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Clinical Radiology
The Royal College of Radiologists

Recommendations for cross-sectional imaging in cancer management, Second edition

Lymphoma

Faculty of Clinical Radiology

Contents

Lymphoma

Clinical background

Lymphoproliferative disorders form a diverse group of malignancies derived from B cells, T cells and natural killer (NK) cells that vary widely in their presentation, clinical course and response to therapy. Lymphoid neoplasms that present with masses are broadly referred to as lymphomas, whereas those where the malignant population are predominantly circulating cells are termed leukaemias. The incidence of non-Hodgkin's lymphoma (NHL) has increased rapidly over the last few decades but now appears to have plateaued,[1,2] while the incidence of Hodgkin's lymphoma (HL) has remained relatively stable over the same period.[1,2] NHL and HL together comprise approximately 5–6% of all malignancies and lymphoma represents the fifth commonest malignancy in most of the Western world.[3]

HL usually presents with lymphadenopathy in one or two contiguous sites. Untreated, it progresses with involvement of adjacent nodal sites and the spleen, before bone marrow, liver or other extranodal involvement. Cure rates are excellent, in excess of 90% in younger patients.[4] NHL is traditionally divided into high- and low-grade lymphomas, although the most recent World Health Organization (WHO) classification (first edition 2000, updated 2008)[5] has moved away from a broad-based categorisation to focus instead on defining individual lymphomas as distinct clinicopathological entities often characterised by specific molecular abnormalities. It is not possible to generalise about the clinical behaviour of NHL, but entities pragmatically regarded as high grade tend to be aggressive, often presenting with generalised lymphadenopathy and B symptoms. They frequently respond well to high-dose chemotherapy, with complete cure being achieved in around 60% of cases.[6] Low-grade lymphomas in general are indolent in behaviour and may be controlled, but not usually cured, with low-dose chemotherapy. As our understanding of lymphoma pathology deepens, however, the broad distinction between low- and high-grade NHL is increasingly recognised as an oversimplification, which does not accommodate entities such as mantle cell lymphoma, which shares features of both categories. In general, extranodal involvement is more frequent in all forms of NHL than in HL, as is involvement of non-contiguous nodal groups. The propensity for extranodal involvement, and for involvement of specific extranodal sites, varies considerably according to the individual subtype of NHL.

The 1988 Cotswolds modification of the Ann Arbor classification is used internationally for the anatomical staging for both HL and NHL and the American Joint Committee on Cancer (AJCC) classification has adopted it for staging purposes.[7,8] Note that for the purposes of classification, lymph node, Waldeyer's ring and splenic involvement are considered nodal or lymphatic sites, and other organ involvement is considered extranodal. Accurate staging is critical to implementing the most appropriate therapy for an individual patient, and imaging plays an essential role in determining the optimal initial therapy, monitoring treatment response and detecting relapse. The success of clinical trials, which are crucial to the development of new and more effective therapies for lymphoma, is also highly dependent on the use of standardised methods for staging and response assessment.

Who should be imaged?

All patients with lymphoma, except those with subtypes of primary cutaneous lymphoma normally limited to the skin such as mycosis fungoides, should be imaged for staging at diagnosis.

Staging objectives

- To stage nodal disease.
- To stage extranodal disease.
- To stage primary cerebral, orbital and head and neck lymphoma.
- To investigate suspected spinal cord compression.
- To assess marrow involvement.
- To evaluate musculoskeletal involvement.

CT is used as the main staging technique, with MRI also being useful in certain clinical situations and increasingly in children. Gallium scanning has now been replaced by ^{18}F-Fluorodeoxyglucose positron emission tomography-computed tomography (^{18}FDG PET-CT) for functional imaging (see below for further ^{18}FDG PET-CT considerations).

