RadioGraphics

FDG PET/CT of Extranodal Involvement in Non-Hodgkin Lymphoma and Hodgkin Disease[1]

CME FEATURE

See accompanying test at http://www.rsna.org/education/rg_cme.html

LEARNING OBJECTIVES FOR TEST 6

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

- Discuss the value of FDG PET/CT for staging and follow-up in patients with extranodal lymphoma.
- Identify common and uncommon PET/CT findings in extranodal lymphoma of various organs.
- Describe common pitfalls of FDG PET/CT for extranodal lymphoma.

Fabio M. Paes, MD • Dimitrios G. Kalkanis, MD • Panagiotis A. Sideras, MD
Aldo N. Serafini, MD

The term *extranodal disease* refers to lymphomatous infiltration of anatomic sites other than the lymph nodes. Almost any organ can be affected by lymphoma, with the most common extranodal sites of involvement being the stomach, spleen, Waldeyer ring, central nervous system, lung, bone, and skin. The prevalence of extranodal involvement in non-Hodgkin lymphoma and Hodgkin disease has increased in the past decade. The imaging characteristics of extranodal involvement can be subtle or absent at conventional computed tomography (CT). Imaging of tumor metabolism with 2-[fluorine-18]fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) has facilitated the identification of affected extranodal sites, even when CT has demonstrated no lesions. More recently, hybrid PET/CT has become the standard imaging modality for initial staging, follow-up, and treatment response assessment in patients with lymphoma and has proved superior to CT in these settings. Certain PET/CT patterns are suggestive of extranodal disease and can help differentiate tumor from normal physiologic FDG activity, particularly in the mucosal tissues, bone marrow, and organs of the gastrointestinal tract. Familiarity with the different extranodal manifestations in various locations is critical for correct image interpretation. In addition, a knowledge of the differences in FDG avidity among the histologic subtypes of lymphoma, appropriate timing of scanning after therapeutic interventions, and use of techniques to prevent brown fat uptake are essential for providing the oncologist with accurate information.

Abbreviations: CNS = central nervous system, FDG = 2-[fluorine-18]fluoro-2-deoxy-D-glucose, MALT = mucosa-associated lymphoid tissue, MZL = marginal zone lymphoma, NHL = non-Hodgkin lymphoma, PET = positron emission tomography, SUV = standardized uptake value

RadioGraphics 2010; 30:269–291 • **Published online** 10.1148/rg.301095088 • **Content Codes:** CT NM OI

[1]From the Department of Radiology, Division of Nuclear Medicine, Jackson Memorial Hospital, University of Miami and Miller School of Medicine, 1080 NW 19th St, 2nd Floor DTC, Miami, FL 33136. Presented as an education exhibit at the 2008 RSNA Annual Meeting. Received April 8, 2009; revision requested May 19 and received June 15; accepted June 22. All authors have no financial relationships to disclose. **Address correspondence to** F.M.P. (e-mail: *fpaes@med.miami.edu*).

The Editor has no relevant financial relationships to disclose.

Introduction

Lymphoma comprises a histologically heterogeneous group of cancers derived from the cells of the immune system, representing approximately 5% of all cancers in the United States at an annual healthcare cost of $4.6 billion. It is estimated that a total of 20,510 deaths will occur due to Hodgkin disease and non-Hodgkin lymphoma (NHL) in 2008 (1). The hallmark of the disease is the enlargement and proliferation of lymph nodes or secondary lymphoid tissues. Although rare, both NHL and Hodgkin disease may arise from or involve almost any organ of the human body. The term *extranodal lymphoma* has been used to describe this uncommon form of lymphoid malignancy, in which there is neoplastic proliferation at sites other than the expected native lymph nodes or lymphoid tissues. Distribution among the nonlymphoid tissues is uneven, with greater predilection for some organs than for others, and includes the gastrointestinal tract, head and neck (Waldeyer ring), orbit, central nervous system (CNS), lung, bone, and skin. The prevalence and distribution among organs vary significantly depending on histologic type and disease stage.

