Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification

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Abstract
The purpose of this work was to modernize recommendations for evaluation, staging, and response assessment of patients with Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). A workshop was held at the 11th International Conference on Malignant Lymphoma in Lugano, Switzerland, in June 2011, that included leading hematologists, oncologists, radiation oncologists, pathologists, radiologists, and nuclear medicine physicians, representing major international lymphoma clinical trials groups and cancer centers. Clinical and imaging subcommittees presented their conclusions at a subsequent workshop at the 12th International Conference on Malignant Lymphoma, leading to revised criteria for staging and of the International Working Group Guidelines of 2007 for response. As a result, fluorodeoxyglucose (FDG) positron emission tomography (PET)–computed tomography (CT) was formally incorporated into standard staging for FDG-avid lymphomas. A modification of the Ann Arbor descriptive terminology will be used for anatomic distribution of disease extent, but the suffixes A or B for symptoms will only be included for HL. A bone marrow biopsy is no longer indicated for the routine staging of HL and most diffuse large B-cell lymphomas. However, regardless of stage, general practice is to treat patients based on limited (stages I and II, nonbulky) or advanced (stage III or IV) disease, with stage II bulky disease considered as limited or advanced disease based on histology and a number of prognostic factors. PET-CT will be used to assess response in FDG-avid histologies using the 5-point scale. The product of the perpendicular diameters of a single node can be used to identify progressive disease. Routine surveillance scans are discouraged. These recommendations should improve evaluation of patients with lymphoma and enhance the ability to compare outcomes of clinical trials.

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INTRODUCTION
The availability of more effective therapies for lymphoma and the increasingly sensitive and specific technologies for disease assessment provide rationale for updated patient evaluation, staging, and response criteria. These should be unambiguous and universally applicable and facilitate the comparison of patients and results among studies and the evaluation of new therapies by regulatory agencies.

Staging defines disease location and extent, suggests prognostic information, allows comparisons among studies, and provides a baseline against which response or disease progression can be compared. Initial staging criteria were designed primarily for Hodgkin lymphoma (HL)1–3 and were superseded by the Ann Arbor classification,4 which subdivided HL patients into four stages and subclassification A and B based on the presence of fevers to greater than 101°F (38.3°C), weight loss, and night sweats and which has been the most widely used classification since its introduction. The Cotswold classification5 first formally incorporated computed tomography (CT) scans and introduced “X” for bulky disease and complete remission unconfirmed (CRu) to describe patients with a residual mass after treatment that was most likely fibrous tissue. The first universally accepted response criteria for non-Hodgkin lymphoma (NHL), used also for HL, were published in 1999 by the National Cancer Institute Working Group6 and revised in 2007 by the International Working Group (IWG)7 to incorporate positron emission tomography (PET) and bone marrow immunohistochemistry and flow cytometry in response assessment, eliminating CRu.
Table 1. Criteria for Involvement of Site

<table>
<thead>
<tr>
<th>Tissue Site</th>
<th>Clinical</th>
<th>FDG Avidity</th>
<th>Test</th>
<th>Positive Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymph nodes</td>
<td>Palpable</td>
<td>FDG-avid histologies</td>
<td>PET-CT</td>
<td>Increased FDG uptake</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nonavid disease</td>
<td>CT</td>
<td>Unexplained node enlargement</td>
</tr>
<tr>
<td>Spleen</td>
<td>Palpable</td>
<td>FDG-avid histologies</td>
<td>PET-CT</td>
<td>Diffuse uptake, solitary mass, miliary lesions, nodules</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nonavid disease</td>
<td>CT</td>
<td>&gt; 13 cm in vertical length, mass, nodules</td>
</tr>
<tr>
<td>Liver</td>
<td>Palpable</td>
<td>FDG-avid histologies</td>
<td>PET-CT</td>
<td>Diffuse uptake, mass</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nonavid disease</td>
<td>CT</td>
<td>Nodules</td>
</tr>
<tr>
<td>CNS</td>
<td>Signs, symptoms</td>
<td></td>
<td>CT</td>
<td>Mass lesion(s)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MRI</td>
<td>Leptomeningeal infiltration, mass lesions</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CSF assessment</td>
<td>Cytology, flow cytometry</td>
</tr>
<tr>
<td>Other (eg, skin, lung, GI tract, bone, bone marrow)</td>
<td>Site dependent</td>
<td></td>
<td>PET-CT*, biopsy</td>
<td>Lymphoma involvement</td>
</tr>
</tbody>
</table>

Abbreviations: CSF, cerebrospinal fluid; CT, computed tomography; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; PET, positron emission tomography. *PET-CT is adequate for determination of bone marrow involvement and can be considered highly suggestive for involvement of other extralymphatic sites. Biopsy confirmation of those sites can be considered if necessary.