Staging of lymphoma (Cotswolds-modified Ann Arbor Classification7)

Stage	Area of involvement
I	One lymph node region or extralymphatic site
II	Two or more lymph node regions on the same side of the diaphragm
III	Involvement of lymph node region or structures on both sides of diaphragm, subdivided as follows: III(1*) – with involvement of spleen and/or splenic hilar, coeliac, and portal nodes III(2*) – with paraaortic, iliac, or mesenteric nodes
IV	Extranodal sites beyond those designated E
Additional qualifiers	
A	No symptoms
B	Fever, sweats, weight loss (more than 10% body weight)
E	Involvement of a single extranodal site, contiguous in proximity to a known nodal site
X*	Bulky disease Mass >1/3 transthoracic diameter at T5 on CXR or any mass >10 cm maximum dimension
CE*	Clinical stage
PS*	PS stands for pathological stage and refers to when staging laparotomy existed but is usually taken to refer to involvement of a given site on imaging denoted by a subscript (eg, M=marrow, H=liver, L=lung, O=bone, P=pleura, D= skin)

**Modification of Ann Arbor System*

CT

Routine CT staging should include the chest, abdomen and pelvis. Head and neck CT may also be indicated. The following are recommended:

- 100–150 ml of intravenous iodinated contrast medium injected at 3–4 ml/sec.
- Post-contrast medium scans through the chest and abdomen and pelvis (portal venous phase) should be acquired. The post-contrast images of the neck can be acquired in either the early arterial or late venous phase.
- Using MDCT, slice thickness will depend on scanner capability. In general, sections are acquired at 1.25–2.5 mm and reformatted at ≤5 mm for viewing.
- Oral contrast medium is recommended for improved visualisation of mesenteric and retroperitoneal lymphadenopathy, and for detection of bowel involvement, which is particularly common in certain subtypes of NHL; for example, mantle cell lymphoma.

Values of $CTDI_{vol}$ should normally be below the relevant national reference dose for the region of scan and patient group (see Appendix and

section on Radiation protection for the patient in CT in Section 2).

MRI

MRI has comparable accuracy to CT in the detection of involved lymph nodes but is considered overall to be a complementary technique to contrast-enhanced CT in lymphoma staging.

MRI is the investigation of choice for suspected central nervous system (CNS) involvement. Gadolinium-enhanced imaging is required and diffusion-weighted sequences are also of value in characterising brain lesions, as cerebral lymphoma commonly shows restricted diffusion.

The excellent spatial resolution and soft tissue contrast of MRI also achieve superior results to CT in imaging extra-nodal soft tissue and intraosseous (marrow space) lesions. ^{18}FDG PET-CT is usually a sensitive imaging tool for detection of bone disease but MRI may be a valuable problem-solving tool, particularly in patients with localised symptoms. MRI is also the optimal imaging modality for local staging of lymphomas of the head and neck region, where detailed anatomical evaluation is more important. It is the investigation of choice in pregnant women and may also be the initial investigation of choice in children due to the lack of ionising radiation. It is also recommended for patients at increased risk of contrast reactions. MRI protocols for individual areas are covered in the other chapters. Soft tissue tumours locally staged by MR that are subsequently demonstrated to be lymphoma will require completion of staging by CT of thorax, abdomen and pelvis.

^{18}FDG PET-CT

The widespread availability of ^{18}FDG PET-CT in the UK has revolutionised the imaging of lymphoma because of its potential to acquire combined structural and functional staging data in a single investigation. This enables the detection of lymphomatous involvement of structurally normal nodes or extranodal organs. ^{18}FDG PET-CT is useful for the assessment of metabolically active disease, where FDG avidity is increased relative to normal tissue due to increased glucose utilisation. ^{18}FDG PET-CT is routinely used to stage disease extent at presentation in both HL and aggressive and intermediate NHL. Aggressive NHL for these purposes includes high-grade lymphomas such as diffuse large B cell lymphoma, lymphoblastic lymphoma, Burkitt's, most subtypes of T cell lymphoma and post-transplant lymphoproliferative disorder (PTLD). Mantle cell lymphoma, although not traditionally grouped with high-grade lymphomas, also behaves aggressively in most cases. There is a substantial body of evidence to show that the addition of ^{18}FDG PET-CT scanning to current staging investigations in lymphoma increases the accuracy of staging and results in changes in clinical management.[9] The degree of FDG uptake is not however of practical utility for grading lymphoma. The vast majority (over 95%) of cases of high grade NHL and HL are FDG-avid,[10] therefore, performing a staging ^{18}FDG PET-CT is the only way to determine whether an individual lymphoma is FDG positive; if this is negative, there is no value in obtaining further PET scans in the course of the patient's management.

