any additional factor
Assessment of outcome	independent blind assessment / record linkage / self report / no description **X**
Was follow up long enough for outcomes to occur	yes **X** / no
Adequacy of follow up of cohorts	complete follow up - all subjects accounted for / subjects lost to follow up unlikely to introduce bias - small number lost **X** follow up rate <…% (select an adequate %) and no description of those lost / no statement
Authors' recommendations and conclusions	This study demonstrates a highly effective strategy for the treatment of advanced-stage DLBCL, one that cured approximately 80%of patients. However, an interim FDG-PET scan did not identify those patients at high risk for a poor outcome. At present, suspected residual active DLBCL on interim restaging FDG-PET scans should be confirmed by biopsy before initiating a change in therapy.

CHAPTER 13
End of treatment evaluation of response to therapy in aggressive non-Hodgkin's lymphoma

Diagnostic accuracy

Systematic reviews

Author, year	Facey 2007
Technology	FDG-PET
Disease	malignant lymphoma
Objective	to assess: ▪ primary diagnosis ▪ staging (before treatment) ▪ response to treatment (during treatment) ▪ **X** restaging (after treatment) (residual disease) ▪ follow up in asymptomatic patients ▪ diagnosis of suspected recurrence ▪ recurrence ▪ impact on management ▪ impact of clinical outcomes
Inclusion criteria	P patients with malignant lymphoma I FDG-PET C erythrocyte sedimentation rate (ESR), Ga scanning, CT R unclear O diagnostic accuracy S prospective, at least 12 (primary studies) or 6 (treatment response planning) patients
Years covered by the search	2000-2005
Study selection data abstraction, quality assessment performed by two authors independently	yes
Comprehensive bibliographic search: at least two databases searched	yes
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	yes
Searched also unpublished studies	no
Language restriction	yes (only studies in English, French, German, Spanish or Italian)

Overall number of references retrieved and n of included studies reported	yes
N. and references of excluded studies reported, reason given	no
Characteristics of included studies clearly reported in tables	yes
Methodological quality of primary studies assessed; criteria reported	no; no
Results of quality assessment used to formulate results and conclusions	yes
Meta-analysis performed with appropriate statistic methods	no, only narrative results
Publication bias assessed	no
N. of included studies study design	total 8 5 to predict prognosis, of which 2 and 1 on HL and NHL patients only, respectively and 2 on a mixed population of patients 3 studies on the investigation of residual mass (2 on HL patients and 1 on a mixed population of patients) unclear
N. of included patients	58 with HL or NHL 65 with HL (median: 32.5, range: 29-36)
Reference standard	follow up
Comparator	Ga scanning, erythrocyte sedimentation rate (ESR), CT
Performance results	narrative results only. PET shows similar sensitivity to CT but better specificity.
Impact on management	not assessed
Impact on clinical outcome	not assessed
Recommendations and conclusions	Five new PSs showed that PET was a better predictor of relapse after therapy than CT. There is no evidence that this information has been used to inform subsequent treatment. There is evidence (one SR reviewing eight PSs of PET, and three additional PSs) that post-therapy PET had similar sensitivity and better specificity than Ga scanning and CT scanning to evaluate residual masses. An economic evaluation in advanced HL showed that PET was highly cost-effective (£ 5 000 per life-year) and predicted large savings in unnecessary consolidation RT when used instead of CT, or after CT-positive scans.

Author, year	**Kirby 2007**
Technology	FDG-PET
Disease	Hodgkin's disease and non-Hodgkin's lymphoma
Objective	to assess: ▪ primary diagnosis ▪ staging (before treatment) ▪ response to treatment (during treatment) ▪ **x** response to treatment (end of treatment) ▪ follow up in asymptomatic patients ▪ diagnosis of suspected recurrence ▪ recurrence ▪ impact on management ▪ impact of clinical outcomes
Inclusion criteria	P patients with Hodgkin's disease or non-Hodgkin's lymphoma I FDG-PET C CT, conventional imaging studies (CIS) R histology, follow up, other imaging techniques O diagnostic accuracy (sensitivity, specificity, PPV, NPV) S retrospective or prospective studies, evaluating post-treatment patients
Years covered by the search	January 1997 to July 2005
Study selection data abstraction, quality assessment performed by two authors independently	unclear
Comprehensive bibliographic search: at least two databases searched	yes
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 studies)
Overall number of references retrieved and n of included studies reported	no
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	unclear; no

