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Recommendation Report PET #12

The Clinical Utility of Positron Emission Tomography in the Diagnosis, Staging, and Clinical Management of Patients with Lymphoma: Recommendation Report

C.T. Kouroukis, M. Cheung, J. Sussman, D. Hodgson, M. Freeman and S. Kellett

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Report Date: March 13, 2015

Evidence-Based Series PET #12 is comprised of 2 sections:	
Section 1:	Guideline Recommendations
Section 2:	Evidentiary Base

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Recommendation Report PET #12: Section 1

The Clinical Utility of Positron Emission Tomography in the Diagnosis, Staging, and Clinical Management of Patients with Lymphoma: Recommendation Report

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QUESTIONS

DIAGNOSIS AND STAGING

What benefit to clinical management does ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) contribute to the initial diagnosis or staging of lymphoma?

DIAGNOSIS OF RECURRENCE AND ROUTINE FOLLOW-UP

What benefit to clinical management does FDG PET/CT contribute after conventional imaging is performed, in patients with suspected or proven recurrence of lymphoma? What benefit to clinical management does FDG PET/CT contribute to routine follow-up at the time of documented recurrence for lymphoma?

RESPONSE EVALUATION (interim and at completion of therapy)

What benefit to clinical management does FDG PET/CT contribute to the interim assessment of treatment response and assessment of residual mass for lymphoma?

TARGET POPULATION

The target population for these recommendations is adult patients suspected of, with a diagnosis of, or recurrence of lymphoma including Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL).

INTENDED USERS

- This recommendation report is intended to guide the Ontario PET Steering Committee in their decision making concerning indications for the use of PET imaging.

- This recommendation report may also be useful in informing clinical decision making regarding the appropriate role of PET imaging and in guiding priorities for future PET imaging research.

RECOMMENDATIONS AND KEY EVIDENCE

These recommendations are based on an evidentiary foundation of one high-quality United Kingdom (UK) Health Technology Assessment (HTA) that included systematic review and primary study literature for the period from 2000 to August 2005 (1). An update of this systematic review was undertaken by the New Zealand Guidelines Group (NZGG) to retrieve the evidence from the period from August 2005 to November 2011 (2). The Program in Evidence-Based Care (PEBC) has endorsed and adapted this evidentiary base for the purpose of this recommendation report; however, 17 additional studies were added post hoc by the PEBC team due to differences in the research objectives of the NZGG and the PEBC. In the NZGG report, systematic reviews were included. This PEBC review did not include these systematic reviews due to overlap in the studies between the reviews; however, the references lists of these systematic reviews were checked to ensure that no primary studies were missed. From this point forward in this document, reference will only be made to the UK HTA (primary studies prior to August 2005) and the primary studies included in this recommendation report (primary studies from August 2005 to November 2011). Pediatric studies were included in the systematic review and qualitatively summarized in Section 2 of this report; however, they were not utilized as part of the evidentiary base for these recommendations.

RECOMMENDATIONS AND KEY EVIDENCE
Diagnosis

Recommendation(s):
A recommendation cannot be made for or against the use of FDG PET/CT for the diagnosis of lymphoma due to insufficient evidence.

***Key Evidence*:**
UK HTA (studies published prior to August 2005)
The UK HTA (1) included one primary study that evaluated the use of PET in eight patients with gastric NHL. Due to its small population, the authors concluded that PET is unlikely to be used routinely for the diagnosis of lymphoma because histological confirmation is always required.

Studies published after August 2005
In adult patients, one study (3) evaluated the utility of FDG PET (no co-registered CT component) in primary central nervous system lymphoma diagnosis. Forty-two scans were performed for the purpose of initial diagnosis and staging. FDG PET scans were abnormal in eight of 42 patients. Biopsies were obtained in six of the patients, of which five revealed malignancy. In three patients, FDG PET revealed systematic NHL. Three patients had false-positive results.

Qualifying Statements:

- FDG PET may disclose higher rates of systemic disease; however, due to false-positive results, FDG PET scans should be subject to clinical follow-up or biopsy.

Staging

Recommendation(s):
When functional imaging is considered to be important in situations where anatomical imaging is equivocal, and/or in potentially curable cases, a FDG PET/CT scan is recommended.

When functional imaging is considered to be important in situations where anatomical imaging is equivocal and treatment choices may be affected in limited stage indolent lymphomas, a FDG PET/CT scan is recommended.

***Key Evidence*:**
UK HTA (studies prior to August 2005)
The UK HTA (1) evaluated several studies relating to the initial staging of HL and NHL. PET was consistently shown to be of superior sensitivity to Gallium (^{67}Ga) scanning, and was more accurate than or comparable with CT for staging.

Studies published after August 2005
In terms of patient management, the addition of FDG PET/CT modified the management of 8% to 32% of patients across included studies, with the majority of patients being upstaged as a result of the identification of distant disease.

Studies evaluating the utility of FDG PET or PET/CT for initial staging in patients with both HL and NHL showed similar results (4-14). In most studies, the specificity was high for both conventional imaging and FDG PET (often >90%); however, the sensitivities varied widely across studies and were generally low due to a prevalence of false-negative cases. In patients with mucosa-associated lymphoid tissue lymphoma, PET scans at baseline were reported to pick up more sites of disease than conventional staging tests (15-18).

In the detection of bone marrow involvement, FDG PET/CT correctly identified bone marrow involvement in approximately 95% of cases and patients were staged appropriately (5,19). FDG PET/CT was also shown to be useful in the planning of directed bone marrow biopsy.

Qualifying Statements:

- There was some evidence to suggest that FDG PET/CT may miss small disease foci; however, in studies that compared FDG PET/CT with ^{67}Ga scanning, the diagnostic accuracy of FDG PET/CT was shown to be superior.

- In most cases, FDG PET/CT changed the management of several patients. Most patients were upstaged due to the identification of advanced disease stage; however, due to poor reporting and short follow-up, the clinical relevance and whether the change resulted in a better clinical outcome of the upstaging was unclear.

Response Evaluation (interim and at completion of therapy)

Recommendation(s):
An FDG PET/CT scan is recommended for the assessment of early response in early stage (I or II) HL following two or three cycles of chemotherapy when chemotherapy is being considered as the definitive single-modality therapy, to inform completion of therapy or if more therapy is warranted.

***Key Evidence*:**
UK HTA (studies prior to August 2005)
The UK HTA (1) included nine primary studies and concluded that there was some weak evidence, consisting mainly of small-scale observational studies, suggesting that FDG PET/CT may be predictive of therapeutic response following two to three cycles of chemotherapy. There was no evidence to suggest that the addition of interim FDG PET/CT changed patient management (such as intensification or change in therapy).

Studies published after August 2005
Evidence suggests that FDG PET/CT scans are superior to conventional anatomical imaging in assessing response to treatment both interim and at completion (10,11,20-31). Interim PET scan results appear to carry powerful prognostic information that can be predictive for treatment failure in patients with NHL and HL undergoing primary therapy. The available evidence indicates that a PET-positive scan at the completion of therapy is associated with poorer prognosis. Also, in patients with relapsed lymphoma who are undergoing salvage chemotherapy and autologous stem cell transplantation, PET scan results appear to be an independent predictive factor for progression-free survival, but are not as strong for overall survival.

Qualifying Statements:

- For interim response to treatment, data around the role of PET in this population are continuing to evolve and patients should be involved in prospective clinical trials conducted in a multidisciplinary setting.

Diagnosis of Suspected Recurrence and Routine Follow-up

Recommendation(s):
In potentially curable cases, when functional imaging is considered to be important and conventional imaging is equivocal, a FDG PET/CT scan is recommended to investigate recurrence of HL or NHL.

An FDG PET/CT scan is recommended for the evaluation of residual mass(es) following chemotherapy in a patient with HL or NHL when further, potentially curative, therapy (such as radiation or stem cell transplantation) is being considered and when biopsy cannot be safely or readily performed.

***Key Evidence*:**
UK HTA (studies prior to August 2005)
The UK HTA (1) included five primary studies that demonstrated that FDG PET/CT was a better predictor of relapse after therapy than CT. When compared with ^{67}Ga scanning and CT scanning, post-therapy FDG PET/CT had a similar sensitivity and better specificity.

Studies published after August 2005
In regard to recurrence, the current recommendation report included six studies evaluating adult patients (11,20,32-35) and three studies evaluating pediatric patients (21,36,37). FDG PET/CT showed a good concordance with conventional imaging in the detection of recurrence; however, due to a prevalence of false-positive results in these studies, PET-positive patients may benefit from clinical follow-up.

In this recommendation report, 11 primary studies (3,7,9,11,14,38-43) investigating FDG PET/CT in the routine follow-up of patients with lymphoma showed similar results with no significant differences between HL and NHL or adult and pediatric patients. Both specificity and sensitivities were high and were in good concordance with conventional imaging. Several studies also provided evidence that a pretransplant FDG PET/CT scan contained predictive information on the long-term clinical outcome of patients (7,44-46).

Qualifying Statements:

- In cases where FDG PET/CT scans have a positive result, patients may benefit from close clinical follow-up or confirmatory biopsy due to a prevalence of false positives in the literature.

Routine Surveillance

Recommendation(s):
An FDG PET/CT scan is not recommended for the routine monitoring and surveillance of lymphoma.

***Key Evidence*:**
Studies published after August 2005
Three studies evaluated the efficacy of FDG PET/CT in the routine surveillance of lymphoma patients (20,32,33). All studies noted increased false positives as well as a lack of evidence of cost effectiveness compared with conventional imaging. The costs incurred as a result of the false positive results were unacceptably high.

Qualifying Statements:

- The current standard of practice in Ontario is to follow patients clinically with history, physical examination, and routine blood work.

Qualifying Statements Applicable to all Recommendations:

- In cases where FDG PET/CT scans have a positive result, patients may benefit from close clinical follow-up or confirmatory biopsy due to a prevalence of false positives in the literature.

- Although most individual studies outlined the technical aspects of how the FDG PET or PET/CT scan was performed and reported, in most studies, the scans were not read by blinded readers and it is unclear whether technical differences may make studies more difficult to compare with one another.

- PET scans are not assumed to be perfect tests and they are associated with variable rates of false-positive and false-negative rates. Practitioners should keep this in mind when interpreting the results of a PET scan.

- With respect to HIV-positive lymphoma patients, only small studies that did not meet the inclusion criteria were found in the systematic literature search; however, the authors are aware of a higher prevalence of false-positive FDG PET/CT results due to higher standardized uptake values in areas of inflammation.

FUTURE RESEARCH

Future research should focus on conducting randomized controlled trials with larger sample sizes focusing on clinically and histologically more homogeneous populations using standardized FDG PET/CT protocols and interpretation criteria. Better standardization of diagnostic criteria with the involvement of well-trained assessors should also be emphasized due to the potential of inter-reader variability. It should also be a priority to incorporate FDG PET/CT scan results in the design of randomized clinical trials to better direct patient management. It is suggested, where possible, that patients be enrolled in clinical trials of PET-directed therapy.

We searched www.clinicaltrials.gov for phase III studies in NHL or HL and PET. The following studies are ongoing:

- Positron Emission Tomography Guided Therapy of Aggressive Non-Hodgkin's Lymphomas
- Very Early FDG-PET/CT-response Adapted Therapy for Advanced Hodgkin Lymphoma (H11)
- ^{18}F-fluorodeoxyglucose (^{18}F-FDG) Positron Emission Tomography in Oncology
- Fluorodeoxyglucose F 18 PET Scan-Guided Therapy or Standard Therapy in Treating Patients With Previously Untreated Stage I or Stage II Hodgkin's Lymphoma
- PET Scan in Planning Treatment in Patients Undergoing Combination Chemotherapy For Stage IA or Stage IIA Hodgkin Lymphoma
- Study Evaluating the Non-inferiority of a Treatment Adapted to the Early Response Evaluated With ^{18}F-FDG PET Compared to a Standard Treatment, for Patients Aged From 18 to 80 Years With Low Risk (aa IPI = 0) Diffuse Large B-cells Non Hodgkin's Lymphoma CD 20+
- Study Evaluating the Non-inferiority of a Treatment Adapted to the Early Response Evaluated With ^{18}F-FDG PET Compared to a Standard Treatment, for Patients Aged From 18 to 80 Years With Low Risk (aa IPI = 0) Diffuse Large B-cells Non Hodgkin's Lymphoma CD 20+
- Fludeoxyglucose F 18-PET/CT Imaging in Assessing Response to Chemotherapy in Patients With Newly Diagnosed Stage II, Stage III, or Stage IV Hodgkin Lymphoma

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Recommendation Report PET #12: Section 2

The Clinical Utility of Positron Emission Tomography in the Diagnosis, Staging and Clinical Management of Patients with Lymphoma: Evidentiary Base

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DRAFT Report Date: March 15, 2015

QUESTIONS

DIAGNOSIS AND STAGING

What benefit to clinical management does ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) contribute to the initial diagnosis or staging of lymphoma?

RESPONSE EVALUATION

What benefit to clinical management does FDG PET/CT contribute to the assessment of treatment response for lymphoma?

DIAGNOSIS OF SUSPECTED RECURRENCE AND ROUTINE FOLLOW-UP

What benefit to clinical management does FDG PET/CT contribute when recurrence of lymphoma is suspected but not proven?

What benefit to clinical management does FDG PET/CT contribute to routine follow-up at the time of documented recurrence for lymphoma?

INTRODUCTION

Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) are lymphoproliferative diseases that can present with different clinical manifestations and may be difficult to diagnose (1). Conventional methods for staging HL and NHL have included chest radiograph, CT or magnetic resonance imaging (MRI), bone scan, gallium scan (^{67}Ga), lymphangiogram, bone marrow biopsy, and laparotomy. While CT and MRI are still widely used to diagnose and stage malignant lymphomas, FDG PET/CT has become increasingly common due to its ability to provide functional imaging, which is essential, particularly in the evaluation of response to

treatment and potential residual disease. The purpose of this recommendation report is to provide a synthesis of the current evidence surrounding FDG PET/CT and provide recommendations with respect to PET in the diagnosis, staging, response evaluation, diagnosis of suspected recurrence, and routine follow-up of both HL and NHL.

