Washington State Health Care Authority

Final Key Questions and Background

Positron Emission Tomography (PET) for Lymphoma

Background:

Clinical need and target population

Lymphoma is a heterogeneous group of cancers that affect cells of the immune system, primarily those involved in the lymphatic system, a complex network of vessels, tissues and organs which carry a fluid called lymph throughout the body. The affected cells are a type of white blood cell called a lymphocyte, which account for 20% to 40% of the total number of white blood cells in adults, and play an integral role in the human immune response by recognizing and destroying infectious organisms and abnormal cells. Lymphoma most often starts in the lymph nodes but can easily spread to other areas if not treated such as the spleen, tonsils, thymus gland and bone marrow, and occasionally even spread to organs outside the lymphatic system. Lymphomas are divided into two major categories: Hodgkin lymphoma (HL, previously called Hodgkin's disease) and non-Hodgkin lymphoma (NHL, all other lymphomas). While HL and NHL occur in the same locations, may be associated with the same symptoms (e.g., swollen lymph nodes), and often have similar appearance on physical examination they can be easily differentiated histologically by the specific type of lymphocyte each involves.

Hodgkin Lymphoma (HL)

HL arises from a malignant transformation of B-lymphocytes. There are two main subtypes of HL: classic HL (further divided into four distinct subtypes) which accounts for 95% of all HLs in adults, and nodular lymphocyte-predominant HL which accounts for the remaining 5%. Classic HL is characterized by the presence of Reed-Sternberg cells (a specific abnormal B lymphocyte); lymphocyte-predominant HL is characterized by the presence of lymphocyte-predominate cells, also called "popcorn cells", and the absence of Reed-Sternberg cells. HL is rare, accounting for 0.5% of all new cancers diagnosed (approximately 8500 cases were diagnosed in 2016) and is more prevalent in younger patients (32% are age 20 to 34 years, with a median age of 39 years). Five year survival rates can be as high 92% among early stage HL patients.

Non-Hodgkin Lymphoma (NHL)

NHL arises from a malignant transformation of either B-lymphocytes (primarily, about 85%) or T-lymphocytes. There are upwards of 60 different subtypes of NHL, the most common being diffuse large B-cell lymphoma (DLBCL) which accounts for 30% to 40% of all cases. It is estimated that over 74,000 individuals are diagnosed with NHL yearly in the US, making it one of the most commonly diagnosed cancers. Patients diagnosed with NHL tend to be older (75% are age 55 or older, with a median age of 66 years) and five-year survival rates are around 70%. Some subtypes of NHL may progress slowly are referred to as indolent and make up about 40% of all NHL in the U.S. Forms include cutaneous T-cell lymphoma, follicular lymphoma, lymphoplasmacytic lymphoma, Waldenström macroglobulinemia, small

cell lymphocytic lymphoma, chronic lymphocytic leukemia and marginal zone lymphoma and mucosa-associated lymphoid tissue (MALT) lymphoma.

Diagnosis and treatment of lymphoma

Each type of lymphoma behaves, spreads, and responds to treatment differently, so an accurate diagnosis is essential to determining the appropriate treatment strategy, expected response to treatment, and monitoring for recurrence. Lymphoma is diagnosed based on physical exam, lymph node biopsy and blood tests. After diagnosis, patients undergoing typical management of lymphoma receive initial staging, treatment, restaging after treatment and subsequent surveillance or further treatment and restaging depending on responsiveness to treatment (generally determined by Computed Tomography (CT) -assessed size reduction of enlarged lymph nodes, extent of bone marrow involvement, immunohistochemistry, flow cytometry and findings on PET scans). Treatment options can include combinations of chemotherapy (including the possibility of higher doses when paired with stem cell transplantation), radiation therapy, targeted therapy (e.g. inhibitor drugs), immunotherapy (including monoclonal antibodies), and in rare cases, surgery. Treatment for indolent forms of NHL ranges from watchful monitoring to aggressive therapy. Treatments are based on type, disease stage, age, co-existent medical conditions and prognostic factors.