Results of quality assessment used to formulate results and conclusions	yes
Meta-analysis performed with appropriate statistic methods	no
Publication bias assessed	no
N. of included studies study design	total: 26; 4/27 only on NHL patients, 13/27 including HL and NHL patients as well; 9/27 only including HL patients unclear
N. of included patients	270 with NHL (median: 66; range: 45-93) 360 with HL (median: 36, range: 26-63) 650 with HL or NHL (median: 40; range: 19-101)
Reference standard	unclear
Comparator	CT, conventional imaging studies
Performance results	FDG-PET, NHL patients only (4/26 studies) sensitivity: range 60-87% specificity: range 94-100% PPV: range 83-100% NPV: range 83-95% accuracy: range 87-90% FDG-PET, studies on a mixed population (13/26 studies) sensitivity: median 86% (43-100%) specificity: median 95% (73-100%) PPV: 88% (56-100%) NPV: 93% (83-100%) accuracy: 91% (80-97%) median PFS at 1-3 years in PET positive pts: 11% (0-31%) median PFS at 1-3 years in PET negative pts: 91% (81-100%)
Impact on management	not assessed
Impact on clinical outcome	not assessed
Recommendations and conclusions	none

Author, year	**Kwee 2008**
Technology	FDG-PET or FDG-PET/CT
Disease	malignant lymphoma
Objective	to assess: ▪ primary diagnosis ▪ staging (before treatment) ▪ response to treatment (during treatment) ▪ **X** restaging (after treatment) (residual disease) ▪ follow up in asymptomatic patients ▪ diagnosis of suspected recurrence ▪ recurrence ▪ impact on management ▪ impact of clinical outcomes
Inclusion criteria	P patients with malignant lymphoma I FDG-PET or FDG-PET/CT (CT and WB-MRI) during and after treatment C other imaging techniques R pathology confirmation or follow up of at least 6 months O diagnostic accuracy S comparative trials, at least 6-month follow up, giving separate results for staging and restaging; excluded studies investigating only bone marrow involvement, with a number of patients <10, not providing absolute numbers of diagnostic performances (necessary to provide confidence intervals)
Years covered by the search	until 25th July 2007
Study selection data abstraction, quality assessment performed by two authors independently	yes
Comprehensive bibliographic search: at least two databases searched	yes
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	unclear
Searched also unpublished studies	no
Language restriction	yes (only studies in English, German, French)
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
Results of quality assessment used to formulate results and conclusions	yes
Meta-analysis performed with appropriate statistic methods	not possible due to different scoring systems used
Publication bias assessed	no
N. of included studies study design	total of 19 (4/19 prospective) 2 on NHL patients, 10 on a mixed population, 7 on HL patients 3 investigating CT, 17 investigating FDG-PET, 4 investigating FDG-PET/CT
N. of included patients	123 with NHL (median 61.5; range: 45-78) 259 with HL (median: 32, range: 23-66) 556 with HL or NHL (median: 45.5; range: 18-101)
Reference standard	histology or follow up≥ 6 months
Comparator	not specified
Performance results	**FDG-PET** NHL patients (5 studies) sensitivity: 60-87% specificity: 80-100% Mixed population (6 studies) sensitivity: 60-100% specificity: 57.1-100% **FDG-PET/CT fusion** NHL: no study Mixed population (3 studies) sensitivity: 92.9-100% specificity: 90.7-100% **CT** NHL: no study NHL+HL (2 studies) sensitivity: 25-100% specificity: 41.7-58.8%
Impact on management	not assessed
Impact on clinical outcome	not assessed

Recommendations and conclusions	In conclusion, the studies included in this systematic review were of moderate methodological quality and used different scoring systems to stage malignant lymphoma. CT remains the standard imaging modality for initial staging of malignant lymphoma, while FDG-PET has an essential role in restaging. Early results suggest that FDG-PET/CT fusion outperforms both CT alone and FDG-PET alone. Data on the diagnostic performance of WB-MRI are lacking. Future well-designed studies, expressing their results according to the Ann Arbor staging system, are needed to determine which imaging modality is most accurate and cost-effective in staging malignant lymphoma.
Notes	

Author, year	**Terasawa 2008**
Technology	FDG-PET
Disease	aggressive NHL
Objective	to assess: ▪ primary diagnosis ▪ staging (before treatment) ▪ response to treatment (during treatment) ▪ **X** response to treatment (end of treatment)/restaging (residual disease) ▪ follow up in asymptomatic patients ▪ diagnosis of suspected recurrence ▪ recurrence ▪ impact on management ▪ impact of clinical outcomes
Inclusion criteria	P patients with Hodgkin's lymphoma or aggressive NHL I FDG-PET C other imaging techniques (CT, MRI, ultrasonography) R histological confirmation and/or follow up O diagnostic accuracy S on at least 10 patients that completed first-line chemotherapy or radiotherapy or chemo-radiotherapy followed by clinical follow up with or without pathological confirmation, with data available on individual patients (units of analysis instead of lesions/organs)
Years covered by the search	from January 1966 to July 2006
Study selection, data abstraction, quality assessment performed by two authors independently	unclear
Comprehensive bibliographic search: at least two databases searched	yes
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	yes
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	yes