METHODS

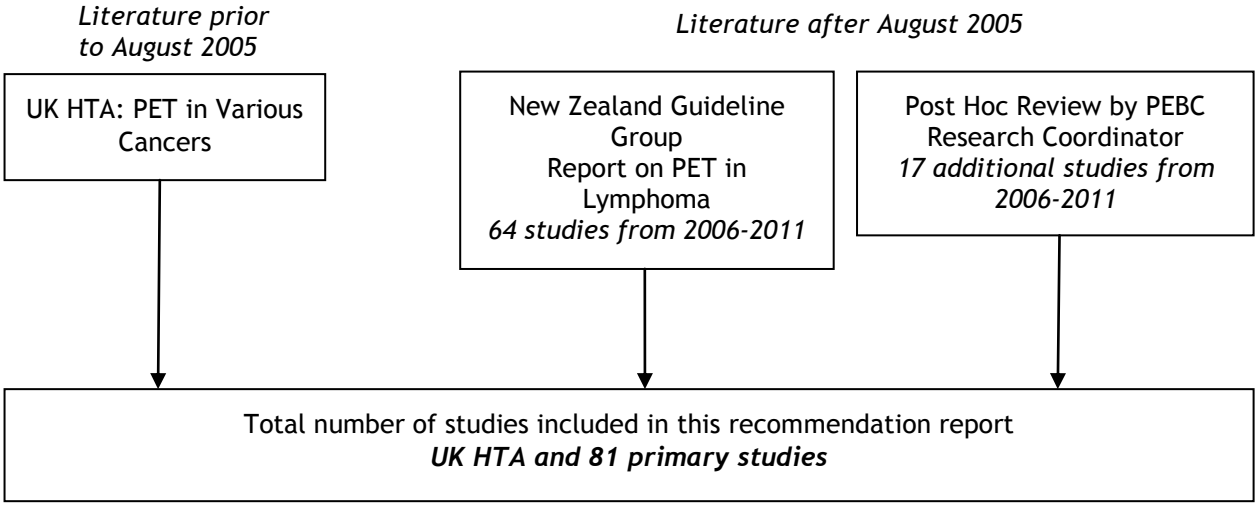
The Evidence-based Series guidelines developed by the Cancer Care Ontario Program in Evidence-Based Care (PEBC) use the methods of the Practice Guidelines Development Cycle (2). For this project, the core methodology used to develop the evidentiary base was the systematic review. Evidence was reviewed by four members of the Hematology Disease Site Group (DSG) (TK, MC, DH, JS), one nuclear medicine specialist (MF) and one PEBC methodologist (SK).

The body of evidence in this review is primarily comprised of a high-quality United Kingdom (UK) Health Technology Assessment (HTA) (3) and prospective and retrospective studies. That evidence forms the basis of the recommendations developed by the Working Group. This systematic review and companion recommendations are intended to promote evidence-based policy in Ontario, Canada. The PEBC is supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC and any associated Programs is editorially independent from the Ministry.

Literature Search Strategy

An a priori decision was made to use an existing systematic review by the New Zealand Guideline Group (NZGG) to serve as the evidentiary base. The NZGG systematic review was comprised of a UK HTA on PET in Various Cancers (3) that synthesized the relevant evidence to 2006, and additional studies published from 2006 to November 2011. The NZGG searched MEDLINE, EMBASE, and all other evidence-based medicine sources on OVID (including the Cochrane Database). The search strategies for MEDLINE and EMBASE are available upon request from the NZGG. The final reference list from the NZGG was reviewed in detail by the research coordinator from PEBC. Due to some variations between the PEBC and NZGG research objectives, it was determined by the PET Steering Committee and Working Group that there were 17 additional studies that contained data relevant to the PEBC research questions. As a result, these studies were added to this PEBC Recommendation Report post hoc. Details on the 17 additional studies can be found in Appendix 1 at the end of this report. In total, this PEBC Recommendation Report included 81 studies from 2006 to November 2011. In their report, the NZGG included systematic reviews. This PEBC review did not include these systematic reviews due to overlap in the studies; however, the references lists of these systematic reviews were checked to ensure that no primary studies were missed. From this point forward the literature will be identified as the UK HTA (literature prior to August 2005) and the 81 total primary studies reviewed for this PEBC Recommendation Report (2006 to November 2011).

Figure 1: Flow Diagram of the Studies Included in This Review



Study Selection Criteria

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they were fully published reports of any one of the following in patients with lymphoproliferative disorders:

1. Systematic reviews or practice guidelines or technology reports evaluating PET scan use.
   - Studies using PET or PET/CT scanning have been included in this systematic review; however, studies using PET/CT technology have been identified as having a higher value due to this technology being the status quo in the clinical setting in Ontario. Any studies utilizing FDG PET only are identified with bold text throughout Tables 1 to 6 of Appendix 2.
2. Any study (randomized controlled trials [RCTs], meta-analyses of RCTs, case control studies, or case series) reporting on the use of PET scans.

The studies were required to report on at least one of the following outcomes: overall survival (OS), disease response and duration, technical aspects regarding PET scan, and correlations or relationships between PET scans and other conventional imaging tests. High-quality evidence was the desired evidence (i.e., RCTs, prospectively conducted studies); however, where high-quality evidence was not available or was unable to answer the research questions, lower level studies were considered but their low quality was taken into consideration when interpreting the results.

Exclusion Criteria

1. Reports that included patients with various types of malignancies in which the results for patients with lymphoproliferative disorders were not reported separately.
2. Letters and editorials.
3. Single case reports or case series with <12 subjects.
4. Reports published in a language other than English.

Critical Appraisal

Diagnostic accuracy studies were appraised by the NZGG using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool, an internationally recognized and validated tool. The QUADAS tool, developed by the NHS centre for Reviews and Dissemination at the University of York, has five items related to verification bias, three items related to review bias, two items relating to generalizability and context and spectrum bias, and four items relating to reporting. Details on the quality assessment of the studies included in this report are available on request from the NZGG. The 17 additional studies identified in the post hoc review by the PEBC research coordinator also underwent quality assessment by the QUADAS tool.

International guidelines were appraised by using the Appraisal of Guidelines for Research and Evaluation (AGREE) Instrument. The AGREE II tool evaluated the process of practice guideline development and the quality of the reporting.

Synthesizing the Evidence

When clinically homogenous results from two or more trials were available, the data were pooled. Further details regarding data synthesis can be requested from the NZGG through the PEBC.

RESULTS

Literature Search Results

The literature search results describe the UK HTA and all 81 primary studies included in this PEBC recommendation report. There were no high-quality randomized or case-control studies. All the studies were case series with variable numbers of patients, with the majority of studies having relatively few patients. A listing of the studies with a summary of their characteristics and results can be found in Tables 1 to 6 in Appendix 2 of this report.

In reviewing the individual studies, many issues arose that may affect the interpretation of the results. Some studies reported on the use of PET scans in one stage of the cancer continuum (i.e., staging only), but others reported on the use of PET scans in several stages of the continuum (i.e., staging, recurrence, routine follow-up, or treatment evaluation). With the latter, some studies may have included all patients in all aspects of the continuum and in other studies this may not be the case. The reference or gold standard to which PET scanning was compared was variable, and included tissue biopsy, comparison with conventional imaging such as CT or MRI, and an evaluation of the patient over time and further follow-up. Many studies did not compare PET scans with ^{67}Ga scanning, which could be considered an alternative functional imaging test for patients with lymphoproliferative disorders. The majority of PET images were not interpreted in a blinded fashion, except for a few studies where the PET readers were blinded to the clinical information and the results of the conventional imaging. It is not apparent whether the PET scans themselves were blinded to the readers.

Diagnosis

RESULTS

The UK HTA included one study on the use of PET in the diagnosis of lymphoma (3). Four primary studies met the inclusion criteria. Of these, three were focused specifically on the diagnosis of lymphoma in pediatric patients. All four studies were retrospective and had relatively small patient populations (<60). Overall, the studies were of poor quality mainly due to insufficiencies in reporting. Details on the individual studies can be found in Table 1 in Appendix 2 of this report.

Study Design	Study Citation(s)
Diagnosis	
Retrospective	(4-7)
Prospective	No Studies

UK HTA (studies published prior to August 2005)

The UK HTA included one primary study that evaluated the use of PET in eight patients with gastric NHL. Due to its small population, the authors were unable to draw any conclusions from the study.

Studies published after August 2005

In adult patients, one study (7) evaluated the utility of FDG PET (no co-registered CT component) in primary central nervous system lymphoma diagnosis. Forty-two scans were performed for the purpose of initial diagnosis and staging. FDG PET scans were abnormal in eight of 42 patients. Biopsies were obtained in six of the patients, of which five revealed malignancy. In three patients, FDG PET revealed systemic NHL. Three patients had false-positive results. Overall, FDG PET may disclose higher rates of systemic disease; however, due to false-positive results FDG PET scans should be subject to clinical follow-up or biopsy.

Three studies evaluated FDG PET/CT in the initial diagnosis of lymphoma in pediatric patients. London et al (5) and Miller et al (6) both evaluated the performance of FDG PET/CT in the diagnosis of HL and NHL in pediatric patients. In both cancer types, FDG PET/CT was superior to conventional imaging with high specificities and sensitivities. Cheng et al (4) evaluated the efficacy of FDG PET/CT in the evaluation of bone marrow involvement for pediatric patients with either HL or NHL.

DISCUSSION

On the whole, there was weak evidence surrounding the use of FDG PET/CT in the diagnosis of lymphoma for adult patients. In diagnosing pediatric patients, FDG PET/CT had high overall sensitivity and specificity. It may also provide substantial value in the determination of bone marrow biopsy site.

Staging

RESULTS

In addition to the UK HTA (3), 23 primary studies were included in this recommendation report for evaluating the diagnostic accuracy of FDG PET or PET/CT in staging of lymphoma. The primary studies for the utility of PET/CT in staging lymphoma are described in detail below.

Lymphoma Type	Study Design	Study Citation(s)
Patient Management		
Hodgkin lymphoma	Prospective	(8-10)
	Retrospective	No studies
Non-Hodgkin lymphoma	Prospective	(11-13)
	Retrospective	(7,14,15)
Undifferentiated patient population (NHL and HL combined)	Prospective	(16-18)
	Retrospective	(19,20)
Pediatric lymphoma	Prospective	(21-24)
	Retrospective	(6)
Diagnostic Accuracy		

Lymphoma Type	Study Design	Study Citation(s)
Hodgkin lymphoma	Prospective	(10,16,22,25,26)
	Retrospective	No studies
Non-Hodgkin lymphoma	Prospective	(17,27,28)
	Retrospective	(15,29-36)
Undifferentiated patient population (NHL and HL combined)	Prospective	(17,37,38)
	Retrospective	(20)
Pediatric lymphoma	Prospective	(39)
	Retrospective	(18,19)

Patient management at initial staging

UK HTA (studies published prior to August 2005)

The UK HTA included seven studies with data on the use of PET or PET/CT in the management of patients (3). FDG PET and PET/CT changed management in approximately 10% to 20% of patients across studies. Three studies in the UK HTA noted that PET or PET/CT incorrectly downstaged nine patients and incorrectly upstaged five patients, thus leading to potential incorrect changes in management.

Studies published after August 2005

Nineteen studies evaluated the impact of FDG PET or PET/CT on patient management at the initial staging of lymphoma. No guidelines or systematic reviews were identified that included data on patient management. In the majority of studies, data on patient management were collected concomitantly with diagnostic accuracy data. Although much of the data in these studies were collected prospectively, histological verification was limited, which introduces the risk that patients were upstaged or downstaged incorrectly.

Five prospective studies (a total of 678 patients with HL) investigated the clinical benefit of FDG PET and PET/CT for initial staging (8-10,22,23), two of which were in children (22,23). In each study, the addition of FDG PET or PET/CT modified the initial staging in several patients. When studies were combined, PET/CT modified the initial staging in 9% to 32% of patients. In many cases, the disease stage was upstaged due to the identification of distant disease not observed on conventional imaging modalities. Three prospective studies and three retrospective studies identified 285 patients with NHL (7,11-15). All studies reported that the addition of FDG PET or PET/CT modified the initial staging in a portion of patients. The changes ranged from 7% to 32% of patients receiving a change in initial staging due to FDG PET/CT results. As with HL, the majority of patients were upstaged due to the identification of advanced disease progression. In a retrospective review of 77 patients with a variety of NHL subtypes, PET scans were used as a part of baseline staging investigations (15). Patients were upstaged or downstaged with either aggressive (upstaged in 22%; downstaged in 10%) or indolent histologies (upstaged in 22%; downstaged in 17%). Finally, three prospective studies and two retrospective studies were identified that did not differentiate between HL and NHL patients (16-20). A total of 596 patients were identified and, in all studies, the addition of FDG PET or PET/CT in initial staging resulted in changes in the management of several patients. More specifically, the changes in the initial staging ranged from 8% to 36% of patients being upstaged or downstaged.

Overall, the addition of FDG PET or PET/CT contributed additional information that resulted in the modification of initial staging in several cases. The majority of patients were upstaged due to the identification of advanced disease progression; however, these changes could not be confirmed due to the absence of histological verification.

Diagnostic Accuracy

UK HTA (studies published prior to August 2005)

The UK HTA evaluated FDG PET and PET/CT for the initial staging of lymphoma (3). The HTA included one systematic review and seven primary studies. The systematic review concluded that FDG PET and PET/CT had sensitivity ranging from 79% to 100%, and a specificity ranging from 90% to 100%. In the seven primary studies identified, FDG PET and PET/CT was shown to be consistently superior to ^{67}Ga scanning in both sensitivity and specificity. When FDG PET and PET/CT results were evaluated against CT-only, the sensitivity and specificities were both comparable.

Primary studies published after August 2005

Twenty-four primary studies were identified that contained diagnostic data on the use of FDG PET in staging of lymphoma. Five studies evaluated the diagnostic utility of FDG PET/CT for the initial staging of patients with HL (10,16,22,25,26). All were prospectively conducted and had patient populations ranging from n=57 to n=99. In all cases, the sensitivity, specificity, positive predictive value and negative predictive value of FDG PET/CT was superior to CT and FDG PET (without CT). Specificities were high for FDG PET and conventional imaging (range, 96.5% to 100% and 98.9% to 100%, respectively) but sensitivities varied (range, 72.7% to 92.3% and 35.3% to 82.6%, respectively). Twelve studies investigated the accuracy of FDG PET or PET/CT for initial staging of patients with NHL. In the majority of studies, the sensitivity and specificity were comparable with conventional staging practices (CT and bone marrow biopsy) where diagnostic statistics were calculated. In general, the sensitivities for both PET/CT and conventional imaging were low (range, 57.6% to 82% and 54% to 63%, respectively).

Twelve studies evaluated the diagnostic accuracy of FDG PET or PET/CT in NHL (15,17,27-36). Three of these were prospectively conducted and the remaining nine were retrospective. Of these 12 studies, five evaluated the utility of PET/CT in patients with mucosa-associated lymphoid tissue (MALT) lymphoma (30-32,38). PET scans at baseline were reported to pick up more sites of disease than conventional staging tests; 81% of initial sites were PET positive and 21% of patients demonstrated PET positivity in regional nodes. One study in MALT lymphoma reported that only subtypes with plasmacytic differentiation showed consistently increased FDG uptake compared with cases without plasmacytic differentiation (31). PET scans were performed at staging and for response assessment in patients with MALT lymphoma in 33 patients (32). Variable results were found and depended on disease stage and location, with PET being universally positive in advanced-stage disease and positive in only 42% of patients with limited-stage disease. In cases with active gastric MALT or aggressive NHL of the stomach, all displayed PET positivity (30). One study found that low-dose unenhanced PET/CT was similar to full-dose, contrast-enhanced PET/CT in detecting lesions at baseline in HL and NHL (38); however, this study did not comment on a comparison with conventional imaging.