The observed rising incidence of NHL and Hodgkin disease in the past 2 decades has been characterized by a marked increase in the occurrence of extranodal lymphoma (2–4). A retrospective review of 3556 cases of NHL revealed that nearly one-third of all cases were extranodal in origin, giving a world standardized incidence of $1.9/10^5$ persons per year (3). The most common sites of involvement were the skin, stomach, and small intestine, with high-grade histologic types predominantly seen (3). The acquired immunodeficiency syndrome epidemic, indolent viral infections (eg, Epstein-Barr virus), altered environmental exposures, and increasing use of immunosuppressive drugs in transplant recipients and patients with collagen vascular disease may, to some extent, explain the changes in the pathophysiologic features and spread of lymphoma, which have led to more extensive extranodal involvement (2).

The presence of extranodal disease also has prognostic implications. Whenever there is secondary involvement of extranodal sites (excluding the spleen) distant from primary nodal disease, the disease is considered to be stage III or IV. However, in patients who present with primary extranodal disease, the disease can still be categorized as stage I or II. In a large series of 91,306 cases, Glass et al (5) found that patients with NHL arising from lymph node sites tended to present with more advanced disease (55.8% with stage III or IV disease), whereas patients with primary extranodal disease and non–lymph node sites presented at an earlier stage (64.7% and 74.0% with stage I and stage II disease, respectively).

The diagnosis of primary versus secondary extranodal lymphoma remains challenging, particularly due to a variety of clinical manifestations, varying metabolic behavior among the histologic types, and (often subtle) anatomic changes at routine radiologic studies. The limitations of conventional cross-sectional imaging, particularly computed tomography (CT), for staging, restaging, and treatment response assessment in all forms of lymphoma are well recognized (6). The routine use of 2-[fluorine-18]fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) in the past decade in the visualization of metabolically active tumor cells has become important in the assessment of lymphoma patients, with FDG PET having clear advantages over contrast material–enhanced CT. FDG PET/CT is now the imaging modality of choice for staging and follow-up in Hodgkin disease and most NHLs. Nevertheless, FDG PET/CT has its limitations, and a familiarity with different extranodal manifestations is crucial for correct image interpretation.

In this article, we review the usefulness of FDG PET/CT in the evaluation of extranodal manifestations of Hodgkin disease and NHL. We discuss and illustrate the common and uncommon extranodal sites of involvement in the human body, with particular attention given to FDG PET/CT findings. In addition, we discuss common false-positive and false-negative findings and various techniques that are available to reduce known pitfalls.

Usefulness of FDG PET/CT in Lymphoma

FDG PET has been widely used for staging of disease, detection of recurrence, and monitoring of treatment response in patients with Hodgkin disease and NHL (7). In the past, the imaging evaluation and follow-up of lymphoma patients was based solely on findings at contrast-enhanced CT. However, contrast-enhanced CT has limited sensitivity in detecting lymphomatous involvement of normal-sized lymph nodes, bone marrow, spleen, and extranodal tissues.

Several studies have shown the value of FDG PET/CT for staging, restaging, and therapy moni-

Table 1
Sensitivity and Specificity of PET/CT and Contrast-enhanced CT for Staging, Restaging, and Detection of Extranodal Lymphoma in NHL and Hodgkin Disease

	Staging		Restaging			Detection of ENL	
Modality	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Accuracy (%)	Sensitivity (%)	Specificity (%)
PET/CT	97	100	96	99	98	88	100
Contrast-enhanced CT	87	85	61	89	84	50	90

Sources.—References 8, 9, 12, and 15.
Note.—ENL = extranodal lymphoma.

toring (8–12). A recent meta-analysis conducted with patient-based data showed a median sensitivity of 90.3% and a median specificity of 91.1% for lymphoma staging with dedicated PET (13). The false-positive rate and maximum accuracy were 10.3% and 87.8%, respectively (13). The addition of CT for anatomic correlation in the newer PET/CT systems has improved staging sensitivity and specificity. In a recent systematic review, the overall sensitivity and specificity of FDG PET/CT for initial staging of NHL and Hodgkin disease were 97% and 100%, respectively (12).

