Imaging for Staging and Response Assessment in Lymphoma[1]

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Lymphoma comprises a heterogeneous group of diseases; remarkable advances have been made in diagnosis and treatment. Diagnostic imaging provides important information for staging and response assessment in patients with lymphoma. Over the years, staging systems have been refined, and dedicated criteria have been developed for evaluating response to therapy with both computed tomography (CT) and fluorine-18 fluorodeoxyglucose positron emission tomography (PET)/CT. The most recent system proposed for staging and response assessment, known as the Lugano classification, applies to both Hodgkin and non-Hodgkin lymphoma. The use of standardized criteria for staging and response assessment is important for making accurate treatment decisions and for determining the direction of further research. This review provides an overview of the updated CT and PET response criteria to familiarize the radiologist with the most important and clinically relevant aspects of lymphoma imaging. It also provides a short clinical update on lymphoma and the associated spectrum of imaging findings.

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Learning Objectives:

After reading the article and taking the test, the reader will be able to:

- Describe the patient population to which the new Lugano classification for staging and response assessment in lymphoma applies
- Describe important imaging parameters for lymphoma assessment outlined in the new Lugano classification
- Discuss the new categories for response assessment with CT and fluorodeoxyglucose PET/CT

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The World Health Organization International Classification of Disease (2008) recognizes more than 50 types of lymphoma based on histopathologic, immunohistochemical, cytogenetic, and molecular analyses (1). Many lymphomas are potentially curable when treated with chemotherapy alone or in combination with radiation therapy; others are only curable when treatment is consolidated with stem cell transplantation. The many types of lymphoma have varying etiologies and risk factors. Immunosuppression from any cause is a well-known risk factor for certain subtypes. Multiple infectious agents have been linked to lymphoma development, including viral agents such as human immunodeficiency virus, human T-cell lymphotropic virus, Epstein-Barr virus, and hepatitis C, as well as bacterial agents such as *Helicobacter pylori*. Genetic mutations creating proto-oncogenes are linked to multiple lymphoma subtypes, such as the chromosome 8:14 translocation in Burkitt lymphoma (2) and the 14:18 translocation of follicular lymphoma (3). In clinical practice, a few subtypes of lymphoma account for the majority of cases. Table 1 summarizes clinical features of the most common lymphoma subtypes.

Essentials

- Lymphoma comprises a heterogeneous group of diseases, with over 50 subtypes; new recommendations for staging and response assessment are described in the Lugano classification and apply to both Hodgkin and non-Hodgkin lymphoma.
- Fluorodeoxyglucose (FDG) PET/CT is an essential imaging test for staging, treatment planning, and response assessment of many lymphomas, in particular Hodgkin lymphoma and diffuse large B-cell lymphoma; the utility of interim PET for response-adapted therapy (escalation or de-escalation of treatment based on early response) is under investigation in many ongoing clinical trials.
- The Lugano classification proposes new definitions relevant to imaging in lymphoma: for splenomegaly, vertical length of spleen greater than 13 cm; for measurable adenopathy, nodal long-axis diameter greater than 1.5 cm (a unidimensional measurement).
- At CT, response is categorized as complete radiologic response (all nodes ≤ 1.5 cm in longest diameter, disappearance of all CT findings of lymphoma), partial remission (≥50% reduction in disease burden), stable disease (<50% decrease in disease burden), or progressive disease (new or increased adenopathy or new extranodal lymphoma).
- At FDG PET/CT, response is graded on the five-point scale and categorized as complete metabolic response (score 1, 2, 3), partial metabolic response (score 4 or 5 with reduced FDG uptake), no metabolic response (score 4 or 5 with no significant change in FDG uptake), or progressive metabolic disease (score 4 or 5 with increased FDG uptake or new lesions compared to previous scan).

Lymphoma Staging

The Ann Arbor staging system, first introduced in 1971 and altered in 1989 to include the "Cotswolds modifications," is applied to both Hodgkin lymphoma and non-Hodgkin lymphoma (4,5). Staging with this system is based on the extent of involvement of nodal groups, as follows: stage I, single lymph node group; stage II, multiple lymph node groups ipsilateral to the diaphragm; stage III, involvement of lymph node groups both above and below the diaphragm; and stage IV, noncontiguous extranodal involvement (eg, liver, lung, or bone marrow).

There are some exceptions to the application of the Ann Arbor staging system: Primary central nervous system (CNS) and primary cutaneous lymphomas (such as mycosis fungoides and Sezary syndrome) are staged using the TNMB (tumor, lymph nodes, metastasis, blood) system (6,7), while Burkitt lymphoma is staged with St Jude staging criteria or a simpler risk-stratification model, with the modifier "R" being used to refer to completely surgically resected disease. Furthermore, as will be discussed, the Lugano classification, recently developed to simplify and standardize staging and response assessment, recommends modifications to the Ann Arbor staging system.

US, CT, and MR Imaging in Lymphoma

Lymphoma may be unifocal, multifocal, or diffuse, affect isolated lymph nodes or any organ system, and demonstrate a range of imaging appearances at almost every site. Normal lymph nodes often have an elongated shape and a fatty hilum. Lymph nodes infiltrated with lymphoma are often visualized incidentally or during a targeted assessment at ultrasonography (US), demonstrating homogeneous echotexture and enlargement. They are often rounded, with a hypoechoic, "pseudocystic" appearance caused by replacement of the node with lymphomatous tissue. On computed tomographic (CT) images, involved lymph nodes are generally enlarged and of homogeneous density. Some lymphoma subtypes, namely small cell lymphocytic lymphoma/chronic lymphocytic leukemia, may manifest as an increased number of small nodes (Fig 1) (8). Lymphoma confined to lymph nodes is considered nodal disease. Extranodal lymphoma refers to involvement of other tissues (Figs 2–4). Involvement may be primary or a manifestation of multifocal disease. "Primary" extranodal

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Abbreviations:
CNS = central nervous system
FDG = fluorodeoxyglucose
SUV = standardized uptake value
ΔSUV = change in SUV

Conflicts of interest are listed at the end of this article.

Table 1

Clinical Characteristics of the Common Lymphoma Subtypes

Disease	Typical Age (y)	Clinical Features	FDG Avidity	Initial Treatment*	Prognosis
Hodgkin lymphoma (10% of all lymphomas)	Median age, 28; second peak age, 60–70	Progresses with involvement of contiguous nodal chains with late hematogenous dissemination; B symptoms in 25%; initial presentation: often neck and mediastinum	Typically high FDG uptake†	Early stage: ABVD chemotherapy and IFRT Advanced stage: ABVD or BEACOPP chemotherapy with or without RT	Aim for cure; early stage disease survival > 90%, advanced stage 60%–90%
Diffuse large B-cell lymphoma (33% of NHL)	Median age, 64	Clinically aggressive; usually present with large nodal masses; 60% of patients present with advanced stage (III or IV) disease and 30% with extranodal disease; may arise as transformation from pre-existing indolent lymphoma; B symptoms in 30%.	Typically high FDG uptake	Anthracycline-based immunochemotherapy (eg, *R*-CHOP or *R*-EPOCH) alone or with RT	Aim for cure; 20%–40% relapse after first-line therapy
Follicular lymphoma (20% of NHL)	Median age, 60	Most common indolent NHL; patients are often asymptomatic; diffuse adenopathy, peripheral and central; typically diagnosed at advanced stage with frequent marrow involvement; lung, liver, or bone involvement is less common; B symptoms infrequent (< 20%)	Variable (low to moderate FDG uptake)	Localized (stage I–II) disease: RT or observation Advanced disease: watchful waiting versus rituximab alone or in combination with chemotherapy	20%–60% disease-free at 10 y for localized disease treated with RT; typically chemo-sensitive, median life expectancy > 10 y
Marginal zone lymphoma (MZL) (9% of NHL)	Median age, 65–70	Three distinct clinicopathologic subtypes; Splenic MZL, nodal MZL, and MALT lymphoma	Variable (none to high FDG uptake)	Splenic MZL: If hepatitis C positive, antivirals; in others, watchful waiting, rituximab alone or with chemotherapy, or splenectomy Nodal MZL: Typically managed similar to follicular lymphoma MALT lymphoma: For select gastric MALT cases, *H.pylori* eradication; otherwise, RT for localized disease, observation, or systemic therapy for advanced stage disease	Widely variable; collectively, typically chemosensitive and radiosensitive, median life expectancy > 10 y
Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma of CLL type (7% of NHL)	Median age, 72	Lymphocytosis alone or with adenopathy and hepatosplenomegaly; frequent bone marrow involvement; transformation to diffuse large B-cell lymphoma is rare (2%–8%)	Variable (low to moderate uptake); high avidity suggests malignant transformation†	Watchful waiting versus immunochemotherapy	Variable; prognosis strongly influenced by individual biologic risk
Mantle cell lymphoma (MCL) (7% of NHL)	Median age, 68	Usually (70%–90%) present with stage IV disease; frequent gastrointestinal and bone marrow involvement; leukemic phase in 75%; transformation (to highly aggressive blastoid variant) in 20%–30%.	Variable (low to high FDG uptake)	Immunochemotherapy with or without stem cell transplantation; in select cases, watchful waiting	Variable; aggressive initial therapy achieves median progression-free survival of > 7 y

Source.—References 3,4,5,20,82,83,84.

