VOLUME 25 · NUMBER 5 · FEBRUARY 10 2007

JOURNAL OF CLINICAL ONCOLOGY

SPECIAL ARTICLE

Use of Positron Emission Tomography for Response Assessment of Lymphoma: Consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma

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Submitted July 13, 2006; accepted November 22, 2006; published online ahead of print at www.jco.org on January 22, 2007.

Presented in part at the 53rd Society of Nuclear Medicine Annual Meeting, June 3-7, 2006, San Diego, CA.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/07/2505-571/$20.00

DOI: 10.1200/JCO.2006.08.2305

ABSTRACT

Purpose

To develop guidelines for performing and interpreting positron emission tomography (PET) imaging for treatment assessment in patients with lymphoma both in clinical practice and in clinical trials.

Methods

An International Harmonization Project (IHP) was convened to discuss standardization of clinical trial parameters in lymphoma. An imaging subcommittee developed consensus recommendations based on published PET literature and the collective expertise of its members in the use of PET in lymphoma. Only recommendations subsequently endorsed by all IHP subcommittees were adopted.

Recommendations

PET after completion of therapy should be performed at least 3 weeks, and preferably at 6 to 8 weeks, after chemotherapy or chemoimmunotherapy, and 8 to 12 weeks after radiation or chemoradiotherapy. Visual assessment alone is adequate for interpreting PET findings as positive or negative when assessing response after completion of therapy. Mediastinal blood pool activity is recommended as the reference background activity to define PET positivity for a residual mass $\geq$ 2 cm in greatest transverse diameter, regardless of its location. A smaller residual mass or a normal sized lymph node (ie, $\leq 1 \times 1$ cm in diameter) should be considered positive if its activity is above that of the surrounding background. Specific criteria for defining PET positivity in the liver, spleen, lung, and bone marrow are also proposed. Use of attenuation-corrected PET is strongly encouraged. Use of PET for treatment monitoring during a course of therapy should only be done in a clinical trial or as part of a prospective registry.

J Clin Oncol 25:571-578. © 2007 by American Society of Clinical Oncology

INTRODUCTION

The use of positron emission tomography (PET) with [^{18}F]fluorodeoxyglucose (FDG) for evaluation of Hodgkin's and non-Hodgkin's lymphomas (HL and NHL, respectively) has increased dramatically during the last few years.[1,2] The widely used International Working Group criteria for response assessment of lymphoma, published in 1999, are based predominantly on computed tomography (CT) and do not include PET as part of response assessment.[3] Considering the more recent widespread use of PET in response assessment of lymphoma, it became clear that the International Working Group criteria warranted revision. For this purpose, the Competence Network Malignant Lymphoma convened an International Harmonization Project at which five subcommittees were formed: Response Criteria, End Points for Clinical Trials, Imaging, Clinical Features, and Pathology/Biology. The Imaging subcommittee's charge was to develop guidelines for performing and interpreting FDG-PET for treatment assessment in lymphoma, to ensure the reliability of the method both in the context of clinical trials and in clinical practice. In addition, the need to identify acceptable approaches of PET imaging to accommodate recent advances in PET imaging technology, particularly the rapid dissemination of PET/CT, was particularly pressing.

Clinical Utility of Consensus Recommendations for PET in Response Assessment of Lymphoma

Despite the widespread use of PET or PET/CT for response assessment of lymphoma, standardized approaches for performing and interpreting PET (PET/CT) scans in this setting are currently lacking, and this compromises treating physicians' confidence in using PET findings to guide patient management. To that end, pertinent consensus recommendations that are developed by experts in this field are expected to be useful to practicing hematologists/oncologists in that they should facilitate greater comparability of PET studies performed at different institutions or interpreted by different imaging physicians and, hence, lead to greater confidence in using PET in patient management as well as in interpreting the results of various clinical trials. Hematologists/oncologists are the primary referring physicians for these PET studies. As ordering physicians, it is important that they understand the clinical information needed by imaging physicians to optimize the interpretation of such studies. It also is important for referring physicians to understand the optimal timing of PET imaging after treatment, the various limitations of PET and pitfalls in PET interpretation, and the most appropriate combinations of imaging studies to achieve accurate and cost-effective evaluation of patients. Similar to practice guidelines, consensus recommendations for oncologic imaging may provide improved patient outcome, improvement in medical practice, means for minimizing inappropriate practice variation, decision support tools for practitioners, points of reference for medical education, criteria for self-evaluation, indicators and criteria for external quality review, assistance with reimbursement and coverage decisions, and identification of areas where additional research is needed.[4]

METHODS

Members of the Imaging subcommittee, composed of nuclear medicine physicians, radiologists, and hematologists/oncologists, were selected for their expertise or special interest in PET of lymphoma. To enhance the focus of this report on the clinically relevant consensus recommendations made, the methodology of the consensus development is available online at www.jco.org.