There are also substantial data on the use of FDG PET for therapy response assessment in Hodgkin disease and aggressive NHL at the conclusion of first-line, salvage, or high-dose therapy (9). The reported pooled sensitivity and specificity for the detection of residual disease after completion of first-line therapy are 84% and 90%, respectively, for Hodgkin disease, and 72% and 100%, respectively, for aggressive NHL (14). FDG PET/CT is extremely useful for therapy response assessment due to its capacity to help distinguish between residual metabolically active tumor and areas of necrosis and fibrosis.

FDG PET/CT has also proved superior to conventional CT in the staging and restaging of NHL and Hodgkin disease (15). NHL can be upstaged with PET/CT in 31% of cases and downstaged in 1% relative to CT findings. In 25% of patients, the treatment approach is changed on the basis of additional PET/CT findings. Hodgkin disease can be upstaged with PET/CT in 32% of cases and downstaged in 15% (11). In NHL, upstaging with PET/CT is evident mostly for stages I and II. The addition of PET/CT to CT changes the treatment strategy in approximately one-fourth of NHL patients and one-third of Hodgkin disease patients and may obviate diagnostic CT in the majority of patients (11). Overall, lymphoma can be correctly staged with FDG PET/CT (93.8% of cases) more often than with conventional diagnostic methods (ie, contrast-enhanced CT and bone marrow biopsy) (89.2%) (16).

The advantages of FDG PET/CT for the staging and restaging of both NHL and Hodgkin disease are mostly attributed to the detection of FDG-avid, normal-sized lymph nodes (usually <1 cm), and of extranodal sites that were previously missed at CT (most commonly the liver, spleen, cortical bone, bone marrow, and skin). In a few cases, paraspinal and pulmonary lesions that were interpreted as benign at CT are seen to be malignant at FDG PET/CT. The overall sensitivity and specificity of PET/CT and contrast-enhanced CT for staging, restaging, and extranodal detection are shown in Table 1 (15,17).

Teaching Point

The current revised response criteria (18,19) suggest the following indications for PET in lymphoma:

1. PET is routinely recommended for the staging of patients with FDG-avid, potentially curable lymphomas (eg, diffuse large B-cell lymphoma and Hodgkin disease) to more accurately delineate disease extent.

2. PET is not routinely recommended prior to treatment for incurable, non-FDG-avid or indolent histologic subtypes (eg, grade 1 follicular lymphoma and mantle cell lymphoma) or for most lymphomas with variable FDG activity, unless the medical oncologist is seeking to assess response to chemotherapy regimens or newer experimental drugs.

3. Midtreatment PET should be performed only as a part of clinical trials.

Teaching Point

FDG Avidity in Various Histologic Subtypes

NHL and Hodgkin disease comprise a very heterogeneous group of malignancies with variable FDG avidity patterns. In cases in which FDG PET/CT is used for imaging lymphoma, the tumor being evaluated must demonstrate significant FDG avidity for proper assessment. Although this information may be inferred from past histologic data, it is desirable to obtain a baseline scan to assess disease extent and to establish the degree and intensity of FDG uptake in lymphoma sites in a given patient; this should always be done when FDG PET/CT will be used for follow-up and treatment response assessment.

The intensity of FDG uptake in lymphoma is determined by many factors, including histologic features (Hodgkin disease versus NHL), grade (indolent versus aggressive NHL), viable tumor cell fraction, tumor cell proliferation, upregulation of glucose metabolism, salvage pathways and tumor-specific pathways, local perfusion (which determines substrate delivery to the cancer cell), and the presence of hypoxia. Because FDG uptake is a multifactorial process, it should not be surprising that there is (sometimes considerable) heterogeneity between lesions of the same histologic subtype and overlap between tumor grades. It has been clearly established that changes in FDG uptake reflect a response to chemotherapy, and that residual abnormal FDG uptake after completion of chemotherapy helps identify patients with a poor prognosis (20). It is less clear what degree of change in FDG uptake should be expected during chemotherapy: In addition to varying with the number of treatment cycles after which imaging is performed, this parameter is likely to vary (qualitatively or quantitatively) with tumor histologic features (generally more rapid response in Hodgkin disease than in aggressive NHL), histologic subtype (large B-cell lymphoma versus other aggressive NHLs), and treatment regimen.