Note.—FDG = fluorodeoxyglucose, MALT = mucosa-associated lymphoid tissue; NHL = non-Hodgkin lymphoma; RT = radiation therapy.

* For initial treatment, ABVD regimen = doxorubicin, bleomycin, vinblastine, dacarbazine; BEACOPP regimen = bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; IFRT = involved field radiation therapy; *R*-CHOP regimen = rituximab, cyclophosphamide, vincristine, doxorubicin, and prednisolone; *R*-EPOCH regimen = rituximab, cyclophosphamide, and infusional doxorubicin, etoposide, and vincristine.

† In general, higher standardized uptake value (SUV) is found with more aggressive lymphoma; SUV > 10 is suspicious for more aggressive lymphoma (29).

Figure 1

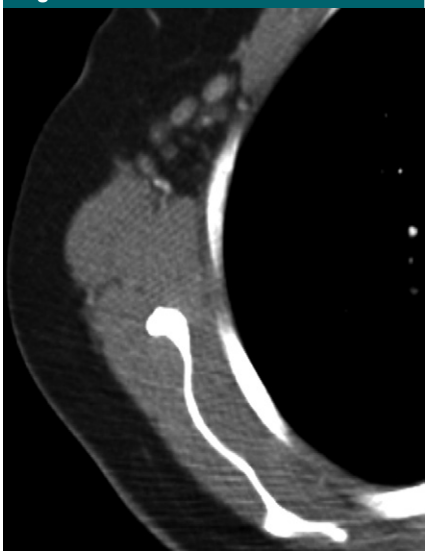


Figure 1: Small cell lymphocytic lymphoma/chronic lymphocytic leukemia in a 57-year-old woman. Contrast-enhanced axial CT scan shows numerous representative small-volume lymph nodes in the right axilla. An increased number of small nodes is often seen in patients with small cell lymphocytic lymphoma. These pathologic small nodes are usually followed in patients with small cell lymphocytic lymphoma/chronic lymphocytic leukemia, with treatment only initiated if nodes increase in size or clinical symptoms develop. These nodes are too small to be considered measurable disease by the Lugano criteria.

Figure 2

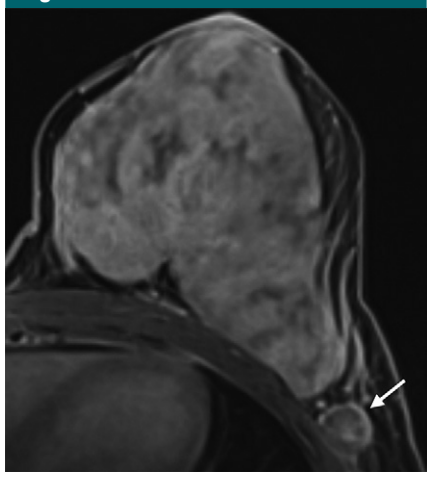
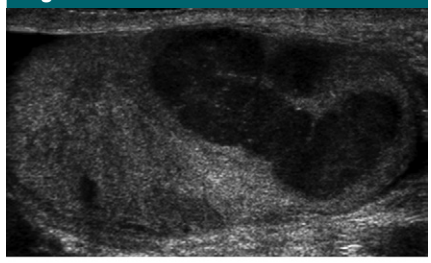
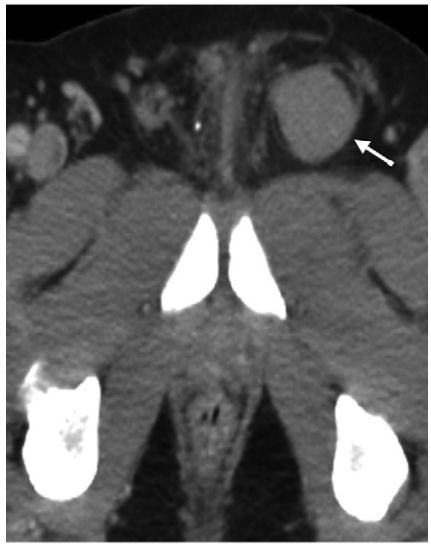


Figure 2: Diffuse large B-cell lymphoma of the left breast in a 33-year-old woman. T1-weighted gadolinium-enhanced fat-saturated axial magnetic resonance (MR) image shows a large mass with predominantly homogeneous enhancement including some areas of heterogeneity. Arrow = left axillary adenopathy. Large breast lymphoma mass is stage IE whereas a large breast lymphoma mass with ipsilateral nodes is typically staged as IIE.

Figure 3



a.



b.

Figure 3: Diffuse large B-cell lymphoma of the left testis in a 49-year-old man. **(a)** US image of left testis (longitudinal plane) depicts multiple well-defined hypoechoic masses. **(b)** Axial contrast-enhanced CT image shows tumor extension along the spermatic cord (arrow; the testis is not depicted on this image). Spread of lymphoma along existing soft tissue structures is often seen.

lymphoma refers to disease restricted to a single organ, although it can be multifocal (for example, with diffuse bone involvement).

As an example, pulmonary lymphoma may manifest as pulmonary masses or as extranodal extension from thoracic nodal masses (Figs 5, 6) (9). Primary pulmonary lymphoma, arising in pulmonary lymphoid tissue, is usually either diffuse large B-cell lymphoma or marginal zone lymphoma arising from bronchial lymphoid tissue, a subtype of mucosa-associated lymphoid tissue lymphoma; both are rare. CT findings in pulmonary lymphoma are variable and may include multiple ill-defined solid or ground-glass nodules or masses, consolidation with air bronchograms, and interlobular septal thickening (Fig 7) (10). On ^{18}F-FDG PET/CT scans in lymphoma patients, pleural effusions usually are not FDG avid and are reactive in etiology, possibly secondary to lymphatic obstruction; presentation with pleural masses or with FDG-avid pleural effusions is rare.

Splenic involvement in lymphoma is common, with most cases representing diffuse large B-cell lymphoma, Hodgkin lymphoma (11), or indolent B-cell lymphomas such as splenic marginal zone lymphoma, chronic lymphocytic leukemia, mantle cell lymphoma, or hairy cell leukemia. Imaging findings vary. Splenomegaly is common but neither sensitive nor specific for lymphoma involvement; no size criterion has been widely accepted (12,13). The following observations strongly suggest splenic involvement with lymphoma: *(a)* massive splenomegaly, *(b)* focal or multifocal solid masses or multiple, tiny nodules, *(c)* adenopathy in the splenic hilum.

On CT images, lymphoma of the abdominal solid organs often manifests as multiple solid masses frequently demonstrating enhancement (14). Diffuse organ involvement is also possible, most commonly affecting the liver and spleen with corresponding organomegaly and variable CT attenuation (15). In the liver, periportal infiltration has been described in association with hepatic masses or portocaval adenopathy (16). The pancreas may be encased by peripancreatic adenopathy, but primary pancreatic lymphoma is rare (17). Renal involvement, typically occurring in the setting of advanced disseminated disease, may appear at imaging as diffuse enlargement or as focal renal masses. In addition, circumferential perirenal soft tissue and direct renal

Figure 4

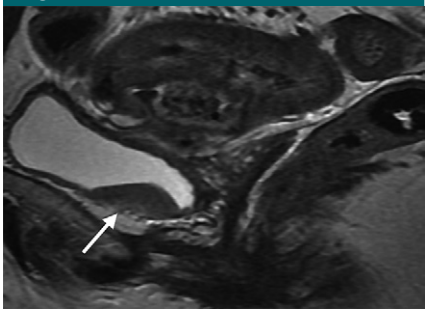


Figure 4: Sagittal T2-weighted MR image of the pelvis in a 71-year-old woman with marginal zone lymphoma of the bladder (arrow), without regional adenopathy. Image shows anteroinferior bladder wall thickening, confirmed as marginal zone lymphoma after biopsy. Lymphoma can arise in any organ or location.