RECOMMENDATIONS

1. Use of PET for Response Assessment of Lymphoma at the Conclusion of Therapy

Numerous studies have demonstrated the value of PET or PET/CT for response assessment of HL and diffuse large B-cell NHL (DLBCL) at the conclusion of front-line, salvage, or high-dose therapy.[5-16] Based on the meta-analysis by Zijlstra et al,[5] pooled sensitivity and specificity of FDG-PET for detection of residual disease after completion of first-line therapy were 84% (95% CI, 71% to 92%) and 90% (95% CI, 84% to 94%), respectively, for HL, and 72% (95% CI, 61% to 82%) and 100% (95% CI, 97% to 100%), respectively, for aggressive NHL. Accurate information regarding tumor status after treatment of these lymphoma subtypes is critical because these are curable lymphomas. The value of PET in this setting is its ability to distinguish between viable tumor and necrosis or fibrosis in residual masses often present after treatment in patients without any other clinical or biochemical evidence of disease.[6-17] Conventional anatomic imaging modalities generally are unable to make this distinction because the morphologic features of these tissues are usually indistinguishable. False-positive PET findings at the site of residual masses can be seen, however, and have been discussed in detail by Juweid and Cheson,[1,2] among others.

The role of PET for response assessment of aggressive NHL subtypes other than DLBCL and of indolent and mantle-cell lymphomas, is less clear. For these generally incurable NHLs, progression-free or overall survival is usually the primary end point in clinical trials evaluating their response to treatment.[18] However, if overall objective response rate and, particularly, complete response rate are major end points in certain clinical trials, PET may be used for their more accurate determination.[18]

2. Requirement for Pretherapy PET Scan for Response Assessment of Lymphoma at the Conclusion of Therapy

Pretherapy PET is not obligatory for assessment of response after treatment of patients with HL, DLBCL, follicular lymphoma, or mantle-cell lymphoma because these lymphomas routinely are FDG avid.[19,20] However, pretherapy PET is strongly encouraged for these subtypes because it can facilitate the interpretation of post-therapy PET.

In contrast, pretreatment PET is mandatory for variably FDG-avid lymphomas, if PET is used to assess their response to treatment. These include aggressive NHL subtypes other than DLBCL, such as T-cell lymphomas, and all subtypes of indolent NHL other than follicular lymphoma, such as extranodal marginal zone lymphoma of mucosa associated lymphoid tissue and small lymphocytic lymphoma reportedly exhibiting modest FDG avidity.[19,21,22] If PET is to be used for response assessment of patients with these histologic subtypes, there needs to be documentation that PET was positive at all disease sites $\geq$ 1.5 cm in diameter noted by CT.

3. Timing of PET Performed for Response Assessment at the Conclusion of Therapy

Studies in an animal model of human lymphoma have shown that post-therapy inflammatory changes may be observed for up to 2 weeks after chemotherapy.[23] These changes may also be observed in clinical lymphoma PET studies for at least 2 to 3 months after radiation therapy or chemoradiotherapy.[11,12] To minimize the frequency of these changes, which potentially confound the interpretation of PET scans, PET should not be performed before at least 3 weeks after chemotherapy and preferably 8 to 12 weeks after completion of radiotherapy.

4. Interpretation of PET Scans Performed for Response Assessment at the Conclusion of Therapy

Visual assessment alone appears to be adequate for determining whether PET is positive or negative at the conclusion of therapy, and quantitative or semiquantitative approaches (eg, using the standardized uptake value [SUV]) do not seem necessary.

The generally used definition of a positive (abnormal) PET finding using visual assessment as focal or diffuse FDG uptake above background in a location incompatible with normal anatomy/physiology seems to be appropriate in the majority of instances. However, the following exceptions are noted.