In general, many studies have shown that low-grade or indolent lymphomas are less FDG avid than are high-grade or aggressive types (21). In NHL, diffuse large B-cell lymphoma and grade 2 or 3 follicular lymphoma demonstrate the highest FDG metabolism. This usually translates into a threefold higher standardized uptake value (SUV) than in a low-grade follicular, marginal zone, or small cell lymphoma, in which the SUVs tend to be lower (22). For Hodgkin disease, although less data exist, some authors have shown a significant difference in FDG avidity among the histologic subtypes, with the nodular sclerosis subtype having the highest SUV and the lymphocyte predominance subtype having the lowest SUV. There is very limited experience with the FDG PET/CT evaluation of T-cell lymphomas (23). Although the most recent data show a higher rate of FDG-positive T-cell lymphoma, a wide range of SUVs among the different histologic subtypes and no significant management changes have been documented in lymphoma staged with PET (24). Table 2 summarizes the most common patterns of FDG avidity among the various histologic subtypes of Hodgkin disease and NHL (23–25).

Marginal Zone Lymphoma

Particular attention should be given to MZLs due to their common extranodal manifestation, the heterogeneity of their FDG avidity, and the extensive controversy in the literature regarding the usefulness of FDG PET/CT for their evaluation. MZL represents a subgroup of indolent B-cell neoplasms and is the third most commonly encountered NHL. There are three distinct subtypes of MZL: MALT MZL, splenic MZL, and nodal MZL. The reported sensitivity of PET for the evaluation of MZL ranges from 0% to 81% (26).

MZL frequently arises in organs of the gastrointestinal tract, which normally demonstrate physiologic FDG uptake. The indolent nature of this disease (low FDG avidity), together with diffuse physiologic background FDG uptake in the gastrointestinal tract, limits the usefulness of PET for the evaluation of these tumors. However, when MZL manifests with nodal disease and involves other extranodal sites such as the lungs, PET/CT has proved useful and reliable for initial staging and posttherapy follow-up.

In patients with biopsy-proved MZL, the most common sites of involvement identified at PET/CT are the stomach, lung, orbit, and parotid gland. PET/CT can help detect active disease in up to 54.5% of all patients at diagnosis, with differing sensitivities among various organs and stages. Sensitivity for gastric involvement (38.9%) is lower than that for involvement of the lung and

Table 2
FDG Uptake in Various Histologic Subtypes of NHL and Hodgkin Disease

Subtype	Uptake
B-cell NHL*	
Diffuse large B-cell lymphoma	High
Burkitt lymphoma	High
Large cell and anaplastic lymphoma	High
Follicular lymphoma (grade 3)	Moderate to high
Follicular lymphoma (grades 1 and 2)	Low to moderate
Mantle cell lymphoma	Low to moderate
Marginal zone lymphoma (MZL) (including mucosa-associated lymphoid tissue [MALT])	None to high
Small lymphocytic lymphoma	None to low
Hodgkin disease†	
Nodular sclerosis type	High
Mixed cellularity type	Moderate to high
Lymphocyte depletion type	Moderate to high
Lymphocyte predominance type	Low
T-cell lymphoma‡	
Extranodal natural-killer/T-cell lymphoma	High
Peripheral T-cell lymphoma	High
Adult T-cell leukemia-lymphoma	Moderate
Cutaneous T-cell lymphoma	Moderate
Mycosis fungoides and Sézary syndrome	Low