Figure 5

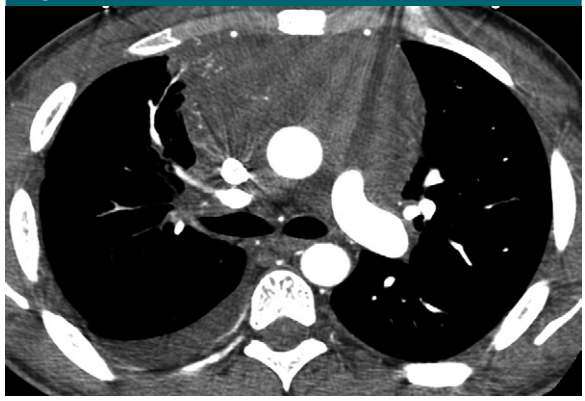


Figure 5: Contrast-enhanced CT of the chest in a 29-year-old woman with Hodgkin lymphoma demonstrates a prevascular anterior mediastinal nodal mass invading the right upper lobe. Mediastinal Hodgkin lymphoma with involvement of several thoracic lymph node groups represents stage II disease; this case, with growth of lymphoma into the lung, represents stage IIE disease. Mediastinal lymphoma with multiple pulmonary lymphomatous nodules but without direct extension into the lung would be considered stage IV disease.

extension from perirenal adenopathy may be seen (Fig 8). Renal lymphoma is usually hypoechoic to normal renal parenchyma on US images, a finding that reflects tissue homogeneity.

Gastrointestinal tract lymphoma is common in non-Hodgkin lymphoma and has variable appearances on CT images. The stomach is most commonly affected, followed by the small bowel and colon; esophageal involvement is rare. Gastric involvement with mucosa-associated lymphoid tissue is hypothesized to be particularly prevalent secondary to chronic inflammation in patients harboring *H. pylori*. Small bowel lymphoma has a predilection for the terminal ileum, likely secondary to the high volume of lymphoid tissue at this site. On CT images, findings include focal or multifocal bowel wall or fold thickening (characteristically without causing upstream obstruction), polyps, ulcers, and aneurysmal dilatation (Fig 9) (18).

Primary lymphoma of bone is uncommon and is typically either diffuse large B-cell lymphoma or follicular lymphoma (17). This entity was described as "reticulum cell sarcoma" before the introduction of newer immunohistochemical markers. The CT appearance of osseous lymphoma is variable; focal lesions are typically lytic but may be sclerotic, as seen with a classic "ivory vertebra," or may demonstrate a mixed lytic/sclerotic appearance. Sclerosis may also develop after chemo- or radiation therapy in treated lesions (19). Either focal bone lesions or diffuse bone marrow involvement may occur in advanced-stage lymphoma. Bone marrow involvement is often assessed with bone marrow biopsy (typically of the

Figure 6

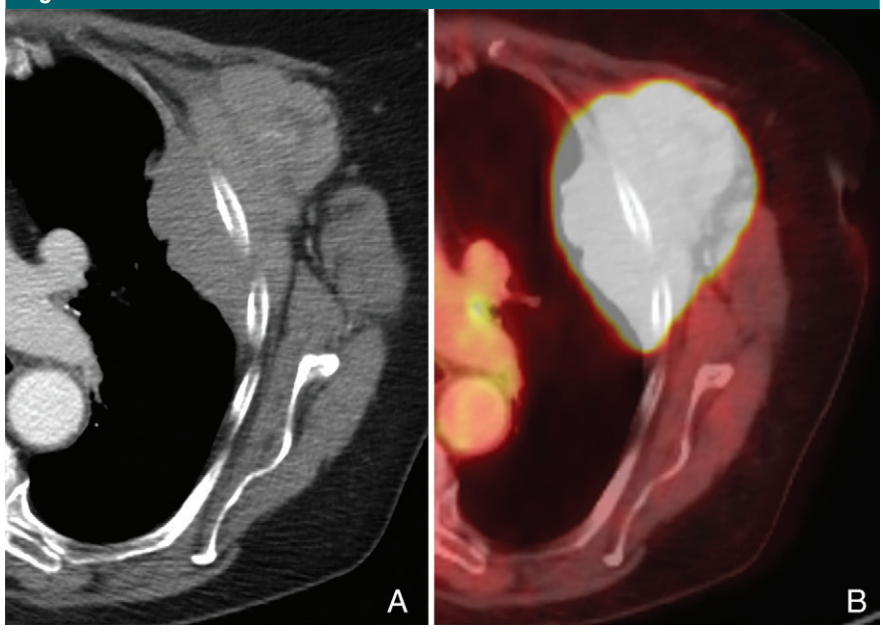
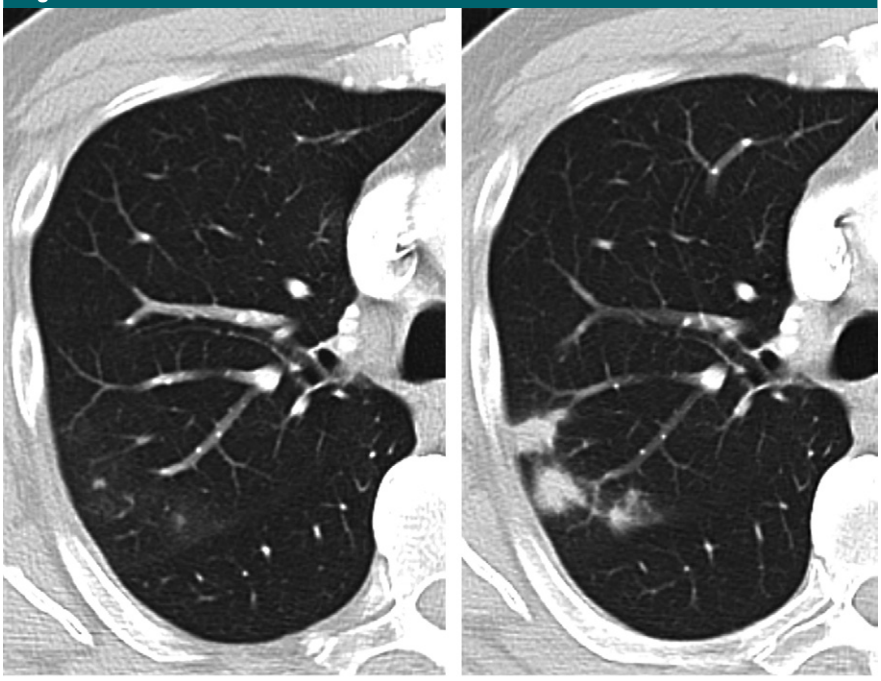


Figure 6: Images in a 93-year-old man with diffuse large B-cell lymphoma. *A*, Contrast-enhanced axial CT image and, *B*, corresponding fused axial fluorine 18 (^{18}F) FDG positron emission tomography (PET)/CT images show a large chest wall mass invading into chest wall, pleura, and lung with very high SUV of 49.3.

Figure 7



a. b.

Figure 7: Follicular lymphoma in a 59-year-old man. **(a)** Initial axial chest CT image shows a few small posterior right upper lobe pulmonary nodules with adjacent ill-defined ground-glass opacities. **(b)** CT image shows increase in size over a follow-up interval of 4 months. Solid organ lesions such as these pulmonary nodules should have a longest diameter greater than 1 cm to be considered measurable disease for response assessment.