After extensive experience with these criteria, and recognizing the progress made after their publication, particularly in imaging techniques, a workshop was held at the 11th International Conference on Malignant Lymphoma in Lugano, Switzerland, in June 2011, which was attended by leading hematologists, oncologists, radiation oncologists, pathologists, radiologists, and nuclear medicine physicians, representing major lymphoma clinical trials groups and cancer centers in North America, Europe, Japan, and Australasia. The aim was to develop improved staging and response criteria for HL and NHL, relevant for community physicians, investigator-led trials, cooperative groups, and registration trials. Subcommittees focused on clinical and imaging issues, and a subsequent workshop at the 12th International Conference on Malignant Lymphoma in 2013 led to the following revisions.

INITIAL EVALUATION

Diagnosis

Lymphoma diagnosis depends on morphology, immunohistochemistry, and flow cytometry reviewed by an experienced lymphoma pathologist and, where appropriate, molecular studies to accurately categorize the lymphoma. A fine-needle aspirate is inadequate for initial diagnosis. An incisional or excisional biopsy is preferred to provide adequate tissue for these examinations, but a core-needle biopsy can be considered when excisional biopsy is not possible and to document relapse; however, a nondiagnostic sample must be followed by an incisional or excisional biopsy. With consent, additional paraffin-embedded, fresh-frozen tissue, or cell suspensions should be stored for future research.

Patient Evaluation

Clinical evaluation requires a comprehensive history including age; sex; absence/presence of fevers to more than 101°F (38.3°C), chills, drenching night sweats, or unexplained weight loss more than 10% of body mass over 6 months; and history of malignancy. Fatigue, pruritus, and alcohol-induced pain in patients with HL should also be noted. Whereas these factors rarely direct treatment, their recurrence may herald disease relapse.

Physical examination includes measurement of accessible nodal groups and the size of the spleen and liver in centimeters below their respective costal margins in the midclavicular line. However, the sensitivity of physical examination is variable among observers. Therefore, organomegaly is formally defined by CT imaging (Table 1).

Anatomic Staging

Historical series and prospective clinical trials have used the Ann Arbor staging system to select patients and report outcomes. Now, stage is only one component of factors in prognostic indices increasingly used for pretreatment risk stratification and selection of therapy. PET-CT scanning has become the standard for assessment of response in most lymphomas. For HL and fluorodeoxyglucose (FDG) -avid NHL subtypes, PET and PET-CT improve the accuracy of staging compared with CT scans for nodal and extranodal sites. PET-CT leads to change in stage in 10% to 30% of patients, more often upstaging, although alteration in management occurs in fewer patients, with no demonstrated impact on overall outcome. However, improving staging accuracy ensures that fewer patients are undertreated or overtreated. PET-CT is particularly important for staging before consideration of radiation therapy. Although most lymphomas are FDG avid, because of greater variability in FDG uptake, metabolic imaging is less reliable in other lymphomas. Whereas mantle-cell lymphoma is routinely FDG avid, limited data suggest that the sensitivity and specificity of identifying bowel involvement are low and should not replace other investigative measures.