Note.—There is a wide range of reported maximum SUVs in patients with similar lymphomas. Usually, visual comparison of the described FDG focus with the blood pool and liver is sufficient to correctly characterize the uptake as low (isointense relative to the blood pool), moderate (nearly isointense relative to the normal hepatic parenchyma), or high (hyperintense relative to the hepatic parenchyma and blood pool). This table provides only a relative assessment of FDG uptake among the histologic subtypes of lymphoma according to the available literature.
*Sources.—References 20, 21.
†Sources.—References 20, 22.
‡Source.—Reference 23.

parotid gland (100%). PET/CT helps detect active disease in up to 100% of patients with advanced (stage III or IV) disease but in only 42.3% with early-stage (stage I or II) disease (26). Note that the site of involvement appears to be more important than the histologic subtype in determining the usefulness of PET/CT in cases of MZL (26).

Potential Pitfalls of PET/CT

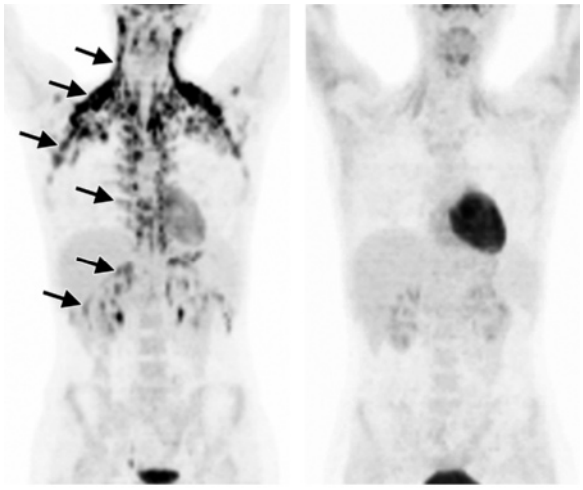
Multiple confounding factors may lead to the erroneous interpretation of a PET/CT study, resulting in a high number of false-positive findings, particularly at posttherapy assessment. Potential imaging pitfalls include brown fat FDG uptake, bone marrow and splenic activation, and recent therapeutic intervention (eg, surgery, radiation therapy, or chemotherapy).

In one study, up to 45% of patients who underwent PET for tumor evaluation had FDG uptake in areas consistent with hypermetabolic brown fat (27). In contrast to white adipose tissue, which is characterized by low metabolism and energy storage function, brown fat is a metabolically active tissue that is responsible for thermogenesis rather than fat storage. This activity is commonly seen at FDG PET/CT in children and

Table 3
Strategies for Decreasing Brown Fat FDG Uptake

Controlled-temperature (warm) environment for patients before FDG injection* (provide blankets if necessary)
High-fat, low-carbohydrate, protein-permitted diet before the examination†
Moderate dose of oral diazepam (>0.8 mg/kg, maximum of 7.5 mg) or intravenous fentanyl (0.75 μg/kg, maximum of 50 μg)‡
Low dose (20 mg) of oral propanolol 60 min before FDG injection§

*Source.—Reference 29.
†Source.—Reference 30.
‡Source.—Reference 31.
§Source.—Reference 32.



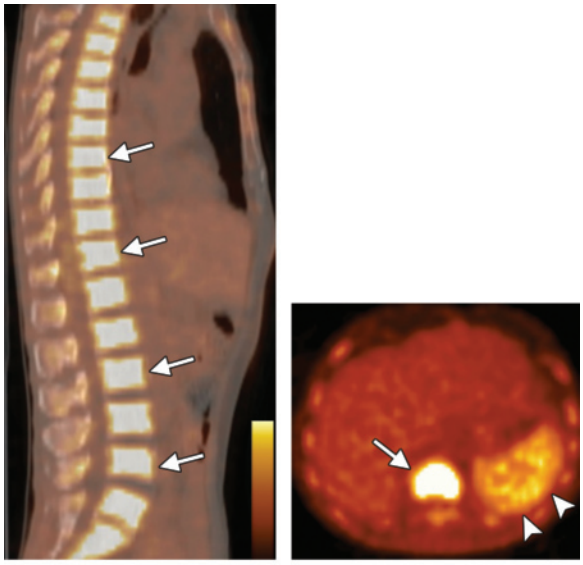
a. b.