Figure 8

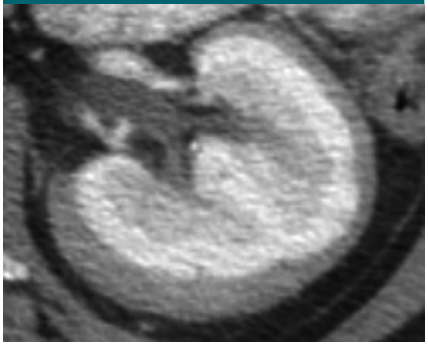
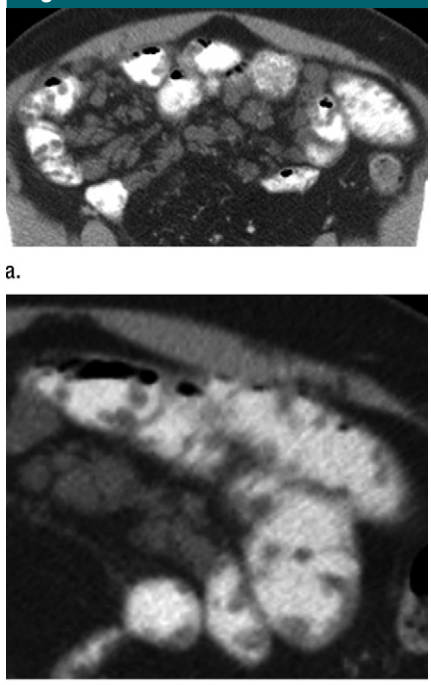


Figure 8: Axial contrast-enhanced CT image in a 53-year-old man with lymphoplasmacytic lymphoma and perirenal growth of soft tissue illustrates infiltrative growth pattern of lymphoma. The renal arteries and veins remain patent despite retroperitoneal adenopathy and infiltrative growth, a finding characteristic of lymphoma. This example illustrates the principle that some sites of lymphoma involvement are not amenable to measurement for response assessment. This perirenal growth is difficult to accurately measure, as are pleural effusions, ascites, and cutaneous lesions. These findings are followed as "nonmeasurable disease."

Figure 9



a. b.

Figure 9: Images in a 59-year-old man with follicular lymphoma. **(a)** Axial contrast-enhanced CT image shows extensive mesenteric adenopathy. **(b)** Magnification shows additional multiple lymphomatous polyps. Multiple lymphomatous polyposis is most typically seen in mantle cell lymphoma, less frequently with follicular lymphoma, and is rare in mucosa-associated lymphoid tissue lymphoma. Patients with follicular lymphoma are often followed clinically with waxing and waning adenopathy over time. Small increase or decrease of 1–2 mm in node size is not significant if the response criteria are applied.

posterior iliac crest) but can be diagnosed in the presence of focal or multifocal increased FDG uptake in bone marrow on pretreatment FDG PET/CT images. MR imaging is also sensitive for detection of focal bone lesions, which present as T1-hypointense masses (Figs 10, 11). The skin is a common site of extranodal involvement of non-Hodgkin lymphoma (19); primary cutaneous lymphoma is rarer. Whole-body FDG PET/CT allows a systemic cutaneous survey (Fig 12).

MR imaging is also the primary imaging modality for CNS evaluation in lymphoma. Primary CNS lymphoma is rare, representing 1% of non-Hodgkin lymphoma cases. Intracranial involvement in patients with advanced, systemic lymphoma is more common, described in 10%–15% of cases (Fig 13) (20). The spectrum of imaging findings is broad. Primary CNS lymphoma in the immunocompetent patient is typically a solid homogeneous T2-hypointense lesion with restricted diffusion and avid central enhancement. In the immunocompromised patient, lesions are more often heterogeneous with peripheral enhancement, mimicking glioblastoma multiforme. On CT images, primary CNS lymphoma deposits are classically hyperattenuating compared with white and gray matter (21). Leptomeningeal infiltration is seen in approximately two-thirds of patients with neurologic involvement, which may manifest on MR images as diffuse thickening or focal enhancing masses of the ependyma, meninges, or cranial or spinal nerves (Fig 14) (22,23).

Figure 10

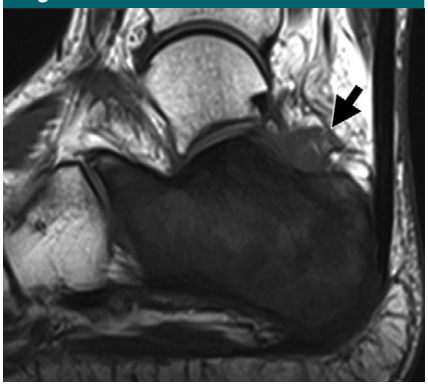


Figure 10: Sagittal T1-weighted MR image of diffuse large B-cell lymphoma of the calcaneus in a 24-year-old woman, with no distant extraosseous manifestation. Image shows homogeneous diffuse calcaneal bone marrow replacement with lymphoma, seen as loss of normal T1 hyperintense marrow signal, with local extraosseous extension of a soft-tissue mass from the posterosuperior calcaneus (arrow). Mass or nodal size can be measured on MR images and applied to the CT response assessment criteria.

Figure 12

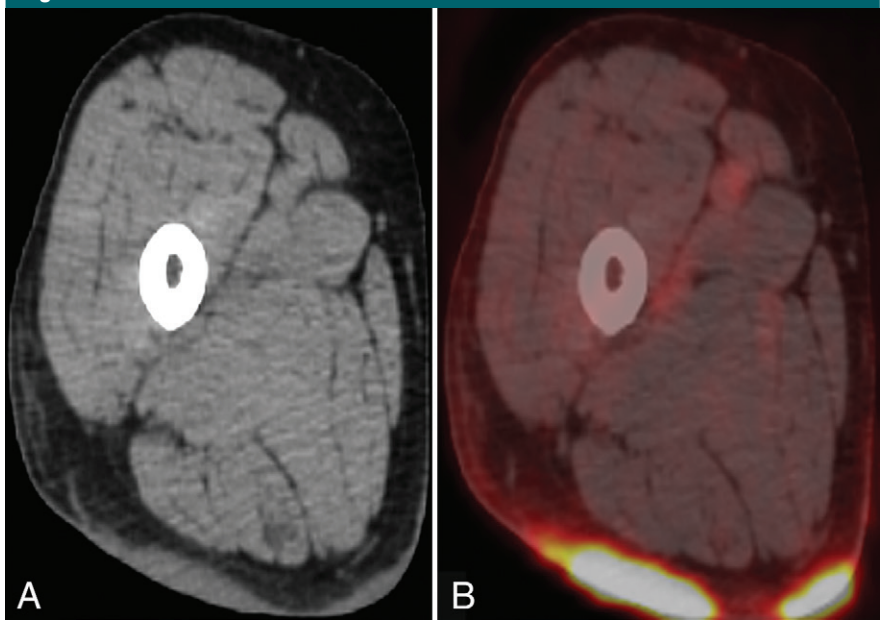


Figure 12: Mycosis fungoides (the most common form of cutaneous T-cell lymphoma) in a 67-year-old man. *A*, Nonenhanced axial CT image shows skin thickening of the posterior thigh. *B*, Corresponding fused axial ^{18}F-FDG PET/CT image shows associated high FDG avidity (SUV, 12.5).

Figure 11

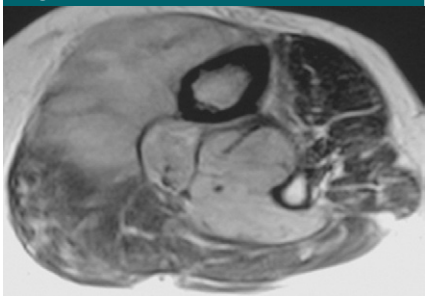


Figure 11: Diffuse large B-cell lymphoma in a 62-year-old woman. Axial T1-weighted gadolinium-enhanced non–fat-saturated MR image shows large lymphoma mass involving several muscles of the left calf but also replacement of the tibial bone marrow by lymphoma. Lymphoma often extends through the Haversian channels, either from the medullary space in bone radiating outward or from the extraosseous soft tissues growing inward. The mass measures 8 × 7 cm in the axial plane and the product of perpendicular diameters is 56. The mass completely disappeared following radiation and chemotherapy, representing complete response. If the mass had only partially reduced in size following therapy, for example to a size of 4 × 4 cm with product of the perpendicular diameters of 16, partial remission (≥ 50% decrease in disease burden) would have been achieved.

Figure 13

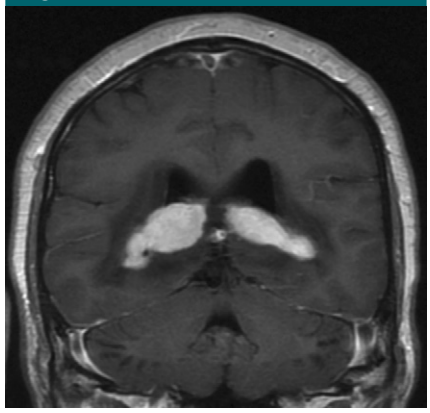


Figure 13: Diffuse large B-cell lymphoma with CNS involvement in a 57-year-old man. Gadolinium-enhanced T1-weighted coronal MR image at the level of the lateral ventricular occipital horns demonstrates enhancing intraventricular masses.

