Role of Imaging in the Staging and Response Assessment of Lymphoma: Consensus of the International Conference on Malignant Lymphomas Imaging Working Group


See accompanying article on page 3059

ABSTRACT

Purpose
Recent advances in imaging, use of prognostic indices, and molecular profiling techniques have the potential to improve disease characterization and outcomes in lymphoma. International trials are under way to test image-based response–adapted treatment guided by early interim positron emission tomography (PET) –computed tomography (CT). Progress in imaging is influencing trial design and affecting clinical practice. In particular, a five-point scale to grade response using PET-CT, which can be adapted to suit requirements for early- and late-response assessment with good interobserver agreement, is becoming widely used both in practice- and response-adapted trials. A workshop held at the 11th International Conference on Malignant Lymphomas (ICML) in 2011 concluded that revision to current staging and response criteria was timely.

Methods
An imaging working group composed of representatives from major international cooperative groups was asked to review the literature, share knowledge about research in progress, and identify key areas for research pertaining to imaging and lymphoma.

Results
A working paper was circulated for comment and presented at the Fourth International Workshop on PET in Lymphoma in Menton, France, and the 12th ICML in Lugano, Switzerland, to update the International Harmonisation Project guidance regarding PET. Recommendations were made to optimize the use of PET-CT in staging and response assessment of lymphoma, including qualitative and quantitative methods.

Conclusion
This article comprises the consensus reached to update guidance on the use of PET-CT for staging and response assessment for [18F]fluorodeoxyglucose-avid lymphomas in clinical practice and late-phase trials.

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INTRODUCTION

Advances in staging and response assessment of lymphomas have occurred with the introduction of prognostic indices,1-4 molecular profiling,5 and more accurate imaging,6 with the potential to improve disease characterization and treatment selection. The International Harmonisation Project (IHP) first published guidelines about the application of positron emission tomography (PET) using [18F]fluorodeoxyglucose (FDG) in lymphoma in 2007, and PET was integrated in revised response criteria.6

The field has continued to evolve. PET combined with computed tomography (CT) has replaced PET alone. Mounting evidence supports the central role of PET-CT in staging7-18 and response assessment in Hodgkin (HL)19-27 and non-Hodgkin lymphomas (NHL).28-34 Multiple international studies are under way to investigate whether PET-CT response can be used to guide therapy to improve patient outcomes.35,36 Concerted efforts have been made to standardize PET-CT methods37-41 and interpretation in the context of trials.42 A five-point scale (5-PS), suited to assess differing degrees of response at mid- and end of treatment, has been developed to score images.43 This scale was recommended as the standard reporting tool at the First International Workshop on PET in Lymphoma in Deauville, France, in 2009,
and these so-called Deauville criteria have been widely applied in trials in preference to earlier criteria.\textsuperscript{44-49} Quantitative applications of FDG-PET are also recognized as objective tools for response monitoring,\textsuperscript{50} although accurate measurement relies on consistent methods for acquisition and processing and rigorous quality assurance of equipment for widespread application.\textsuperscript{38,39,42-44}

In response to changing requirements for PET-CT, to accommodate assessments at staging and during and after treatment, especially for response-adapted therapies, a workshop was convened at the International Conference on Malignant Lymphoma (ICML) in 2011, attended by representatives from major cooperative groups. ICML working groups were established to update guidelines. The imaging group reported to colleagues at follow-up workshops at the Fourth International Workshop on PET in Lymphoma in Menton, France, in 2012 and the 12th ICML in Lugano, Switzerland, in 2013. This article represents the consensus reached regarding the use of PET-CT in lymphoma in clinical practice and late-phase trials.

\section*{METHODS}

The following areas, pertinent to imaging, were identified as requiring updating at the 2011 workshop:

- Relevance of existing imaging staging, including the influence of bulk and assessment of bone marrow involvement

- Use of early or interim PET-CT and requirements for standardization of methods, including reporting

- Potential prognostic value of quantitative analyses using PET and CT

Experts in nuclear medicine and radiology applied to lymphoma undertook a literature review and shared knowledge about research in progress. Recommendations were formulated as follows (Table 1):

- Based on established current knowledge (type 1)
- To identify emerging applications (type 2)
- To highlight key areas requiring further research (type 3)

Recommendations were presented at the Fourth International Workshop on PET in Lymphoma, and a working paper was circulated for comment and updated after presentation at the 12th ICML.