Four studies evaluated the accuracy of FDG PET or PET/CT for initial staging in patients with a combined HL or NHL patient population. The results of the patient populations were pooled and were not able to be differentiated. Five of these studies investigated initial staging (18-20,37,39) and two evaluated bone marrow involvement (16,29). In four studies involving adult patients (18-20,37), FDG PET or PET/CT was in concordance with, or superior to, conventional imaging.

DISCUSSION

The available evidence for this category comes from case series in patients with HL and various histologies of NHL. The studies compared PET with conventional imaging

techniques, most commonly CT, MRI, and, less frequently, ^{67}Ga scanning. Only a few studies attempted biopsy proof of disease at sites of PET uptake. Given these limitations, most studies suggest that PET may change the stage in patients with lymphoproliferative disorders. This may be more relevant, based on one study in patients with follicular lymphoma, mantle cell lymphoma or T cell lymphoma where the diagnostic properties of ^{67}Ga scans appeared to be poorer. It cannot be determined whether upstaging or downstaging led to a treatment change that may have been associated with a clinical benefit because the studies did not provide comparator groups or histological follow-up.

Overall, the studies evaluating the utility of FDG PET or PET/CT for initial staging in patients with both HL and NHL showed similar results. In most studies, the specificity was high for both conventional imaging and FDG PET, oftentimes over 90%; however, the sensitivities varied widely across studies and were generally low due to a prevalence of false-negative cases. In PET-negative cases, clinical follow-up and/or additional imaging may be warranted for these cases. The use of FDG PET or PET/CT in identifying bone marrow involvement also showed similar results across the UK HTA as well as the primary studies. The results suggest that PET has good agreement with conventional staging practices in PET-positive cases; however, in PET-negative cases (particularly in patients with indolent NHL) a bone marrow biopsy may be still needed.

Response Evaluation (interim and at completion of therapy)

RESULTS

The UK HTA included nine primary studies that evaluated PET or PET/CT for interim response to treatment; they did not include studies for the use of PET or PET/CT at the completion of treatment. In addition to the UK HTA (3), 26 primary studies evaluated the value of FDG PET or PET/CT for interim response to treatment, 18 studies at treatment completion, and four studies for pretransplant planning.

Lymphoma Type	Study Design	Study Citation(s)
Interim response to treatment		
Hodgkin lymphoma	Prospective	No studies
	Retrospective	No studies
Non-Hodgkin lymphoma	Prospective	(40)
	Retrospective	No studies
Undifferentiated patient population	Prospective	(37)
	Retrospective	No studies
Pediatric lymphoma	Prospective	(41)
	Retrospective	(6,21)
Survival	Prospective	(40,42-49)
	Retrospective	(50-61)
Response at completion of therapy		
Hodgkin lymphoma	Prospective	(41)
	Retrospective	(61,62,68)
Non-Hodgkin lymphoma	Prospective	(40)
	Retrospective	(1,14,30,63)
Undifferentiated patient population	Prospective	(37)
	Retrospective	(20)
Pediatric lymphoma	Prospective	No studies
	Retrospective	(21)
Survival	Prospective	(23,64)

Lymphoma Type	Study Design	Study Citation(s)
	Retrospective	(60,65,66,69)
Pretransplant planning		
Pretransplant planning		(27,48,56,67)

Interim Response to Treatment

Diagnostic Accuracy

UK HTA (studies published prior to August 2005)

The UK HTA included nine studies that included information on the diagnostic accuracy of PET or PET/CT to evaluate interim response to treatment (3). The primary studies indicated that scans performed at mid-therapy may be predictive of treatment outcome; however, there was no evidence on actual changes to the management of patients.

Primary studies published after August 2005

Five primary studies evaluated the efficacy of FDG PET or PET/CT in assessing the interim response to treatment following two to three cycles of chemotherapy (6,21,37,40,41). Two of these studies evaluated FDG PET in an adult population and three studies evaluated FDG PET in a pediatric population. In adults, the sensitivity of FDG PET or PET/CT was 63% and 92% and the specificity was 59% and 93%, respectively. In pediatric patients, the sensitivities and specificities were relatively higher. The sensitivities ranged from 75% to 100% and the specificities ranged from 68% to 100%.

Survival

UK HTA (studies published prior to August 2005)

The UK HTA did not have data that pertained to the use of PET or PET/CT to predict patient survival at mid-therapy.

Primary studies published after August 2005

In addition to diagnostic data, several studies provided data on the utility of an interim-treatment FDG PET or PET/CT scan in predicting event-free survival (EFS) in patients with lymphoma. Seven studies provided patient outcome data in patients with HL (42-46,50,51) and 14 in patients with various NHL subtypes (40,47-49,52-61). The majority of FDG PET or PET/CT scans were conducted after two to three cycles of various chemotherapy regimens. In patients with HL and NHL, an FDG PET or PET/CT scan provided important prognostic information for progression-free survival (PFS). In cases where an FDG PET scan came back negative, PFS or EFS was >80%.

In a prospective study of 108 patients with HL (46), treatment consisted of escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) if the International Prognostic Score (IPS) was ≥3 and standard BEACOPP if the score was <3. All patients underwent PET/CT scans and ^{67}Ga scans at baseline and after two cycles of treatment. In the event of a positive scan, patients subsequently received four cycles of escalated BEACOPP whereas four cycles of standard BEACOPP were given with a negative scan. The relapse rate was 27% in PET-positive patients versus 2.3% in those with a negative scan ($p<0.02$). For the high-risk group (IPS ≥3), the five-year EFS and OS rates were 85% (95% confidence interval [CI], 73% to 98%) and 91% (95% CI, 82% to 100%), respectively, with a median follow-up of 49 months. The five-year EFS and OS rates for the lower risk group were 84% (95% CI, 74% to 94%) and 90% (95% CI, 81% to 99%), respectively, with a median follow-up of 46 months. With a median follow-up of 47 months, the five-year EFS for all the patients was 85% (95% CI, 77% to 92%) and the OS from diagnosis is 90% (95% CI, 84% to 97%). The negative predictive value of normal interim ^{67}Ga or PET scans was 85% and

98%, respectively (p<0.001). The positive predictive values were low in both groups. The authors suggested that the EFS and OS results for the high-risk IPS group of patients looked appealing compared with other studies.

In another prospective study in 260 patients with HL (44), PET scanning was performed at baseline and after two cycles of adriamycin, bleomycin, vinblastine, and dacarbazine. Therapy was not changed based on the results of the PET scan. ^{67}Ga scans were not performed. The two-year PFS was worse in patients with a positive PET scan (12.8% versus 95%, p<0.0001). In a multivariate analysis, only PET scanning was a significant factor in predicting treatment outcome. The other univariate predictors that failed to remain significant in the multivariate analysis included stage IV disease, a high white blood cell count, the presence of lymphopenia, and bulky disease.

In a prospective study in aggressive histology lymphoma (49) (diffuse large B-cell lymphoma [DLBCL]-majority, mantle cell lymphoma, peripheral T-cell lymphoma), 40 patients underwent PET and ^{67}Ga scans at baseline and after three cycles of combination anthracycline-containing chemotherapy. The PET and ^{67}Ga scans were concordant in 82% of patients. In DLBCL, the two-year EFS was better with negative PET scans (85% versus 30%, p=0.003) and with negative ^{67}Ga scans (78% versus 33%, p=0.018), without much difference between the two imaging modalities. PET sensitivity tended to be higher than ^{67}Ga but was not statistically significantly different, and no differences were found between PET and ^{67}Ga in terms of specificity and diagnostic accuracy. PET scans performed after a median of three cycles of chemotherapy in DLBCL identified patients with a higher risk for treatment failure, where 71% of patients progressed at a median of 6.5 months (57). However, in this retrospective study, it was not clear whether these patients were consecutively PET scanned or whether there was any bias in ordering the PET scan. In a retrospective study, germinal centre phenotype was examined along with early-response evaluation using PET in 81 patients with DLBCL. Although the prognostic value of the germinal centre phenotype was not confirmed in this study, PET scan positivity was strongly associated with a lower three-year EFS (46% versus 80%, p=0.0003).

A retrospective study examined the value of PET scans prior to high-dose chemotherapy and autologous stem cell transplantation (ASCT) in 211 patients with recurrent or refractory HL (61). The presence of disease according to PET or ^{67}Ga was an independent predictor of a poor prognosis, PFS, and OS at three years (69% versus 23% and 87% versus 58%, p<0.0001).

Response at Completion of Treatment

Diagnostic Accuracy

UK HTA (studies published prior to August 2005)

The UK HTA did not include evidence for the utility of PET or PET/CT at the completion of treatment.

Primary studies published after August 2005

Thirteen studies evaluated the diagnostic utility of FDG PET or PET/CT at the completion of the preferred treatment regimen to evaluate the patients' response to treatment (1,14,20,21,27,30,37,40,41,62,63,66,68). Sensitivities varied widely (range, 45% to 100%). Specificities were better, ranging from 88% to 96.9%. In two studies that evaluated pediatric patients, sensitivities and specificities were higher relative to conventional imaging (21,41).

In a retrospective study of adults with HL (66) who were treated with the Stanford V regimen, PET scans were performed at baseline and at the completion of chemotherapy, at eight weeks and 12 weeks, respectively, for patients with favourable stage I/II and those with

bulky disease or stage III/IV disease. Radiotherapy was preplanned from baseline and was not influenced by the results of the post-therapy PET scan. ^{67}Ga scans were not used in this study. Of a total of 81 patients, all patients had positive PET scans at baseline, and six had residual PET abnormalities all in sites in which radiation therapy was planned. Four of the six patients experienced relapse compared with three of the 75 patients with negative PET scans. The PET-positive patients had an inferior freedom from progression after a median follow-up of four years (33% versus 96%, $p<0.0003$). In a Cox model, PET positivity after chemotherapy was a significant predictor of PFS even after controlling for bulk and IPS of >2. There was no apparent benefit in administering radiotherapy to these patients. The OS in both the PET-positive and PET-negative groups was 100% at a median follow-up of four years.

In another study of 26 patients with HL who had a residual imaging abnormality or suspected relapse, high positive and negative predictive values for PET scans were found (62). Of 14 patients who were PET scanned after completing therapy, three had a positive PET scan and active lymphoma was confirmed in all three by needle biopsy. Of the patients with suspected relapse, nine of the 20 patients had a positive PET scan: eight of the nine had active lymphoma confirmed by tissue biopsy, and one case was believed to be a false positive. Of the 10 negative PET scans, patients were still in clinical remission with an average follow-up of 14 months, and one scan was believed to be indeterminate but the patient had not relapsed. Conventional imaging included CT and MRI.

In another study previously mentioned in the section on staging (20), PET scans were compared with conventional imaging in 100 patients with NHL and 69 patients with HL after treatment, which was three months after completion of primary therapy. PET changed results of monitoring therapy in 52% of cases. PET results were confirmed in 74% of cases for post-treatment. PET scans performed better for monitoring disease therapy compared with conventional imaging for sensitivity (0.91 versus 0.69, $p<0.02$), specificity (0.90 versus 0.38, $p<0.00001$), positive predictive value (0.77 versus 0.42, $p<0.001$), and accuracy (0.83 versus 0.55, $p<0.02$).

Survival

UK HTA (studies published prior to August 2005)

The UK HTA did not have data that pertained to the use of PET or PET/CT to predict patient survival at completion of treatment.

Primary studies published after August 2005

Several studies also evaluated the efficacy of FDG PET or PET/CT to predict patient survival outcomes. Six studies evaluated survival at the completion of treatment (23,60,64-66,69). Differences in PFS and EFS were significantly different in patients with a positive PET scan and a negative PET scan. In terms of survival, patients with a negative PET scan progressed better than those with a positive PET scan at the completion of treatment. FDG PET or PET/CT did not predict OS as well as it did PFS or EFS.

Pretransplant Planning

Four studies evaluated FDG PET or PET/CT in pretransplant planning (27,48,56,67). Overall, the studies indicated that pre- and post-transplantation FDG PET scans contain important prognostic information in terms of eligibility for transplant and survival after transplant. A positive pretransplant PET indicated a high risk of ASCT failure, which was increased by a positive post-transplant PET image. For patients with lymphoma who have positive pre-ASCT PET images, more investigations using new treatment approaches will be required. For patients who have negative pre-ASCT PET images, obtaining post-ASCT PET images does not seem to be mandatory.

DISCUSSION

This category contains some recently published studies that report on relevant outcomes, such as treatment failure, and some studies reporting on the outcome of the PET scan taking into account other prognostic factors. PET scan results appear to carry powerful prognostic information that can be predictive for treatment failure in patients with NHL and HL undergoing primary therapy. Also, in patients with relapsed lymphoma who are undergoing salvage chemotherapy and ASCT, PET scan results appear to be an independent predictive factor for PFS, but not for OS. One study in HL suggested improved outcomes, in a retrospective manner, when PET scans are used to define a treatment algorithm.

Diagnosis of Suspected Recurrence and Routine Follow-up

RESULTS

The UK HTA included five primary studies and one systematic review pertaining to the use of PET or PET/CT for suspected recurrence after therapy (3). Eleven studies investigated the diagnostic accuracy of FDG PET/CT in suspected recurrence of lymphoma when compared with conventional imaging practices (20,29,42,62,63,70-72), three of which were specifically in pediatric patients (21,73,74). Two studies evaluated FDG PET or PET/CT in NHL, six studies evaluated HL and the remaining study had a patient population of both NHL and HL that could not be differentiated. Two studies included data on the utility of FDG PET/CT in the management of patients (7,20).

The UK HTA did not evaluate the use of PET or PET/CT for routine follow-up. Ten primary studies investigated the diagnostic accuracy of FDG PET or PET/CT for routine follow-up compared with conventional imaging (7,19,27,36,39,69,75-79). Four studies evaluated the utility of FDG PET/CT in the management of patients in routine follow-up (19,20,80,81).