The Evolving Role of PET Imaging in Lymphoma

Advances in molecular imaging with ^{18}F-FDG PET (which is usually combined with unenhanced or contrast-enhanced CT as FDG PET/CT) have facilitated the use of imaging not only for diagnosis and staging but also for response assessment in lymphoma patients (24,25). The definition of a persistent PET-positive lesion is fundamental for response assessment with FDG PET. When FDG PET/CT was first included in clinical criteria for response assessment (in the 2007 International Harmonization Project criteria), a PET-positive lesion was defined as "focal or diffuse FDG uptake above background in a location incompatible with normal anatomy or physiology," without a specific SUV cutoff (26,27). In addition, the change in SUV (ΔSUV) between baseline and interim PET can serve to quantify metabolic response and also has prognostic implications (28). For example, reduction of maximum SUV by more than 66% after two cycles of chemotherapy in diffuse large B-cell lymphoma indicates satisfactory response to therapy and is therefore related to good prognosis (29,30). Intensity of FDG uptake as quantified by SUV has also been linked to the clinical aggression of the lymphoma subtype (31,32), which may become relevant if

Figure 14

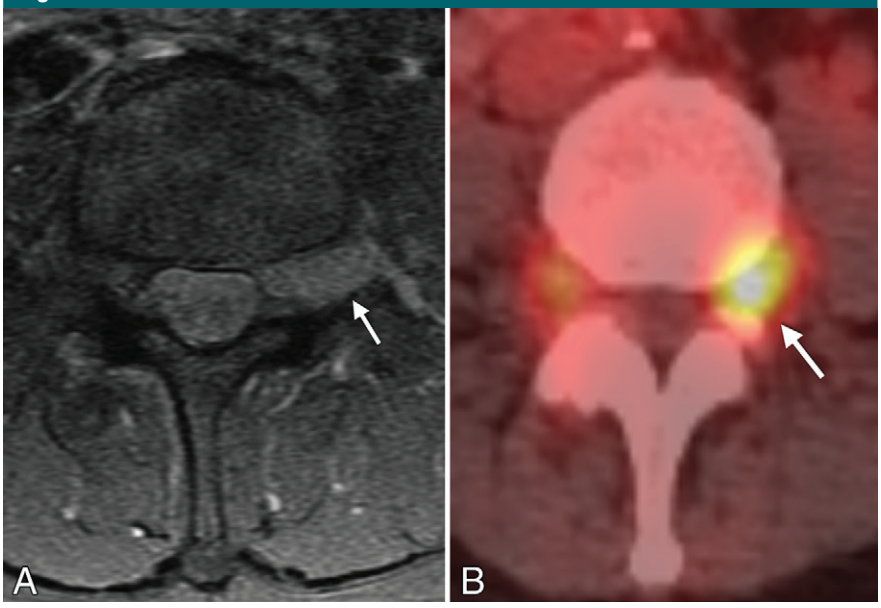


Figure 14: Neurolymphomatosis in a 73-year-old female patient with chronic lymphocytic leukemia. *A*, Axial T1-weighted gadolinium-enhanced fat-saturated MR image shows thickening and enhancement of the left T6 nerve root (arrow). *B*, Corresponding axial ^{18}F-FDG PET demonstrates increased FDG uptake of nerve root (SUV, 2.5). Several additional nerve roots were also involved, including right T7 nerve root.

transformation of a previously indolent lymphoma is clinically suspected.

Currently, functional imaging with FDG PET/CT is often obtained in FDG-avid lymphoma, but indications depend on specific diagnosis and presentation. A baseline pretreatment scan is always recommended to allow meaningful comparison later (33,34). Combined FDG PET/CT has been found to be more accurate than CT alone for response assessment. For example, one analysis showed that in identifying lymph node involvement, FDG PET/CT was 94% sensitive and 100% specific, while contrast-enhanced CT alone was 88% sensitive and 86% specific. For organ involvement, FDG PET/CT showed sensitivity of 88% and specificity of 100%, whereas contrast-enhanced CT alone had sensitivity of 50% and specificity of 90% (35). With FDG PET/CT, non-Hodgkin lymphoma will be upstaged in 31% and downstaged in 1% of patients relative to CT (usually patients with stage I or II disease), thereby potentially changing treatment in 25%. Hodgkin lymphoma will be upstaged in 32% and downstaged in 15% of patients with FDG PET/CT, thus possibly leading to treatment change in up to 33% (9).

FDG PET/CT is of particular benefit for the assessment of extranodal lymphoid tissue. In particular, FDG PET/CT often demonstrates bone marrow lesions that are occult on CT images, although the specificity of such findings varies among disease types (36–38). Diffuse FDG uptake in bone marrow is nonspecific and often observed in response to cytokine stimulation, especially in Hodgkin lymphoma, without lymphomatous infiltration of bone marrow. Sensitivity and specificity of FDG PET/CT for detection of focal or diffuse marrow involvement are reported at 94% and 100%, respectively, at least for typically FDG-avid diffuse large B-cell lymphoma (39,40). Recent data show that bone marrow involvement can be excluded with high certainty with a negative FDG PET/CT study in patients with Hodgkin lymphoma (41,42). The new Lugano classification (43) states that bone marrow biopsy may be obviated in patients with Hodgkin lymphoma and aggressive non-Hodgkin lymphoma if FDG PET/CT is clearly positive for marrow involvement. Bone marrow biopsy may remain necessary in other patients depending on the clinical question and lymphoma histology. In the spleen, focal lesions with FDG avidity above background in typically avid lymphomas are strongly suggestive of splenic lymphoma, as is diffuse FDG avidity of the pretreatment spleen greater than that of the liver. FDG uptake by gastrointestinal tract lymphoma is variable but may be detected on FDG PET/CT images in 60% (for mucosa associated lymphoma [44]) to 100% (for large cell lymphoma) of cases.

After therapy, diffuse splenic or bone marrow FDG avidity following administration of hematopoietic stimulating agents may complicate the interpretation of FDG PET/CT images, limiting the ability to assess for possible residual disease in these organs. Furthermore, cortical bone lesions heal slowly compared with bone marrow and, because of osseous remodeling, have prolonged FDG uptake that limits the ability to assess for residual malignancy. Treatment with the monoclonal antibody rituximab as part of the *R*-CHOP regimen in diffuse large B-cell lymphoma may induce a strong inflammatory "flare" response and is a well-known cause of "false-positive" FDG avidity on interim FDG PET/CT scans (43,45,46).

Lymphoma Treatment

Treatment of lymphoma depends on the subtype and clinical stage. The aim of treatment for Hodgkin lymphoma and the aggressive non-Hodgkin lymphomas, such as diffuse large B-cell lymphoma or peripheral T-cell lymphoma, is cure. Indolent non-Hodgkin lymphoma is generally incurable and current treatment is dedicated to prolonging survival, although new therapies are being investigated (47).

Hodgkin Lymphoma

Among patients with early-stage Hodgkin lymphoma, the cornerstone of therapy is chemotherapy, most commonly with the ABVD regimen (consisting of doxorubicin, bleomycin, vinblastine,

and dacarbazine) with or without consolidative radiation therapy. For advanced-stage Hodgkin lymphoma, combination chemotherapy is the standard of care, in the United States usually with the ABVD regimen. In select higher-risk scenarios, the BEACOPP regimen (consisting of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) may be chosen. Consolidative radiation therapy may be considered for initially bulky disease. This treatment paradigm has evolved from earlier models, when extended-field radiation therapy (such as mantle-field radiation, inverted Y, or total lymphoid irradiation) was a dominant component of lymphoma treatment, allowing cure of advanced Hodgkin lymphoma for the first time in the decades following 1970. Recent advances include progressive minimization of radiation therapy fields, as achieved with involved-nodal radiation therapy or involved-site radiation therapy, which limit radiation therapy to initially involved sites of disease with minimal margins. For patients in whom disease is refractory to initial treatment or in whom there is subsequent relapse, routine treatment is second-line chemotherapy and, for responders, consolidative high-dose therapy with autologous stem cell rescue (autotransplant). Radiation therapy is often incorporated if not delivered as part of first-line therapy if the relapse is limited to tissues that may be safely irradiated.