\section*{RECOMMENDATIONS}

\subsection*{Interpretation of PET-CT Scans}

PET-CT is increasingly used for staging and response assessment in lymphoma,\textsuperscript{8} both for early assessment during treatment,\textsuperscript{19,20,22-23,28,29,31,55-59} and for remission assessment at the end of treatment.\textsuperscript{26,27,30,32-34,60,61} Almost all lymphomas are FDG avid,\textsuperscript{62-64} Table 2, but most published data are related to the use of PET in HL, diffuse large B-cell lymphoma (DLBCL), and follicular lymphoma (FL). PET scans are usually reported using visual assessment,\textsuperscript{43} noting the location of increased focal uptake in nodal and extranodal sites, and these-so-called Deauville criteria have been widely applied in trials in preference to earlier criteria.\textsuperscript{44-49} Quantitative applications of FDG-PET are also recognized as objective tools for response monitoring,\textsuperscript{50} although accurate measurement relies on consistent methods for acquisition and processing and rigorous quality assurance of equipment for widespread application.\textsuperscript{38,39,42-44}

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which is distinguished from physiologic uptake and other patterns of disease with increased FDG uptake including infection and inflammation,\(^{68,69}\) according to distribution and/or CT characteristics.

Focal FDG uptake within the bone or marrow, liver, and spleen is highly sensitive for involvement in HL\(^ {70,71}\) and aggressive NHL\(^ {74,77}\) and may obviate the need for bone marrow biopsy.\(^ {70,78,79}\) Diffuse increased uptake may occur with abnormal focal uptake, but in HL, diffuse uptake without focal activity often represents reactive hyperplasia\(^ {70,80}\) and should not be confused with lymphomatous involvement. PET-CT can miss low-volume involvement, typically \(< 20\%\) of the marrow,\(^ {79,80}\) and coexistent low-grade lymphoma in DLBCL, although this rarely affects management.\(^ {70}\) The sensitivity of PET for diffuse marrow involvement is limited in FL,\(^ {18}\) mantle-cell lymphoma, and most indolent lymphomas.\(^ {77,82}\) where biopsy is required for staging.

High physiologic FDG uptake occurs in the brain, and although intracerebral lymphoma often shows intense uptake,\(^ {83}\) leptomeningeal disease, which may be diffuse and of low volume, may be missed. Magnetic resonance imaging (MRI) is preferred to assess suspected CNS involvement.

PET scans are best reported using a fixed display and color table scaled to the standardized uptake value (SUV)\(^ {90}\) to assist with consistency of reporting, for serial scans, and to reduce the effect of patient size. The SUV is the radioactivity most commonly corrected for patient weight and administered activity.

**Recommendation.** Staging of FDG-avid lymphomas is recommended using visual assessment, with PET-CT images scaled to a fixed SUV display and color table. Focal uptake in HL and aggressive NHL is sensitive for bone marrow involvement and may obviate the need for biopsy. MRI is the modality of choice for suspected CNS lymphoma (type 1).

Resolution of uptake at sites of initial disease indicates metabolic response.\(^ {9} \) Reduction of uptake may also indicate satisfactory response, but the degree of uptake that is indicative of response\(^ {43} \) is dependent on the timing of the scan during treatment\(^ {85,86} \) and the clinical context, including prognosis, lymphoma subtype,\(^ {21,30,60} \) and treatment regimen.\(^ {22,56} \) The availability of a baseline scan is considered optimal for the accuracy of subsequent response assessment.\(^ {30,43,87,88} \)

The IHP criteria\(^ {9} \) specified that uptake should be \( \leq \) the mediastinal blood pool for lesions \( \geq 2 \) cm or the adjacent background for smaller lesions to define metabolic response at the end of treatment. In early-response assessment, treatment is incomplete, so the emphasis is on the degree of response and a continuous or close-to-continuous scale is desirable rather than positive or negative response categories.\(^ {43} \) Early attempts to address this used three response groups (ie, negative, minimal residual uptake, and positive),\(^ {19,37,89,90} \) Further refinement led to the development of the 5-PS,\(^ {42} \) which better represents different grades of uptake.

The 5-PS was intended as a simple, reproducible scoring method, with the flexibility to change the threshold between good or poor response according to the clinical context and/or treatment strategy.\(^ {42} \) For example, a lower level of FDG uptake might be preferred to define a so-called negative result in a clinical trial exploring de-escalation to avoid undertreatment. A higher level of uptake might be preferred to define a so-called positive result in a trial exploring escalation to avoid overtreatment. The 5-PS has been validated for use at interim\(^ {25,28,34,44,58,91-93} \) and the end of treatment\(^ {24,94} \) and was adopted as the preferred reporting method at the First International Workshop on PET in Lymphoma in Deauville, France (ie, Deauville criteria),\(^ {43} \) and in several international trials.\(^ {32,44,46-49,95-97} \)

The 5-PS scores the most intense uptake in a site of initial disease, if present, as follows:

- 1. No uptake
- 2. Uptake \( \leq \) mediastinum
- 3. Uptake \( > \) mediastinum but \( \leq \) liver
- 4. Uptake moderately higher than liver
- 5. Uptake markedly higher than liver and/or new lesions
- X. New areas of uptake unlikely to be related to lymphoma

Good interobserver agreement has been reported in HL,\(^ {42,92,98} \) DLBCL,\(^ {93} \) and FL.\(^ {34} \)

The UK RAPID (Response Adapted Therapy Using Positron Emission Tomography in Early-Stage Hodgkin Lymphoma) study used the 5-PS in patients with early HL. iPET remained an independent predictor of 3-year progression-free survival (PFS) on multivariable analysis, despite use of a response-adapted design.\(^ {44} \) Conservative scoring was used, with a score of 1 or 2 regarded as complete metabolic response (CMR); patients with CMR after three cycles of ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) were randomly assigned to radiotherapy (RT) or no further treatment. Retrospective analysis of an international cohort of 260 patients with advanced HL using scores 1, 2, and 3 to define CMR after two ABVD cycles reported a negative predictive value (NPV) of 94\% and positive predictive value (PPV) of 73\% for 3-year PFS.\(^ {25} \) iPET and end-of-treatment PET using scores 1, 2, and 3 for CMR were both independent predictors of 2-year survival.
ICML Recommendations for Using PET-CT in Lymphoma

PET-CT should be used for staging in clinical Scores 4 and 5 with reduced uptake from Upstaging occurs more often than Currently, prognostic indices Studies Comparing PET or PET-CT With CT Alone for Staging of Lymphomas so imaging-determined stage 17 FL 82 FL 8 5 2001 PET 19 NS 14 /H11005 Disease 18 61 HL and NHL 0 29 /H11005 3051 5 6 HL and NHL 0 29 /H11005 2000 PET 2006 PET 42 FL stages I-II on CT 45 0 29 /H11005 2002 PET 0 3 2008 Mostly PET 99 HL 0 1 2008 PET-CT 18 2008 PET-CT 142 FL 11 1 NS /H11569

Table 3. Studies Comparing PET or PET-CT With CT Alone for Staging of Lymphomas

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>PET or PET-CT</th>
<th>No. of Patients</th>
<th>Disease</th>
<th>Upstaging (%)</th>
<th>Downstaging (%)</th>
<th>Management Change (%)</th>
</tr>
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<tbody>
<tr>
<td>Bangerter et al\textsuperscript{106}</td>
<td>1998</td>
<td>PET</td>
<td>44</td>
<td>HL</td>
<td>12</td>
<td>2</td>
<td>14</td>
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<tr>
<td>Partridge et al\textsuperscript{107}</td>
<td>2000</td>
<td>PET</td>
<td>44</td>
<td>HL</td>
<td>41</td>
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<td>25</td>
</tr>
<tr>
<td>Jerusalem et al\textsuperscript{108}</td>
<td>2001</td>
<td>PET</td>
<td>33</td>
<td>HL</td>
<td>10</td>
<td>10</td>
<td>3</td>
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<tr>
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<td>2002</td>
<td>PET</td>
<td>22</td>
<td>HL</td>
<td>18</td>
<td>0</td>
<td>5</td>
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<tr>
<td>Munker et al\textsuperscript{110}</td>
<td>2004</td>
<td>PET</td>
<td>73</td>
<td>HL</td>
<td>29</td>
<td>3</td>
<td>NS</td>
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<td>Naumann et al\textsuperscript{111}</td>
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<td>PET</td>
<td>88</td>
<td>HL</td>
<td>13</td>
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<td>20</td>
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<td>Hutchings et al\textsuperscript{9}</td>
<td>2006</td>
<td>Mostly PET-CT</td>
<td>99</td>
<td>HL</td>
<td>19</td>
<td>5</td>
<td>9</td>
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<td>Rigacci et al\textsuperscript{110}</td>
<td>2007</td>
<td>Mostly PET</td>
<td>186</td>
<td>HL</td>
<td>14</td>
<td>1</td>
<td>6</td>
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<td>Buchmann et al\textsuperscript{112}</td>
<td>2001</td>
<td>PET</td>
<td>52</td>
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<td>8</td>
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<tr>
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<td>14</td>
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<td>18</td>
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<tr>
<td>Rasani et al\textsuperscript{13}</td>
<td>2006</td>
<td>PET-CT</td>
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<td>HL (n = 32), NHL (n = 68)</td>
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<td>Elstrom et al\textsuperscript{17}</td>
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<td>PET-CT</td>
<td>61</td>
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<td>5</td>
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<td>Poesi et al\textsuperscript{13}</td>
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<td>PET</td>
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<td>HL (n = 30), NHL (n = 35)</td>
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<td>5*</td>
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<td>Karam et al\textsuperscript{114}</td>
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<td>PET</td>
<td>17</td>
<td>FL</td>
<td>41</td>
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<td>29</td>
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<tr>
<td>Janikova et al\textsuperscript{175}</td>
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<td>Mostly PET</td>
<td>82</td>
<td>FL</td>
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<td>18</td>
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<tr>
<td>Wirth et al\textsuperscript{116}</td>
<td>2008</td>
<td>PET</td>
<td>42</td>
<td>FL stages I-II on CT</td>
<td>29</td>
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<tr>
<td>Le Dortz et al\textsuperscript{17}</td>
<td>2010</td>
<td>PET-CT</td>
<td>45</td>
<td>FL</td>
<td>8</td>
<td>0</td>
<td>18</td>
</tr>
<tr>
<td>Luminari et al\textsuperscript{118}</td>
<td>2013</td>
<td>PET-CT</td>
<td>142</td>
<td>FL</td>
<td>11</td>
<td>1</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviations: CT, computed tomography; FL, follicular lymphoma; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; NS, not stated; PET, positron emission tomography.