Lymphoma Type	Study Design	Study Citation(s)
Diagnosis of Suspected Recurrence		
Diagnostic Accuracy		
Hodgkin lymphoma	Prospective	(42,72)
	Retrospective	(62,68,71)
Non-Hodgkin lymphoma	Prospective	No studies
	Retrospective	(63,70)
Undifferentiated patient population	Prospective	No studies
	Retrospective	(20)
Pediatric lymphoma	Prospective	No studies
	Retrospective	(21,73,74)
Patient Management		
Hodgkin lymphoma	Prospective	No studies
	Retrospective	No studies
Non-Hodgkin lymphoma	Prospective	No studies
	Retrospective	(7)
Undifferentiated patient population	Prospective	No studies
	Retrospective	(20)
Routine Follow-up		
Diagnostic Accuracy		
Hodgkin lymphoma	Prospective	(76)
	Retrospective	(75)
Non-Hodgkin lymphoma	Prospective	(27)
	Retrospective	(7,36,69,77,78)

Lymphoma Type	Study Design	Study Citation(s)
Undifferentiated patient population	Prospective	No studies
	Retrospective	(19,79)
Pediatric lymphoma	Prospective	(39)
	Retrospective	No studies
Patient Management		
Hodgkin lymphoma	Prospective	No studies
	Retrospective	No studies
Non-Hodgkin lymphoma	Prospective	No studies
	Retrospective	No studies
Undifferentiated patient population	Prospective	(80,81)
	Retrospective	(19,20)

Diagnosis of Suspected Recurrence

Patient Management at the Identification of Recurrence

UK HTA (studies prior to August 2005)

The UK HTA included five primary studies and one systematic review pertaining to the use of PET or PET/CT for suspected recurrence after therapy (3). While it was found that PET was a better predictor of relapse after therapy, it did not contain information on whether the additional information provided by PET/CT had an impact on patient management.

Primary studies published after August 2005

Two retrospective studies (7,20) were identified that provided evidence on how additional information provided by FDG PET or PET/CT changed clinical management of lymphoma patients at the time of identification of recurrence. Mohile et al (7) performed 15 FDG PET scans in 11 patients. Of these patients, seven had negative PET scans and developed no evidence of systemic lymphoma at follow-up. In the remaining four patients, three had a change in therapy after the addition of information provided by FDG PET. The second study (20) evaluated 169 adult patients with histologically confirmed HL or NHL. The addition of FDG PET modified the diagnosis of recurrence in 14 of 48 cases (29%) and was proven correct in seven cases.

Diagnostic Accuracy at the Identification of Recurrence

UK HTA (studies prior to August 2005)

The UK HTA evaluated FDG PET or PET/CT for routine follow-up of lymphoma (3). Evidence from five primary studies indicated that FDG PET or PET/CT was a better predictor of relapse after therapy than CT. In one systematic review, post-therapy PET has a similar sensitivity and better specificity than ^{67}Ga scanning and CT scanning to evaluate residual masses.

Primary studies published after August 2005

Eleven primary studies evaluated the utility of FDG PET or PET/CT for identifying recurrence. Eight of these studies had an adult patient population (20,42,62,63,68,70-72) and three had a pediatric patient population (21,73,74). In adult patients, the sensitivity of FDG PET for the detection of recurrence was high (range 93% to 100%) with the exception of one study (sensitivity 69%). The range of specificities varied more widely (range 71.4% to 96%). The results of the pediatric studies were similar to the adult patients with sensitivities remaining high (100%) and specificities varying (57.1% to 100%).

Routine Follow-up

Patient Management

UK HTA (studies prior to August 2005)

The UK HTA did not include studies pertaining to the use of PET or PET/CT for patient management at routine follow-up

Primary studies published after August 2005

Two prospective studies and two retrospective studies were included that contained data on the effect of FDG PET/CT on the clinical management of lymphoma patients at the time of routine follow-up (19,20,80,81).

One prospective study included 11 patients with relapsed HL and 28 patients with aggressive NHL (81). The results of this study showed that PET modified restaging after the completion of therapy in 31% of patients. An additional prospective study included 100 patients diagnosed with intermediate or high-grade NHL (80). The results of this study indicated that PET and CT performed separately (side-by-side evaluation) modified the staging after completed therapy in a higher number of patients than a combined PET/CT (75% versus 47%). One retrospective study of 95 patients with HL and NHL found that PET modified the staging after completed therapy in 17% of patients (19). One retrospective review of 169 patients with HL and NHL found that PET modified staging in 35.7% of cases ($p<0.00001$) (20).

Diagnostic Accuracy

UK HTA (studies prior to August 2005)

The UK HTA did not include studies pertaining to the diagnostic accuracy of PET or PET/CT at routine follow-up

Primary studies published after August 2005

Ten primary studies evaluated the accuracy of FDG PET or PET/CT for routine follow-up in adult lymphoma patients. In two studies that specifically evaluated HL only, the sensitivities were 90% and 64% and specificities were 80% and 100%, respectively (75,76). In five studies evaluating NHL, the sensitivities ranged from 75% to 100% and the specificities ranged from 93% to 100% (27,36,69,77,78). The final two studies did not differentiate between HL and NHL (19,79). The sensitivities were 82% and 98%, respectively, and specificities were 96% and 95%, respectively. One study evaluated routine follow-up in pediatric lymphoma patients. Lopci et al (39) evaluated nine HL patients and 11 NHL patients with FDG PET/CT versus conventional imaging. FDG PET/CT was superior to conventional imaging with a sensitivity and specificity of 100% and 93%, respectively, compared with 94% and 72%, respectively, for conventional imaging.

DISCUSSION

FDG PET and PET/CT showed a good concordance with conventional imaging in the detection of recurrence; however, due to a prevalence of false-positive results, PET-positive patients may benefit from clinical follow-up.

Overall, the 11 studies investigating FDG PET or PET/CT in the routine follow-up of patients with lymphoma showed similar results with no significant differences among HL, NHL, or pediatric patients. Both specificity and sensitivities were high and were in good concordance with conventional imaging.

CONFLICT OF INTEREST

In accordance with the PEBC Conflict of Interest (COI) Policy, the guideline authors, Hematology DSG members, and internal and external reviewers were asked to disclose potential conflicts of interest.

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Appendix 1: Studies Identified Outside of the New Zealand Guidelines Group Systematic Review by a Post Hoc Review by the Program in Evidence-Based Care Research Coordinator

First author name, Publication date, Reference	N	Lymphoma type	Prospective or Retrospective Study	Purpose
Staging				
Ambrosini, 2006 (30)	15	NHL	Retrospective	Evaluated the usefulness of FDG PET in patients with gastric lymphoma, in particular those affected by MALT type and aggressive gastric NHL.
Bruzzi, 2006 (34)	37	CLL	Retrospective	Evaluated the accuracy of PET/CT for the diagnosis of Richter's transformation of CLL to diffuse large cell lymphoma.
Cerci, 2011 (25)	210	HL	Prospective	Prospective trial to evaluate the cost-effectiveness of FDG PET scan in initial staging of patients with HL.
Hoffmann, 2006 (31)	19	MALT	Retrospective	Evaluated whether the histological features of plasmacytic differentiation might explain the heterogeneous behaviour of MALT lymphoma regarding FDG uptake.
Nogami, 2007 (28)	50	NHL	Prospective	Compared the diagnostic performance of PET alone, CT alone, side-by-side reading, and fused images for restaging or follow-up of patients with malignant lymphoma.
Perry, 2007 (32)	33	NHL (MALT)	Retrospective	Evaluated the diagnostic accuracy of PET/CT in patients with MALT lymphoma and assessed its reliability in clinical staging and monitoring response.
Rodriguez-Vigil, 2006 (38)	47	NHL, HL	Prospective	Comparison of unenhanced and enhanced PET/CT. Study suggests no benefit to enhanced PET/CT.
Sattar, 2006 (15)	77	NHL	Retrospective	Investigated 77 untreated patients with different histologies of NHL both with conventional imaging techniques and FDG PET.
Tsukamoto, 2007 (35)	255	NHL, HL	Retrospective	Comparison of PET and ^{67}Ga, similar except ^{67}Ga poorer for follicular, mantle cell, NK/T cell subtypes.
Picardi, 2011 (26)	103	HL	Prospective	Prospectively evaluated event-free survival in 103 HL patients staged with fused FDG PET/CT to identify those at greatest risk for abdominal relapse.
Schaefer, 2007 (29)	50	HL, NHL	Retrospective	Evaluated the diagnostic impact and clinical significance of FDG-avid bone lesions detected by FDG PET/CT in patients with lymphoma.
Response Evaluation				
Dann, 2007 (46)	108	HL	Prospective	Prospective study to evaluate the best regimen to achieve prolong progression-free survival and minimize toxicity in HL.
Jabbour, 2007 (61)	211	HL	Retrospective	Determine the prognostic value of functional imaging in predicting outcome of patients with recurrent/refractory HL before undergoing high-dose chemotherapy with autologous stem cell transplantation.

First author name, Publication date, Reference	N	Lymphoma type	Prospective or Retrospective Study	Purpose
Gallamini, 2006 (45)	108	HL	Prospective	Predictive value on therapy outcome of an early evaluation of treatment response by FDG PET scan performed after two courses of conventional standard-dose chemotherapy in advanced-stage Hodgkin disease.
Ng, 2007 (57)	45	NHL (DLBCL)	Retrospective	Assessed whether particular patterns of residual abnormality on PET were more predictive of an adverse outcome.
Strobel, 2007 (82)	68	NHL, HL	Retrospective	Evaluated the necessity of FDG PET/CT after end of treatment in lymphoma patients who had an interim FDG-PET/CT.
Diagnosis of Recurrence and Routine Follow-up				
Bjurberg, 2006 (62)	26	HL	Retrospective	Compared the value of FDG-PET with conventional imaging in patients with residual disease or suspected relapse in HL.

CT: Computed tomography; CLL: Chronic lymphocytic leukemia; DLBCL: Diffuse large B-cell lymphoma; FDG: ^{18}F-fluorodeoxyglucose; ^{67}Ga: Gallium; HL: Hodgkin lymphoma; NK/T: Natural killer/T-cell; MALT: Mucosa-associated lymphoid tissue; NHL: Non-Hodgkin lymphoma; PET: Positron emission tomography

Appendix 2: Evidentiary Base

Table 1: Included Studies for the Initial Diagnosis of Lymphoma using Positron Emission Tomography or Positron Emission Tomography/Computed Tomography

Reference (study design)	Objective	Country	PET or PET/CT (dose)	Reference standard	Age (mean/median)	Unit of analysis	Lymphoma type and tumour site	Sens (Comp Test)	Spec (Comp Test)	Sens PET	Spec PET	PPV	NPV
Mohile, 2008 (7) Retrospective single gate	FDG PET in disclosing systemic foci of disease	USA	**PET only** Dose 12 to 16 mCi	Biopsy	Adults 35 to 80 years (median 65 years)	Patients	NHL (n=42) Primary CNS	Biopsy was comparator. No sens or spec reported		100%	92%	63%	100%
Cheng, 2011 (4) Retrospective single gate	FDG PET/CT vs. BMB in evaluation of bone marrow involvement in pediatric patients	USA	PET/CT (dose not reported)	Bone marrow biopsy	Children 6 to 24 years (mean not reported)	Patients	HL (n=31)	NR		100%	100%	100%	100%
							NHL (n=23)	NR		100%	93%	88%	100%
London, 2011 (5) Retrospective single gate	FDG PET and CI to detect malignant lesions and predict poor lesion response to therapy	Australia	PET/CT Dose 370 MBq	Histopathology/ clinical follow-up >6 months	Children (mean 12.8 years)	Lesions	HL (n=2646 lesions, 30 patients)	77.1% (CI)	99% (CI)	98%	100%	100%	100%
							NHL (n=1630 lesions, 22 patients)	63.3% (CI)	99.4% (CI)	94%	100%	100%	100%
Miller, 2006 (6) Retrospective single gate	FDG PET/CT in diagnosing pediatric patients with HL and NHL	Israel	PET/CT Dose 0.2 mCi/kg	CI, CT and clinical follow-up	Children aged 3 to 20 years (mean age 12.9±5.1 years)	Lesions	HL (n=24) NHL (n=7)	74.8% (CT)	23.1% (CT)	99%	100%	100%	86%

BMB: Bone marrow biopsy; CI: Conventional imaging; Comp Test: Comparison test; CSM: Conventional staging methods; CT: Computed tomography; FDG : ^{18}F-fluorodeoxyglucose; HL: Hodgkin lymphoma; NHL: Non-Hodgkin lymphoma; NPV: Negative predictive value; NR: Not reported; PET: Positron emission tomography; PPV: Positive predictive value; Sens: Sensitivity; Spec: Specificity

Table 2: Included Primary Studies for Staging Lymphoma using Positron Emission Tomography or Positron Emission Tomography/Computed Tomography

Reference (study design)	Objective	Country	PET or PET/ CT (dose)	Reference standard	Age	Unit of analysis	Lymphoma type	Sens Comp	Spec Comp	Sens PET	Spec PET	PPV	NPV
Hodgkin Lymphoma													
Hutchings, 2006 (10) Prospective single gate	Value of FDG PET and PET/CT for staging of HL patients, impact on the choice of treatment	Denmark	**PET only** Dose 400 MBq	CT and clinical follow-up	Adults aged 18.6 to 79.2 years (mean age 40.9 years)	Regions	HL (n=99)	82.6%	98.9%	92.3%	97.6%	94.9%	96.3%
						Organs		37%	99.7%	86%	96.5%	78.2%	97.9%
			PET/CT Dose 400 MBq			Regions		82.6%	98.9%	92.2%	99.3%	98.4%	96.2%
						Organs		37%	99.7%	72.7%	97.2%	80%	95.8%
Pelosi, 2008 (16) Prospective single gate	FDG-PET/CT versus BMB in the detection of bone marrow disease in patients with HL or NHL	Italy	PET/CT Dose 222 to 370 MBq	Bone marrow biopsy	Adults and children aged 11-84 years (median age 46.6 years)	Patients	HL (n=82)	35.3% (P=0.035)	100%	76.5%	100%	100%	94.2%
Cerci, 2011 (25) Prospective	Cost-effectiveness of FDG PET scan in initial staging of patients with HL	Brazil/Italy	**PET only** 296-444 MBq	Clinical and imaging follow-up	Median = 33.7 years	Patients	HL (n=210)	87.3%	96.8%	97.9%	95.3%	97.9%	93.8%
Picardi, 2011 (26) Prospective	FDG-PET/CT to identify those at risk for abdominal relapse	Italy	PET/CT 5.3±1 MBq/kg	histologically proven HL	Age 18-74 years; median 30 years	Patients	HL (n=103)	Thirty-one of 103 patients staged with FDG-PET/contrast-enhanced CT were found to have spleen involvement and 10 patients liver involvement. Fourteen of the 100 patients staged with separate procedures were found to have spleen involvement and 3 patients liver involvement. FDG-PET/contrast-enhanced CT-guided treatment resulted in a 95% EFS, whereas separate FDG-PET and diagnostic CT-guided treatment resulted in an 81% EFS (p=0.002).					