The potential role of ^{18}FDG PET-CT in low grade NHL remains under study. At present, it is recommended in early-stage (that is, localised) follicular lymphoma where radiotherapy is under consideration. In this scenario, 97% of cases have been shown to be FDG-avid and management is changed in 44% of cases.11 Evidence to date indicates that most cases of low-grade lymphoma are FDG-avid, with small lymphocytic lymphoma and marginal zone lymphoma showing the lowest positivity rates in the largest published series (85% and 55% respectively).[12] As many of these diseases are indolent and in early stages sometimes managed with a 'watch and wait' policy, ^{18}FDG PET-CT staging does not form part of their routine clinical management. It may, however, be useful for problem-solving in individual cases. Increased FDG uptake may be seen in patients with low-grade lymphomas which undergo high-grade transformation but biopsy is indicated to confirm transformation before treatment.[13]

Staging recommendations

- Staging of patients with HL and aggressive NHL and to serve as a baseline for comparison with treatment response scan.
- Staging of patients with early-stage follicular lymphoma (FL) to be considered for radiotherapy treatment.

- Staging of suspected post-transplant lymphoproliferative disorder (PTLD); see Appendix 1.[14]

PET-CT imaging techniques

Patient scheduling
Sequential PET-CT exams for a patient should ideally be performed in the same centre using the same PET-CT system as the baseline scan. The patient preparation, ^{18}FDG administration, image acquisition and reconstruction for scans should be matched as closely as possible for each subsequent patient scan during therapy.[15]

Patient preparation
Non-diabetic patients should fast for four to six hours before the start of the PET-CT study.

Plain (non-sugary/unflavoured) water should be taken during the period of fasting and the uptake period to ensure good hydration.

Diabetics on oral medication should be given a late morning appointment, asked to fast for four hours, and take their usual hypoglycaemic medication that morning.

Diabetics on insulin should eat and administer their insulin as normal before the four-hour fast. If blood glucose level is >11 mmol/l (>200 mg/dl), consideration should be given to rescheduling the scan. Insulin should not be administered to lower blood glucose as this increases uptake into skeletal and cardiac muscle increasing the background and can reduce uptake into tumour sites.

The blood glucose level of all patients should be measured on arrival at the imaging centre. This should be performed using a calibrated glucometer or similar bedside device.

Patients should avoid strenuous exercise for six hours prior to the scan.

Patients should be weighed without shoes and coats using a calibrated device.

If local protocols include a diagnostic staging CT scan using intravenous and/or bowel contrast as part of the routine clinical PET-CT examination, there is debate about whether this should be performed as a separate examination after the PET-CT scan. In a clinical trial setting where quantitative analysis is to be used, CT using contrast should be avoided for attenuation of PET data. In this case, a separate low-dose CT without contrast should be acquired before the PET acquisition and this scan should be used for attenuation correction of the PET images.[16–18]

Radiopharmaceutical administration
Route of administration
Intravenous administration via butterfly cannula under quiet conditions.

Suggested administered activity
The injected activity is dependent on the PET-CT system utilised and the patient weight.

Users should not exceed the ARSAC DRL of 400 MBq but it is suggested:

- To administer 5.4 MBq/kg ^{18}FDG for 2D acquisition or 3.5 MBq/kg for 3D acquisition
- That although scan duration can be modified according to patient weight, a minimum of 3 minutes per bed position scan time should be used
- For larger patients (>90 kg), it is strongly recommended to increase the scanning time rather than increasing the injected dose.

Procedure
Assay the FDG injectate residue, and record the net activity injected and time of injection.

Uptake period
- During the ^{18}FDG administration, uptake phase and the PET-CT exam, the patient should be relaxed and kept warm to avoid uptake in the muscles or brown fat.
- Patients should be asked to void immediately prior to the PET-CT scan to reduce bladder activity.
- The PET emission acquisition is typically acquired 60–90 minutes after the FDG administration.
- The response scans must be performed at the same time after injection as the baseline scan +10 minutes, but not less than 55 minutes post-injection.