(1) *Mild and diffusely increased FDG uptake* at the site of moderate-sized or large residual masses (ie, $\geq$ 2 cm in diameter), regardless of their location, with intensity lower than or equal to that of

mediastinal blood pool structures should be considered negative for the presence of residual lymphoma, whereas diffuse or focal uptake exceeding that of mediastinal blood pool structures should be considered indicative of lymphoma. This mild degree of uptake usually is related to post-therapy inflammatory changes with mild macrophage infiltration rather than lymphoma, and may be present several weeks after completion of chemotherapy. However, many (if not most) residual masses assessed after therapy conclusion do not have FDG uptake greater than background connective tissue. In contrast, patients with persistent lymphoma usually have moderate to intense uptake exceeding the activity of mediastinal blood pool structures. Because of the effect of partial volume averaging, any increased uptake above surrounding background in lymph nodes or nodal masses less than 2 cm in diameter, including normal sized lymph nodes by CT, should be considered positive for lymphoma. Obviously, the use of mediastinal blood pool activity as a reference background tissue only applies to attenuation-corrected scans, which, with the advent of PET/CT, currently are the most widely used for PET image interpretation (Figs 1 to 3). The aforementioned definition of PET positivity/negativity at the site of residual masses recently was validated by Olsen et al,[24] who reported high predictive values using this definition in the post-therapy assessment of 50 patients with HL or aggressive NHL.

(2) *New lung nodules* that are ≥ 1.5 cm by CT (ie, approximately ≥ twice the spatial resolution of a typical PET or PET/CT