Technology of interest

Positron emission tomography (PET) is a type of nuclear medicine imaging that utilizes small amounts of radioactive materials called radiotracers to examine and measure physiological functions in the body. The more energy a group of cells needs, the more the radiotracer will build up in that location. For lymphoma, the radioactive particle most commonly used for PET is ^{18}fluorine, which binds to glucose to form fluorodeoxy-D-glucose (FDG). Most types of lymphoma are metabolically active and use more glucose compared with normal structures (i.e. are termed FDG avid). This results in greater uptake of the radioactive FDG creating a “hot” spot on the PET image. In general, ^{18}FDG-PET is not routinely used for initial diagnosis of lymphoma as histologic samples obtained via biopsy are required; however, ^{18}FDG-PET may assist in identification of the best place for biopsy (e.g. most metabolically active site, locations where biopsy may be difficult, previous non-diagnostic needle biopsy). ^{18}FDG-PET has become widely used as an imaging tool for staging of lymphoma after histological diagnosis and for interim evaluation (e.g. restaging and evaluation of treatment response) although there is some debate regarding the value of interim PET based on the quality of evidence available and inconsistency regarding criteria for PET interpretation in the literature. More recent literature provides guidance regarding standards for interpretation. The Lugano Criteria are currently used. For staging, ^{18}FDG-PET/CT has been formally incorporated in to the standard staging and a modification of the Ann Arbor descriptive terminology is used to for anatomic distribution of disease extent. The 5–Point Scale (Deauville criteria) is used for treatment response evaluation and product of the perpendicular diameters of a single node can be used to identify progressive disease. Some guidelines recommend interim PET and it is generally performed at least once and has become a standard for assessment of treatment response for most lymphomas. All treatments have been associated with a broad range side effects depending on the therapies used, and may include fertility issues, damage to the thyroid, heart and lungs as well as increased risk for infection, stroke and secondary cancers. Interim PET/CT imaging may facilitate the ability to discriminate between

those for whom additional or intensified treatment may be important and those for whom additional therapy may not be necessary or some forms of therapy (e.g. radiation) may not be needed. This may permit optimization of therapy and maintenance of treatment efficacy while decreasing or avoiding treatment-related side-effects or sequelae. Recently, studies have emerged which explore the role of interim PET findings for adapting therapy with this goal in mind. To evaluate the value of PET/CT, studies comparing treatment given based on PET/CT results with treatment that would have been given without PET/CT information are of primary interest. Interim PET is not generally performed for indolent lymphoma. There are data suggesting that $^{18FDG\text{-}PET}$ may be a predictor of prognosis when performed early during treatment. PET is generally not used for routine surveillance following treatment completion, largely due to concerns regarding false-positive findings and lack of impact on patient outcomes.

Today, most PET scans are performed on combination PET/CT scanners. The combined PET/CT scans provide images that pinpoint the anatomic location of abnormal metabolic activity within the body and provide more accurate staging and evaluation than the two scans performed separately. Most clinical guidelines recommend the use of PET in conjunction with diagnostic CT, whether each test is done separately or via an integrated PET/CT scanner for initial staging and re-staging at critical points after treatment. The combination of PET with diffusion weighted MRI is an emerging technology for the evaluation of lymphoma. While PET/CT involves radiation exposure, the risk of adverse events specifically related to its use is generally considered to be low. In contrast, treatment-related adverse events are common and may be severe.

Policy context/reason for selection:

This topic was originally reviewed in 2011. It is being re-reviewed in 2018 due to newly available published evidence.

Objectives

The aim of this report is to update the 2011 HTA on positron emission tomography (PET) for lymphoma by summarizing information on diagnostic accuracy (e.g., sensitivity, specificity, predictive values) for context and systematically reviewing, critically appraising and analyzing new research evidence evaluating the clinical effectiveness (i.e., the ability of PET to stage, and influence therapeutic decisions, clinical management and clinical outcomes), safety, differential efficacy and safety in subpopulations, and cost-effectiveness of PET for lymphoma in adult and pediatric patients. The combination of PET with diffusion weighted MRI is an emerging technology for the evaluation of lymphoma. Currently this combination is not widely used, so the focus of this report will be on PET/CT as it is the current standard of care. Evidence on PET/MRI will be included as appropriate.