*False negative.
lymphomas with low FDG avidity. PET-CT may be used to select the best site to biopsy (type 1).

**Role of Contrast-Enhanced CT**

The CT part of a PET-CT scan may be performed with contrast enhancement (ceCT) at full dose to obtain a high-quality CT examination or without contrast using a lower dose. Lower-dose CT is used to correct for the attenuation of radioactivity within the patient and to localize abnormalities seen on PET, with less radiation than a full diagnostic examination. However, whichever protocol is used, CT must be acquired during shallow breathing or end of expiration to avoid misregistration and artifacts.

Direct comparison of unenhanced lower-dose PET-CT and cePET-CT suggests management is rarely altered by ceCT, although ceCT may identify additional findings and improve detection of abdominal or pelvic disease. However, full-dose ceCT involves additional radiation, which should be considered when deciding which examination to perform. ceCT is desirable for RT planning performed in the treatment position and is required for accurate nodal measurements for trial purposes.

Small errors in the measurement of FDG uptake in tumor may occur with contrast media because of an effect on attenuation correction; these errors are unlikely to be clinically important. Contrast may cause errors in comparison of uptake between tumor and reference sites by causing FDG uptake to be overestimated in the mediastinum and liver by 10% to 15%. Several organizations (eg, European Association Nuclear Medicine, Society Nuclear Medicine, and Radiological Society North America) recommend that a low-dose CT scan with normal breathing be performed before a PET scan, followed by full diagnostic high-dose ceCT with repositioning of the arms and breath hold, if quantitative measures and ceCT are required.

In practice, many patients undergo separate ceCT before PET-CT. If baseline ceCT demonstrates no additional relevant findings, lower-dose CT during PET-CT examination will be sufficient for response assessment.

**Recommendation.** ceCT when used at staging or restaging should ideally occur during a single visit in combination with PET-CT, if not already performed. The baseline findings will determine whether cePET-CT or lower-dose unenhanced PET-CT will suffice for additional imaging examinations (type 2).

**Relevance of Initial Disease Bulk**

The presence of bulky disease is a negative prognostic factor in some lymphomas. Bulk is considered an adverse factor in early-stage HL but not in advanced HL. In DLBCL, bulk is predictive of inferior survival in favorable-prognosis disease but not in poor-prognosis disease, probably because its influence is superseded by other factors reflecting disease burden. The longest diameter of the largest involved node is included in the FL International Prognostic Index 2. Unidimensional measurements are used for bulk, but these do not assess total tumor burden. Newer methods of contouring are being developed for CT and PET to measure the total tumor volume. The prognostic value of these methods remains to be evaluated.

**Recommendation.** Bulk remains an important prognostic factor in some lymphomas. Volumetric measurement of tumor bulk and total tumor burden, including methods combining metabolic activity and anatomic size or volume, should be explored as potential prognosticators (type 3).

**Role of iPET**

Interim imaging is frequently performed in clinical practice and trials and is recommended by some international guidelines. The purpose is to ensure the effectiveness of treatment and exclude the possibility of progression. PET-CT shows metabolic response earlier than anatomic response and has the potential to replace CT. Studies have shown that iPET is a strong prognostic indicator in HL and aggressive NHL, outperforming the International Prognostic Score and International Prognostic Index. These findings highlight the potential of using iPET to tailor treatment according to individual response. However, it is important to emphasize that there is no conclusive evidence that changing treatment according to iPET improves outcome, a question currently being addressed in clinical trials worldwide.