clearly reported in tables	
Methodological quality of primary studies assessed; criteria reported	yes; yes
Results of quality assessment used to formulate results and conclusions	yes
Meta-analysis performed with appropriate statistic methods	meta-analysis not performed: too few data points to reliably estimate the summary ROC curves and confidence regions for summary sensitivity and specificity
Publication bias assessed	yes
N. of included studies study design	19 (3 on aggressive NHL only, 6 on HL and aggressive NHL as well, 10 on HL patients only) 14/19 retrospective; only 1 assessing FDG-PET/CT accuracy age: 2-85 median time from therapy completion to PET: 1-5.2 months; median follow up: 9.3-62 months
N. of included patients	254 with NHL (median: 29.5, range: 5-73) 474 with HL (median: 31, range: 5-71)
Reference standard	clinical follow up with or without histological confirmation
Comparator	none reported
Performance results	**FDG-PET, NHL patients** sensitivity: 33-77% specificity: 82-100% **FDG-PET, NHL patients with residual mass at CT** sensitivity: 33-87% specificity: 75-100% Meta-analysis not performed because there were too few data points to reliably estimate the summary ROC curves and confidence regions for summary sensitivity and specificity
Impact on management	not assessed
Impact on clinical outcome	not assessed
Recommendations and conclusions	The currently available data show that 18F-FDG-PET has good overall accuracy in detecting residual disease only in patients with HD who have completed first-line therapy. The current literature has methodological weaknesses that may overestimate accuracy. Because data from original studies are limited, our review could not find robust evidence to answer the question of whether clinicians should routinely use PET to assess the post-therapeutic response, suggesting that they should be cautious about making clinical decisions based solely on a PET result.
Notes	

Author, year	**Zijlstra 2006**
Technology	FDG-PET
Disease	Hodgkin's disease and (aggressive) non-Hodgkin's lymphoma
Objective	to assess: ▪ primary diagnosis ▪ staging (before treatment) ▪ response to treatment (during treatment) ▪ **X** response to treatment (end of treatment) ▪ follow up in asymptomatic patients ▪ diagnosis of suspected recurrence ▪ recurrence ▪ impact on management ▪ impact of clinical outcomes
Inclusion criteria	P histologically proven Hodgkin's disease and (aggressive) non-Hodgkin's lymphoma I dedicated FDG-PET C not specified R histology or follow up of at least 12 months O diagnostic accuracy (sensitivity, specificity, PPV, NPV) S retrospective or prospective studies of at least 10 patients in which evaluation of post-treatment patients following first-line therapy
Years covered by the search	until January 2004
Study selection data abstraction, quality assessment performed by two authors independently	yes
Comprehensive bibliographic search: at least two databases searched	yes
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	only reference list of retrieved articles
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; yes ("The studies included were of moderate methodological quality, with a 40% score for internal validity, and a 64% score for external validity)
Results of quality assessment used to formulate results and conclusions	yes
Meta-analysis performed with appropriate statistic methods	yes
Publication bias assessed	no
N. of included studies study design	15 2/15 only on NHL, 8/15 including HL as well NHL patients, 5/15 only including HL patients prospective (6/15), retrospective (9/15); consecutive enrolment in 2/15 studies prospective + retrospective (1/15)
n. of included patients	138 with NHL (median: 69; range: 45-93) 202 with HL (median: 37, range: 26-60) 418 with HL or NHL (median: 52; range: 32-88)
Reference standard	histology (only for a minority of patients), radiology and follow up (median >18 months)
Comparator	
Performance results	diagnostic accuracy FDG-PET, NHL patients (5 studies/15) sensitivity: 72% (95% CI 61-82) specificity: 100% (95% CI 94-100) negative likelihood ratio (LR-): 0.28 (95% CI 0.20-0.41) positive likelihood ratio (LR+): 37 (95% CI 11-127)
Impact on management	not assessed
Impact on clinical outcome	impossible to assess due to the "variability of the applied endpoints (overall survival, progression-free survival, relapse-free survival, disease-free survival) […] and the lack of specified data for Hodgkin's and non-Hodgkin's lymphoma as separate entities. There was no apparent inverse relation between sensitivity and specificity for either HD or NHL (Spearman -0.4 and -0.3, respectively)"
Recommendations and conclusions	The presently available evidence on the diagnostic performance of FDG-PET in evaluating the response to first-line therapy for HD and NHL is useful. Standardization of procedures is required before implementation in clinical practice. FDG-PET appears to be the most helpful non invasive modality for differentiating tumor recurrence from fibrosis when CT scanning shows a residual mass. If abnormal FDG-uptake is seen, further investigation is mandatory. In the case of a negative PET-scan, no further investigations at that particular time point are necessary, but minimal residual disease and the risk of a late relapse cannot be completely excluded.
Notes	