Figure 1. Hypermetabolic brown fat in a 24-year-old woman with a history of diffuse large B-cell lymphoma of the neck. **(a)** Three-dimensional maximum intensity projection image from PET/CT data obtained at the end of therapy shows diffuse symmetric FDG uptake in the neck and in the supraclavicular and paraspinal regions (arrows), findings that are highly suggestive of brown fat activity. The first study was obtained in a routine temperature-controlled ("warm") environment, and even then, there was significant brown fat activity, so that evaluation for residual metabolically active disease in the neck was significantly limited. **(b)** Fused PET/CT image obtained 1 week later, again in a warm environment but now with the administration of a low dose of propranolol 60 minutes prior to FDG injection, shows resolution of the brown fat activity and no evidence of residual disease.

young adults who have been exposed to a cold environment and quite often (but not always) manifests as symmetric high uptake in the suboccipital, cervical, supraclavicular, mediastinal, and paraspinal areas (Fig 1). Nevertheless, this pattern of FDG distribution can mimic or obscure malignant lymphadenopathy at PET if no correlation with CT findings is made. Site-by-site comparison of such findings with CT findings can ameliorate this confusion because low-attenuation brown fat can be distinguished from soft-tissue-attenuation lymph nodes. Furthermore, with combined PET/CT, the misinterpretation of brown fat activity as malignant is less likely, since corresponding low-attenuation areas can be identified on the coregistered CT scans. In those rare instances in which correct metabolic-anatomic correlation remains difficult, misinterpretation as nodal and extranodal uptake may persist, leading to false-positive results. In such cases, brown fat uptake can be misidentified as adjacent soft-tissue, thymic, lung, or muscular involvement by lymphoma. The presence of brown fat can also decrease tumor uptake by decreasing the pool of FDG available for the tumor tissues (28). The strategies that are available for decreasing brown fat FDG uptake are listed in Table 3 (29–32). No single technique is capable of completely blocking brown fat uptake, and sometimes a combination of methods should be attempted.

Teaching Point

Bone marrow involvement is indicative of a worse prognosis in patients with lymphoma. Although PET has proved superior to CT and equivalent to bone marrow biopsy for the detection of bone marrow involvement in lymphoma patients, the development of diffuse bone marrow activation in the weeks following chemotherapy and the use of growth factors constitutes a known limitation in making the correct diagnosis. The pattern of FDG uptake in bone marrow activation is typically diffuse, involving the axial skeleton in a symmetric fashion and, sometimes, the spleen and thymus (Fig 2). It is important to know when the patient received treatment, par-



a. b.

Figure 2. Bone marrow and splenic activation in a 50-year-old man who had completed R-CHOP (rituximab, cyclophosphamide, vincristine, doxorubicin, and prednisone) chemotherapy for large cell lymphoma 4 weeks earlier. Sagittal fused PET/CT image **(a)** and axial PET scan **(b)** show diffuse reactive bone marrow activity (arrows) and hematopoietic expansion in the spleen (arrowheads in **b**). Hematopoietic expansion is an expected finding in patients after chemotherapy, particularly after the use of colony-stimulating factors, and represents the active recovery process of dormant progenitor cells in the primary (bone marrow) and secondary (spleen and thymus) lymphoid organs. The combination of diffuse uptake in the spleen with diffuse bone marrow uptake favors a diagnosis of hematopoietic expansion rather than splenic involvement by lymphoma.

ticularly treatment with colony-stimulating factors, and to understand that diffusely increased FDG uptake in the bone marrow may persist for more than 4 weeks after treatment. The presence of bone marrow activation also limits the ability to identify cortical bone, anterior mediastinal (thymic) involvement, and diffuse splenic involvement. Nevertheless, whenever the distribution of FDG uptake becomes more multifocal and heterogeneous, the presence of lymphomatous involvement should be suspected.