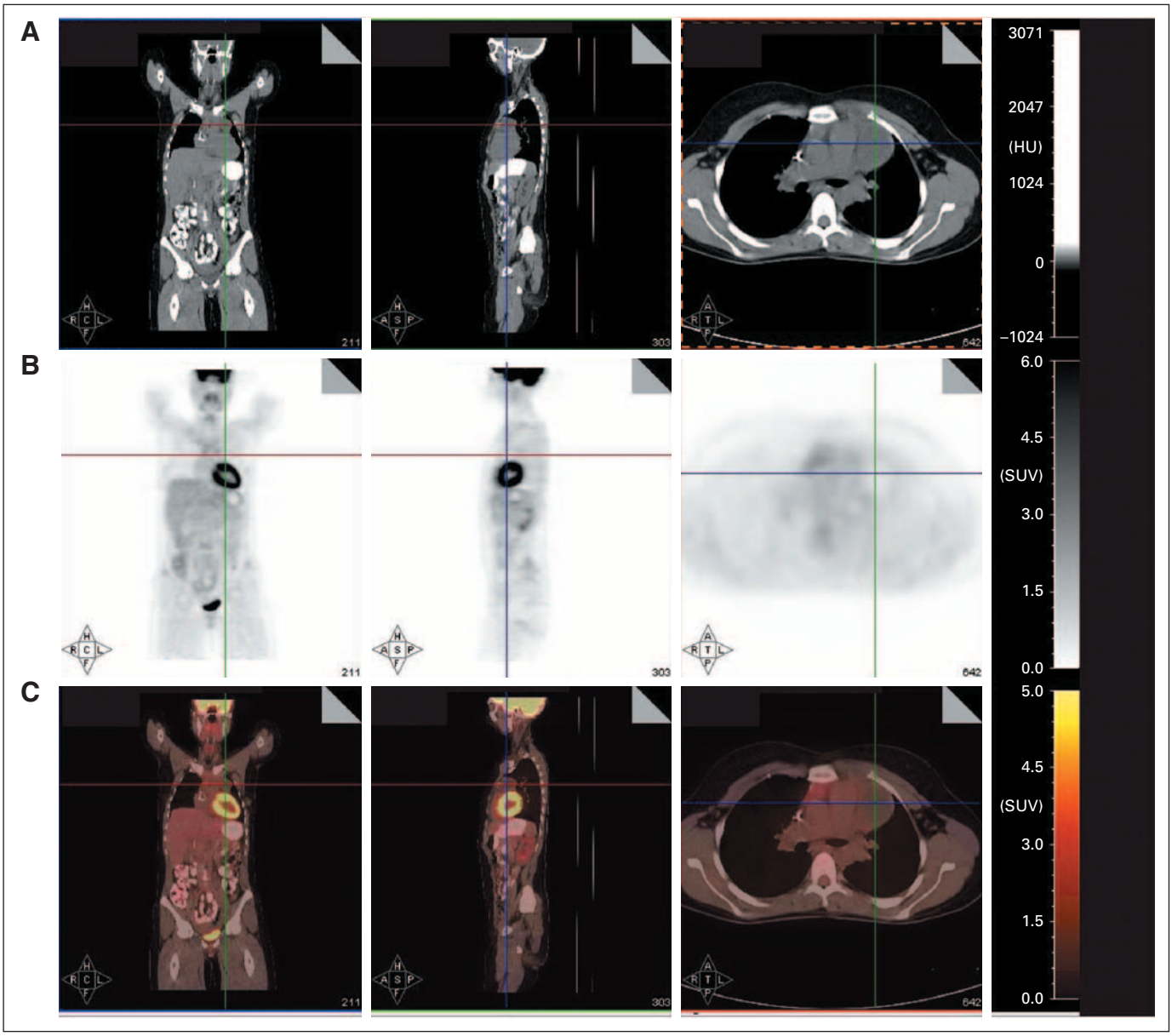

Fig 1. Positron emission tomography (PET) –negative residual mass in a patient with nodular sclerosis Hodgkin's disease. This patient underwent a restaging PET/computed tomography (CT) scan 1 month after treatment with six cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine; the scan showed a residual mass in the mediastinum measuring 5.0 × 3.7 cm, with [^{18}F]fluorodeoxyglucose uptake clearly less than that of mediastinal blood pool structures (the mass actually appears photopenic compared with surrounding mediastinal background activity). This patient is currently without evidence of disease after 25 months of follow-up post-therapy. (A) CT images; (B) PET images; (C) fused PET and CT images. HU, Hounsfield unit; SUV, standardized uptake value.