Synoptic table of primary studies assessing diagnostic accuracy at the end-of-treatment evaluation of response to therapy in patients with aggressive non-Hodgkin's lymphoma

Author, year	Disease	Patient number	Techno-logy	Reference test	FDG-PET sensitivity	FDG-PET specificity	FDG-PET PPV	FDG-PET NPV	FDG-PET accuracy	Comparator	Comp. sensitiv.	Comp. specific.	Comp. PPV	Comp. NPV	Comp. accuracy
Altamirano 2008	HL or NHL	28 (7 HL, 21 aggress. NHL)	FDG-PET	follow up (median 18 months, range: 6-24 months)	100%	95%				CT	83%	63%			
Bucerius 2006	HL or NHL	79 (30 HL, 49 aggress. NHL)	FDG-PET	histopathology and/or follow up	69%	90%				CT	91%	38%			
Riad 2010	HL or NHL	51 (45 HL, 6 aggress. NHL)	FDG-PET/CT	histopathology and/or follow up	100%	98%				conventional imaging methods (CT, MRI, US)	83%	67%			
Talavera Rubio 2009	HL or NHL	29	FDG-PET/CT	biopsy (2 pts), or clinical follow up (mean: 14,5 months)	96%	98%				contrast-enhanced CT	95%	95%			

Primary studies

Author, year	Altamirano 2008
Country	Mexico
Technology	18F-FDG-PET
Disease	Hodgkin's lymphoma and non-Hodgkin's lymphoma
Objective	to determine the diagnostic accuracy of 18FDG after three cycles and at the end of chemotherapy in non-Hodgkin's lymphoma (NHL) or Hodgkin's lymphoma (HL)
Patients characteristics	40 patients but only 28 patients where studied 15 patients were female (53.6%) and 13 were male (46.4%) with a mean age of 43 years (range: 15-74 years) 7 patients corresponded to HL diagnosis (25%) and 21 to NHL (75%)
Index test	18F-FDG-PET
Comparator	CT
Reference standard	follow up; guidelines established by the International response evaluation criteria in solid tumors Group (RECIST)
Outcomes considered	sensitivity, specificity, diagnostic accuracy, PPV, NPV
Study design	prospective cross-sectional study
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not clear
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	no
Independent and blind interpretation of index test and reference standard results	yes
Withdrawals from the study explained	not applicable

Pre-test probability	
Results	18F-FDG-PET sensitivity: 100% specificity: 95% accuracy: 96% PPV: 90% NPV: 100% CT sensitivity: 83% specificity: 63% accuracy: 68% PPV: 41% NPV: 92%
Authors' recommendations and conclusions	18FDG had greater prognostic values than CT after the third and last cycle of chemotherapy. PET after three cycles of chemotherapy is predictive of 18-month outcome in patients with intermediate and aggressive NHL and HL and may help in the identification of patients who would benefit from more intensive treatment or from a change in chemotherapy.

Author, year	**Bucerius 2006**
Country	Germany
Technology	FDG-PET
Disease	Hodgkin's lymphoma and non-Hodgkin's lymphoma
Objective	to compare the performance of FDG-PET and conventional imaging (CI) at three different time points during the course of the disease including diagnosis of recurrence
Patients characteristics	169 patients (59 female, 110 male: aged 45.9±14,8 years; range 15-80 years) with histologically proven HD (69-41%) or NHL (100-59%); staging at baseline (42 patients), monitoring response to treatment (79 patients), diagnosis of recurrence (48 patients)
Index test	FDG-PET
Comparator	CT
Reference standard	histological examination and/or clinical follow up
Outcomes considered	sensitivity, specificity, diagnostic accuracy, PPV, NPV
Study design	retrospective cross-sectional study
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	yes
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	no
Execution of the reference standard described	no
Independent and blind interpretation of index test and reference standard results	yes
Withdrawals from the study explained	not applicable
Pre-test probability	

Results	FDG-PET sensitivity: 69% specificity: 90% accuracy: 83% PPV: 77% NPV: 85% CT sensitivity: 91% specificity: 38% accuracy: 55% PPV: 42% NPV: 90%
Authors' recommendations and conclusions	FDG-PET appears to be superior to CI for monitoring response to treatment.