PET-CT is already widely used for pretreatment assessment, often outside of clinical trials, to assign stage and has already been incorporated into response assessment. Although physical examination remains important, and despite concerns that more sensitive staging can
result in stage migration, impairing the use of historically controlled data, PET-CT is critical as a baseline measurement before therapy to increase the accuracy of subsequent response assessment\(^2\)\(^7\)\(^8\) (Table 1). Therefore, the consensus was that PET-CT should be recommended for routine staging of FDG-avid, nodal lymphomas (especially all histologies except chronic lymphocytic leukemia/small lymphocytic lymphoma, lymphoplasmacytic lymphoma/Waldenström’s macroglobulinemia, mycosis fungoides, and marginal zone NHLs, unless there is a suspicion of aggressive transformation) as the gold standard.\(^2\)\(^4\)

The following recommendations are intended for lymphomas with primarily nodal involvement, although they are also applicable to primary extranodal diffuse large B-cell lymphoma (DLBCL). Separate criteria have been proposed for primary extranodal\(^2\)\(^9\)\(^3\)\(^0\) and cutaneous lymphomas.\(^3\)\(^1\)

**Imaging**

PET-CT is preferred for staging of FDG-avid lymphomas, and CT scan is preferred in the other lymphomas. A chest x-ray is no longer required in lymphoma staging because it less accurate than CT.\(^3\)\(^5\) Moreover, CT identifies more hilar nodes and may better discriminate between a single large nodal mass and an aggregate of individual nodes. Bulk is a negative prognostic factor,\(^1\)\(^1\)\(^3\)\(^1\)\(^3\)\(^1\)\(^5\) but there is little agreement on its definition, which is disease, stage, and treatment specific.

These criteria strongly recommend PET-CT for staging of routinely FDG-avid histologies, especially in clinical trials. A contrast-enhanced CT scan should be included for a more accurate measurement of nodal size if required for trials; if necessary, to more accurately distinguish bowel from lymphadenopathy; and in the setting of compression/thrombosis of central/ mediastinal vessels. Contrast-enhanced CT is also preferred for radiation planning. Variably FDG-avid histologies should be staged with a CT scan.

For patients staged with PET-CT, focal uptake in nodal and extranodal sites that is in keeping with lymphoma, according to the distribution and/or CT characteristics, is considered involvement with lymphoma, including spleen, liver, bone, thyroid, and so on. For patients staged with CT, up to six of the largest target nodes, nodal masses, or other lymphomatous lesions that are measurable in two diameters (longest diameter [LDi] and shortest diameter) should be identified from different body regions representative of the patient’s overall disease burden and include mediastinal and retroperitoneal disease, if involved. A measurable node must have an LDi greater than 1.5 cm. Measurable extranodal disease (eg, hepatic nodules) may be included in the six representative, measured lesions. A measurable extranodal lesion should have an LDi greater than 1.0 cm. All other lesions (including nodal, extranodal, and assessable disease) should be followed as nonmeasured disease, except for cutaneous, GI, bone, spleen, liver, kidneys, pleural or pericardial effusions, ascites. In patients in whom a discordant histology or malignant transformation is suspected, a PET-CT may identify the optimal site to biopsy for confirmation.\(^2\)\(^0\)\(^2\)\(^1\)

**Tumor Bulk**

A single nodal mass, in contrast to multiple smaller nodes, of 10 cm or greater than a third of the transthoracic diameter at any level of thoracic vertebrae as determined by CT is retained as the definition of bulky disease for HL.\(^5\) A chest x-ray is not required to determine bulk because of its high concordance with CT.\(^3\)\(^2\) However, a variety of sizes have been suggested for NHL,\(^5\)\(^3\)\(^3\) with limited evidence suggesting 6 cm as best for follicular lymphoma\(^1\)\(^5\) and 6 to 10 cm in the rituximab era for DLBCL.\(^3\)\(^4\) However, none of the proposed sizes have been validated in the current therapeutic era. Therefore, the recommendation for HL and NHL is to record the longest measurement by CT scan, with the term X no longer necessary.

**Spleen Involvement**

A wide range of normal spleen sizes has been reported,\(^3\)\(^5\)\^-\(^3\)\(^7\)\(^3\)\(^7\) related to race, body size, and height.\(^3\)\(^8\) A spleen may be of normal size and still contain lymphoma or may be enlarged as a result of variations in blood volume, use of hematopoietic growth factors, or lymphoma-unrelated causes. Splenic involvement is best determined by PET-CT and may be characterized by homogeneous splenomegaly, diffuse infiltration with miliary lesions, focal nodular lesions, or a large solitary mass.\(^3\)\(^9\) There is no agreement on whether single, multiple, or volumetric measurements should be used to measure spleen size\(^3\)\(^5\) or what cutoff to use for splenomegaly. For simplicity, a single measurement that correlates well with volume\(^4\)\(^0\)\^-\(^4\)\(^\)\(^1\) is preferable to a volumetric measurement or estimation by equations, with special software, which are unlikely to be used routinely.