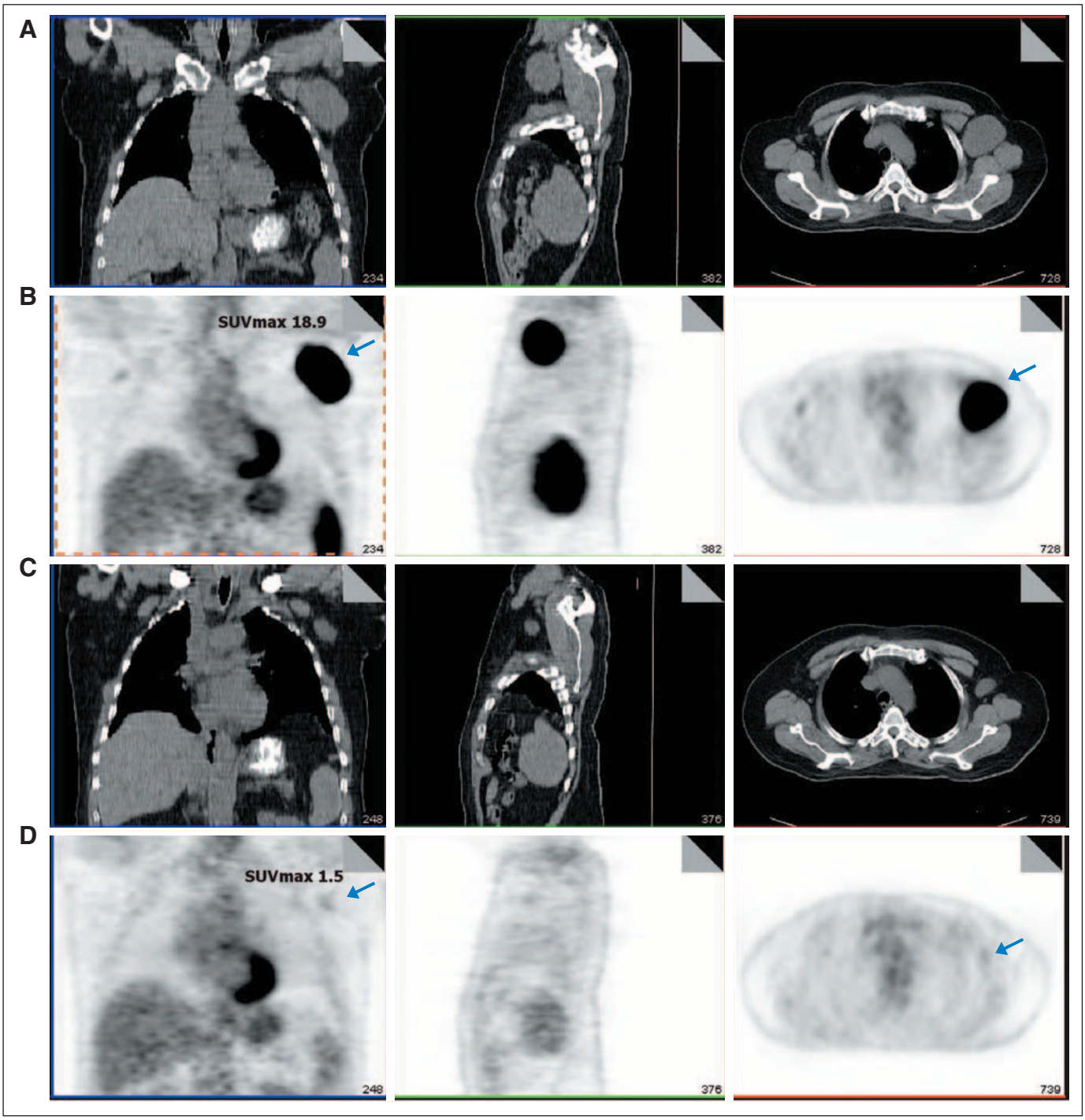

Fig 2. Positron emission tomography (PET) –negative residual mass in a patient with grade 3 follicular/diffuse large B-cell non-Hodgkin's lymphoma. This patient had extensive lymphomatous involvement by staging PET/computed tomography (CT) in the right neck, axillae, paratracheal, periaortic, and both inguinal regions in addition to involvement of the spleen. PET/CT performed 1 month after completion of six cycles of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone showed resolution of disease except for a residual 3.2 × 2.0 cm mass in the left axilla exhibiting mild [^{18}F]fluorodeoxyglucose uptake similar to that of mediastinal blood pool structures. An excisional biopsy of the left axillary node showed diffuse sclerosis with patchy chronic inflammation and scattered foamy histiocytes, but no evidence of lymphoma. The patient is currently without evidence of disease after 18 months of follow-up post-therapy. (A) Pretherapy CT; (B) pretherapy PET; (C) post-therapy CT; (D) post-therapy PET. SUV, standardized uptake value; max, maximum.

system) in patients with no evidence of pulmonary lymphoma before therapy should only be considered suggestive of lymphoma if their uptake exceeds that of mediastinal blood pool structures. Unfortunately, for new lung nodules less than 1.5 cm, the degree of uptake is unreliable for assessment of these lesions because of partial volume averaging and, therefore, residual lymphoma cannot be excluded in these small nodules that fail to show FDG uptake. New lung nodules in patients without established pulmonary lymphoma at