Key Questions:

Contextual questions:

In patients with histologically proven HL and NHL included in the report, what are the accuracy and reliability of ^{18}FDG-PET alone or in combination with CT for initial staging, interim evaluation (including re-staging, monitoring during treatment, evaluation of treatment response and prognosis) and surveillance of patients in remission? Specifically, provide a summary of the:

- Sensitivity and specificity and prognostic value (positive and negative predictive values)
- Inter- and intra-rater reliability (reproducibility)

In addition, a brief summary of the diagnostic accuracy and use of PET/CT for initial diagnosis will be provided. Summaries of accuracy will be based on highest quality systematic reviews which critically appraise included studies. Contextual information on the combination of PET with MRI will be presented. Contextual questions are not systematically reviewed, and use a "best evidence" approach.

Research key questions:

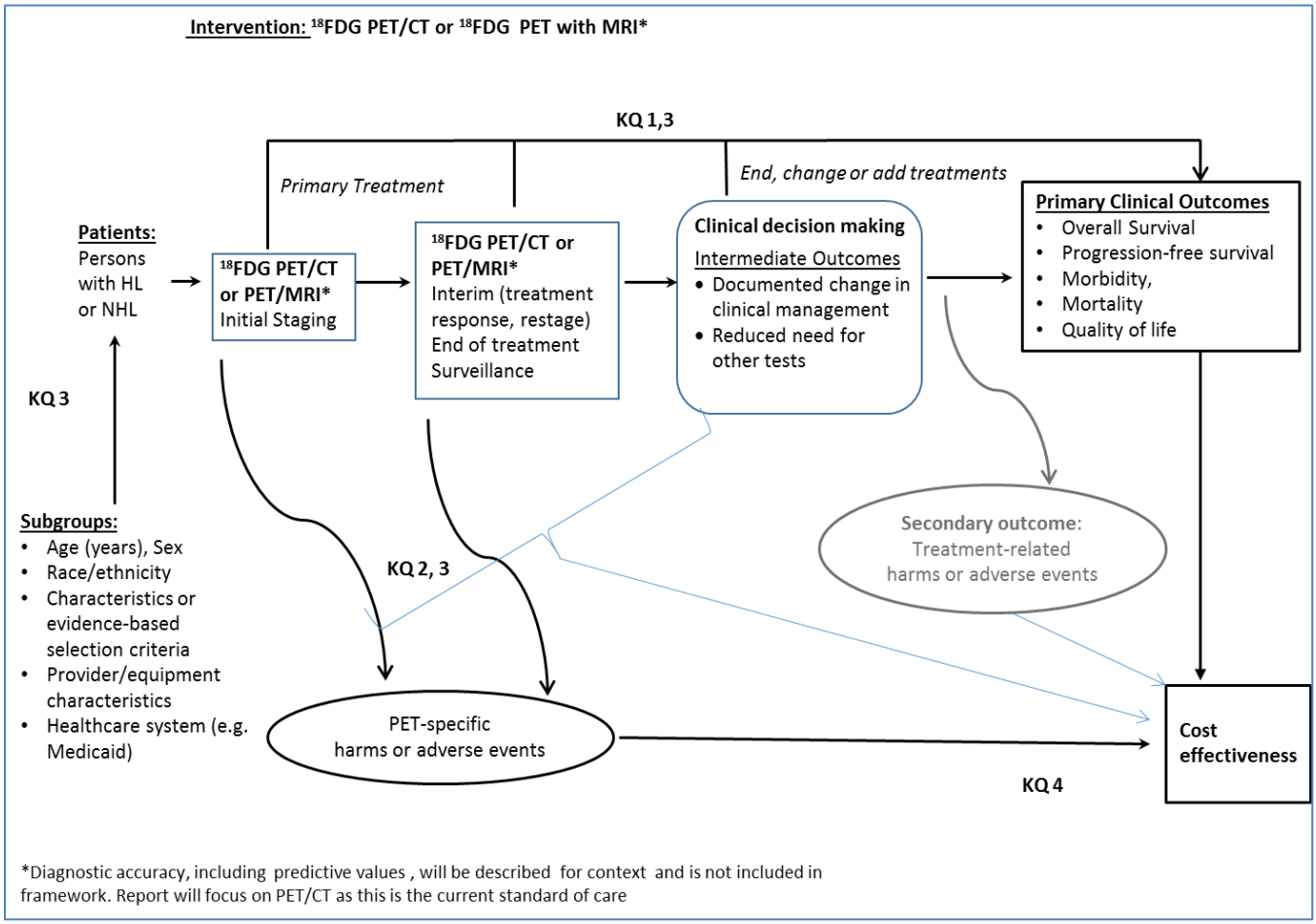
The focus of this portion of the report is on the clinical impact of ^{18}FDG PET/CT as this is the current standard of care. Information related to the PET/MRI combination will be included if relevant. In patients with histologically proven HL or NHL undergoing PET/CT for initial staging, interim evaluation (including re-staging, monitoring during treatment, and evaluation of treatment response) or surveillance:

1. What is the evidence of clinical effectiveness of ^{18}FDG imaging in combination with CT (PET/CT) results?
    a. How do ^{18}FDG PET/CT results impact therapeutic decisions or clinical management? Do test results lead to use of effective treatment strategies (e.g. including initial treatment following staging or treatment acceleration, deceleration or termination at interim imaging) compared with treatment strategies not using such test results?
    b. How do clinical outcomes (e.g. overall survival) differ based on PET/CT-related treatment decisions compared with decisions made in the absence of such test results?
    c. Does the use of ^{18}FDG PET for treatment decisions lead to reduction in treatment-related adverse events/sequelae in general compared with treatment decisions that do not involve PET/CT?
    d. Is there a reduction in the need for other tests?
    e. How do end of treatment ^{18}FDG PET/CT results impact clinical decision making compared with clinical decisions that do not involve PET/CT??
    f. How does surveillance ^{18}FDG PET/CT results impact clinical decision making compared with clinical decisions that do not involve PET/CT?
2. What is the safety profile of ^{18}FDG PET/CT for lymphoma?
    a. What adverse events are reported: type and frequency directly attributable to ^{18}PET/CT (mortality, major morbidity, radiation exposure, other)?

Final

3. What is the evidence that ^{18}FDG PET/CT imaging in patients with known lymphoma has differential efficacy or safety in subpopulations? Including consideration of:
   a. Patient age, sex, characteristics or evidence-based patient selection criteria
   b. Type of scanning machine and software, reader training, and other operational factors
   c. Provider type, setting or other provider characteristics
   d. Health care system type, including worker's compensation, Medicaid, state employees
4. What is the evidence of short and long-term cost-effectiveness of ^{18}FDG PE/CT for patients with lymphoma compared with other imaging or clinical care not involving ^{18}FDG PET/CT?

Analytic Framework:



Scope for Research Key Questions:

Focus: Comparative clinical effectiveness of ^{18}FDG PET/CT after initial histologic diagnosis of lymphoma