Image acquisition
The PET and CT scan region should include the base of the brain to the upper thigh. In cases where a whole-body PET-CT (from skull vertex to feet) is required to be performed due to the possibility of disease in the extremities, a whole-body PET-CT (skull vertex to feet) may be preferred.

Patients should be scanned with arms above the head if tolerated. Patient positioning should be matched on the response scans.

Separate body and head and neck scans can be performed if locally accepted practice. If a separate head and neck is acquired, the arms should be by down the sides.

Image reconstruction

- Attenuation correction should be performed using the low-dose CT.
- Iterative reconstruction should be used; for example, ordered subset expectation maximisation (OSEM) or similar.
- Both attenuation corrected and non-attenuation corrected PET images should be reconstructed.

Response assessment to treatment

Post-treatment assessment in lymphoma should be performed with the same imaging modality as employed for staging. For HL and aggressive NHL, this is normally ^{18}FDG PET-CT (please see Appendix 1),[14] whereas for low-grade NHL this will typically be CT, or possibly MRI in selected cases such as head and neck lymphoma (combined with CT chest, abdomen and pelvis for disease elsewhere). Mid-treatment CT is not routinely indicated, but may be required to investigate a clinical suspicion of poor response in cases where CT alone has been used for staging or if there is no clinical or other radiographic (such as chest X-ray) means of assessing response.

Assessment of early response to chemotherapy
The use of ^{18}FDG PET-CT to assess the effectiveness of therapy now forms a routine part of clinical assessment. This may be performed to confirm response at the end of treatment but increasingly is undertaken as an interim scan after as few as two cycles of chemotherapy. There are now a substantial number of studies demonstrating that interim FDG PET scanning in HL and aggressive NHL are predictive of progression-free and overall survival.[19–24] The role of interim PET to enable early treatment adaptation is currently under investigation in several Phase II and Phase III clinical trials to determine:

- Whether a reduction in the number of cycles of therapy and/or omission of radiotherapy for patients with good response and early disease can be achieved without adverse effect on survival
- Whether escalation of chemotherapy or early transplant can improve cure rates for patients with poor response.

PET reporting criteria in lymphoma
Efforts have been made to establish international criteria for reporting PET. Semi-quantitative assessment using standardised uptake values (SUVs) may complement visual criteria but is not used currently outside clinical trials.

The International Harmonisation Project (IHP) published guidelines on the performance and interpretation of PET in lymphoma in 2007 (please see Appendix 2).[25] Visual evaluation alone was considered adequate for ^{18}FDG PET-CT assessment after the completion of therapy. In the IHP criteria, mediastinal blood pool activity is used as the reference background activity to define FDG-PET positivity for a residual mass greater than 2 cm in greatest transverse diameter, regardless of location.[25] A smaller residual mass or a lymph node of normal size was considered positive if its activity was greater than that of the surrounding background tissue. The guidelines also include separate criteria for defining FDG-PET positivity in the liver, spleen, lung and bone marrow.

Some criticisms have been made of the IHP criteria, in particular with regard to their use for interim ^{18}FDG PET-CT, where it is recognised that residual minimal uptake especially in Hodgkin lymphoma can be associated with good prognosis.[26] The use of lymph node size (greater or less than 2 cm) to determine what reference standard is used has been criticised. Size measurement of lymph nodes around this

diameter has been shown, however, to be an area of high inter-observer variability, which may reduce reproducibility of the assessment.

The Deauville/London criteria were suggested as a method of visual assessment at an international meeting held in Deauville in 2009.[27] It has been reported to have good inter-observer agreement in adult and paediatric Hodgkin lymphoma.[28–30] The Deauville/London criteria are widely used in the UK for reporting both interim and post-treatment lymphoma ^{18}FDG PET-CT scans.

Deauville/London PET criteria (applies to response scans)
The five-point scale below describes uptake in sites of disease involved on the staging scan:

1. No uptake
2. Uptake ≤mediastinum
3. Uptake ≥mediastinum but ≤liver
4. Uptake moderately greater than liver uptake
5. Markedly increased uptake greater than liver uptake and/or new sites of disease.