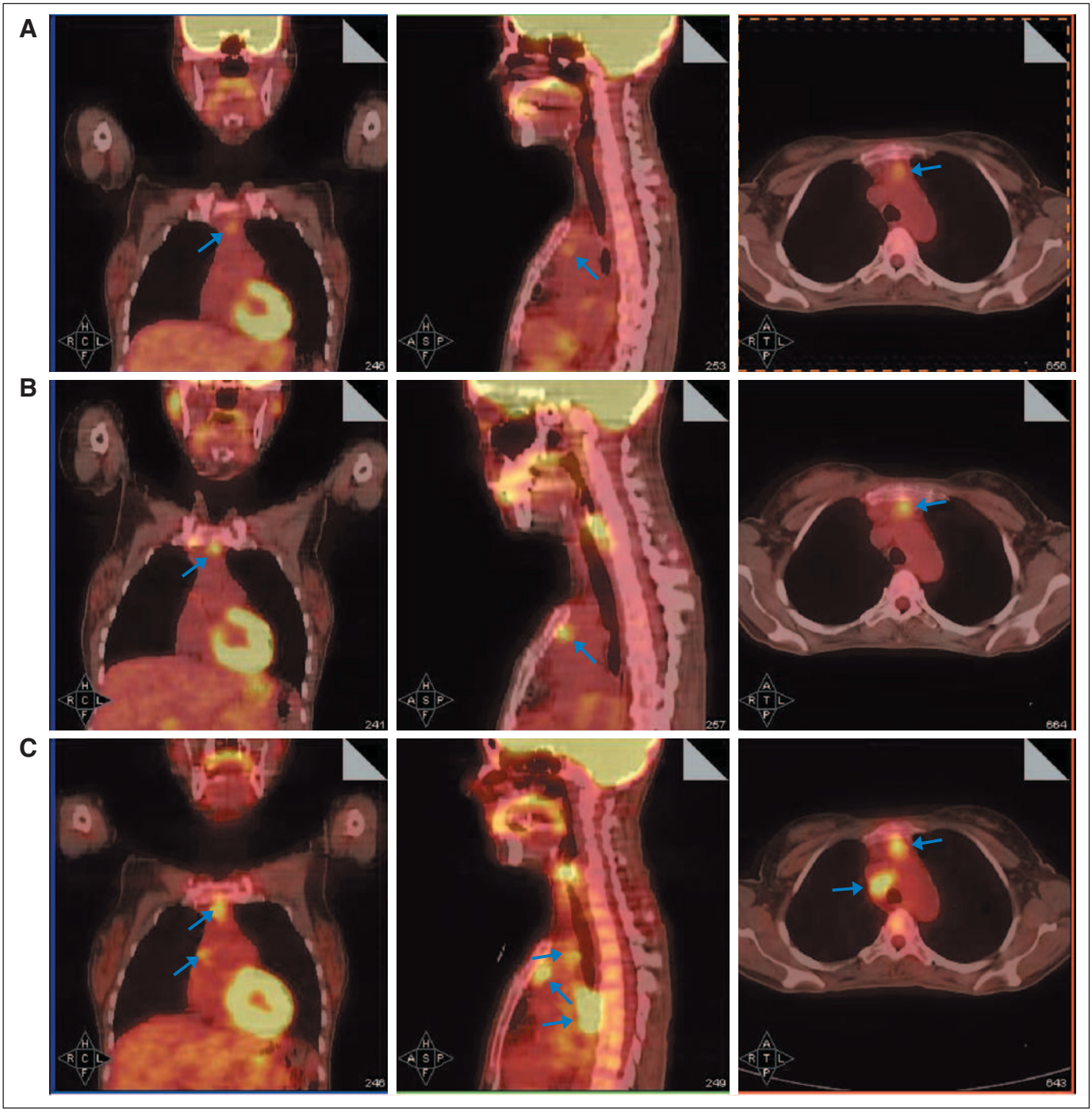

Fig 3. Positron emission tomography (PET) –positive residual mass in a patient with initial diagnosis of stage IIA nodular sclerosis Hodgkin's disease. This patient underwent a restaging PET/computed tomography (CT) scan 2 months after treatment with six cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine. (A) Fused PET/CT images show increased uptake clearly greater than that of mediastinal blood pool structures within the residual anterior mediastinal mass, consistent with persistent disease. (B) A follow-up PET/CT scan performed 2 months later shows substantially more intense uptake in the same area, again suggesting persistent disease. (C) A third follow-up scan performed 4 months thereafter also demonstrates intense uptake in the same area but now with additional new sites of disease in the right paratracheal, right hilar, and subcarinal regions, indicating frank disease progression. The patient then underwent high-dose chemotherapy and autologous stem-cell transplantation. Reprinted with permission.[2]

baseline and who have evidence of complete response at all previously known disease sites should be considered negative for lymphoma regardless of their size or uptake because these typically represent infectious or inflammatory lesions.

(3) *Residual hepatic or splenic lesions more than* 1.5 cm on CT should be considered positive for lymphoma if their uptake is greater than or equal to that of the liver or spleen, respectively; their uptake should be lower than that of the liver or spleen to be considered

negative for lymphoma, whereas persistent hepatic/splenic lesions less than 1.5 cm in diameter should only be considered positive if their uptake is greater than that of the liver or spleen, and negative if their uptake is equal to or lower than that of the liver or spleen.