Author, year	**Riad 2010**
Country	Egypt
Technology	18F-FDG-PET/CT
Disease	Hodgkin's lymphoma and non-Hodgkin's lymphoma
Objective	to evaluate the performance of 18F-FDG-PET/CT and to compare diagnostic accuracy of 18F-FDG-PET/CT with conventional imaging modalities(CIM) in the evaluation of early treatment response in Hodgkin's and non-Hodgkin's lymphoma
Patients characteristics	152 total patients (35 female and 117 male) with histologically proven malignant lymphoma 8 117 HD, 35, NHL) range age 3-18 years They were divided into four groups: Group I: 41 patients for initial staging Group II: 51 patients (45 HD, 6 NHL) for evaluating early treatment response after two to three cycles of chemotherapy. Five patients were stage I, 20 were stage II, 18 were stage III and 8 were stage IV Group III: 42 patients for evaluating treatment response 4-8 weeks after the end of their treatment Group IV: 18 patients evaluated for long-term follow up
Index test	18F-FDG-PET
Comparator	conventional imaging modalities (CIM - CT, MRI, US, physical examination, bone marrow biopsy when available)
Reference standard	histopathological exam and clinical follow up
Outcomes considered	sensitivity, specificity, diagnostic accuracy, PPV, NPV
Study design	retrospective cross-sectional study
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 clear
Execution of the index and comparator tests adequately described	yes

Did patients receive the same reference standard regardless of the index test result	no
Execution of the reference standard described	no
Independent and blind interpretation of index test and reference standard results	not clear
Withdrawals from the study explained	not applicable
Pre-test probability	
Results	18F-FDG-PET/CT sensitivity: 100% specificity: 90.9% accuracy: 92.8% PPV: 75% NPV: 100% CIM sensitivity: 55.5% specificity: 57.5% accuracy: 57.1% PPV: 26.3% NPV: 82.6%
Authors' recommendations and conclusions	PET/CT in paediatric lymphoma is more accurate than CIM. We recommend that it should be the first modality for all purposes in initial staging, evaluating treatment response and follow up.

Author, year	**Talavera Rubio 2009**
Country	Spain
Technology	18F-FDG-PET/CT
Disease	Hodgkin's lymphoma and non-Hodgkin's lymphoma
Objective	to define the utility of intravenous contrast administration in the PET-CT (PET-CTc) in patients with lymphoma in order to determine its possible indications
Patients characteristics	142 patients with malignant lymphoma but only those with a final diagnosis established (78, 47 males and 31 females) were included FDG-PET was used to evaluate end-of treatment response in 28 patients (15 female and 13 male, mean age: 43 years, range: 15-74 years) 7 patients had HL (25%) and 21 NHL (75%)
Index test	18F-FDG-PET
Comparator	CT
Reference standard	clinical and radiological follow up every 6 months; median follow up 18 months (range 6-24 months)
Outcomes considered	sensitivity, specificity, diagnostic accuracy, PPV, NPV
Study design	prospective cross-sectional study
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	not clear
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	yes
Execution of the reference standard described	no
Independent and blind interpretation of index test and reference standard results	not clear

Withdrawals from the study explained	not applicable
Pre-test probability	
Results	18F-FDG-PET/CT sensitivity: 100% specificity: 95% accuracy: 96% PPV: 90% NPV: 100% CT sensitivity: 83% specificity: 63% accuracy: 68% PPV: 41% NPV: 92%
Authors' recommendations and conclusions	18FDG had greater prognostic values than CT after the third and last cycle of chemotherapy. PET after three cycles of chemotherapy is predictive of 18-month outcome in patients with intermediate and aggressive NHL and HL and may help in the identification of patients who would benefit from more intensive treatment or from a change in chemotherapy.

CHAPTER 14
Follow up of patients treated for aggressive non-Hodgkin's lymphoma, with no suspicion of recurrence

Diagnostic accuracy

Systematic reviews

None included.

Synoptic table of primary studies on follow up of asymptomatic patients treated for aggressive non-Hodgkin's lymphoma

Author, year	Disease	N. of patients	Mean/ median age	Mean/ median follow up (months)	Range follow up	Pre-test probability	Index test	Reference test	Compa-rator	Sens. index	Spec. index	PPV index	NPV index
El-Galaly, 2011	diffuse large B-cell lymphoma: 43 T-cell lymphoma: 6 follicular lymphoma grade 3: 1 Burkitt lymphoma: 2	52	61	18	3-25	7,7%	FDG-PET/CT	follow up, biopsy or radiological findings	none	100%	81%	31%	100%
Petrausch, 2010b	DLBCL	35	60	16,5	6-93	8,6%	FDG-PET/CT	biopsy (suspected recurrence) and follow up	none	100%	97%	75%	100%
Zinzani, 2007c	DLBCL + PMLBCL	94	52	22	8-46	7,4%	FDG-PET	PET+: histological findings	none	100%	98%	78%	100%