It is preferable when reporting to describe the scan appearances rather than simply give a score alone; when a score is given it should be prefixed by the classification; for example, Deauville score 3. The significance of the above scores in determining positivity or negativity in an individual case depends on lymphoma subtype whether the scan is interim or at the end of treatment. Score 1 or 2 is generally regarded as a complete metabolic response. Repeat scans at the end of treatment are generally not recommended where the Deauville score is 1 or 2. Score 4 or 5 is generally regarded as indicating active lymphoma. The interpretation of Score 3 is likely to depend on the clinical or research situation and whether a high positive or negative predictive value is required from the test; that is, the willingness to undertreat or overtreat.[9]

Response assessment recommendations
Early interim PET to assess response to treatment after two cycles of chemotherapy in HL and aggressive NHL.

Where possible patients should be entered into current UK trials investigating the role of PET in response adapted therapy.

Evaluation of residual masses, and post-treatment assessment or restaging
^{18}FDG PET-CT is also indicated for evaluation of the residual post-therapy mass, where structural imaging alone cannot accurately distinguish between remaining tumour and reparative granulation tissue/fibrosis. It must, however, be borne in mind that post-treatment inflammatory/reactive changes may be similarly FDG-avid to small volumes of residual viable tumour, potentially leading to false-positive or negative findings if PET-CT is performed within an insufficient interval post-therapy. The inflammatory post-therapeutic response may persist for up to two weeks after chemotherapy alone and up to at least 12 weeks following radiotherapy or chemoradiotherapy. As this response may well be strongly FDG-avid, it is recommended that follow-up PET-CT be delayed until after three weeks (preferably after six to eight weeks) post-chemotherapy and at least 12 weeks post-radiotherapy/chemoradiotherapy. It is usual to perform a CT of neck, chest, abdomen and pelvis at this time but this can be omitted where the facility to perform PET-CT with intravenous contrast exists. The negative predictive value for FDG in the assessment of residual masses is around 90% but the positive predictive value is more variable and biopsy is usually indicated before treatment is initiated based on a 'positive' PET scan.[9,31]

PET-CT is also useful in assessment of response to secondline therapy and appears to be related to prognosis in the pre-transplant setting in patients undergoing autologous bone marrow transplant.[32]

Response assessment recommendations
1. End of treatment response assessment in HL and aggressive NHL in patients with positive staging and/or positive interim scans.
2. Assessment of response to secondline treatment and subsequent treatments for FDG-avid lymphoma.
3. Prior to bone marrow transplant to assess volume of disease and suitability for transplant.
4. To determine disease extent and identify a suitable biopsy site in patients with low-grade lymphomas in whom there is suspected high-grade transformation (please see Appendix 1).[14]

Follow-up

No clear evidence-based consensus exists on the optimal imaging modality, interval or duration of routine follow-up in lymphoma, either following treatment or in the 'watch and wait' scenario often employed in early-stage low-grade NHL. An important general principle in follow-up imaging is that the benefits must be perceived to outweigh the costs and the risks of increased radiation exposure. Review of retrospective series suggests that whatever the imaging schedule employed, most relapses are still detected clinically. Routine imaging with CT or ^{18}FDG PET-CT is not advised given the lack of evidence supporting its role. Either CT or ^{18}FDG PET-CT may be used to investigate suspected relapse, dependent upon the level of clinical concern, local availability and the known FDG avidity of the individual's tumour. The need for histological confirmation of positive findings should be discussed at a multidisciplinary team (MDT) meeting.

Recommendation
Imaging should be used for the evaluation of clinically suspected relapse in symptomatic patients only (please see Appendix 1).[14] Either CT or ^{18}FDG PET-CT may be used to investigate relapse.

Radiotherapy planning

CT is currently the mainstay of radiotherapy treatment planning for lymphoma. As might be expected given its superiority to CT in the staging of HL and aggressive NHL, ^{18}FDG PET-CT has been postulated to be more accurate than CT in defining disease extent pre-radiotherapy.[33] The technique is increasingly being incorporated into the planning process of radiotherapy for lymphomas, especially in cases where more conformal radiotherapy is planned, and it has been suggested that as radiotherapy volume definition focuses on involved-node radiotherapy rather than intensity-modulated radiation therapy (IMRT), its role is likely to grow.[34–36] To date, there is however, insufficient clinical data available on ^{18}FDG PET-CT in target definition for lymphoma radiotherapy planning to indicate its routine use for this purpose.