There is a preponderance of data reporting the predictive value of iPET, most often after two cycles in HL (Appendix Table A1, online only). In DLBCL, early indication of poor response is especially important because salvage treatment of progressive or relapsed disease is less effective in the rituximab era. However, although early data favored iPET over PET, more recent data have suggested iPET is less predictive for response with immunotherapy (Appendix Table A2, online only), and end-of-treatment PET is a better predictor.

Visual assessment with iPET in HL results in consistently high NPV, with ≥2-year PFS of approximately 95%, and acceptable PPV, with PFS between 13% and 27%; for advanced disease treated with ABVD. Initial reports using visual analysis for iPET in DLBCL were favorable, but more recent studies have demonstrated good NPV, with ≥2-year PFS rates of 73% to 86% for patients with so-called negative scans, but more variable PPV. PPV for PET-positive patients in recent studies has ranged from 18% to 74%. The drop in PPV may be related to improved outcomes with rituximab or better supportive care, or may possibly occur because so-called false-positive metabolic activity is more frequent with immunotherapy. A different cutoff or combination of factors may be required for modern management of DLBCL.

**Recommendation.** If midtherapy imaging is performed, PET-CT is superior to CT alone to assess early response. Trials are evaluating the role of PET–response–adapted therapy. Currently, changing treatment solely on the basis of iPET-CT is not recommended, unless there is clear evidence of progression (type 1).

The use of quantitation to improve on visual assessment has been explored in DLBCL. Change in the maximum SUV (SUVmax) in tumor before and after treatment has been evaluated as a measure of response. Receiver operator curve analysis in 92 patients with DLBCL scanned after two cycles and 80 patients scanned after four cycles was predictive of PFS, whereas visual analysis was not. Other groups have also reported that SUVmax predicts response, but with thresholds ranging from 66% to 91%, suggesting that consistency in scanning protocols, matching conditions for serial scans, and proper calibration and scanner maintenance are mandatory for...
The optimum cutoff is also likely influenced by timing, with a tendency for a higher cutoff later during treatment. Although the goal of quantitation is more objective assessment, it remains necessary to integrate with clinical information to exclude confounding variables.

The $\bar{S}UV_{max}$ analysis is being prospectively applied in the PETAL (Positron Emission Tomography Guided Therapy of Aggressive Non-Hodgkin’s Lymphomas) and GAINED (GA in Newly Diagnosed Diffuse Large B Cell Lymphoma) studies exploring response-adapted treatment with immunochemotherapy. Combining $\bar{S}UV_{max}$ with CT metrics in early nonbulky HL and with age-adjusted International Prognostic Index in DLBCL has been reported to improve response prediction. Another measure proposed is SUVpeak, a 1-cm$^3$ volume containing the hottest area of tumor, which may be less sensitive to noise and resolution and possibly more reproducible. Changes in the metabolic tumor volume (MTV) and total lesion glycolysis (TLG) calculated as MTV $\times$ SUVmean are additional exploratory measures. However, preliminary reports have suggested changes in MTV and TLG are not predictive in DLBCL. The results of the UK National Cancer Research Institute PET R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone) substudy measuring PFS in 200 patients with DLBCL where clinicians were blinded to iPET are awaited. This and other studies may provide insight into whether quantitation will improve the performance of iPET in DLBCL.

Assessment Before High-Dose Chemotherapy and Autologous Stem-Cell Transplantation

Various studies have reported that PET-CT using FDG is prognostic in patients with relapsed or refractory HL or DLBCL after salvage chemotherapy before high-dose chemotherapy and autologous stem-cell transplantation (ASCT) and is superior to CT alone. Three-year PFS and EFS rates of 31% to 41% have been reported for patients with PET-positive scans, compared with 75% to 82% for patients with PET-negative scans.

PET may have a role in selecting patients for high-dose chemotherapy and ASCT after salvage treatment and in identifying patients with poor prognosis who could benefit from alternative regimens or consolidation. PET could also be used as a surrogate end point to test the addition of novel therapies to current reintroduction regimens.

Recommendation. Assessment with PET-CT could be used to guide decisions before high-dose chemotherapy and ASCT, but additional studies are warranted (type 3).