Non-Hodgkin Lymphoma

Cure can be achieved in the majority of patients with the most common type of aggressive non-Hodgkin lymphoma (diffuse large B-cell lymphoma) with combination chemotherapy-immunotherapy or combined-modality therapy. A standard regimen in patients with advanced-stage disease is six cycles of *R*-CHOP (the anti-CD20 antibody rituximab in combination with cyclophosphamide, vincristine, doxorubicin, and prednisone). Patients with limited-stage disease can be treated with an abbreviated course of *R*-CHOP (three to four cycles) followed by involved-field radiation therapy with similar outcomes to full-course chemotherapy. Bulky disease at any stage is typically treated with six cycles of *R*-CHOP with or without radiation therapy. Other regimens have been studied including consecutive *R*-CHOP and ICE (consisting of ifosfamide, carboplatin, and etoposide) chemotherapy (48), and infusional chemotherapy with a dose-adjusted *R*-EPOCH regimen (rituximab, etoposide, prednisone, vincristine, and doxorubicin) (49); the role for consolidation of first remission with autotransplant for high-risk patients remains uncertain (50), and investigators are evaluating incorporation of targeted therapy into first-line regimens (51,52).

The treatment of relapsed lymphoma continues to evolve rapidly. Currently, many emerging drug therapies show promise, including targeted biologic therapies such as monoclonal antibodies, antibody drug conjugates, small molecule inhibitors of critical oncogenic pathways such as the phosphatidylinositol 3-kinase (PI3 K) pathway or B-cell receptor pathway, radioimmunotherapy, and immunomodulators (53). Treatment paradigms across all subtypes of lymphoma have changed dramatically over the past decade and will continue to change as novel therapies emerge.

Response Assessment

Staging and Response Assessment: Historical Development

The introduction of radiation therapy and clinical introduction of CT and later FDG PET/CT imaging contributed significantly to the evolution of staging and response assessment systems in lymphoma:

1971: The Ann Arbor staging classification was published, with anatomic stages related to radiation therapy fields (54).

1989: Cotswolds modifications were added to create the modified Ann Arbor system after the introduction of CT for staging assessment (55).

1999: The International Working Group criteria defined five categories of clinical response based on CT imaging of lesion size (56). The category "complete remission—unconfirmed" applied to residual adenopathy after treatment and caused confusion.

2007: The International Harmonization Project criteria for response assessment defined clinical response based on PET/CT imaging of metabolic activity (26,57). FDG avidity was defined relative to the mediastinal blood pool; this was a shortcoming of these criteria. The Deauville criteria were subsequently proposed in 2009 (58) for grading FDG avidity on PET.

2014: The Lugano classification was published (43).

The Lugano Classification

The Lugano classification (43) represents a major change from the Ann Arbor staging system and the International Working Group criteria for response assessment. The classification was developed following meetings in 2011 and 2013. The goal of the Lugano classification is the simplification and standardization of response assessment and reporting. The new classification also addresses the role of FDG PET/CT for staging and interim treatment response assessment. Given the expected rapid clinical application of the new staging criteria, it is important for radiologists and nuclear medicine specialists to be aware of the associated implications for lymphoma imaging.

In short, FDG PET/CT has been fully incorporated into staging and response assessment of FDG-avid lymphoma. Lymphoma types with low or variable FDG uptake should still be staged with CT. Although FDG PET/CT is strongly recommended for staging FDG-avid lymphomas, a diagnostic contrast-enhanced CT examination should still be included at initial staging for optimal anatomic assessment, which may be completed as part of the FDG PET/CT (59). Contrast-enhanced CT will allow more accurate measurement of node size if required for clinical trials and will help better discern adenopathy from surrounding soft-tissue structures than the low-dose nonenhanced CT previously routinely performed for FDG PET/CT (43).

Table 2

Lugano Criteria for Response Assessment on CT and FDG-PET/CT

Modality	Clinical Application	Complete Response	Partial Remission/ Partial Response	Stable Disease/ No Response	Progressive Disease
CT	All lymphoma (if CT is performed for tumor size measurement); primary assessment modality for non–FDG-avid lymphoma	Complete radiologic response: Nodal sites reduced to ≤1.5 cm in LDi Complete disappearance of radiologic evidence of disease	Partial remission: For multiple lesions, ≥50% decrease in SPD of up to six target measurable nodes and extranodal sites If only a single lesion is present, ≥50% decrease in the PPD	Stable disease: <50% decrease from baseline in SPD of up to six dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met	May be based on a single dominant lesion; progressive disease is assigned with at least one of the following: 1. New or increased adenopathy; an individual node must be abnormal with: *(a)* LDi > 1.5 cm AND *(b)* PPD increase by ≥ 50% from nadir AND *(c)* LDi or SDi increase from nadir; the increase in LDi or SDi from nadir (the smallest recorded measurement) must be > 0.5 cm for lesions ≤ 2 cm and > 1.0 cm for lesions > 2 cm 2. Splenic volume increase: *(a)* With prior splenomegaly: increase in length by > 50% of its prior increase beyond baseline; for example, splenic length increases from 15 cm (2 cm above baseline splenomegaly of 13 cm) to >16 cm (>3 cm above baseline) *(b)* Without prior splenomegaly: length increase by at least 2 cm *(c)* New or recurrent splenomegaly 3. New or larger nonmeasured lesions 4. Recurrent previously resolved lesions 5. New extranodal lesion > 1 cm in any axis (new lesions < 1 cm in any axis are included if these are "unequivocally attributable" to lymphoma) 6. A new node > 1.5 cm in any axis
FDG PET/CT	FDG-avid lymphoma (including Hodgkin lymphoma and diffuse large B-cell lymphoma)	Complete metabolic response: Score of 1, 2, 3 in nodal or extranodal sites with or without a residual mass	Partial metabolic response: Score of 4 or 5 with reduced uptake compared with baseline and residual mass(es) of any size	No metabolic response: Score of 4 or 5 with no obvious change in FDG uptake	Score 4 or 5 in any lesion with an increase in intensity of uptake from baseline and/or New FDG-avid foci consistent with lymphoma

Note.—Modified after the recommendations of the Lugano classification (43). This table represents a short version of the response criteria with focus on CT and FDG PET/CT findings. Please see original article for complete details of response assessment (for example, determining bone marrow involvement). Nonmeasurable disease such as pleural effusions or ascites should be mentioned in the radiology report but are not used to quantify response assessment on CT. LDi = longest transverse diameter of a lesion; SDi = shortest axis perpendicular to LDi; PPD = product of perpendicular diameters, the product of the LDi, and its perpendicular diameter (if only have one lesion); SPD = sum of the product of the perpendicular diameters of multiple lesions (if have multiple measurable lesions).

The new criteria for response assessment using CT and FDG PET/CT are summarized in Table 2. Four categories for CT have been outlined: *(a)* complete radiologic response, all nodes less than or equal to 1.5 cm in longest diameter, disappearance of all CT findings of lymphoma; *(b)* partial remission, 50% or greater decrease in disease burden; *(c)* stable disease, less than 50% decrease in disease burden; and *(d)* progressive disease, new or increased adenopathy or new extranodal lymphoma.

Response assessment with FDG PET/CT is based on metabolic activity, indicated by FDG uptake. The SUV serves as a marker of metabolic activity, and response assessment is now based on visual assessment of FDG uptake and categorized according to the "five-point scale." The five-point scale incorporates the Deauville criteria initially proposed for assessment on interim FDG PET/CT images (24,43,58). The five-point scale includes the following categories:

1. No FDG uptake > background.
2. FDG uptake ≤ mediastinum.
3. FDG uptake > mediastinum but ≤ liver.
4. FDG uptake moderately > liver.
5. FDG uptake markedly > liver and/or new lesions.

X. New areas of FDG uptake unlikely to be related to lymphoma.

The five-point scale is now applied to both interim and end-of-treatment FDG PET/CT response assessment. Four categories of response have been outlined (24,43) as follows: *(a)* complete metabolic response—score of 1, 2, or 3; *(b)* partial metabolic response—score of 4 or 5 with reduced FDG uptake; *(c)* no metabolic response—score of 4 or 5 without significant change in FDG uptake; and *(d)* progressive metabolic disease—score of 4 or 5 with increased FDG uptake or with new lesions.