Recommendation
CT remains the standard modality for radiotherapy treatment planning. Prospective trials are needed to investigate the role of ^{18}FDG PET-CT in tailoring radiotherapy fields.

Future imaging applications

Whole-body MRI/whole-body diffusion-weighted imaging (WBDWI)
Whole-body MRI is an emerging imaging modality which holds considerable promise for staging and treatment response assessment in lymphoma.[37–40] Its excellent spatial resolution and the functional imaging component offered by whole-body diffusion-weighted imaging (WBDWI) may offer a viable alternative to CT and ^{18}FDG PET-CT. Current studies of its role in lymphoma imaging are mainly limited to small or pilot series, with much larger studies being needed to validate the accuracy of whole-body MRI and WBDWI as compared to the current standard modalities.

Non-FDG novel tracers
As noted above, ^{18}FDG PET-CT suffers from relatively poor sensitivity in detecting some low-grade lymphomas as well as a lack of specificity in distinguishing neoplasia from benign tissue with a high glycolytic index such as inflammatory/reparative processes. A number of novel radiotracers have been investigated as alternative agents in lymphoma imaging and have shown promising results but their use is still at an experimental level. ^{18}F-fluoro-L-thymidine (FLT) uptake is highly correlated with proliferation rate and it has been suggested that it might be able to distinguish between high- and low-grade lymphomas.[41,42] The amino acid tracers 11C-methionine (MET) and ^{18}F-fluoroethyl-L-tyrosine (FET) reflect the increased transport and protein synthesis of malignant tissue and are postulated to be more tumour-specific.[43,44]

Hybrid PET-MRI
Integrated PET/MRI systems are being introduced into routine clinical practice and will offer true multifunctional imaging, including spectroscopy, functional MRI, and arterial spin labelling, complemented by the metabolic/molecular information of PET. PET/MRI is likely to prove useful for evaluation of CNS lymphomas, extranodal lymphomas and bone marrow involvement in particular, and may provide an impetus for the development of

improved functional imaging protocols and more targeted radiotracers.[45–47]

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Appendix 1. PET-CT recommended indications

Below are recommended indications for PET-CT.[14]

- Staging of patients with Hodgkin's lymphoma (HL) and aggressive non-Hodgkin's lymphoma (NHL) and as baseline for comparison with treatment response scan.
- Staging of patients with early-stage follicular lymphoma (FL) considered for radiotherapy treatment.
- Interim response assessment of patients with HL and aggressive NHL after two cycles of chemotherapy.
- End of treatment response assessment of HL and aggressive NHL in patients with positive interim scans.
- Evaluation of suspected relapse for FDG-avid lymphomas in symptomatic patients.
- Assessment of response to secondline treatment and subsequent treatments for FDG-avid lymphoma.
- Staging of suspected post-transplant lymphoproliferative disorder (PTLD).
- Prior to bone marrow transplant to assess volume of disease and suitability for transplant.
- To determine extent and identify a suitable biopsy site in patients with low-grade lymphomas in who there is suspected high-grade transformation.

Appendix 2. Response definitions for clinical trials

The following are response definition for clinical trials.[25]

Complete remission (CR)
1. Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present before therapy.

2a. Typically FDG-avid lymphoma: in patients with no pre-treatment PET scan or when the PET scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative.

2b. Variably FDG-avid lymphomas/FDG avidity unknown: in patients without a pre-treatment PET scan, or if a pre-treatment PET scan was negative, all lymph nodes and nodal masses must have regressed on CT to normal size (≤1.5 cm in their greatest transverse diameter for nodes >1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their long axis and more than 1.0 cm in their short axis before treatment must have decreased to ≤1.0 cm in their short axis after treatment.

3. The spleen and/or liver, if considered enlarged before therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies, and nodules related to lymphoma should disappear. However, determination of splenic involvement is not always reliable because a spleen considered normal in size may still contain lymphoma, whereas an enlarged spleen may reflect variations in anatomy, blood volume, the use of haematopoietic growth factors, or causes other than lymphoma.