Most studies use 10 to 12 cm for vertical length. Our recommendation is to use a cutoff for splenomegaly of more than 13 cm.

**Liver Involvement**

Given variability in body habitus and the impact of numerous medical conditions, liver size by physical examination or CT scan is not a reliable measure of hepatic involvement by lymphoma. Similar to splenic involvement, diffusely increased or focal uptake, with or without focal or disseminated nodules, supports liver involvement.

**Bone Marrow Involvement**

Bone marrow biopsy (BMB) has been standard in lymphoma staging,\(^5\) although it is often performed even when the likelihood of involvement is low. The high sensitivity of PET-CT for bone marrow involvement has recently called into question the continued use of BMB in several common histologies.\(^4\)\(^2\)\^-\(^4\)\(^\)\(^6\) In one study in HL, 18% of patients had focal skeletal lesions on PET-CT, but only 6% had positive BMB,\(^4\)\(^6\) all with advanced disease on PET-CT. None of the patients would have been allocated to another treatment based on BMB results. Patients with early-stage disease rarely have involvement in the absence of a suggestive PET finding, and those with advanced-stage disease rarely have involvement in the absence of disease-related symptoms or other evidence of advanced-stage disease. Thus, if a PET-CT is performed, a bone marrow aspirate/biopsy is no longer required for the routine evaluation of patients with HL.

In DLBCL, PET-CT is also more sensitive than BMB but has been reported to miss low-volume diffuse involvement of 10% to 20% of the marrow.\(^5\)\(^2\)\^-\(^4\)\(^\)\(^7\)\(^\)\(^\)\(^9\) Nevertheless, patients with clinical early-stage disease rarely have involvement in the absence of a suggestive PET finding. In one study in DLBCL, 27% of patients were found to have marrow involvement (94% by PET-CT and only 40% by BMB). BMB was negative in 21 of 28 patients with focal disease on PET-CT and did not upstage any patients. Two cases (1.5%) of bone marrow involvement went undetected by PET-CT, with a 10% infiltrate of large cells. Thus, a PET-CT scan indicating bone or marrow involvement is...
usually sufficient to designate advanced-stage disease, and a BMB is not required. Patients with a positive BMB generally have other factors consistent with advanced stage or poor prognosis. If the scan is negative, a BMB is indicated to identify involvement by discordant histology if relevant for a clinical trial or patient management. The data in all other lymphoma histologies are insufficient to change the standard practice, and a 2.5-cm unilateral BMB is recommended, along with immunohistochemistry and flow cytometry.

**PROGNOSTIC GROUPS AND TREATMENT ALLOCATION**

The increased use of systemic and multimodality approaches has made Ann Arbor stage less relevant in directing the choice of therapy. Nevertheless, we recommend a modification of the Ann Arbor classification (Table 2) for anatomic description of disease extent. However, regardless of stage, general practice is to treat patients based on limited (stages I and II, nonbulky) or advanced (stages III or IV) disease, with stage II bulky disease considered limited or advanced as determined by histology and a number of prognostic factors. The designation E for extranodal disease is relevant only for limited extranodal disease in the absence of nodal involvement (IE) or in patients with stage II disease and direct extension to a non-nodal site. E is not relevant to patients with advanced-stage disease.

The Ann Arbor classification subdivides patients according to the absence (A) or presence (B) of disease-related symptoms. However, these features are frequently neither recorded nor accurate. Moreover, in the International Prognostic Index, Follicular Lymphoma International Prognostic Index, Follicular Lymphoma International Prognostic Index 2, and Mantle Cell International Prognostic Index, constitutional symptoms do not confer an unfavorable outcome. Thus, only patients with HL need be assigned the designations A or B because symptoms only direct treatment in that disease.