Reference (study design)	Objective	Country	PET or PET/CT (dose)	Reference standard	Age	Unit of analysis	Lymphoma type	Sens Comp	Spec Comp	Sens PET	Spec PET	PPV	NPV
Kabickova, 2006 (22) Prospective single gate	FDG PET and CSMs for initial staging of children and adolescents with HL	Czech Republic	PET/CT Dose 5.25 MBq/ 70 kg body weight	Routine staging (x-ray, CT, US, bone scanning, and bone marrow biopsy)	Children aged 4 to 19 years (mean age 15.5 years)	Lymph nodes	HL (n=57)	88.4%	NE	100%	100%	100%	100%
						Regions/ organ		87.3%	99.5%	90%	100%	100%	98.1%
Non-Hodgkin Lymphoma													
Qiao, 2010 (27) Prospective single gate	FDG PET in the staging of NHL patients prior to autologous stem cell transplant	China	PET/CT Dose 240 to 259 MBq	Clinical follow-up and imaging and biopsy	Adults and children aged 11 to 68 years (mean age 43.1 years)	Patients	NHL (n=31)	NR: histologically proven NHL		75%	86.7%	85.7%	76.5%
Schaefer, 2007 (29) Retrospective single gate	FDG-avid bone lesions detected by FDG-PET/CT in patients with lymphoma	Switzerland	PET/CT 370 MBq	Clinical follow-up	Mean age 41.7±15.5 years; 27 female, 23 male	Lesions	HL (n=22) NHL (n=28)	In 50 patients, 193 FDG-avid lesions were found by PET/CT. BMB (n=43) was positive in 12 patients (27.9%). In CT, 32 of 193 (16.6%) lesions were detected without the PET information. Additional PET/CT information regarding uni- or multifocal bone involvement resulted in lymphoma upstaging in 21 (42%) patients compared with combined CT and BMB.					
Ambrosini, 2006 (30) Retrospective single gate	^{18}F-FDG-PET in patients with gastric lymphoma (MALT and aggressive gastric NHL)	Italy	**PET only** 5.3 MBq/kg	Clinical follow-up and histology	6 males, 9 females; median age 53 years, range 33 to 72 years	Patients	Extranodal MZL (n=9) or gastric non-MALT high-grade NHL (n=6)	FDG-PET was positive in all cases of gastric non-MALT aggressive NHL with known active disease (4 cases were studied at presentation, 2 at first relapse). In 3 patients, PET showed pathological ^{18}F-FDG uptake in the gastric lymph nodes, revealing metastatic sites not detected by other diagnostic procedures (US and CT).					
Hoffmann, 2006 (31) Retrospective single gate	FDG PET for imaging of pMALT lymphoma	Austria	**Whole-body FDG PET only** 380	Histological verification	35 total (ages 33-93)	Patients	pMALT (n=19) MALT (n=16)	Diverging results were found for the two groups of patients, with 16 of 19 pMALT patients rated positive as opposed to three of 16 patients with normal MALT histology (p=0.001). Thus, a sensitivity of 84% versus 19% was found in the two groups.					

Reference (study design)	Objective	Country	PET or PET/CT (dose)	Reference standard	Age	Unit of analysis	Lymphoma type	Sens Comp	Spec Comp	Sens PET	Spec PET	PPV	NPV
			MBq										
Perry, 2007 (32) Retrospective single gate	Diagnostic accuracy of FDG PET/CT in patients with MALT lymphoma	Israel	FDG PET/CT 370 to 666 MBq	Biopsy	Median age 63.5 years (39 to 88 years)	Patients	MALT (n=33)	Sensitivity in gastric MALT (38.9%) was lower when compared with nongastric MALT (75%). PET/CT detected active disease in 100% patients with advanced disease (stage III–IV) but only in 42.3% with early stage disease (I–II). Of the 33 patients in the study cohort, 12 had a follow-up PET/CT that detected relapse in 3 patients.					
Fueger, 2009 (33) Retrospective single gate	PET/CT in staging of patients with indolent lymphoma	USA	**PET only** Dose 7.77 MBq/kg	Clinical follow-up and imaging and biopsy	Adults aged 21 to 78 years (mean age 56 years)	Nodes	NHL Indolent lymphoma (n=45)	54.2%	98.3%	57.6%	96.2%	79.1%	89.9%
			PET/CT Dose 7.77 MBq/kg							77.3%	98.3%	92%	94.4%
Bruzzi, 2006 (34) Retrospective single gate	PET/CT for the diagnosis of Richter's transformation of chronic lymphocytic leukemia to DLBCL	USA	PET/CT	Biopsy	Adults aged 40 to 82 years	Patients	DLBCL	NR	NR	94%	90%	79%	97%
Nogami, 2007 (28) Prospective single gate	PET/CT in staging patients with NHL	Japan	PET and PET/CT 111 to 148 MBq	Histological confirmation and/or clinical follow-up for at least 12 months	30 men and 20 women; mean age 53.8 years; range 20 to 76 years	Patients	NHL (n=50)	48.2% (CT)	96.4% (CT)	83.9% (PET alone) 98.2% (fused)	99.5% (PET alone) 99.3% (fused)	Accuracy: 99.8%	
Tsukamoto, 2007 (35) Retrospective single gate	PET/CT in staging	Japan	**PET only** 275 to 370	Pathologic specimens were reviewed by at least 2	NR	Disease sites	913 disease sites in 255 NHL patients	Of 913 disease sites in 255 patients, FDG-PET identified >97% of disease sites of HL and aggressive and highly aggressive NHL. For indolent lymphoma, the detection rate of FDG-PET was 91% for follicular lymphoma (FL); 82% for extranodal marginal zone B-cell lymphoma of MALT.					

Reference (study design)	Objective	Country	PET or PET/CT (dose)	Reference standard	Age	Unit of analysis	Lymphoma type	Sens Comp	Spec Comp	Sens PET	Spec PET	PPV	NPV
			MBq	independent pathologists									
Sattar, 2006 (15) Retrospective single gate	PET in initial staging of different histological varieties of NHL	USA	**PET only** (370 to 555 MBq)	Clinical follow-up	Range: 20 to 80 years; mean 55 years; median 53.2 years	Patients	NHL (n=77)	76 of 77 cases of NHLs were positive by PET imaging. PET imaging resulted, both in high/intermediate grade and indolent NHLs, in a higher stage in more than 20% of cases.					
Bishu, 2007 (36) Retrospective single gate	PET in peripheral T-cell lymphomas	USA	**PET only** Dose 370 to 740 MBq	Biopsy, clinical imaging and clinical follow-up	Adults aged 16 to 85 years (mean age 40 years)	Lesions	NHL (peripheral T cell lymphoma) (n=24)	NR	NR	82%	NR	100%	0%
Pelosi, 2008 (17) Prospective single gate	PET/CT in patients with HL or NHL and its impact on therapy	Italy	**PET only** Dose 222 to 370 MBq	Bone marrow biopsy	Adults and adolescents aged 11 to 84 years (median age 46.6 years)	Patients	NHL (n=112)	65.6%	97.5%	59.4%	97.5%	90.5%	85.7%
Hodgkin and Non-Hodgkin lymphoma													
Altamirano, 2008 (37) Prospective single gate	FDG PET/CT before, after three cycles and at the completion of chemo. in NHL and HL.	Mexico	**PET only** Dose 370 to 555 MBq (10 to 15 mCi)	Biopsy, clinical follow-up and imaging (^{67}Ga; CT)	Adults aged 15 to 74 years (mean age 43 years)	Patients	NHL (n=21) HL (n=7)	64% (^{67}Ga); 100% (CT)	0% (^{67}Ga); 100% (CT)	100%	100%	100%	0%
Bucerius, 2006 (20)	FDG-PET and CI in patients	Germany	**PET**	CI (CT/MRI)	Adults aged	Patients	HL (n=69)	97% (CI)	83% (CI)	100%	100%	100%	100%

Reference (study design)	Objective	Country	PET or PET/CT (dose)	Reference standard	Age	Unit of analysis	Lymphoma type	Sens Comp	Spec Comp	Sens PET	Spec PET	PPV	NPV
Retrospective single gate	with HL and NHL at three time points		**only** Dose 350 to 450 MBq		15 to 80 years (mean age 45.9±14.8 years)		NHL (n=100)						
Rodrigues-Vigil, 2006 (38) Prospective	Low-dose PET/CT and contrast-enhanced full-dose PET/CT in lesion detection and initial staging	Spain	FDG PET/CT 370 MBq	Biopsy-proven and untreated lymphoma	Mean age, 50 years; range, 15 to 83 years	Patients	HL (n=16) NHL (n=31)	For region-based analysis, no significant differences were found between unenhanced low-dose PET/CT and contrast-enhanced full-dose PET/CT, although full-dose PET/CT showed fewer indeterminate findings and a higher number of extranodal sites affected than did low-dose PET/CT. Agreement between the 2 types of PET/CT was almost perfect for disease stage (k=0.92; p<0.001).					
Pelosi, 2008 (17) Prospective single gate	Role of FDG PET/CT in the staging of HL and NHL	Italy	PET/CT Dose range 222 to 370 MBq	Bone marrow biopsy; Contrast-enhanced CT	Median age 46.7 years (range 17 to 83 years)	Patients	HL (n=30) NHL (n=35)	NR (PET/CT correctly staged 61 of 65 cases and CI correctly staged 58 of 65 cases (p=NS); no data on TP, TN, FP, FN of CI)		50%	89.5%	40%	92.7%
Pediatric Patients													
Hernandez-Pampaloni, 2006 (83) Retrospective 2006	PET/CT in initial staging in pediatric lymphoma patients	USA	PET/CT Dose 130 µCi/kg	Clinical follow-up	Children aged 5 to 22 years (mean age 15 years)	Patients	HL (n=18) NHL (n=6)	79% (CT)	88% (CT)	78%	98%	94%	80%
Imataki, 2009 (19) Retrospective single gate	FDG PET/CT in staging and response evaluation of patients with HL and NHL	Japan	PET/CT	Overall clinical information and follow-up for >3 months	Not reported	Patients	HL and NHL (n=33)	87%	100%	87%	100%	100%	43%

Reference (study design)	Objective	Country	PET or PET/ CT (dose)	Reference standard	Age	Unit of analysis	Lymphoma type	Sens Comp	Spec Comp	Sens PET	Spec PET	PPV	NPV
Lopci, 2008 (39) Prospective single gate	FDG PET in staging of pediatric lymphomas	Italy	**PET only** Dose 5.3 MBq/kg	Clinical follow-up and imaging (CT) and biopsy	Children aged 6 to 14 years (mean age 10 years)	Lesions	HL (n=9) NHL (n=11)	94%	72.4%	100%	93%	89%	100%

BMB: Bone marrow biopsy; CI: Conventional imaging; Comp: Comparison test; CSM: Conventional staging methods; CT: Computed tomography; DLBCL: Diffuse large B-cell lymphoma; DLCL: Diffuse large cell lymphoma; FDG : ^{18}F-fluorodeoxyglucose; FN: False negative; FP: False positive; HL: Hodgkin lymphoma; MALT: Mucosa-associated lymphoid tissue; MRI: Magnetic resonance imaging; MZL Marginal zone lymphoma; NHL: Non-Hodgkin lymphoma; NPV: Negative predictive value; NR: Not reported; PET: Positron emission tomography; pMALT: Plasmacytically differentiated MALT; PPV: Positive predictive value; Sens: Sensitivity; Spec: Specificity; TN: True negative; TP: True positive; US: Ultrasound

Table 3: Included Primary Studies Investigating the Accuracy of Positron Emission Tomography or Positron Emission Tomography/Computed Tomography in Response Evaluation

Reference (study design)	Objective	Country	PET or PET/CT (dose)	Timing of PET or PET/CT	Reference standard	Age	Unit of analysis	Follow-up time	Lympho-ma type	Sens (Comp Test)	Spec (Comp Test)	Sens PET	Spec PET	PPV	NPV
Interim response to treatment															
Cashen, 2011 (40) Prospective single gate	FDG PET/CT for end-of-treatment evaluation	USA	PET/CT Dose 370 to 555 MBq (10 to 15 mCi)	Following 2 cycles	International Harmonisation Protocol and clinical outcomes	Adults aged 29 to 80 years (mean age 58 years)	Patients	Median 40 months	Stage III or IV DLBCL (n=50)	NR	NR	63%	59%	42%	77%
Altamirano, 2008 (37) Prospective single gate	FDG PET during and at the completion of chemo in patients with intermediate and aggressive NHL or HL	Mexico	**PET only** Dose 370 to 555 MBq (10 to 15 mCi)	Following 3 cycles	Biopsy, clinical follow-up and imaging	Adults aged 15 to 74 years (mean age 43 years)	Patients	Median 18 months	NHL (n=21) HL (n=7)	79% (CT)	50% (CT)	92%	93%	92%	93%
Furth, 2009 (41) Prospective single gate	Early and late response assessment by FDG-PET	Germany	**PET only** No details	Following 2 cycles	Clinical and follow-up examinations, histology, clinical data, x-rays and ultrasound	Children aged 9 to 18 years (mean age 15 years)	Patient	26 to 72 months (mean 46 months	HL (n=40)	100%	3% (CI)	100%	68%	14%	100 %
Miller, 2006 (6) Retrospective single gate	FDG PET/CT in pediatric patients with HL and NHL	Israel	PET/CT Dose 0.2 mCi/kg	Following 2 cycles	CI, CT and clinical follow-up	Children aged 3 to 20 years (mean 12.9±5.	Patients	Mean 15.4 months	HL (n=24) NHL (n=7)	NR (follow-up CT of 76 residual masses, only 11 were involved with tumour resulting in a PPV of 14%.)		75%	100%	100%	96%

Reference (study design)	Objective	Country	PET or PET/CT (dose)	Timing of PET or PET/CT	Reference standard	Age	Unit of analysis	Follow-up time	Lympho-ma type	Sens (Comp Test)	Spec (Comp Test)	Sens PET	Spec PET	PPV	NPV
						1 years)									
Riad, 2011 (21) Retrospecti ve single gate	FDG PET/CT in pediatric lymphomas	Egypt	PET/CT 3.7 MBq/kg	Following 2 to 3 cycles	Pathologica l correlation and clinical follow-up	Children aged 3 to 18 years	Patients	NR	HL (n=45) NHL (n=6)	83% (CIM)	66.6% (CIM)	100%	97.7%	85.7 %	100 %
Response at completion															
Bucerius, 2006 (20) Retrospecti ve single gate	FDG PET in patients with HL or NHL at 3 time points	Germany	**PET only** Dose 350 to 450 MBq	CI (CT/MRI)	Histological examinatio n or clinical follow-up	Adults aged 15 to 80 years (mean age 46 years)	Patients	3 months	HL (n=69) NHL (n=100)	91% (CI)	38% (CI)	69%	90%	77%	85%
Cashen, 2011 (40) Prospective single gate	Interim ^{18}F-FDG PET/CT for end-of-treatment evaluation	USA	PET/CT Dose 370 to 555 MBq (10 to 15 mCi)	At completio n of treatment (6 cycles)	Internationa l Harmonisati on Protocol and clinical outcomes	Adults aged 29 to 80 years (mean age 58 years)	Patients	Median 40 months	Stage III or IV DLBCL (n=42)	NR	NR	42%	93%	71%	80%
Bodet-Milin, 2010 (1) Retrospecti ve single gate	FDG PET for impact on patients with MCL	France	**PET only** Dose 5 to 7 MBq/kg	At completio n of treatment (within 3 weeks)	CI, biopsy and clinical follow-up	Adults aged 43 to 80 years (median age 62 years)	Patients	Median 21 months	MCL (n=44)	100% (IWC for NHL)	76% (IWC for NHL)	100%	88%	62.5 %	100 %
Gill, 2008 (63) Retrospecti ve single gate	Response to treatment and recurrence in MCL with CT or FDG PET/CT	Australia	**PET only** Dose not reported	At completio n of treatment (within 1 month)	CT, bone marrow biopsy and clinical follow up	Adults aged 33 to 82 years (median age 59 years)	Scans	9 to 139 months (median 46 months)	MCL (n=28)	NR	NR	67%	88%	58%	91%