4. If the bone marrow was involved by lymphoma before treatment, the infiltrate must have cleared on repeat bone marrow trephine biopsy. The biopsy sample on which this determination is made must be adequate (with a goal of a >20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry but that demonstrates a small population of clonal lymphocytes by flow cytometry will be considered a CR until data become available demonstrating a clear difference in patient outcome.

CRu
The use of the above definition for CR and that below for PR eliminates the category of complete remission/unconfirmed (CRu).

Partial remission (PR)
The designation of PR requires all of the following.

1. At least a 50% decrease in sum of the product of the diameters (SPD) of up to six of the largest dominant nodes or nodal masses. These nodes or masses should be selected according to all of the following: they should be clearly measurable in at least two perpendicular dimensions; if possible they should be from disparate regions of the body; and they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
2. No increase should be observed in the size of other nodes, liver, or spleen.
3. Splenic and hepatic nodules must regress by ≥50% in their SPD or, for single nodules, in the greatest transverse diameter.
4. With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present.
5. Bone marrow assessment is irrelevant for determination of a PR if the sample was positive before treatment. However, if positive, the cell type should be specified (for example, large-cell lymphoma or

small neoplastic B cells). Patients who achieve a CR by the above criteria, but who have persistent morphologic bone marrow involvement, will be considered partial responders.
6. When the bone marrow was involved before therapy and a clinical CR was achieved, but with no bone marrow assessment after treatment, patients should be considered partial responders. No new sites of disease should be observed.
7. Typically FDG-avid lymphoma: for patients with no pre-treatment PET scan or if the PET scan was positive before therapy, the post-treatment PET should be positive in at least one previously involved site.
8. Variably FDG-avid lymphomas/FDG avidity unknown: for patients without a pre-treatment PET scan, or if a pre-treatment PET scan was negative, CT criteria should be used.

In patients with follicular lymphoma or mantle cell lymphoma, a PET scan is only indicated with one or at most two residual masses that have regressed by more than 50% on CT; those with more than two residual lesions are unlikely to be PET negative and should be considered partial responders.

Stable disease
Stable disease (SD) is defined as the following.

1. A patient is considered to have SD when he or she fails to attain the criteria needed for a CR or PR, but does not fulfill those for progressive disease (see relapsed disease [after CR]/progressive disease [after PR, SD]).
2. Typically FGD-avid lymphomas: the PET should be positive at prior sites of disease with no new areas of involvement on the post-treatment CT or PET.
3. Variably FDG-avid lymphomas/FDG avidity unknown: for patients without a pre-treatment PET scan or if the pre-treatment PET was negative, there must be no change in the size of the previous lesions on the post-treatment CT scan.

Relapsed disease (after CR)/progressive disease (after PR, SD)
Lymph nodes should be considered abnormal if the long axis is more than 1.5 cm regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if its short axis is more than 1.0. Lymph nodes ≤1.0 × ≤1.0 cm will not be considered as abnormal for relapse or progressive disease.

1. Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.
2. At least a 50% increase from nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesions (such as splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1.0 cm must increase by ≥50% and to a size of 1.5 × 1.5 cm or more than 1.5 cm in the long axis.
3. At least a 50% increase in the longest diameter of any single previously identified node more than 1.0 cm in its short axis.
4. Lesions should be PET-positive if observed in a typical FDG-avid lymphoma or the lesion was PET positive before therapy unless the lesion is too small to be detected with current PET systems (<1.5 cm in its long axis by CT).

Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these recommendations, the spleen is considered nodal disease. Disease that is only assessable (such as pleural effusions, bone lesions) will be recorded as present or absent only, unless, while an abnormality is still noted by imaging studies or physical examination, it is found to be histologically negative.

In clinical trials where PET is unavailable to the vast majority of participants, or where PET is not deemed necessary or appropriate for use (for example, a trial in patients with marginal zone lymphoma), response should be assessed as above, but only using CT scans. However, residual masses should not be assigned CRu status, but should be considered partial responses.

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