### Table 2. Revised Staging System for Primary Nodal Lymphomas

<table>
<thead>
<tr>
<th>Stage</th>
<th>Involvement</th>
<th>Extranodal (E) Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limited</td>
<td>One node or a group of adjacent nodes</td>
<td>Single extranodal lesions without nodal involvement</td>
</tr>
<tr>
<td>II bulky*</td>
<td>II as above with “bulky” disease</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Advanced</td>
<td>Nodal disease without splenic involvement</td>
<td>Not applicable</td>
</tr>
<tr>
<td>IV</td>
<td>Additional noncontiguous extranodal involvement</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

**Summary**

Excisional biopsy is preferred for diagnosis, although core-needle biopsy may suffice when not feasible.

Clinical evaluation includes careful history, relevant laboratory tests, and recording of disease-related symptoms. PET-CT is the standard for FDG-avid lymphomas, whereas CT is indicated for nonavid histologies.

A modified Ann Arbor staging system is recommended; however, patients are treated according to prognostic and risk factors. Suffixes A and B are only required for HL.

The designation X for bulky disease is no longer necessary; instead, a recording of the largest tumor diameter is required.

If a PET-CT is performed, a BMB is no longer indicated for HL; a BMB is only needed for DLBCL if the PET is negative and identifying a discordant histology is important for patient management.

### ASSESSMENT OF RESPONSE AFTER TREATMENT

End-of-treatment assessment is more accurate with PET-CT, especially for patients with radiologic (CT) CRu or partial response (PR) in HL, DLBCL, and follicular lymphoma. PET–CT–based criteria eliminate CRu and improve the prognostic value of PR. In early- and advanced-stage patients with HL, a negative predictive value of 95% to 100% and positive predictive value of more than 90% have been reported.

In aggressive NHL, studies have reported a negative predictive value of 80% to 100% but a lower positive predictive value, ranging from 50% to 100%. If further treatment based on residual metabolically active disease on PET-CT is being considered, either biopsy or follow-up scan is advised. In these lymphoma subtypes, response assessment with PET-CT may be preferred.

The IHWG criteria for reviewing PET scans were based on visual interpretation and intended for end-of-treatment evaluation, using mediastinal blood pool as the comparator. The current recommendation is to use the 5-point scale, both for clinical trials including interim analysis and for end-of-treatment assessment (Table 3). Interim PET-CT is used to assess early treatment response and, at end of treatment, to establish remission status. A score of 1 or 2 is considered to represent complete metabolic response at interim and end of treatment. FDG uptake declines during therapy in chemotherapy-sensitive disease, and residual FDG uptake higher than normal liver uptake is frequently seen at interim in patients who achieve complete metabolic response at the end of treatment. More recent data also suggest that most patients with uptake higher than mediastinum but less than or equivalent to liver (score of 3) have good prognosis at the end of treatment with standard therapy in HL. PET-CT–based criteria eliminar CRu and improve the prognostic value of PR. In early- and advanced-stage patients with HL, a negative predictive value of 95% to 100% and positive predictive value of more than 90% have been reported.

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with lymphoma represents treatment failure at interim and at the end-of-treatment assessment.

In most cases, lack of significant response can be interpreted visually. Although ideally a quantitative cutoff might improve consistency, there is insufficient evidence to quantify precisely the reduction in uptake that predicts adequate response using FDG-PET for lymphoma, which is dependent on disease type, timing, and treatment given. Recent data suggest that the CT scan may play a complimentary role in patients with HL who have either a positive interim or post-treatment PET-CT, with a greater reduction in tumor mass correlating with an improved outcome.64,65 How best to use this information remains to be determined.

CT-based response is preferred for histologies with low or variable FDG avidity and in regions of the world where PET-CT is unavailable. However, in the absence of a PET-CT scan, a mass that has decreased in size but persists is considered at best a PR in the absence of biopsy documenting absence of lymphoma, and the former term CRu is not to be considered.7 In trials exploring new agents in multiply relapsed disease where data are lacking regarding PET-CT and where assessment of disease control is more important than likelihood of cure, CT-based response may also be more relevant (Table 3).

At interim or end of therapy, tests that were abnormal before treatment should be repeated, including assessment of extranodal sites. Response assessment is detailed in Table 3 and in the following sections.

**Nodes or Extranodal Lesions That Split When Disease Is Responding**

If a confluent nodal mass splits into several discrete nodes, the individual product of the perpendicular diameters (PPDs) of the nodes should be summed together to represent the PPD of the split lesion; this PPD is added to the sum of the PPDs of the remaining lesions to measure response. If subsequent growth of any or all of these discrete nodes occurs, the nadir of each individual node is used to determine progression (as if each individual node was selected as a target lesion at baseline).