Reference (study design)	Objective	Country	PET or PET/CT (dose)	Timing of PET or PET/CT	Reference standard	Age	Unit of analysis	Follow-up time	Lympho-ma type	Sens (Comp Test)	Spec (Comp Test)	Sens PET	Spec PET	PPV	NPV
Le Dortz, 2010 (14) Retrospecti ve single gate	PET/CT in restaging of patients with FL	France	PET/CT Dose 5 MBq/kg	At completio n of treatment (6 cycles)	Clinical, biological and imaging	Adults aged 47 to 78 years (mean age 60 years)	Patient	24 to 50 months (median 35 months)	FL	100% (CT)	51% (CT)	100%	96.9%	92.3 %	100 %
Altamirano, 2008 (37) Prospective single gate	FDG PET at interim and at the end of chemothera py NHL or HL	Mexico	**PET only** Dose 370 to 555 MBq (10 to 15 mCi)	At completio n of treatment	Biopsy, clinical follow-up and imaging	Adults aged 15 to 74 years (mean age 43 years)	Patients	Median 18 months	NHL (n=21) HL (n=7)	83% (CT)	63% (CT)	100%	95%	90%	100 %
Furth, 2009 (41) Prospective single gate	FDG-PET for response assessment in pediatric HL	Germany	**PET only** No details	At completio n of treatment (within 14 to 17 days)	Clinical and follow-up examinatio ns, histology, clinical data, x-rays and ultrasound	Children aged 9 to 18 years (mean age 15 years)	Patients	26 to 72 months (mean 46 months	Advance d stage HL (n=29)	50% (CI)	11% (CI)	100%	78%	25%	100 %
Jabbour, 2007 (61) Retrospecti ve	PET/CT in predicting outcome of patients with recurrent/ refractory HL before chemo.	USA	**PET only** 555 MBq	1 PET scan between salvage chemoth erapy and before ASCT.	Clinical and follow-up examinatio ns, histology	Youths and adults (aged 11 to 77 years)	Patients	With a median follow-up of 2.8 years among patients without progressio n after ASCT	68 PET and 144 ^{67}Ga consecuti ve recurrent/ refractory HL patients	When evaluated separately, 68% of PET positive and 74% of the ^{67}Ga-positive patients recurred. Recurrences were seen in 23% and 27% of the PET-negative and ^{67}Ga-negative patients, respectively; a small difference between the PET and ^{67}Ga groups may be related to the longer follow-up on the ^{67}Ga patients.					
Riad, 2011 (21) Retrospecti	Evaluate the performanc	Egypt	PET/CT 3.7 MBq/kg	At completio n of	Pathologica l correlation	Children aged 3	Patients	Not reported	HL (n=29)	55.5% (CIM)	57.1% (CIM)	100%	90.9%	75%	100 %

Reference (study design)	Objective	Country	PET or PET/CT (dose)	Timing of PET or PET/CT	Reference standard	Age	Unit of analysis	Follow-up time	Lympho-ma type	Sens (Comp Test)	Spec (Comp Test)	Sens PET	Spec PET	PPV	NPV
ve single gate	e of FDG PET/CT in pediatric lymphomas			treatment (within 4 to 8 weeks)	and clinical follow-up	to 18 years			NHL (n=13)						

ASCT: autologous stem cell transplant; CI: Conventional imaging; Comp Test: Comparison test; CT: Computed tomography; DLBCL: Diffuse large B-cell lymphoma; DLCL: Diffuse large cell lymphoma; FDG : ^{18}F-fluorodeoxyglucose; FL: Follicular lymphoma; ^{67}Ga: Gallium; HL: Hodgkin lymphoma; IWC: International Workshop Criteria; MCL: Mantle cell lymphoma; MRI: Magnetic resonance imaging; NHL: Non-Hodgkin lymphoma; NPV: Negative predictive value; NR: Not reported; PET: Positron emission tomography; PPV: Positive predictive value; Sens: Sensitivity; Spec: Specificity

Table 4: Included Primary Studies Investigating Positron Emission Tomography for Identifying Recurrence and Routine Follow-up in Patients with Lymphoma

Reference (study design)	Objective	Country	PET or PET/CT (dose)	Reference standard	Age	Unit of analysis	Lymphoma type	Sens (Comp Test)	Spec (Comp Test)	Sens PET	Spec PET	PPV	NPV
Diagnosis of Suspected Recurrence													
El-Galaly, 2011 (70) Retrospective single gate	Clinical impact of PET/CT	Denmark	PET/CT (Dose not reported)	Biopsy/radiological findings with contrast-enhanced CT	Adults aged >18 years (mean age 61 years)	Patients	Aggressive NHL (n=52)	NR	NR	100%	81%	28%	100%
Gill, 2008 (63) Retrospective single gate	Response to treatment and recurrence in MCL with FDG PET/CT	Australia	**PET only** Dose not reported	CT, bone marrow biopsy and clinical follow-up	Adults aged 33 to 82 years (median age 59)	Scans	MCL (n=28)	NR	NR	93%	96%	96%	92%
Lee, 2010 (71) Retrospective single gate	Surveillance PET/CT for HL patients in first remission	USA	PET/CT (Dose not reported)	Tissue biopsy or CI	Adults aged 18 to 81 years (median age 33 years)	Scans	HL (n=474)	PPV of CT=28.6 No data on Sens and Spec		100%	92.01%	22.9%	100%
Cerci, 2010 (42) Prospective single gate	FDG-PET in patients with HL with unconfirmed complete remission (or partial remission) after first-line treatment	Brazil	**PET only** Dose 296 to 444 MBq (8 to 12 mCi)	Biopsy and clinical follow-up and CI	Adults (median age 29.3 years)	Patients	HL (n=50)	87% (CT)	73.6% (CT)	100%	92%	92.3%	100%
Crocchiolo, 2009 (72) Prospective single gate	PET/CT in identifying relapse during follow-up of HL patients in complete remission	Italy	PET/CT Dose 270 MBq	Biopsy and clinical follow-up and CI	Adults aged 17 to 83 years (median age 35 years)	Scans	HL (n=28)	NR	NR	100%	71.4%	54%	100%

Reference (study design)	Objective	Country	PET or PET/CT (dose)	Reference standard	Age	Unit of analysis	Lymphoma type	Sens (Comp Test)	Spec (Comp Test)	Sens PET	Spec PET	PPV	NPV
	after upfront or salvage treatment												
Bucerius, 2006 (20) Retrospective single gate	FDG PET in a series of patients with HL or NHL at 3 time points during their course of disease	Germany	**PET only** Dose 350 to 450 MBq	CI (CT/MRI)	Adults aged 15 to 80 years (mean age 46)	Patients	HL (n=69) or NHL (n=100)	100 (CI)	88% (CI)	98%	75%	95%	86%
Schaefer, 2007 (68) Retrospective single gate	PET/CT in patients with HL after first-line therapy	Switzerland	PET/CT Dose 370 MBq	Biopsy and clinical follow-up	Adolescents and adults aged 11 to 76 years (mean age 35 years)	Patients	HL (n=66)	NR (CT)	NR (CT)	100%	91%	85%	100%
Meany, 2007 (73) Retrospective single gate	Post-treatment PET scan results	USA	**PET only** (Dose not reported)	Biopsy and clinical follow-up	Children aged 5 to 19 years (mean age 14 years)	Patients	HL (n=23)	NR	NR	100%	57.1%	18.2%	100%
Bjurberg, 2006 (62) Retrospective	Value of FDG-PET in patients with residual disease or suspected relapse in HL	Sweden	**PET only** average activity of 342 MBq	Clinical follow-up	Adults 17 to 54 years (median 29 years)	Scans	HL (n=30)	PPV = 40% NPV=80%		NR	NR	100%	91%
Levine, 2006 (74) Retrospective single gate	Examine the use of PET scans in pediatric patients with HL	Canada	PET/CT Dose 0.14 mCi/kg	Biopsy, clinical follow-up or repeat PET scan follow-up	Children and adolescents aged 3 to 26 years (median age 15 years)	Scans	HL (n=47)	NR	NR	100%	84%	11%	100%

Reference (study design)	Objective	Country	PET or PET/CT (dose)	Reference standard	Age	Unit of analysis	Lymphoma type	Sens (Comp Test)	Spec (Comp Test)	Sens PET	Spec PET	PPV	NPV
Riad, 2011 (21) Retrospective single gate	FDG PET/CT in pediatric lymphomas in response after 2 to 3 cycles of chemo, from 3 to 8 weeks after chemo treatment	Egypt	PET/CT Dose 3.7 MBq/kg	Pathological correlation (n=13) and clinical follow-up (n=139)	Children aged 3 to 18 years	Patients	HL (n=117) NHL (n=35)	100% (CIM)	38.4% (CIM)	100%	100%	100%	100%
Routine Follow-up													
Pracchia, 2007 (75) Retrospective single gate	FDG PET for the detection of residual tumour of patients with HL	Brazil	**PET only** Dose 185 to 370 MBq	Clinical follow-up, CT and/or biopsy	Adults aged 17 to 50 years (median age 29 years)	Patients	HL (n=38)	NR	NR	90%	80%	82%	89%
Markova, 2009 (76) Prospective single gate	PET after 4 cycles of combination therapy with BEACOPP in patients with advanced-stage HL	Germany	**PET only** No details	Standardized staging investigations- no details	Adults aged 16 to <70 years	Patients	HL (n=49)	NR	NR	64.3%	100%	100%	87.5%
Qiao, 2010 (27) Prospective single gate	value of ^{18}F-FDG PET/CT imaging for the clinical outcome	China	PET/CT Dose 240 to 259 MBq	Clinical follow-up and imaging and biopsy	Adults and children aged 11 to 68 years (mean age 43.1 years)	Patient	NHL (n=142)	NR: histologically proven HL		75%	93.3%	92.3%	77.8%
Zinzani, 2007 (69) Retrospective single gate	PET in patients with follicular lymphoma	Italy	**PET only** Dose 370 MBq	CI including CT, biopsy and clinical follow-up	Adults aged 31 to 78 years (median	Patients	Follicular lymphoma (n=45)	NR	NR	83%	97%	91%	94%

Reference (study design)	Objective	Country	PET or PET/CT (dose)	Reference standard	Age	Unit of analysis	Lymphoma type	Sens (Comp Test)	Spec (Comp Test)	Sens PET	Spec PET	PPV	NPV
	after induction treatment				age 55 years)								
Bishu, 2007 (36) Retrospective single gate	Evaluate the diagnostic accuracy of PET in PTCL	USA	**PET only** Dose 370 to 740 MBq	Biopsy, clinical imaging and clinical follow-up	Adults aged 16 to 85 years (mean age 40)	Lesions	PTCL (n=28)	NR	NR	92%	100%	50%	100%
Alinari, 2006 (77) Retrospective single gate	^{18}F-FDG PET in patients with extranodal marginal zone lymphoma of the MALT type	USA and Italy	**PET only** Dose 5.3 MBq/kg	Histology and CI/follow-up	Adults aged 31 to 82 years (median age 57 years)	Patients	MALT lymphoma (n=26)	NR	NR	81%	NE	NE	NE
Karam, 2006 (78) Retrospective single gate	FDG-PET scanning in low-grade lymphomas	USA	**PET only** Dose 16 to 19 mCi	Repeat biopsy and/or long-term follow-up	Adults (no further details reported)	Patients	Follicular lymphoma (n=30)	91% (CT)	50% (CT)	100%	95%	91%	100%
Imataki, 2009 (19) Retrospective single gate	PET in surveillance of HL and NHL	Japan	**PET only** Dose 180 to 230 MBq	Overall clinical information and follow-up for >3 months	Not reported	Patients	HL and NHL (n=62)	81% (CT)	78% (CT)	82%	97%	96%	87%
Fuster, 2006 (79) Retrospective single gate	FDG PET in the detection of bone marrow involvement in malignant lymphoma	Spain	**PET only** Dose 2.52 MBq/kg to 5.18 MBq/kg	Bone marrow biopsy	Adults (mean age 53±15 years)	Patients	HL (n=18) NHL (n=88)	NR	NR	86%	99%	97%	95%

Reference (study design)	Objective	Country	PET or PET/CT (dose)	Reference standard	Age	Unit of analysis	Lymphoma type	Sens (Comp Test)	Spec (Comp Test)	Sens PET	Spec PET	PPV	NPV
Mohile, 2008 (7) Retrospective single gate	FDG PET to detect systemic disease in the staging and restaging of PCNSL	Italy	**PET only** Dose 12 to 16 mCi	Clinical follow-up, imaging	Adults aged 35 to 80 years (median age 65)	Scans	PCNSL (n=49)	NR (CT, BMB)	NR (CT, BMB)	100%	88%	76%	100%
Lopci, 2008 (39) Prospective single gate	PET/CT in comparison with CI in pediatric lymphomas	Italy	PET/CT Dose 5.3 MBq/kg	Clinical follow-up and imaging and biopsy	Children aged 6 to 14 years (mean age 10 years)	Scans	HL (n=9) NHL (n=11)	94% (CI)	72.4% (CI)	100%	93%	88%	100%

ASCT: autologous stem cell transplant; BEACOPP: Bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, prednisone; BMB: Bone marrow biopsy; CI: Conventional imaging; Comp Test: Comparison test; CT: Computed tomography; DLBCL: Diffuse large B-cell lymphoma; DLCL: Diffuse large cell lymphoma; FDG : ^{18}F-fluorodeoxyglucose; ^{67}Ga: Gallium; HL: Hodgkin lymphoma; MALT: Mucosa-associated lymphoid tissue; MCL: Mantle cell lymphoma; MRI: Magnetic resonance imaging; NE: Not estimable; NHL: Non-Hodgkin lymphoma; NPV: Negative predictive value; NR: Not reported; PCNSL: Primary central nervous system lymphoma; PET: Positron emission tomography; PPV: Positive predictive value; PTCL: Peripheral T-cell lymphoma; Sens: Sensitivity; Spec: Specificity