In interpreting the five-point scale, a score of 1 or 2 is interpreted as negative for lymphoma, while a score of 4 or 5 is considered positive (Figs 15, 16). A score of 3 likely also represents complete metabolic response at interim with resulting good prognosis and is therefore usually also considered as negative (24). However, in some trials pursuing a de-escalation of therapy strategy, a score of 3 may be considered as inadequate response to avoid undertreatment (60).

Additional Recommendations in the Lugano Classification

Recommendations of the Lugano classification include the following:

1. Although FDG PET/CT is now recognized as the reference standard for FDG-avid lymphomas, the importance of CT for anatomic assessment is addressed in the Lugano classification, in which contrast-enhanced CT is recommended at the time of initial staging and for radiation therapy planning. Regardless of imaging modality, all clinical data need to be incorporated for diagnostic assessment.

2. The Cotswold modifications have been updated. Evaluation of bulky disease and B symptoms has traditionally been inaccurate; removal of the associated modifiers "X" and "B" may help to standardize staging. Although the current definition of bulky disease in Hodgkin lymphoma is retained (namely a mass ≥ 10 cm or 1/3 of the transthoracic diameter), the associated "X" modifier is no longer applied in Hodgkin lymphoma or non-Hodgkin lymphoma. Instead, the longest diameter of a mass is simply recorded for staging purposes. The modifier "B" is only applied in patients with Hodgkin lymphoma as presence of B symptoms only affects Hodgkin lymphoma treatment.

3. The Lugano classification recommends modification of the Ann Arbor classification for anatomic description of disease extent. Patients are now to be more simply categorized as having "limited" (previously Ann Arbor stage I or II) or "advanced" (previously Ann Arbor stage III or IV) disease.

4. CT (or FDG PET/CT): Tumor burden is to be calculated at baseline staging. Choose up to six of the largest nodes, nodal complexes, or other lymphoma deposits (for example, extranodal solid organ disease). Lesions chosen must be amenable to accurate measurement in two dimensions. Eligible lymph nodes are those with longest diameter greater than 1.5 cm. Eligible extranodal lesions are those with longest diameter greater than 1.0 cm. Measure the longest diameter and shortest diameter of each lesion in the transverse plane. Multiply the longest diameter and shortest diameter for each lesion to give the "product of the diameters." Add these to give the "sum of the product of the diameters," or SPD. As an example, for two nodes measuring 2 × 3 cm and 4 × 5 cm, the SPD would be (2 × 3) + (4 × 5) = 6 + 20 = 26 (Fig 11). The SPD calculated at time of staging will serve as the baseline for sequential quantification of tumor burden at interim and end-of-therapy FDG PET/CT.

Quantification of Treatment Response with FDG PET/CT

The Lugano classification recommends a five-point scale for response assessment with FDG PET/CT; this is based on visual analysis. A different approach is quantification of treatment response in lymphoma. Quantification of treatment response has become an interesting research area and is the subject of ongoing investigations in lymphoma imaging (29,61–63). A short introduction is provided below.

Response on FDG PET/CT images can be quantified by measuring changes in metabolic activity, expressed as the ΔSUV: ΔSUV (%) = (SUVcurrent − SUVbaseline)/SUVbaseline. Usually, the highest SUV in *any* lesion on the baseline scan and the highest SUV in *any* lesion on the follow-up study (not necessarily the same disease site on both studies) are measured.

The ΔSUV is an exploratory measure. For diffuse large B-cell lymphoma, a ΔSUV greater than 66% (after two cycles of chemotherapy) or 77% (after four cycles of chemotherapy) has been proposed as an indicator of good treatment response associated with better survival (29). Data in Hodgkin lymphoma are less robust, but a ΔSUV of 71% after two cycles of chemotherapy has been tentatively proposed (63).

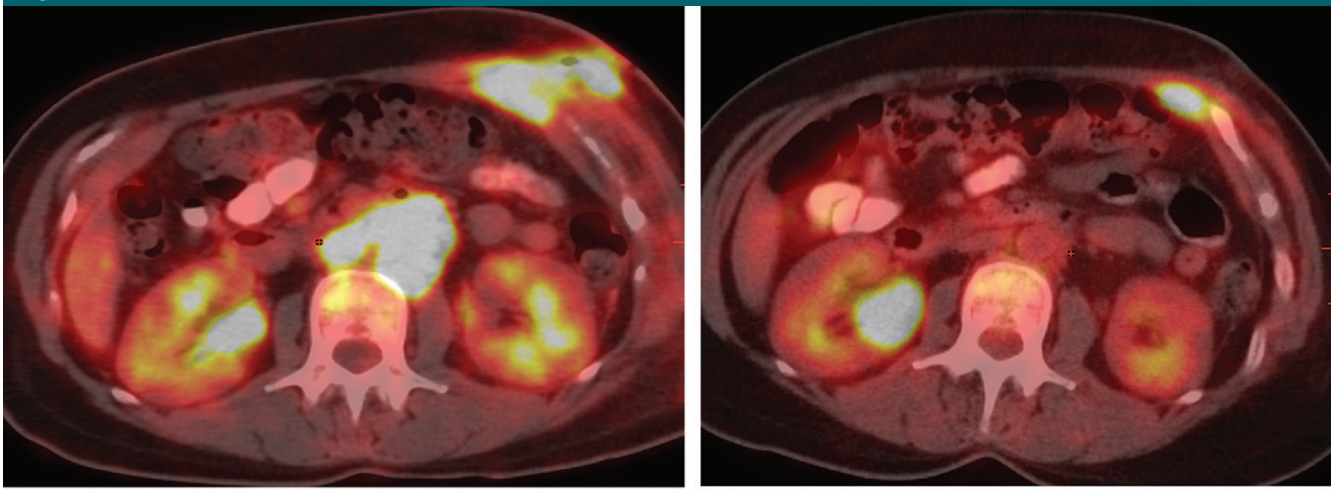
The ΔSUV approach improves interobserver agreement as compared with visual analysis using the five-point scale. However, ΔSUV is still currently an exploratory measure and should only be used as part of research protocols. The usual limitations of SUV measurement also apply to the ΔSUV approach (SUV varies depending on various technical parameters, the patient's dietary condition, and FDG uptake time).

Discussion of New Response Criteria

The new Lugano classification represents a consensus statement of clinical experts in lymphoma and is therefore expected to serve as a unified guideline for all physicians involved in lymphoma diagnosis and management. In particular, the new response criteria should facilitate a simple assessment of response to guide clinical management and are not intended as an academic or mathematical exercise in SUV evaluation or tumor burden calculation. As a result of these criteria, radiologists and nuclear medicine specialists have a renewed opportunity to guide clinical management based on imaging findings.

Several features of the new criteria for response assessment deserve particular attention and discussion:

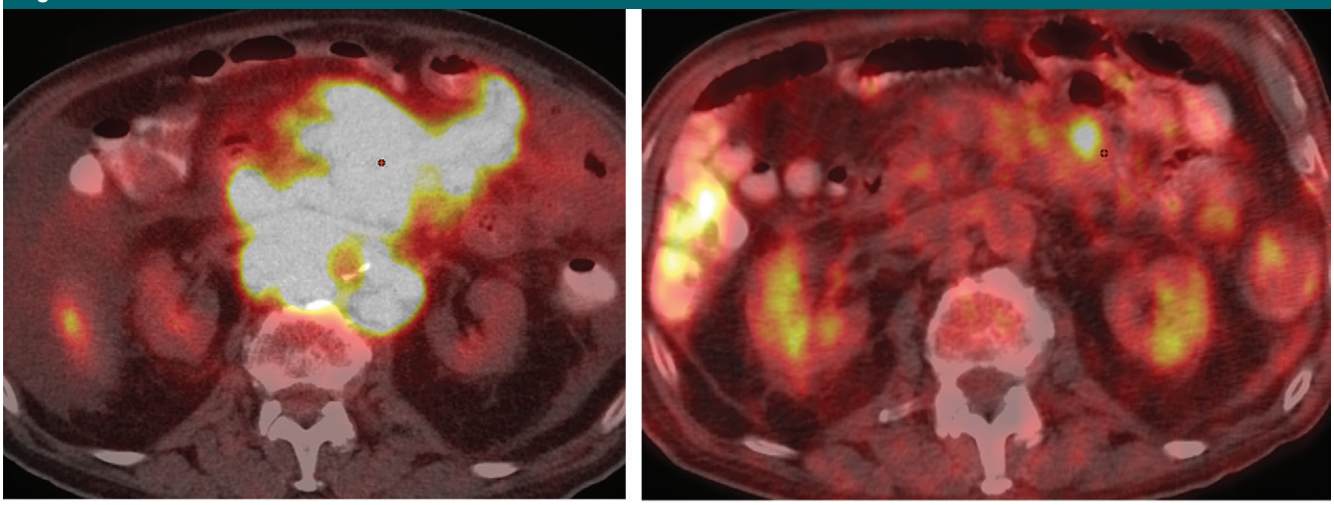
Figure 15



a. b.