**Nodes or Extranodal Lesions That Become Confluent When Disease Is Progressing**

If a group of target lymph nodes becomes confluent, the PPD of the current confluent mass should be compared with the sum of the PPDs of the individual nodes, with more than 50% increase in the PPD of the confluent mass compared with the sum of individual nodes necessary to indicate progressive disease. The LDi and shortest diameter are no longer needed to determine progression.

**Additional Response Assessment Guidelines**

The presence of residual symptoms in the absence of detectable disease by imaging does not preclude the designation CR. In the context of an agent associated with a flare reaction, caution must be exercised not to confuse the possible tumor flare with progressive disease. It is recommended that either a biopsy be performed or the lesion be reassessed in at least 2 weeks, and if there is continued evidence of tumor progression, the date of progressive disease is the previous evaluation.
**Table 3. Revised Criteria for Response Assessment**

<table>
<thead>
<tr>
<th>Response and Site</th>
<th>PET-CT–Based Response</th>
<th>CT-Based Response</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complete</strong></td>
<td></td>
<td>Complete radiologic response (all of the following)</td>
</tr>
<tr>
<td>Lymph nodes and extralymphatic sites</td>
<td>Complete metabolic response</td>
<td>Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi</td>
</tr>
<tr>
<td></td>
<td>Score 1, 2, or 3* with or without a residual mass on 5PS†</td>
<td>No extralymphatic sites of disease</td>
</tr>
<tr>
<td></td>
<td>It is recognized that in Waldeyer’s ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake.</td>
<td></td>
</tr>
<tr>
<td>Nonmeasured lesion</td>
<td>Not applicable</td>
<td>Absent</td>
</tr>
<tr>
<td>Organ enlargement</td>
<td>Not applicable</td>
<td>Regress to normal</td>
</tr>
<tr>
<td>New lesions</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>No evidence of FDG-avid disease in marrow</td>
<td>Normal by morphology; if indeterminate, IHC negative</td>
</tr>
<tr>
<td><strong>Partial</strong></td>
<td></td>
<td>Partial remission (all of the following)</td>
</tr>
<tr>
<td>Lymph nodes and extralymphatic sites</td>
<td>Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size</td>
<td>≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites</td>
</tr>
<tr>
<td></td>
<td>At interim, these findings suggest responding disease</td>
<td>When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value</td>
</tr>
<tr>
<td></td>
<td>At end of treatment, these findings indicate residual disease</td>
<td>When no longer visible, 0 × 0 mm</td>
</tr>
<tr>
<td>Nonmeasured lesions</td>
<td>Not applicable</td>
<td>For a node &gt; 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation</td>
</tr>
<tr>
<td>Organ enlargement</td>
<td>Not applicable</td>
<td>Absent/normal, regressed, but no increase</td>
</tr>
<tr>
<td>New lesions</td>
<td>None</td>
<td>Spleen must have regressed by &gt; 50% in length beyond normal</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan</td>
<td>None</td>
</tr>
<tr>
<td><strong>No response or stable disease</strong></td>
<td>No metabolic response</td>
<td>Stable disease</td>
</tr>
<tr>
<td>Target nodes/nodal masses, extranodal lesions</td>
<td>Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment</td>
<td>&lt; 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met</td>
</tr>
<tr>
<td>Nonmeasured lesions</td>
<td>Not applicable</td>
<td>No increase consistent with progression</td>
</tr>
<tr>
<td>Organ enlargement</td>
<td>Not applicable</td>
<td>No increase consistent with progression</td>
</tr>
<tr>
<td>New lesions</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>No change from baseline</td>
<td>Not applicable</td>
</tr>
<tr>
<td><strong>Progressive disease</strong></td>
<td>Progressive metabolic disease</td>
<td>Progressive disease requires at least 1 of the following PPD progression:</td>
</tr>
<tr>
<td>Individual target nodes/nodal masses</td>
<td>Score 4 or 5 with an increase in intensity of uptake from baseline and/or</td>
<td>An individual node/lesion must be abnormal with:</td>
</tr>
<tr>
<td>Extranodal lesions</td>
<td>New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment</td>
<td>LDi &gt; 1.5 cm and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increase by &gt; 50% from PPD nadir and</td>
</tr>
<tr>
<td></td>
<td>New or recurrent splenomegaly</td>
<td>An increase in LDi or SDi from nadir</td>
</tr>
<tr>
<td></td>
<td>New or clear progression of preexisting nonmeasured lesions</td>
<td>0.5 cm for lesions ≤ 2 cm</td>
</tr>
<tr>
<td>Nonmeasured lesions</td>
<td>None</td>
<td>1.0 cm for lesions &gt; 2 cm</td>
</tr>
</tbody>
</table>