Table 5: Primary Studies with Data on Survival

Reference	Study design	Type of PET imaging	Patients	Treatment	Timing of PET scan	Follow-up time	Survival outcomes
PET Scan at Mid-Treatment							
Cerci, 2010 (42)	Prospective	PET	115 patients with newly diagnosed HL	ABVD	Following 2 cycles	3 years	EFS 53% positive PET vs. 91% negative PET (p<0.001)
Gallamini, 2011 (50)	Retrospective	PET	165 patients with advanced-stage HL	ABVD for first two cycles, then negative PET patients remained on ABVD, positive PET patients received BEACOPP	Following 2 cycles	2 years	FFS 62% positive PET vs. 95% negative PET
Avigdor, 2010 (43)	Prospective	PET/CT	44 patients with advanced-stage HL	Escalated BEACOPP	Following 2 cycles	4 years	PFS 53% positive PET vs. 87% negative PET (p=0.01)
Castagna, 2009 (51)	Retrospective	PET	24 patients with relapsed/refractory HL who were receiving salvage chemotherapy	IGEV	Following 2 cycles	2 years	PFS 10% positive PET vs. 93% negative PET (0.004) OS 32% positive PET vs. 93% negative PET (p=0.024)
Kobe, 2008 (64)	Prospective	PET	817 patients with advanced-stage HL	BEACOPP	Following 6 to 8 cycles	1 year	PFS 86% positive PET vs. 96% negative PET (p=0.011)
Gallamini, 2007 (44)	Prospective	PET only	260 patients with advanced-stage HL	ABVD	Following 2 cycles	2 years	PFS 13% positive PET vs. 95% negative PET (p<0.0001)
Gallimini, 2006 (45)	Prospective	PET only	108 with newly diagnosed HL	ABVD/ COPP/EBV/CAD	Following 2 cycles	Diagnosis: 603 days (mean); Final restaging: 359 days (mean)	Eighty-eight patients attained CR while 20 showed disease progression during therapy or within 6 months after having reached CR; one patient relapsed. PET-2 was positive in 20 patients: 17 progressed during therapy, one relapsed and two remained in CR. In contrast, 85/88 (97%) patients with a negative PET-2 remained in CR; 3 progressed or relapsed early after the end of the chemotherapy. Thus, the PPV of a PET-2 was 90% and the NPV was 97%. The sensitivity, specificity and overall accuracy of PET-2 were 86%, 98% and 95%, respectively. The 2-year probability of FFS for PET-2 negative and for PET-2 positive patients was

Reference	Study design	Type of PET imaging	Patients	Treatment	Timing of PET scan	Follow-up time	Survival outcomes
							96% and 6%, respectively (log rank test = 116.7, p<0.01).
Advani, 2007 (66)	Retrospective	PET	81 patients with HL	Stanford V	Following treatment (8 to 12 weeks)	4 years	FFP 33% positive PET vs. 96% negative PET (p=0.0003)
Dann, 2007 (46)	Prospective	PET/CT	112 patients	BEACOPP	Following 2 cycles	5 years	Following a positive interim scan, 4 cycles of escalated BEACOPP were administered, whereas 4 cycles of standard BEACOPP were given to patients with a negative scan. The complete remission rate, the 5-year EFS, and OS rates were 97%, 85% and 90%, respectively. Relapse or progression occurred in 27% of patients with interim positive PET/CT versus 2.3% of negative scans (p<0.02). Early FDG-PET/CT is a useful tool for adjustment of chemotherapy on an individual basis. Similar EFS and OS rates were observed for patients in both risk groups.
Cahu, 2011 (52)	Retrospective	PET	54 patients with on-cutaneous T-cell/natural killer (T/NK) lymphomas	Various	Following 3 to 4 cycles	4 years	OS 47% positive PET vs. 76% negative PET (p=0.16) PFS 49% positive PET vs. 69% negative PET (p=0.10)
Cashen, 2011 (40)	Prospective	PET/CT	50 patients with advanced-stage DLBCL	R-CHOP	Following 2 to 3 cycles	3 years	PFS 63% positive PET vs. 85% negative PET (p=0.04)
Trotman, 2011 (65)	Retrospective	PET/CT	122 patients with follicular lymphoma	R-CHOP R-CVP	Following 6 to 8 cycles	3.5 years	PFS 33% positive PET vs. 71% negative PET (p<0.001)
Yang, 2011 (53)	Retrospective	PET/CT	161 patients with newly diagnosed DLBCL	R-CHOP	Following 3 to 4 cycles	3 years	PFS interim (3 to 4 cycles) 37% positive PET vs. 88% negative (p<0.01) OS 31% positive PET vs. 86% negative PET (p<0.01) PFS 29% positive PET vs. 86% negative PET (p<0.01)
Zinzani, 2011 (54)	Retrospective	PET	91 patients with newly diagnosed DLBCL	MACOP-B (n=12) R-CHOP (n=66)	Mid-treatment (various,	18 months	EFS 18% positive PET vs. 75% negative PET

Reference	Study design	Type of PET imaging	Patients	Treatment	Timing of PET scan	Follow-up time	Survival outcomes
			(n=78) or PMLBCL (n=13)	R-VNCOB-P (n=13)	depending on treatment given)		(p=0.0001)
Kasamon, 2011 (55)	Review	PET/CT	59 newly diagnosed patients with B-cell lymphoma	Standard chemotherapy	Following 2 to 3 cycles	2 years	EFS 67% positive PET vs. 89% negative PET
Dupuis, 2009 (47)	Prospective	PET	103 patients with untreated DLBCL	CHOP or R-CHOP	Following 4 cycles	5 years	EFS 36% positive PET vs. 80% negative PET
Derenzini, 2008 (48)	Prospective	PET/CT	72 patients with DLBCL (n=51) or FL (n=21)	IEV	Following 1-3 cycles and before ASCT	2 years	PFS 35% positive PET vs. 87% negative PET (p<0.00001) OS 67% positive PET vs. 94% negative PET (p=0.009)
Fruchart, 2006 (49)	Prospective	PET	40 patients with NHL; the majority had DLBCL	CHOP (or R-CHOP) ACVBP (or R-ACVBP)	Following 2 cycles of CHOP or 3 cycles of ACVBP	2 years	OS 36% positive PET vs. 84% negative PET (p=0.002) EFS 30% positive PET vs. 85% negative PET (p=0.003)
Filmont, 2007 (56)	Retrospective	PET/CT	60 patients (50 NHL, 10 HL)	BEAM	Following 3 to 4 cycles and before ASCT	1 year	EFS 43% positive PET vs. 80% negative PET (p=0.0002) OS 92% positive PET vs. 53% negative PET (p=0.0003)
Ng, 2007 (57)	Retrospective	PET	45 patients with DLBCL	CHOP	Median of 3 cycles	Median of 62 months	Of 45 eligible patients, 14 (31%) were PET-positive after a median of 3 chemotherapy cycles (range 1 to 5), of which 10 (71%) progressed at a median of 6.5 months. An interim positive PET was a statistically significant adverse prognostic factor for treatment failure (p<0.0001, log-rank analysis) with a hazard ratio for a positive interim-treatment PET of 9 (95% confidence interval = 4 to 55) and PPV of 71% and NPV of 90%. Notably, four patients with low-grade FDG-avidity limited to sites previously involved by biopsy-proven osseous lymphoma, remain progression-free (median follow-up 62 months).
Zinzani, 2007 (69)	Retrospective	PET/CT	45 patients with previously untreated	CHOP FM	Following 6 cycles	2 years	PFS 20% positive PET vs. 90% negative PET

Reference	Study design	Type of PET imaging	Patients	Treatment	Timing of PET scan	Follow-up time	Survival outcomes
			FL				(p=0.0031)
Zhao, 2007 (58)	Retrospective	PET/CT	61 patients with NHL	Various, but the majority received CHOP or R-CHOP	Following 3 to 4 cycles	2 years	PFS 23% positive PET vs. 72% negative PET (p<0.0005)
Kahn, 2006 (59)	Retrospective	PET	77 patients with NHL	CHOP	Following 4 to 6 cycles	2 years	OS 53% positive PET vs. 85% negative PET (p<0.001)
Kostakoglu, 2006 (60)	Retrospective	PET/CT	47 patients with newly diagnosed DLBCL (n=24) or HL (n=23)	Patients with DLCL received CHOP or R-CHOP. Patients with HL received ABVD	Following 1 cycle	2 years	PFS 12.5% positive PET vs. 100% negative PET (p<0.0001) Results did not differ when DLBCL and HL patients were analysed separately
Strobel, 2007 (82)	Retrospective	PET/CT	38 (n=HL) 30 (n=NHL)	AVBD/CHOP	Following 2 to 4 cycles and at the end of treatment	Not reported	In 31 (82%) HL patients, interim PET demonstrated CR that was still present on end PET. The remaining 7 HL patients (18%) had PR on interim PET. For NHL, 22 (73%) patients had CR on interim PET analysis that was still present on end PET. In the remaining 8 NHL patients, interim PET revealed PR in 7 and stable disease in 1 patient. None of all interim PET complete responders progressed until the end of therapy. Of the 196 PET/CT's carried out in this study population, 53 end PETs (27.0%) were carried out in interim complete responders.
PET Scan at Treatment Completion							
Kostakoglu, 2006 (60)	Retrospective	PET/CT	47 patients with newly diagnosed DLCL (n=24) or HL (n=23)	Patients with DLCL received CHOP or R-CHOP. Patients with HL received ABVD	Completion of treatment	2 years	PFS 8.3% positive PET vs. 90% negative PET (p<0.0001) Results did not differ when DLCL and HL patients were analyzed separately
Cahu, 2011 (52)	Retrospective	PET	54 patients with on-cutaneous T-cell/natural killer (T/NK) lymphomas	Various	Completion of treatment	4 years	OS 75% positive PET vs. 62% negative PET (p=0.71) PFS 67% positive PET vs. 61% negative PET (p=0.73)
Before and After Transplant							

Reference	Study design	Type of PET imaging	Patients	Treatment	Timing of PET scan	Follow-up time	Survival outcomes
Qiao, 2010 (27)	Retrospective	PET/CT	31 patients with NHL (no further details reported)	ASCT	Pre- ASCT	1 year	PFS 29% positive PET-CT vs. 88% negative PET-CT (p<0.0005)
		PET/CT	31 patients with NHL (no further details reported)	ASCT	At completion of ASCT	1 year	PFS 23.1% positive PET-CT vs. 88.9% negative PET-CT (p<0.0005)
Dickinson, 2010 (67)	Retrospective	PET	39 patients with primary-refractory or relapsed DLBCL	Salvage chemotherapy (various regimens) ASCT	Following salvage therapy (median 3 cycles) therapy and before ASCT	3 years	PFS 35% positive PET vs. 81% negative PET (p =0.003) OS 39% positive PET vs. 81% negative PET (p=0.01)
Filmont, 2007 (56)	Retrospective	PET/CT	60 patients (50 NHL, 10 HL)	BEAM	Following ASCT	1 year	EFS 25% positive PET vs. 81% negative PET (p<0.0001) OS 50% positive PET vs. 90% negative PET (p<0.0001)
Derenzini, 2008 (48)	Prospective	PET/CT	72 patients with DLBCL (n=51) or FL (n=21)	IEV	Following 1 to 3 cycles and before ASCT	2 years	PFS 35% positive PET vs. 87% negative PET (p<0.00001) OS 67% positive PET vs. 94% negative PET (p=0.009)
Hines-Thomas, 2008 (23)	Prospective	PET	41 patients	Not reported	Following treatment (number of cycles not reported)	3 years	RFS 79% positive PET vs. 87% negative PET (p=0.022)

ABVD: Adriamycin, bleomycin, vinblastine, dacarbazine; ACVBP: Doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone; ASCT: Autologous stem cell transplant; BEACOPP: Bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, prednisone; BEAM: Carmustine, etoposide, cytarabine, melphalan; BMB: Bone marrow biopsy; CAD: Lomustine, doxorubicin, vindesine; CHOP: Cyclophosphamide, doxorubicin, vincristine, prednisone; CI: Conventional imaging; Comp Test: Comparison test; COPP: Cyclophosphamide, oncovin, procarbazine, prednisone; CR: Complete remission; CT: Computed tomography; CVP: Cyclophosphamide, vincristine, prednisone; DLBCL: Diffuse large B-cell lymphoma; DLCL: Diffuse large cell lymphoma; EBV: Epidoxirubicin, bleomycin, vinblastine; EFS: Event-free survival; FDG : ^{18}F-fluorodeoxyglucose; FFS: Failure-free survival; FL: Follicular lymphoma; FM: Fludarabine, mitoxantrone; HL: Hodgkin lymphoma; IEV: Ifosfamide, epirubicin, etoposide; IGEV: Ifosfamide, gemcitabine, vinorelbine; MACOP-B: Cyclophosphamide, doxorubicin, methotrexate, vincristine, bleomycin, prednisone; MALT: Mucosa-associated lymphoid tissue; MCL: Mantle cell lymphoma; MRI: Magnetic resonance imaging; NE: Not estimable; NHL: Non-Hodgkin lymphoma; NPV: Negative predictive value; NR: Not reported; OS: Overall survival; PCNSL: Primary central nervous system lymphoma; PET: Positron emission tomography; PFS: Progression-free survival; PMLBCL: Primary mediastinal large B-cell lymphoma; PPV: Positive predictive value; PR: Partial remission; R: Rituximab; RFS: Relapse-free survival; R-VNCOB-P: Rituximab, etoposide, mitoxantrone, cyclophosphamide, vincristine, prednisone, bleomycin; vs.: Versus

Table 6: Studies in Positron Emission Tomography in Patient Management

Reference	Objective	Country	Study design	Participants	Age	Purpose of PET or PET/CT	Comparison	Impact on physician decision making
Staging								
Papajik, 2011 (11)	PET/CT for determining the stage and extent of the disease	Czech Republic	Prospective multicentre follow-up	117 male and female patients with newly diagnosed NHL	Median age 59 years(range 26 to 79 years)	Staging and management	PET/CT combined vs. PET and CT performed separately	PET/CT modified the staging in 11 patients (9.4%) - 5 patients upstaged - 6 patients downstaged PET/CT led to modification in the treatment approach in 3 of 117 patients (2.6%)
Riad, 2010 (21)	FDG PET/CT in pediatric lymphomas for the purpose of initial staging, evaluating treatment response early after 2 to 3 cycles of chemotherapy, from 3 to 8 weeks after chemo treatment and for long-term follow-up.	Egypt	Retrospective review	41 male and female pediatric patients with HL (n=39) and NHL (n=2)	Age range 3 to 18 years	Staging and treatment response	PET/CT at various time points vs. CI	Of the 41 patients diagnosed with lymphoma there was 73% concordance. PET/CT modified the staging in 11 of 41 cases (26.8%) -5 patients upstaged (12.2%) -6 patients downstaged (14.6%)
Le Dortz, 2010 (14)	FDG PET/CT in staging, prognosis evaluation and restaging of patients with follicular lymphoma.	France	Retrospective review	45 male and female patients with follicular lymphoma	Mean age 60 years (range 47 to 78 years)	Staging and treatment response	PET/CT vs. CT	PET/CT modified the staging/treatment options in 8 patients (18%) - 5 patients upstaged from early to advanced stage - 3 patients upstaged from stage I-III to advance
Cerci, 2009 (8)	FDG-PET in the initial staging of HL patients	Brazil	Prospective follow-up	82 male and female patients with HL	Median age 32 years (range 16 to 82 years)	Initial staging and treatment response	A combination of the initial PET and CT results with the results of the PET performed after the second chemotherapy cycle and CT	Of the 82 patients diagnosed with lymphoma there was 68.2% concordance. PET modified the staging in 10 patients (20.7%) -17 patients upstaged (20.7%) - 9 patients downstaged (10.9%) Changes to staging would have led to a change in the treatment strategy in 15.8% (13/82) of the patients.