Primary studies

Author, year	El-Galaly 2011
Technology	FDG-PET/CT
Disease	Aggressive NHL
Objective	To investigate the value of routine PET/CT surveillance
Patients characteristics	total number of patients: 52 (100%) sex (male, female): 31, 21 median age at diagnosis (years): 61 diffuse large B-cell lymphoma: 43 (82%) T-cell lymphoma: 6 (12) follicular lymphoma grade 3: 1 (2%) Burkitt lymphoma: 2 (4%) Ann Arbor stage I at diagnosis: 13 (25%) stage II at diagnosis: 8 (15%) stage III at diagnosis: 14 (27%) stage IV at diagnosis: 17 (33%) extra-nodal disease: 22 (42%) B-symptoms at diagnosis: 25 (48%) elevated lactate dehydrogenase at diagnosis 23: (44%) high risk (IPI 4-5): 6 (12%) high-intermediate risk (IPI 3): 10 (19%) low-intermediate risk (IPI 2): 15 (29%) low risk (IPI 0-1): 21 (40%)
Index test	FDG-PET/CT
Comparator	
Reference standard	follow up, biopsy or radiological findings
Country	Denmark
Outcomes considered	specificity, sensitivity, and cost-effectiveness
Study design	retrospective
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

<table>
<tr><td>Execution of the index and comparator tests adequately described</td><td>yes</td></tr>
<tr><td>Did patients receive the same reference standard regardless of the index test result</td><td>no</td></tr>
<tr><td>Execution of the reference standard described</td><td>no</td></tr>
<tr><td>Independent and blind interpretation of index test and reference standard results</td><td>no</td></tr>
<tr><td>Withdrawals from the study explained</td><td>no withdrawals</td></tr>
<tr><td>Pre-test probability</td><td>7.69% (4/52)</td></tr>
<tr><td>Results</td><td>
<table>
<tr><th></th><th colspan="2">1st surv. PET/CT</th><th colspan="2">2nd surv. PET/CT</th><th colspan="2">3rd surv. PET/CT</th><th colspan="2">4th surv. PET/CT</th></tr>
<tr><th></th><th>n</th><th>%</th><th>n</th><th>%</th><th>n</th><th>%</th><th>n</th><th>%</th></tr>
<tr><td>TP</td><td>1</td><td>2</td><td>1</td><td>2</td><td>1</td><td>3</td><td>1</td><td>7</td></tr>
<tr><td>FP</td><td>4</td><td>8</td><td>5</td><td>12</td><td>5</td><td>17</td><td>1</td><td>7</td></tr>
<tr><td>TN</td><td>47</td><td>90</td><td>36</td><td>86</td><td>23</td><td>80</td><td>13</td><td>86</td></tr>
<tr><td>FN</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Total</td><td>52</td><td>100</td><td>42</td><td>100</td><td>29</td><td>100</td><td>15</td><td>100</td></tr>
</table>
specificity: 89% (based on number of scans); 81% (recalculated on number of patients)

sensitivity: 100%

PPV: 21% (based on number of scans); 31% (recalculated on number of patients)

NPV: 100%

The median SUVmax
▪ in false-positive PET/CTs was 6.4 (range 2.1-12.8)
▪ in true-positive PET/CTs was 10.5 (range 5.8-14), (p=0.06 for difference between the two groups)
The PPV was increased to 60% if only PET/CTs showing clear CT pathology with SUVmax above 5.5 were interpreted as positive
The NPV largely remained unaffected at 99%
Additional cost for early discovery of one relapse:
US$ 241,224 (differential cost of doing PET/CT instead of contrast-enhanced CT in our cohort)
</td></tr>
</table>

Authors' recommendations and conclusions	Routine PET/CT surveillance in asymptomatic patients with aggressive NHL in CR is effective in detecting disease recurrence. PET/CT surveillance is severely limited by the considerable number of false-positive PET/CTs and the high costs of the procedure. Our analysis supports the initiation of collaborative prospective validation studies including a health technology assessment.
Notes	

Author, year	**Petrausch 2010b**
Technology	FDG-PET/CT
Disease	NHL: diffuse large B-cell lymphoma
Objective	to evaluate the impact of FDG-PET/CT during follow up of patients with diffuse large B-cell lymphoma (DLBCL) being in complete remission or unconfirmed complete remission after first-line therapy
Patients characteristics	overall, 75 patients with confirmed DLBCL: 45 male, 30 female age: mean 60; range from 23 to 90 years follow up: median: 16.5 months; range 6-93 months asymptomatic patients (n = 35), (n, %) morphological residual mass: yes: 14, 40% no: 21, 60% stage of disease: early (IA-IIB): 23, 65.7% advanced (IIIA-IVB): 12, 34.3% extra-nodal disease: yes: 17, 50% no: 17, 50% advanced age (years): <60: 20, 57.2% >60: 15, 42.8% symptomatic patients (n = 40), (n, %) morphological residual mass: yes: 32, 80% no: 8, 20% stage of disease: early (IA-IIB): 17, 42.5% advanced (IIIA-IVB): 23, 57.5% extra-nodal disease: yes: 20, 50% no: 20, 50% advanced age (years): <60: 14, 35% >60: 26, 65 %
Index test	FDG-PET/CT
Comparator	
Reference standard	biopsy (suspected recurrence) and follow up
Country	Switzerland
Outcomes considered	diagnostic accuracy
Study design	retrospective