Diffusely increased splenic uptake that is greater than that of the normal liver should be considered compatible with lymphoma unless the patient has a history of recent cytokine administration, in which case increased splenic uptake may be observed for up to at least 10 days after cessation of cytokine administration, depending on the cytokine administered.[25]

(4) *Clearly increased (multi)focal bone (marrow) uptake* should be interpreted as positive for lymphoma; diffusely increased bone marrow uptake, even if more intense than the liver, is usually due to post-therapy marrow hyperplasia and should not be misinterpreted as diffuse lymphomatous marrow involvement. Furthermore, a negative PET in the bone marrow does not exclude mild or moderate bone marrow involvement. Bone marrow biopsy, therefore, remains the standard procedure for assessment of bone marrow.

There are only limited data regarding the use of quantitative or semiquantitative assessment for interpretation of the PET results after therapy.[11,26] In a PET/CT study, Freudenberg et al[26] used a cutoff SUV_{max} of 2.5 to differentiate benign from malignant findings in the restaging of 27 lymphoma patients. Using this cutoff, the specificity of PET for excluding lymphoma was 100% and the sensitivity for detecting residual/recurrent lymphoma was 86%. The validity of using cutoffs of absolute SUV or percent reduction in SUV from baseline for PET interpretation at the conclusion of therapy has not yet been evaluated in rigorous prospective trials in large numbers of patients. Such trials are ongoing and could potentially identify optimum cutoff SUVs that may differ depending on the type of treatment administered and possibly other factors.

If the SUV is to be used to differentiate benign from malignant PET findings, a standardized approach for SUV determination is critical. Thus, to ensure the comparability of the SUVs among various sites, strict adherence to predefined reconstruction algorithms and timing of PET imaging after FDG injection is required.

5. Use of PET for Response Assessment During Treatment

PET or PET/CT scanning during treatment of patients with HL and aggressive NHL appears to be justified if the information provided by the scan clearly will be used to alter management. As pointed out by Juweid and Cheson,[1,2] several studies have demonstrated a correlation between a visual normalization of FDG uptake as early as after one to four cycles of chemotherapy or chemoimmunotherapy and patient outcome.[27-30] There is some evidence, however, that a dichotomous interpretation based on visual assessment alone may not be sufficiently reliable to distinguish patients with a more favorable from those with less favorable outcome, largely because of an apparent variability in visual scan interpretation between various PET readers. Some readers are more focused on the residual post-therapy uptake in the tumor region, whereas others are more focused on the change in uptake from baseline when rendering their qualitative interpretation.[31,32] Therefore, it is possible that semiquantitative assessment, for example using the SUV, may prove to be necessary for a more uniform and potentially more accurate assessment of midtherapy PET studies. The role of PET scanning during treatment is likely to increase once clinical trials demonstrate that the information provided by PET affects patient management or ultimate patient outcome. If PET is obtained during a course of therapy, it should be performed as close as possible (ie, within 4 days) before the subsequent cycle; for example, on days 17 to 21 of a 21-day cycle or days 10 to 14 of a 14-day cycle.

6. Use of CT and PET or PET/CT for Response Assessment in Lymphoma Clinical Trials

In clinical trials, CT scans routinely are used to objectify responses. Not only is CT able to evaluate nonpalpable lesions, but also is more reliable and reproducible than manual assessment of palpable nodes. At initial staging, an intravenous (IV) contrast-enhanced diagnostic CT (CECT) scan should be performed routinely using either a dedicated CT scanner or a PET/CT system (see Standardization of PET and CT Imaging Parameters). If PET will be used for response assessment, baseline PET is strongly encouraged for lymphomas that are routinely FDG avid, and is obligatory for lymphomas with variable FDG avidity. Although data from large prospective studies comparing IV contrast-enhanced PET/CT with PET plus a separately performed dedicated CECT are not yet available, IV contrast-enhanced PET/CT likely provides at least equal information to that provided by the sum of the latter two modalities and, therefore, represents an adequate alternative. This recommendation is supported by mostly retrospective or small studies showing that PET/CT performed even without IV contrast provides similar information to that provided by PET and a separately performed CECT.[26,33,34]