PET-CT in Subtypes Other Than HL, DLBCL, and FL

Small retrospective studies have suggested that post-treatment scans can predict survival in treatment of mantle-cell lymphoma. In primary mediastinal B-cell lymphoma, a recent prospective study reported that 54 (47%) of 115 patients achieved CMR after first-line chemotherapy, and a PET response-adapted approach is currently being tested (IELSG-37 [International Extranodal Lymphoma Study Group]). However, another study involving 51 patients treated with dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) plus rituximab reported that 10 of 15 patients had FDG uptake 6 weeks after treatment, which later diminished or stabilized, suggesting treatment-related inflammation with this regimen. There are limited data regarding T-cell lymphomas, with higher uptake reported in more aggressive subtypes and lower uptake in cutaneous lymphomas. In mycosis fungoides, higher uptake has been reported in the presence of large-cell transformation and extracutaneous disease, which adversely affects prognosis. There are few data on response assessment; one report in noncutaneous mature natural killer/T-cell lymphoma suggested iPET was predictive of response, whereas another found that neither

End-of-treatment remission assessment is more accurate with PET-CT than CT alone in patients with HL, DLBCL, and high–tumor burden FL (Appendix Table A3, online only). High accuracy for PET-CT has been reported in patients after treatment with ABVD and BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) for advanced HL. In a study where PET was used to guide RT, patients treated with BEACOPP (but no RT) with a PET-negative positive response had PFS equivalent to that of patients with complete response (CR) or unconfirmed CR. In aggressive NHL, studies involving > 300 patients have reported consistently high NPV of 80% to 100% but more variable PPV of 50% to 100%. In the presence of residual metabolically active tissue, if salvage treatment is being considered, a biopsy may be required. If residual disease is considered unlikely, the scan could be repeated later.

Recommendation. PET-CT is the standard of care for remission assessment in FDG-avid lymphoma. For HL and DLBCL, in the presence of residual metabolically active tissue, where salvage treatment is being considered, a biopsy is recommended (type 1). The significance of a residual mass if CMR is achieved is unclear, with some reports suggesting improved outcomes when CMR is associated with a radiologic CR in HL and DLBCL, whereas others suggest outcomes are unaffected by the presence of a residual mass. It is proposed that the size of the residual mass be recorded where possible, and if relapse occurs, it should be documented whether this occurred within the residual mass.

Recommendation. Investigation of the significance of PET-negative residual masses should be collected prospectively in clinical trials. Residual mass size and location should be recorded on end-of-treatment PET-CT reports where possible (type 3).

In FL, PET predicts inferior outcomes in patients with high tumor burden who remain PET positive after first-line immunochemotherapy. Post-treatment PET seems to be a better predictor than iPET. Currently, data are insufficient regarding assessment after maintenance therapy. This suggests a potential role for PET in evaluating new approaches in response-adapted studies in FL after first-line treatment with rituximab-containing chemotherapy.

Recommendation. Emerging data support the use of PET-CT after rituximab-containing chemotherapy in high–tumor burden FL. Studies are warranted to confirm this finding in patients receiving maintenance therapy (type 2).
interim nor end-of-treatment PET were predictive.67 Prospective studies are warranted.

**DISCUSSION**

In response to developments involving PET-CT, recommendations from the ICML imaging group have been made to update practice. These include guidance on reporting of PET-CT for staging and response assessment of HL, DLBCL, and aggressive FL using the 5-PS. PET-CT is recommended for midtreatment assessment in place of CT alone, if imaging is clinically indicated, and for remission assessment. Quantitative imaging parameters for assessing disease burden and response should be explored as potential prognosticators. The standardization of PET-CT methods is mandatory for quantitative analysis and desirable for best clinical practice.

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**Manuscript writing:** All authors

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ICML Recommendations for Using PET-CT in Lymphoma


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Appendix

Table A1. Studies Including ≥ 50 Patients With HL Reporting Outcomes According to Visual Assessment With Interim PET