Figure 15: **(a)** Pretreatment FDG PET/CT image in a 61-year-old woman with diffuse large B cell lymphoma documents retroperitoneal adenopathy with SUV of 16.4 and uptake in the anterior abdominal wall secondary to previous surgery. **(b)** Interim scan shows resolved retroperitoneal adenopathy with no FDG uptake, consistent with a score of 1 on the five-point scale, as well as improving postsurgical inflammation in the anterior abdominal wall.

Figure 16



a. b.

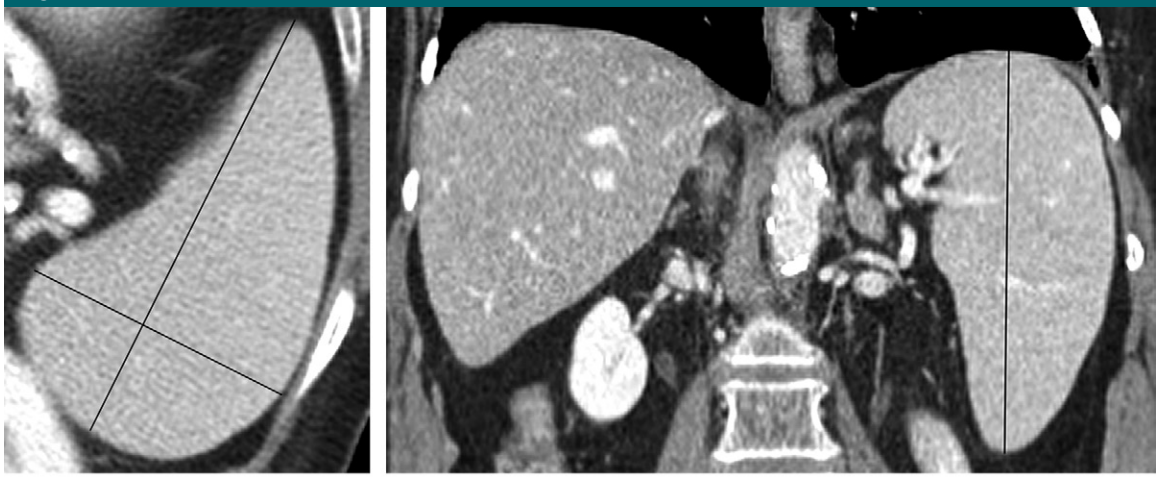
Figure 16: **(a)** Pretreatment FDG PET/CT image demonstrates a mesenteric and retroperitoneal mass with an SUV of 23.5 in an 81-year-old woman with diffuse large B cell lymphoma. **(b)** On interim FDG PET/CT scan, the residual mesenteric mass has reduced FDG uptake with an SUV of 5.6. Uptake with an SUV of 5.6 is moderately higher than liver uptake (SUV of 2.3 in this patient); therefore this would be scored as 4 on the five-point scale.

1. Future studies are needed to further validate these new response criteria. The overall trend is toward a more simplified response assessment. Bidirectional measurements remain important in the Lugano classification but unidimensional measurements were finally introduced for spleen and lymph node size and may become even more important in the future.

2. The trend toward simplification of response assessment may lead in the future to a single set of response criteria for both hematologic and solid organ malignancies that could be used in place of the currently disparate lymphoma response criteria and Response Evaluation Criteria In Solid Tumors (RECIST) systems.

3. The proposed five-point scale is a visual measure of FDG PET/CT response assessment; the risk of a degree of subjectivity in the interpretation of FDG avidity has not been eliminated.

Figure 17



a. b.

Figure 17: A practical approach to measuring the splenic size in lymphoma patients includes three measurements. **(a)** The largest transverse diameter and the perpendicular diameter are measured in the axial plane and **(b)** the craniocaudal diameter is measured in the coronal plane. According to the Lugano classification, splenomegaly is defined as vertical splenic length greater than 13 cm. It should be noted that shrinkage of the spleen after treatment is best appreciated in the coronal plane. Black line indicates the measurement plane on axial and coronal contrast-enhanced CT images in this 72-year-old female patient with lymphoma.

This may limit comparisons on serial scans or between different patients or centers in clinical trials. The ΔSUV approach has been proposed to eliminate interobserver variability in interpreting interim PET scans. Recent studies also suggest that the ΔSUV approach provides better prognostic information than the five-point visual scale (64), but further validation and improved standardization of PET imaging between centers is needed (65–67) before this method can be applied widely in daily clinical practice.

4. The definition of measurable adenopathy mandated by the Lugano classification includes a longest nodal diameter of greater than 1.5 cm. Radiologists must be aware that this is a definition for CT. A much smaller 1.0-cm lymph node may be involved with lymphoma and show avid FDG uptake.

5. Splenomegaly is now defined as size greater than 13 cm in the vertical length (43) (Fig 17). In our experience, only a few patients will meet this definition of splenomegaly in the absence of hematologic disease, splenic disease, portal hypertension, or other causes of pathologic splenic enlargement.

6. Finally, radiologists must be aware that findings on CT and FDG PET/CT images may (rarely) be "discordant." Discrepancy may arise when CT images demonstrate a marked reduction in tumor burden but FDG PET/CT images show increasing SUV in a smaller lesion, or new small lesions.

Interim Imaging

In the ongoing clinical effort to optimize outcomes while minimizing toxicity in the treatment of lymphoma, early response assessment with an interim FDG PET/CT scan is often performed. Interim FDG PET/CT scans are those completed after initiation but before completion of therapy, often after either the second or fourth cycle of a standard six-cycle course (4). Reduction in lesion size and metabolic activity are indicative of response and interim FDG PET/CT negativity is associated with improved outcomes (68–71). The greatest potential benefit of interim FDG PET/CT evaluation is the potential to inform "response-adapted therapy," whereby treatment could be de-escalated in intensity in the setting of a satisfactory early response or escalated if early response is inadequate (72). Both approaches have shown promise in Hodgkin lymphoma (73–75). Several major clinical trials are ongoing in the US and worldwide to further study the value of response-adapted therapy based on findings of interim FDG PET/CT scans (76). Currently, changing therapy based on findings at interim PET alone is not currently recommended except in the setting of obvious disease progression (24).

Imaging after Completion of Treatment

A negative FDG PET/CT scan after the end of treatment excludes residual viable tumor with high certainty in both Hodgkin lymphoma and diffuse large B-cell lymphoma, with higher negative predictive value in Hodgkin lymphoma (77). Although a negative FDG PET/CT scan generally supersedes a finding from a posttherapy CT examination, the risk of recurrence may be somewhat higher with residual structural disease greater than 2 cm, even when the FDG PET/CT scan is negative for metabolic activity (78). Otherwise, no consensus has been achieved in defining the role of imaging for monitoring

lymphoma patients after completion of therapy with curative intent. In general, clinical symptoms and signs provide the earliest evidence of recurrent disease, reported as accounting for up to 80% of presentations (79). Surveillance FDG PET/CT scans, those performed after patients have achieved remission, have been shown to have high false-positive rates (80) and are not generally recommended. Surveillance CT imaging is still widely performed but may not be necessary in all patients (81).

The Lugano criteria provide a consensus statement on follow-up imaging advising against routine surveillance FDG PET/CT scans in asymptomatic patients and recommending imaging with CT for follow-up as indicated by clinical signs or symptoms or as required by a clinical trial. Limitation of radiation exposure is also advised. In practice, posttreatment imaging in lymphoma patients varies widely by center and will probably remain variable despite the new consensus guidelines.

Conclusion

The lymphomas are a heterogeneous group of malignancies, all of which arise from a given stage in lymphocyte ontogeny but which have highly variable clinical and imaging manifestations. Diagnostic imaging plays a critical role in the initial evaluation, monitoring, and follow-up of lymphoma patients. Improved familiarity with the Lugano classification, and with potential pitfalls in imaging interpretation, will allow the radiologist to provide added value as a member of the clinical oncology team.

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