As previously described, PET/CT is an accurate method for evaluating tumor viability in the posttherapy setting. However, appropriate timing of the procedure is fundamental in preventing false-positive or false-negative results. Recent therapeutic intervention may lead to inaccurate results due to nonspecific changes caused by accumulation of inflammatory cells removing the debris of dead tumor cells, "flare phenomena," or "stunning" of the residual tumor cells. The recommended timing for performing end-of-therapy PET varies with the treatment modality. Posttherapy PET should be performed at least 4–6 weeks after surgery or chemotherapy and 8–12 weeks after external beam radiation therapy or radioimmunotherapy (20,33,34). These waiting times represent a trade-off between a reliable clinical response and the chances of false-positive and false-negative findings. Whenever there is a question regarding a possible nonspecific inflammatory finding, it may be pertinent and helpful to perform repeat PET/CT a few weeks later.

Teaching Point

Pertinent clinical information and adherence to a standardized protocol are crucial to ensure accurate interpretation. There should be consistency between baseline and follow-up studies in terms of patient preparation, image acquisition, and processing. This is particularly important for reliable comparison and quantitative analysis. Generally, patients undergoing PET/CT must fast for 4–6 hours and their measured serum glucose level must be less than 200 mg/dL (11 mmol/L) prior to FDG administration. Diabetic patients should not receive short-acting insulin on the day of the study, and if the serum glucose level exceeds the aforementioned limit, the study should be rescheduled. PET/CT should be started 50–70 min after FDG administration.

Visual-only evaluation of the images can be used for accurate interpretation; however, quantitative analysis using SUV measurement has been shown to have additional prognostic value in the assessment of early treatment response (35). Although maximum SUVs normalized for body surface area or total body weight are widely used quantitative measures of FDG uptake, other methods such as peak SUV normalized for lean body mass and total lesion glycolysis have been recently proposed in the PERCIST (PET Response Criteria in Solid Tumors) criteria (36). The use of a standardized protocol is also essential to properly assess treatment response and to allow data comparison in multicenter trials (36,37).

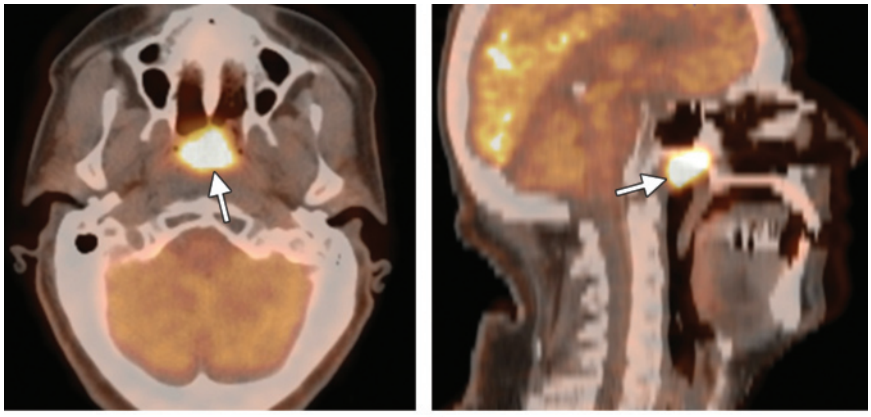


Figure 3. Primary diffuse large B-cell carcinoma of the nasopharynx. Axial **(a)** and sagittal **(b)** fused PET/CT images show fullness of the nasopharynx with a focus of abnormally increased FDG uptake (arrow). Note the absence of FDG activity in the tonsils and cervical lymph nodes. The most important possibility in the differential diagnosis in such cases is carcinoma of the nasopharynx.