Reference	Objective	Country	Study design	Participants	Age	Purpose of PET or PET/CT	Comparison	Impact on physician decision making
							scans performed after the 4th cycle of chemotherapy	
Ngeow, 2009 (12)	Value of PET/CT over conventional CT and BMB in the initial evaluation of patients with lymphoma	Singapore	Prospective follow-up	122 male and female patients with HL and NHL	Median age 54 years (range 17 to 80 years)	Initial staging	PET only vs. CT scan	Initial staging Of the 122 patients diagnosed with HL and NHL there was 60% concordance. PET/CT resulted in 21 patients being upstaged (17%) B- cell NHL n=12 T-cell NHL n=3 HL n=6
Imataki, 2009 (19)	Compare the efficacy of CT, with FDG PET/CT	Japan	Retrospective review	95 patients with HL and NHL	Not reported	Staging	PET only vs. CT scan	Initial staging Of the 95 patients diagnosed with lymphoma there was 75.8% concordance. PET/CT modified the staging in 8 patients (8.4%) - 5 patients upstaged (5.3%) - 3 patients downstaged (10.9%) n=3 DLBCL, n=2 HL, n=1 FL and 2 T-cell NHL
Scott, 2009 (13)	PET impact on staging and management and to compare PET and ^{67}Ga scans in low-grade NHL.	Australia	Prospective follow-up	74 male and female patients with low grade NHL	Median age 58 years (range 32 to 82 years)	Staging and management	Pre-PET-only vs. post-PET-only evaluation	Initial staging PET modified staging in 24/74 patients (32%) -21 patients upstaged (28%) -3 patients downstaged (4%) Change in treatment strategy Altered management plan based on the PET; 25 patients (34%; 95% CI, 23% to 45%). Pre-PET n =74 (%) Post-PET n =74 (%) Radiotherapy 25 (34) 15 (20) Radiotherapy and Chemotherapy 8 (11) 9 (12)

Reference	Objective	Country	Study design	Participants	Age	Purpose of PET or PET/CT	Comparison	Impact on physician decision making
								Chemotherapy 21(28) 27 (37) Other; Observation 16 (21) 18 24) Surgical excision biopsy 3 (4.1) 3 (4.1) Biopsy then chemotherapy 1 (1.4) 2 (2.7) Impact of PET on patient management; • high in 20 (27%) • medium in 5 (6.8%) • low in 44 (59%) • none in 5 (6.8%) Change in management plan intent; 7 patients (9.5%) had treatment intent altered by PET, with all 7 changed from curative to palliative management. Actual treatment that patients received; 55 patients whose post-PET management plan and actual treatment were the same (74%) and 19 patients whose actual treatment differed from that planned post- PET. In 17 of the 19 patients the actual treatment implemented was thought to be appropriate given the PET results.
Mohile, 2008 (7)	Ability of body FDG PET to detect systemic disease in the staging and restaging of PCNSL	USA	Retrospective review	49 adult patients with PCNSL	Median age 65 years (range 35 to 80 years)	Initial staging	PET-only vs. clinical, biological and imaging data	<u>Initial staging</u> PET resulted in 3 of 42 patients being diagnosed with NHL (7%) <u>Restaging for recurrent disease</u> PET confirmed NHL diagnosis in 3 of 11 patients (27%)
Pelosi, 2008 (16)	Compare the usefulness of FDG PET/CT vs. BMB in the detection of BMD in patients with HL or aggressive	Italy	Prospective follow-up	65 adult patients with newly diagnosed HL and NHL	Median age 46.7 years (range 17 to 83 years)	Initial staging and management	PET/CT vs. BMB	<u>Initial staging</u> Of the 65 patients diagnosed with lymphoma there was 83.1% concordance in 54/65 patients (83.1%); PET-CT correctly modified the staging in 7 patients (10.8%) and incorrectly modified the staging in 11 patients

Reference	Objective	Country	Study design	Participants	Age	Purpose of PET or PET/CT	Comparison	Impact on physician decision making
	NHL and its impact on therapy							(16.9%) - 8 patients upstaged (seven true positive and one false positive) - 3 downstaged (all false negative) <u>Change in treatment strategy</u> PET – Upstaging led to a change in oncological treatment for 5 of 7 upstaged patients (7.7%) - Involved-field radiation of a bone lesion was added to chemotherapy in 2 patients - Chemotherapy regimen was reinforced in 3 patients
Pelosi, 2008 (17)	FDG PET/CT in the staging of HL and NHL	Italy	Prospective follow-up	194 consecutive male and female patients with newly diagnosed HL and NHL	Median age 46.6 years (range 11 to 84 years)	Staging and management	PET/CT vs. BMB	<u>Change in treatment strategy</u> A change in treatment regimen based on PET findings was suggested in 12 patients (6.2%) -Chemotherapy regimen changed in 10 patients (5 HL and 5 NHL) -Radiation therapy added in 2 patients due to the detection of a vertebral lesion (1 HL and 1 NHL)
Rigacci, 2007 (9)	PET in staging of HL	Italy	Prospective follow-up	186 consecutive male and female patients with newly diagnosed HL	Median age 35.2 years (range 14 to 79 years)	Staging and management	PET only vs. CT scan	<u>Initial staging</u> Of the 186 patients diagnosed with lymphoma there was 84% concordance. PET modified the staging in 30 of 186 patients (16%) - 27 patients upstaged (14.5%) 3 patients downstaged (1.6%) <u>Change in treatment strategy</u> The treatment strategy was modified based on PET/CT findings in 11 of 30 patients (37%) after the definition of final stage
Hernandez-Maraver, 2006 (18)	PET/CT in work-up of NHL and HL	Spain	Prospective follow-up	47 consecutive male and female patients with	<u>HL group</u> Median age 17 years (range 20 to 61 years)	Lesion detection and staging	PET/CT combined vs. PET and CT performed separately	<u>Initial staging</u> Of the 47 patients diagnosed with lymphoma there was a 61.5% concordance. PET modified the staging/treatment

Reference	Objective	Country	Study design	Participants	Age	Purpose of PET or PET/CT	Comparison	Impact on physician decision making
				untreated biopsy-proven HL and NHL.	NHL group Median age 59 years (range 15 to 83 years)			options in 11 patients (23%) (10 NHL and 1 HL) (McNemar test p=0.012) Change in treatment strategy A different treatment strategy based on PET/CT findings was suggested for 7 patients (14.8%).
Bucerious, 2006 (20)	FDG-PET and CI in a series of patient with HL and NHL at three time points during disease	Germany	Retrospective review	169 consecutive patients with histological diagnosis of HL (n=69) or NHL (n=100).	Mean age 45.9 years (range 15 to 80 years)	Staging and management	PET only at diagnosis vs. PET only after treatment and PET only at recurrence	Initial staging PET modified staging in 15 of 42 cases (35.7%), p<0.005
Hutchings, 2006 (10)	FDG PET/CT for the staging of HL patients, and the impact on the choice of treatment	Denmark	Prospective follow-up	99 consecutive (66 of whom had PET/CT) male and female patients with newly diagnosed HL	Mean age 40.9 years (range 18.6 to 79.2 years)	Staging and management	PET/CT combined vs. PET and CT performed separately vs. CT scan results, histology and follow-up	Initial staging PET modified staging in 24/74 patients (32%). -21 patients upstaged (19%) -3 patients downstaged (5%) Change in treatment strategy A different treatment strategy based on PET findings was suggested for seven patients (9%).
Kabickova, 2006 (22)	FDG PET/CT and conventional staging methods for initial staging of children and adolescents with HL	Czech Republic	Prospective follow-up	57 male and female pediatric patients with newly diagnosed or relapsed HL	Mean age 15.5 years (range 3.9 to 18.9 years)	Initial staging	PET only vs. CI and BMB	Initial staging Of the 47 patients diagnosed with lymphoma there was a 96.5% concordance. PET correctly modified the staging in 9 patients (15.8%) and incorrectly modified the staging in 2 patients (3.5%) - 7 patients upstaged (all true positive) - 4 patients downstaged (two true negative and two false negative)
Hines-Thomas, 2008 (23)	PET in treatment planning on pediatric HL patients	USA	Prospective follow-up	44 male and female pediatric patients with HL	Median age 12.5 years (range 4 to 21 years)	Diagnosis, identification of recurrence, and treatment planning	PET only vs. ^{67}Ga & CT scans	Initial staging PET modified the staging in 4 of 44 cases (9%) - 4 patients upstaged (9%) Change in treatment strategy PET- Upstaging led to a change in

Reference	Objective	Country	Study design	Participants	Age	Purpose of PET or PET/CT	Comparison	Impact on physician decision making
								radiation dose for 1 patient (2.2%)
Mody, 2007 (24)	Clinical utility of FDG PET in the management of pediatric patients with lymphomas	USA	Prospective follow-up	26 male and female pediatric patients with biopsy-proven HL and NHL	Age range 8 to 19 years	Diagnosis, staging and management	PET only vs. conventional imaging and ^{67}Ga scan	HL Staging Staging was modified in 5 of 26 patients (19%) compared with ^{67}Ga scan. Staging was modified in 3 of 26 patients (11%) compared with CI. Change in management Changed management in 4 of 26 (15%) patients compared with CI. Changed management in 5 of 26 (19%) patients compared with ^{67}Ga scan. NHL Staging Staging was modified in 5 of 26 patients (19%) compared with both ^{67}Ga and CI Change in management Changed management in 5 of 26 (19%) patients compared with both.
Miller, 2006 (6)	Role of FDG PET/CT in pediatric patients with HL and NHL	Israel	Retrospective review	31 pediatric patients with newly diagnosed HL (n=24) and NHL (n=7)	Mean age 12.9 years (range 3 to 20 years)	Staging and management	PET/CT at diagnosis vs. later in course of disease	Initial staging Of the 31 patients diagnosed with lymphoma there was 67.6% concordance. PET/CT modified the staging in 10 patients (32.3%) -7 patients upstaged (22.6%) -3 patients downstaged (9.6%)
Diagnosis of Suspected Recurrence and Routine Follow-up								
Imataki, 2009 (19)	Compare the efficacy of CT with FDG PET	Japan	Retrospective review	95 patients with HL and NHL	Not reported	Staging	**PET only** vs. CT scan	Restaging after chemotherapy Of the 95 patients diagnosed with lymphoma there was 74.2% concordance. PET-CT modified the staging/treatment options in 16 patients (16.8%) - 5 patients upstaged (5.3%) - 11 patients downstaged (11.6%)

Reference	Objective	Country	Study design	Participants	Age	Purpose of PET or PET/CT	Comparison	Impact on physician decision making
								n=3 DLBCL, n=6 HL, n= 5 FL and n= 2 T-cell NHL
Bucerious, 2006 (20)	FDG-PET and CI in a series of patient with HL and NHL at three time points during their course of disease	Germany	Retrospective review	169 consecutive patients with histological diagnosis of HL (n=69) or NHL (n=100).	Mean age 45.9 years (range 15 to 80 years)	Staging and management	PET at diagnosis vs. PET after treatment and PET at recurrence	Restaging/Monitoring response to treatment PET modified staging in 54 of 103 cases (52.4%), p<0.00001 Restaging at diagnosis of recurrence PET modified staging in 14 of 148 cases (29.2%), p=NS
La Fougere, 2006 (80)	FDG PET/CT in patients with malignant lymphoma compared with separately performed PET and CT.	Germany	Prospective follow-up	100 male and female patients diagnosed with intermediate or high-grade HL and NHL	Median age 32 years (range 16 to 82 years)	Initial staging and restaging after completed therapy	PET/CT combined vs. PET and CT performed separately	Restaging after completed therapy PET and CT performed separately (side-by-side evaluation) modified the staging/treatment options in 21 of 28 patients (75%) - 1 patient upstaged (3.6%) - 20 patients downstaged (71.4%) PET-CT combined modified the staging/treatment options in 18 of 38 patients (47%) - 1 patient upstaged (2.6%) - 17 patients downstaged (45%)
Schot, 2006 (81)	PET in a study population with relapsed lymphoma receiving re-induction therapy followed by ablative therapy and ASCT	Netherlands	Prospective follow-up	39 male and female patients with relapsed HL (n=11) and aggressive NHL (n=28)	Median age 49 years (range 19 to 68 years)	Identification of recurrence and treatment planning	PET only before treatment vs. PET only after treatment	Restaging Overall treatment changed in 12 of 39 patients (31%) -4 patients were upstaged after induction chemotherapy -5 patients upstaged after 2nd cycle DHAP
Mohile, 2008 (7)	FDG PET in disclosing systemic foci of disease and to consider whether this test should be incorporated into	USA	Retrospective review	49 adult patients with (PCNSL	Median age 65 years (range 35 to 80 years)	Initial staging	PET only vs. clinical, biological, and imaging data	Restaging for recurrent disease PET confirmed NHL diagnosis in 3 of 11 patients (27%)

Reference	Objective	Country	Study design	Participants	Age	Purpose of PET or PET/CT	Comparison	Impact on physician decision making
	the routine staging of PCNSL.							

ASCT: Autologous stem cell transplantation; BMB: Bone marrow biopsy; BMD: Bone marrow disease; CI: Conventional imaging; CT: Computed tomography; DHAP: Dexamethasone, cytarabine, cisplatin; DLBCL: Diffuse large B-cell lymphoma; FDG : ^{18}F-fluorodeoxyglucose; FL: Follicular lymphoma; ^{67}Ga: Gallium; HL Hodgkin lymphoma; NHL Non-Hodgkin lymphoma; NS: Nonsignificant; PCNSL: Primary central nervous system lymphoma; PET: Positron emission tomography; vs.: Versus