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>No. of Patients</th>
<th>Disease Stage</th>
<th>Chemotherapy</th>
<th>No. of Cycles Before PET</th>
<th>No. PET Negative</th>
<th>PFS/EFS At (years) PET Negative (%) PET Positive (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hutchings et al</td>
<td>2005</td>
<td>85</td>
<td>I-IV</td>
<td>Mostly ABVD (n = 79)</td>
<td>2-3</td>
<td>72</td>
<td>5   92 39</td>
</tr>
<tr>
<td>Hutchings et al</td>
<td>2006</td>
<td>77</td>
<td>I-IV</td>
<td>Mostly ABVD (n = 70)</td>
<td>2</td>
<td>61</td>
<td>2   96 0</td>
</tr>
<tr>
<td>Gallamini et al</td>
<td>2007</td>
<td>260</td>
<td>IIB-IV</td>
<td>Mostly ABVD (n = 249)</td>
<td>2</td>
<td>210</td>
<td>2   96 6</td>
</tr>
<tr>
<td>Markova et al</td>
<td>2009</td>
<td>50</td>
<td>IIB-IV</td>
<td>BEACODPP</td>
<td>4</td>
<td>36</td>
<td>2   97 86</td>
</tr>
<tr>
<td>Ceci et al</td>
<td>2010</td>
<td>104</td>
<td>I-IV</td>
<td>ABVD</td>
<td>2</td>
<td>74</td>
<td>3   90 53</td>
</tr>
<tr>
<td>Barnes et al</td>
<td>2011</td>
<td>96</td>
<td>II (nonbulky)</td>
<td>ABVD</td>
<td>2-4</td>
<td>79</td>
<td>4   91 87</td>
</tr>
<tr>
<td>Zinzani et al</td>
<td>2012</td>
<td>304</td>
<td>I-IIA (n = 147)</td>
<td>ABVD</td>
<td>2</td>
<td>128</td>
<td>9   95 31</td>
</tr>
<tr>
<td>Zinzani et al</td>
<td>2012</td>
<td>104</td>
<td>IIB-IV</td>
<td>ABVD</td>
<td>2</td>
<td>123</td>
<td>9   89 29</td>
</tr>
<tr>
<td>Biggi et al</td>
<td>2013</td>
<td>260</td>
<td>IIB-IV</td>
<td>ABVD</td>
<td>2</td>
<td>215</td>
<td>3   95 28</td>
</tr>
</tbody>
</table>

Abbreviation: ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; BEACODPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; EFS, event-free survival; HL, Hodgkin lymphoma; PET, positron emission tomography; PFS, progression-free survival.

Prospective study.

Table A2. Studies Including ≥ 50 Patients With Aggressive NHL Reporting Outcomes According to Visual Assessment With Interim PET

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>No. of Patients</th>
<th>Chemotherapy</th>
<th>No. of Cycles of Therapy</th>
<th>No. PET Negative</th>
<th>PFS/EFS At (years) PET Negative (%) PET Positive (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spaepen et al</td>
<td>2002</td>
<td>70</td>
<td>Mostly CHOP (n = 56)</td>
<td>3-4</td>
<td>37</td>
<td>2   85 0</td>
</tr>
<tr>
<td>Haioun et al</td>
<td>2005</td>
<td>90</td>
<td>CHOP or ACVBP/ACE (n = 53) plus rituximab (n = 37)</td>
<td>2-3</td>
<td>60</td>
<td>5   82 43</td>
</tr>
<tr>
<td>Mikhaeel et al</td>
<td>2005</td>
<td>121</td>
<td>Mostly CHOP (n = 97)</td>
<td>2-3</td>
<td>26</td>
<td>2   85 63</td>
</tr>
<tr>
<td>Cashen et al</td>
<td>2011</td>
<td>50</td>
<td>R-CHOP</td>
<td>2-3</td>
<td>26</td>
<td>2   73 60</td>
</tr>
<tr>
<td>Micallef et al</td>
<td>2011</td>
<td>76</td>
<td>ER-CHOP</td>
<td>2</td>
<td>60</td>
<td>2   86 29</td>
</tr>
<tr>
<td>Yang et al</td>
<td>2011</td>
<td>159</td>
<td>R-CHOP</td>
<td>3-4</td>
<td>116</td>
<td>3   84 66</td>
</tr>
<tr>
<td>Yoo et al</td>
<td>2011</td>
<td>155</td>
<td>R-CHOP</td>
<td>2-4</td>
<td>100</td>
<td>3   84 66</td>
</tr>
<tr>
<td>Zinzani et al</td>
<td>2011</td>
<td>91</td>
<td>Mostly R-CHOP (n = 66), rituximab (n = 91)</td>
<td>Midtreatment</td>
<td>56</td>
<td>5   75 18</td>
</tr>
<tr>
<td>Safar et al</td>
<td>2012</td>
<td>112</td>
<td>R-CHOP (n = 81), R-ACVBP (n = 31)</td>
<td>2</td>
<td>70</td>
<td>3   84 47</td>
</tr>
<tr>
<td>Pregno et al</td>
<td>2012</td>
<td>88</td>
<td>R-CHOP</td>
<td>2-4</td>
<td>66</td>
<td>2   85 72</td>
</tr>
<tr>
<td>Nols et al</td>
<td>2013</td>
<td>73</td>
<td>R-CHOP (n = 48), R-miniCHOP (n = 8), ACVBP (n = 17), CHOP (n = 1)</td>
<td>3-4</td>
<td>53</td>
<td>2   84 47</td>
</tr>
</tbody>
</table>

Abbreviations: ACE, doxorubicin, cyclophosphamide, and etoposide; ACVBP, doxorubicin, cyclophosphamide, vincristine, bleomycin, and prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; E, etoposide; EFS, event-free survival; HL, non-Hodgkin lymphoma; PET, positron emission tomography; PFS, progression-free survival; R, rituximab.