Spectrum of patients representative of the individuals who will receive the test in practice	unclear		
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	unclear		
Execution of the index and comparator tests adequately described	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	no		
Withdrawals from the study explained	no withdrawals		
Pre-test probability	30% overall 8.6% asymptomatic patients 50% symptomatic patients		
Results		Signs ClinRel	No signs ClinRel
	all patients, n = 75	40	35
	PET/CT positive	23 (57.5%)	4 (11.5%)
	biopsy positive	20 (50%)	3 (8.6)
	<60 years, n = 34	14	20
	PET/CT positive	4 (28.6%)	1 (5%)
	biopsy positive	4 (28.6%)	1 (5%)
	>60 years, n = 41	26	15
	PET/CT positive	19 (73.1%)	3 (20%)
	biopsy positive	16 (61.5%)%	2 (13.3%)
	PPV = 85%		
	Asymptomatic patients on follow up (calculated by ASSR reviewer from raw data) sensitivity: 100% specificity: 97%		

Authors' recommendations and conclusions	FDG-PET/CT detects recurrent DLBCL after first-line therapy with high PPV. However, it should not be used routinely and if only in selected high-risk patients to reduce radiation burden and costs. FDG-PET/CT during follow up is indicated for patients <60 years with clinical signs of relapse and in patients >60 years with and without clinical signs of relapse.
Notes	

Author, year	**Zinzani 2007c**		
Technology	FDG-PET		
Disease	mediastinal lymphoma		
Objective	to verify the reliability of positive PET scans of the mediastinum in following up patients with mediastinal lymphoma		
Patients characteristics		HD	Aggressive NHL
	n. of patients	57	94
	age (years)		
	median	26	52
	range	16-42	28-65
	sex		
	male	30	54
	female	27	40
	histology		
	DLBCL		84
	PMLBCL		10
	stage		
	I-II	52	85
	III-IV	5	9
	bulky disease	25	52
Index test	FDG-PET		
Comparator			
Reference standard	histological findings		
Country	Italy		
Outcomes considered	diagnostic accuracy		
Study design	retrospective		
Spectrum of patients representative of the individuals who will receive the test in practice	unclear		
Patients selection criteria clearly described	yes		
Verification by reference standard of all subjects	yes		
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	yes		
Execution of the index and comparator tests adequately described	yes		

Did patients receive the same reference standard regardless of the index test result	yes (different biopsy technique based on index test results)
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	no
Withdrawals from the study explained	no withdrawals
Pre-test probability	NHL: 7.45% (7/94); [All: 11.26% (17/151)]
Results	True Positive PET/Positive PET all 57% - 17/30 NHL 77.78% - 7/9; Calculated PET accuracy parameters for HD: sensitivity: 100% specificity: 98% PPV: 78% NPV: 100%
Authors' recommendations and conclusions	A positive PET scan of the mediastinum of a patient being followed up for a mediastinal lymphoma should not be considered sufficient for diagnostic purposes in view of its lack of discrimination. Histological confirmation can safely be carried out with various biopsy techniques, the choice of which should be made on the basis of the findings of the clinical and imaging studies of the individual case.
Notes	

CHAPTER 15
Staging of recurrence in patients treated for aggressive non-Hodgkin's lymphoma

Diagnostic accuracy

Systematic reviews

Author, year	Wu 2012
Technology	FDG-PET or FDG-PET/CT
Disease	malignant lymphoma
Objective	to assess: ▪ primary diagnosis ▪ **X** staging (before treatment) ▪ response to treatment (during treatment) ▪ restaging (after treatment) (residual disease) ▪ follow up in asymptomatic patients ▪ diagnosis of suspected recurrence ▪ recurrence ▪ impact on management ▪ impact of clinical outcomes
Inclusion criteria	P patients with malignant lymphoma I FDG-PET or FDG-PET/CT or MRI C not specified R histopathology and/or close clinical and imaging follow up of at least 6 months O diagnostic accuracy S articles of ten or more patients included, raw data available (excluded reviews, case reports, letters etc)
Years covered by the search	January 1995 - July 2010
Study selection data abstraction, quality assessment performed by two authors independently	yes
Comprehensive bibliographic search: at least two databases searched	yes
Searched also specialized register, conference proceedings, reviews, textbooks and reference list of retrieved studies	no
Searched also unpublished studies	no
Language restriction	yes (only studies in English and Chinese)