After treatment, a CECT scan usually is performed to objectify responses. In patients with HL and DLBCL, CECT should be complemented with PET imaging. Increasingly, PET/CT scans are used for response assessment. In this case, a separate CECT or use of IV contrast as part of the PET/CT examination is not required if no involvement of the liver or spleen was seen at initial staging. If hepatic or splenic involvement was demonstrated at initial staging, a separate CECT or an IV contrast-enhanced PET/CT should be performed for response assessment because of the limitation of nonenhanced CT in detecting hepatic or splenic lesions, particularly when these are small. On the other hand, PET/CT performed without IV contrast appears to be adequate for response assessment of lymphomatous involvement of nodes or other extralymphatic organs, including the detection of many small pulmonary lesions that may not be detectable by PET.[26,33-35] Regardless of whether the post-therapy PET/CT is performed with or without IV contrast, it is critical that the interpreting physician also reports the size of residual or new lesions and not only the degree of their metabolic activity.

Finally, it should be noted that only dedicated PET or PET/CT systems and not coincidence imaging should be used for response assessment of lymphoma.[36,37] Nonattenuation-corrected PET scans are also strongly discouraged in favor of attenuation-corrected scans.

7. Standardization of PET and CT Imaging Parameters

Several recommendations related to standardization of PET imaging parameters pertaining to response assessment of cancer in general, such as patient preparation and image acquisition. These recommendations were recently addressed by Shankar et al.[38] The Imaging subcommittee generally agrees with those recommendations, noting that the recommendations made by our subcommittee in the current report (eg, with respect to PET timing relative to prior therapy) are more lymphoma specific and should, therefore, be adhered to in lymphoma trials. In brief, as outlined by Shankar et al,[38] patients undergoing PET imaging should receive an FDG

dose of 3.5 to 8 MBq/kg of body weight, with a minimum dose of 185 MBq in adults (5 mCi) and 18.5 MBq (0.5 mCi) in children. Patients should have fasted for at least 4 hours before FDG injection. Blood glucose level should not exceed 200 mg/dL (11 mmol/L) at the time of FDG injection. If the blood glucose exceeds this level, the FDG-PET study should be rescheduled and an attempt made to control the blood sugar.

Whole-body acquisition using a PET or PET/CT system should encompass at least the region between the base of the skull and the mid thigh, and can be acquired in either two- or three-dimensional mode. Whole-body imaging should begin 60 ± 10 minutes after the administration of FDG. The PET projection data should be corrected for random coincidences, scatter, and attenuation in accordance with manufacturer's recommendations. The reconstructed PET or PET/CT images must be displayed on a computer workstation so that transaxial, sagittal, and coronal images can be viewed simultaneously.

Although CT standards and technology continue to evolve, some general principles should be adopted for all studies. Contrast enhancement in the arterial and/or portal venous phase is essential at initial staging and for follow-up studies whenever hepatic or splenic involvement was documented previously. Oral contrast material should also be administered to optimize differentiation of bowel from other abdominopelvic structures. Multidetector CT technology will minimize scan time and maximize anatomic coverage.

Optimization of the CT portion of a PET/CT examination also continues to evolve, as discussed in more detail by Delbeke et al.[39]

8. Transfer of PET Images Between Various Institutions

To ensure an adequate interpretation of PET and CT scans, scans transferred between institutions as part of a clinical trial (eg, to a central imaging core laboratory or repository) should always be submitted in Digital Imaging and Communications in Medicine (DICOM) format. BMP files, JPG files, or hard copies (films) are unacceptable for adequate interpretation of PET and CT scans transferred between institutions.

Limitations of Proposed Consensus Recommendations

A limitation of the recommendations proposed in this report is that, except for the use of PET or PET/CT in patients with HL and DLBCL at the conclusion of therapy, most recommendations are based on the authors' expertise and the limited literature available, some still in abstract form. Thus, although the expert panel believes that adherence to these guidelines would greatly facilitate patient care and comparison among studies, perhaps their most important function is to identify important questions for further research, particularly in settings where only limited or preliminary data are currently available. It is anticipated that these guidelines will promote continuing dialogue between hematologists/oncologists and imaging physicians to achieve the greatest benefit from PET imaging in patients with lymphoma.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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Acknowledgment

We thank Drs Volker Diehl, MD, and Beate Pfistner, MD, for organizing and leading the IHP meetings, and Richard Wahl, MD, who provided input for these guidelines.