Prospective study.
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>No. of Patients</th>
<th>Disease and Stage</th>
<th>No. PET Negative</th>
<th>PPV</th>
<th>PFS/EFS at (years)</th>
<th>PET Negative (%)</th>
<th>PET Positive (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spaepen K et al: Br J Haematol 115:272-278, 2001</td>
<td>2001</td>
<td>60</td>
<td>IIA-IVB HL</td>
<td>55</td>
<td>91</td>
<td>2</td>
<td>91</td>
<td>0</td>
</tr>
<tr>
<td>Cerci et al</td>
<td>2010</td>
<td>50</td>
<td>I-IV HL (patients in CRu/PR on CT)</td>
<td>23</td>
<td>92</td>
<td>—</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Engert et al</td>
<td>2012</td>
<td>739</td>
<td>IIB-IV HL</td>
<td>548</td>
<td>95</td>
<td>NA</td>
<td>5</td>
<td>92</td>
</tr>
<tr>
<td>Barnes et al</td>
<td>2011</td>
<td>96</td>
<td>I-II nonbulky HL</td>
<td>83</td>
<td>94</td>
<td>46</td>
<td>4</td>
<td>94</td>
</tr>
<tr>
<td>Spaepen et al</td>
<td>2001</td>
<td>93</td>
<td>Aggressive NHL</td>
<td>90</td>
<td>100</td>
<td>70</td>
<td>—</td>
<td>NS</td>
</tr>
<tr>
<td>Micallef et al</td>
<td>2011</td>
<td>69</td>
<td>DLBCL</td>
<td>61</td>
<td>90</td>
<td>50</td>
<td>2</td>
<td>78</td>
</tr>
<tr>
<td>Pregno et al</td>
<td>2012</td>
<td>88</td>
<td>DLBCL</td>
<td>77</td>
<td>100</td>
<td>82</td>
<td>2</td>
<td>83</td>
</tr>
<tr>
<td>Trotman et al</td>
<td>2011</td>
<td>122</td>
<td>High-tumor burden FL</td>
<td>90</td>
<td>NS</td>
<td>NS</td>
<td>3.5</td>
<td>71</td>
</tr>
<tr>
<td>Dupuis et al</td>
<td>2012</td>
<td>106</td>
<td>High-tumor burden FL</td>
<td>83</td>
<td>NS</td>
<td>NS</td>
<td>2</td>
<td>87</td>
</tr>
</tbody>
</table>

Abbreviations: CRu, unconfirmed complete response; CT, computed tomography; DLBCL, diffuse large B-cell lymphoma; EFS, event-free survival; FL, follicular lymphoma; FTF, freedom from treatment failure; HL, Hodgkin lymphoma; NA, not applicable; NHL, non-Hodgkin lymphoma; NPV, negative predictive value; NS, not stated; PET, positron emission tomography; PFS, progression-free survival; PPV, positive predictive value; PR, partial response.

†Prospective study.

Prospective study.

†Treatment guided by end-of-treatment PET.
Fig A1. (A) Pretreatment scan: computed tomography, positron emission tomography, and fused images showing disease in left neck (arrow). (B) Example of score 1: complete metabolic response with no uptake in normal-size lymph nodes at site of initial disease in left neck (arrow).
Fig A2. (A) Pretreatment scan: computed tomography, positron emission tomography, and fused images showing disease in left axilla. (B) Example of score 2: residual uptake of intensity < mediastinal blood pool in lymph nodes in left axilla (arrow). Maximum standardized uptake value (SUVmax) in lymph nodes was 1.2; SUVmax in mediastinal blood pool was 1.7.
Fig A3. (A) Pretreatment scan: computed tomography, positron emission tomography, and fused images showing disease in right neck and mediastinum (arrow). (B) Example of score 3: residual uptake of intensity > mediastinal blood pool but < liver in residual mediastinal mass (arrow). Maximum standardized uptake value (SUVmax) in mass was 1.7; SUVmax in liver was 2.2.
Fig A4. (A) Pretreatment scan: computed tomography, positron emission tomography, and fused images showing disease in mediastinum. (B) Example of score 4: residual uptake of intensity > liver in residual mediastinal mass (arrow). Maximum standardized uptake value (SUVmax) in mass was 4.5; SUVmax in liver was 3.2.
Fig A5. (A) Pretreatment scan: computed tomography, positron emission tomography, and fused images showing disease in right neck, mediastinum, and right axilla. (B) Example of score 5: residual uptake in mediastinum with intensity markedly higher than normal liver. Maximum standardized uptake value (SUV\text{max}) in mass was 13.0; SUV\text{max} in liver was 2.3.