*Score 1: normal physiologic uptake, 2: increased uptake, 3: high physiologic uptake.
†PPD progression:* 
- LDi: Longitudinal diameter increase
- SDi: Short axis diameter increase
- PPD progression: Longitudinal diameter increase of at least 1.5 cm, with or without a residual mass, and/or increase in active lesion size greater than 50% from nadir. Splenic length increase in setting of splenomegaly must be at least 2 cm from baseline.
Accurate pretreatment evaluation and response assessment are critical to the optimal management of patients with lymphoma. With increasing knowledge of the disease, new prognostic factors, and a better understanding of tumor biology comes a need to update prior systems. Despite the importance of a physical examination, imaging studies have become the standard. The present recommendations are directed primarily at initial staging and assessment, and their role in the multiply relapsed setting and early clinical trials remains to be confirmed. A major departure from the Ann Arbor system and the IWG criteria is that PET-CT is included in staging for FDG-avid lymphomas, because it is more sensitive than CT and provides a baseline against which response is more accurately assessed.

A new node must be unequivocal and must be at least 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma. Any disease not truly assessable is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, Waldeyer’s ring or in extranodal sites (eg, GI tract, liver, bone marrow), PET uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

**Table 3. Revised Criteria for Response Assessment (continued)**

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<th>Response and Site</th>
<th>PET-CT-Based Response</th>
<th>CT-Based Response</th>
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Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.

A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not preferable to be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not preferable to be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not preferable to be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not preferable to be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not preferable to be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not preferable to be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not preferable to be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not preferable to be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not preferable to be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not preferable to be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not preferable to be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not preferably to be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation.

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**CONCLUDING REMARKS**

Accurate pretreatment evaluation and response assessment are critical to the optimal management of patients with lymphoma. With increasing knowledge of the disease, new prognostic factors, and a better understanding of tumor biology comes a need to update prior systems. Despite the importance of a physical examination, imaging studies have become the standard. The present recommendations are directed primarily at initial staging and assessment, and their role in the multiply relapsed setting and early clinical trials remains to be confirmed. A major departure from the Ann Arbor system and the IWG criteria is that PET-CT is included in staging for FDG-avid lymphomas, because it is more sensitive than CT and provides a baseline against which response is more accurately assessed. Patients should be treated based on prognostic factors. Subclassification of A and B is now only indicated if prognostically important (ie, HL). Patients, including those with HL and most with DLBCL, can be spared a staging BMB, and a routine chest x-ray is unnecessary for staging, although it may be useful for monitoring select patients with HL. Although the current definition of bulk is retained for HL, further correlations between maximum tumor diameter and outcome are needed to provide a clinically meaningful definition of bulk with current treatment approaches for NHL. Response assessment is preferred for FDG-avid lymphomas where possible, using the 5-point scale, whereas CT-based response remains important in lymphomas with low or variable FDG avidity, and in multiply relapsed disease, CT criteria for progressive disease can be based on an increase of a single lesion. The better we are able to exploit the biology of lymphomas for therapeutic benefit, the more our treatment strategies will be determined by relevant receptors and pathways, with even less reliance on Ann Arbor staging. Hopefully, the current recommendations will provide the necessary standardization of clinical trial conduct and interpretation that leads to improved therapies for patients with lymphoma.

**AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

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**AUTHOR CONTRIBUTIONS**

Conception and design: All authors
Collection and assembly of data: All authors
Data analysis and interpretation: All authors
Manuscript writing: All authors
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REFERENCES

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