Table 1. Inclusion and exclusion criteria

Study Component	Inclusion	Exclusion
Population	Adults, adolescents or children with biopsy-proven HL or NHL. Diagnoses of interest include (to be evaluated separately): • Hodgkin lymphoma (HL) or aggressive non-Hodgkin lymphoma (NHL) • Indolent NHL • Other NHL with focus on most common types	• Studies with <80% of population with HL or NHL • Studies with <80% of population who got PET
Interventions	• FOCUS: Positron emission tomography (PET) to measure glucose metabolism (18FDG-PET) in addition to computed tomography (CT) (including combined PET/CT equipment) • Combination of PET with MRI (including diffusion weighted MRI)	• 3'-deoxy-3'-^{18}F-fluorothymidine (i.e., ^{18}F-FLT-PET) or other uncommonly used tracers for lymphoma; Investigational or non-FDA approved tracers • Outdated PET technology or methods; gamma PET, CDET • Studies of PET alone (i.e. in the absence of either separate CT or done on combination PET/CT equipment.
Comparator	• Other imaging (CT alone, MRI, including diffusion weighted MRI) • Standard clinical protocols or standard prior tests/evaluations (including history and physical examination, laboratory studies, biopsy) that do not involve ^{18}FDG PET	• Indirect comparisons of imaging methods or protocols
Outcomes	• **Primary outcomes:** Improvement in clinical outcomes based on PET/CT –based clinical decision making (focus on overall survival, event-free or progression-free survival, morbidity and mortality), quality of life • **Secondary outcomes:** Summary of adverse treatment effects based on PET-related treatment decisions • **Indirect outcomes:** Documentation of impact on therapeutic decisions or clinical management (e.g., reduced need for other tests, change in patients' management [e.g., continuation or discontinuation of therapy], change in treatments planned or given, change in stage) • **Safety:** Adverse events directly attributable to PET/CT; type and frequency (e.g. incidental findings, repeat/additional procedures, radiation exposure, other)	• Technical efficacy (i.e., the ability of a diagnostic test to conform to technical specifications) • Impact on diagnosis, therapeutic decisions, and clinical outcomes of patients with diagnosis other than Hodgkin or non-Hodgkin lymphoma. • Studies that focus on specific PET features

Study Component	Inclusion	Exclusion
	• Economic: Cost-effectiveness outcomes (e.g., cost per improved outcome) or cost-utility outcomes (e.g., cost per quality adjusted life year (QALY), incremental cost effectiveness ratio (ICER) or similar)	
Timing	• Initial staging, interim evaluation, end of treatment, surveillance	• Initial diagnosis
Study Design	Focus will be on PET/CT studies with the least potential for bias. • KQ 1-2: **Effectiveness:** ○ Updated, high quality systematic reviews that include research published subsequent to the prior report will be considered. ○ RCTs and prospective, longitudinal observational studies will be sought that compare treatment strategies based on PET/CT results with strategies that do not involve PET/CT results are of primary interest. In the absence of such studies, studies comparing treatments given based on PET findings will be included with a focus on RCTs which randomize patients to treatment based on PET/CT findings.* ○ Treatment and response planning and clinical decision making studies must provide specifics regarding use of PET/CT results to inform treatment assessment or therapy planning; preference will be given to prospective comparative studies. **Safety:** Studies characterizing direct PET/CT harms (including incidental findings, repeat biopsy, radiation safety); Included studies which describe the impact of PET/CT– related decision making on treatment-related adverse events. • KQ 3: Studies which stratify on patient or other characteristics and formally evaluate statistical interaction (effect modification) • KQ 4: Only full, formal economic studies (i.e., cost-effectiveness, cost-utility, cost-minimization, and cost-benefit studies) comparing PET/CT with other imaging or clinical care not involving FDG PET/CT will be considered.	• Studies of diagnostic accuracy, including prognosis (covered in the contextual questions) • Technical papers (e.g. SUVs, FDG uptake, phantom studies, quantitation papers) • Studies solely evaluating bone marrow involvement seen on PET (e.g. evaluation of bone marrow only, use of PET in lieu of bone marrow biopsy or comparing PET with bone marrow biopsy) • Indirect comparisons of imaging modalities or treatment strategies • Incomplete economic evaluations such as costing studies • Studies with fewer than 30 patients for HL and DBCL and fewer than 15 patients for more rare lymphoma • Case reports • Studies whose abstracts do not allow study characteristics to be determined. • SUV studies that only evaluate prognosis, not treatment response or planning with a view to evaluating patient management
Publication	• Studies published in English in peer reviewed journals, technology assessments or publically available FDA reports • Studies published subsequent to the 2011 report (Search dates February 2011 to May 2018)	• Abstracts, conference proceedings, posters, editorials, letters • Duplicate publications of the same study that do not report different outcomes or follow-up times • Single reports from multicenter trials

Study Component	Inclusion	Exclusion
	• For question 5, full formal economic analyses (e.g., cost-effectiveness, cost-utility studies) published in English in a peer reviewed journal	• White papers • Narrative reviews • Articles identified as preliminary reports when full results are published in later versions • Incomplete economic evaluations such as costing studies

* In the absence of such studies, contextual information on treatments and outcomes in untested patients will be described.