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
Results of quality assessment used to formulate results and conclusions	no
Meta-analysis performed with appropriate statistic methods	yes
Publication bias assessed	yes
N. of included studies study design	32 (5 on PET/CT, 20 on PET and 8 on MRI) retrospective (14/32), prospective (11/32), ND (7/32)
N. of included patients	1 845 (775 with NHL, 690 with HL, 380 with HL or NHL)
Reference standard	histopathology and/or close clinical and imaging follow up of at least 6 months
Comparator	MRI
Performance results	bone marrow involvement detection PET/CT sensitivity: mean 91.6% (95% CI 85.1-95.9) (highly heterogeneous, heterogeneity chi-squared = 45.63) specificity: mean 90.3% (95% CI 85.9-93.7%) (heterogeneity chi-squared = 10.18) PET sensitivity: mean 81.5% (95% CI 77.3-85.3%) (highly heterogeneous, heterogeneity chi-squared = 187.03) specificity: mean 87.3% (95% CI 84.9-89.5%) (highly heterogeneous, heterogeneity chi-squared = 270.59) MRI sensitivity: mean 90.3% (95% CI 82.4-95.5%) (heterogeneity chi-squared = 25.83) specificity: mean 75.9% (95% CI 69.8-81.2%) (heterogeneity chi-squared = 21.12)
Impact on management	not assessed
Impact on clinical outcome	not assessed

Recommendations and conclusions	PET/CT was a highly sensitive and specific modality in diagnosing patients with bone marrow involvement in lymphoma, Compared with MRI and PET alone, PET/CT can play much more important roles in staging of lymphoma.
Notes	

Primary studies

Author, year	**Bucerius 2006**
Country	Germany
Technology	FDG-PET
Disease	Hodgkin's lymphoma and non-Hodgkin's lymphoma
Objective	to compare the performance of FDG-PET and conventional imaging (CI) at three different time points during the course of the disease including diagnosis of recurrence
Patients characteristics	169 patients (59 female, 110 male: aged 45.9±14,8 years; range 15-80 years) with histologically proven HD (69) or NHL (100); staging at baseline (42 patients), monitoring response to treatment (79 patients), diagnosis of recurrence (48 patients)
Index test	FDG-PET
Comparator	CT
Reference standard	histological examination and/or clinical follow up
Outcomes considered	sensitivity, specificity, diagnostic accuracy, PPV, NPV
Study design	retrospective cross-sectional study
Spectrum of patients representative of the individuals who will receive the test in practice	yes
Patients selection criteria clearly described	yes
Verification by reference standard of all subjects	yes
Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	yes
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	no
Execution of the reference standard described	no
Independent and blind interpretation of index test and reference standard results	yes
Withdrawals from the study explained	not applicable
Pre-test probability	

Results	FDG-PET sensitivity: 98% specificity: 75% accuracy: 94% PPV: 95% NPV: 86% CT sensitivity: 100% specificity: 88% accuracy: 98% PPV: 98% NPV: 100%
Authors' recommendations and conclusions	The extent of disease could be more reliably assessed by FDG-PET than by CT for staging at baseline and monitoring response treatment but not for diagnosis of recurrence.

Author, year	**Mohile 2008**
Technology	FDG-PET
Disease	primary central nervous system lymphoma
Objective	to determine the utility of FDG-PET in disclosing systemic foci of disease and to consider whether this test should be incorporated into the routine staging of PCNSL
Patients characteristics	49 patients (only 11 patients for recurrence) with a median age of 65 years (range: 35-80 years) who underwent 57 body FDG-PET scans were identified using the electronic medical record
Index test	FDG-PET
Comparator	conventional examinations
Reference standard	histology and follow up
Country	USA
Outcomes considered	sensitivity
Study design	retrospective study
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 clear
Execution of the index and comparator tests adequately described	yes
Did patients receive the same reference standard regardless of the index test result	no
Execution of the reference standard described	yes
Independent and blind interpretation of index test and reference standard results	not clear
Withdrawals from the study explained	not applicable
Pre-test probability	27.3%

Results	FDG-PET for systemic recurrence sensitivity: 100% specificity: 87.5% change in management the 3 patients for whom FDG-PET revealed recurrent systemic NHL all had a negative CT CAP, and two had a negative bone marrow biopsy. Treatment was modified in all (3/11 = 27.3%)
Authors' recommendations and conclusions	This is the first study to evaluate the role of body FDG-PET in the staging evaluation of PCNSL. Although it reflects a relatively large collection of patients, it is inherently limited by its retrospective nature. In particular, there may have been clinical suspicions in the patients selected for FDG-PET that were not evident by record review. Therefore, our findings need to be confirmed and validated in prospective studies in which FDG-PET is employed in the staging of PCNSL patients and compared to the yield of CT CAP and bone marrow biopsy. An emerging role for FDG-PET in staging could have important implications for the management of PCNSL as well as our understanding of this disease.

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. **(*)**
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228. Linee guida per la stesura e l'utilizzo della Carta dei servizi delle ASP. Bologna. **(*)**