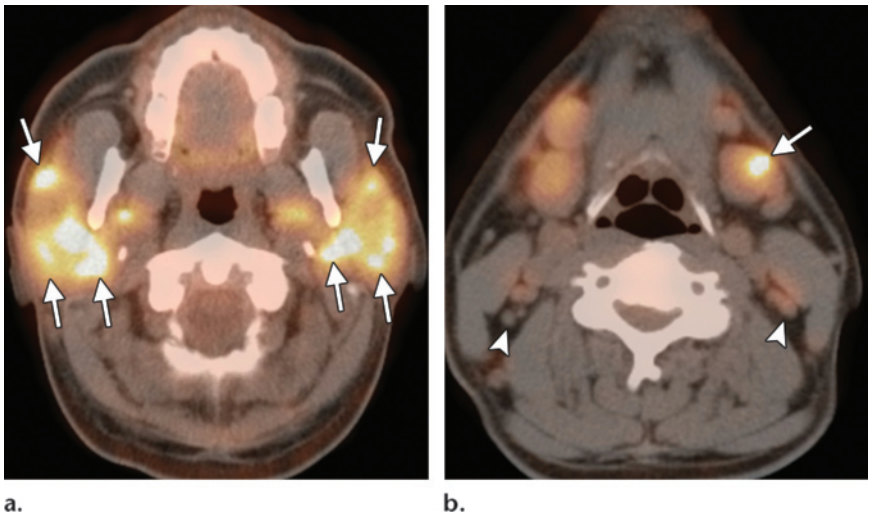


Figure 4. Primary follicular lymphoma of the parotid and submandibular glands. Axial fused PET/CT images show multifocal areas of abnormal FDG uptake in the parotid glands (arrows in **a**) and left submandibular gland (arrow in **b**). Mildly FDG-avid bilateral subcentimeter level II cervical nodes are also noted (arrowheads in **b**).

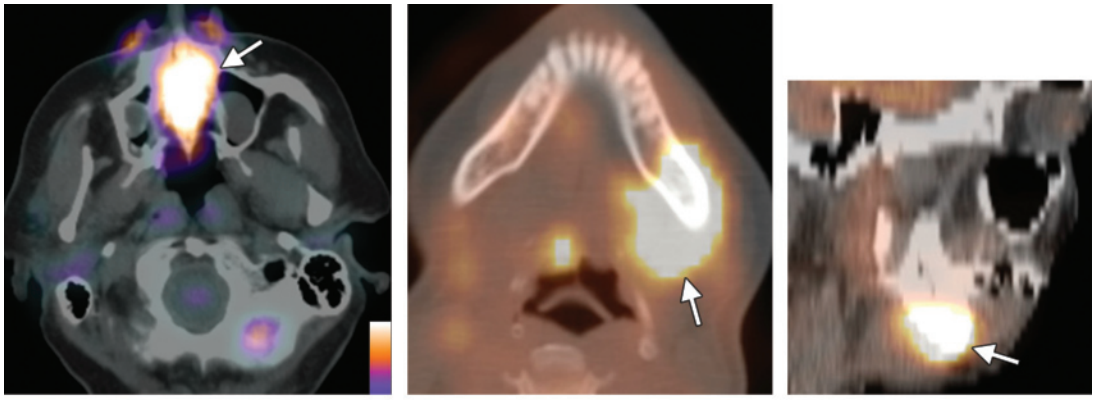
Extranodal Lymphoma

Lymphoma of the Head and Neck

The head and neck region is the second most common site of NHL. Primary head and neck extranodal lymphoma accounts for up to 20% of all NHL cases and can arise from the tonsils, mandible, hard palate, nasopharynx, parotid glands, nasal cavity, paranasal sinuses, pharynx, larynx, thyroid gland, and ocular adnexa.

The Waldeyer ring is the primary site of NHL in approximately one-third of all cases of extranodal disease (33,38). Whether the Waldeyer ring should be considered a nodal or an extranodal site is still controversial. The most common type of lymphoma involving the head and neck region is diffuse large B-cell lymphoma (39). Several studies have classified diffuse large B cells in the Waldeyer ring as extranodal disease (38,40,41). High FDG uptake is associated with a high proliferation rate, and the higher the SUV of a diffuse large B-cell lesion in the head and neck region, the worse the clinical outcome (38).

Physiologic or reactive FDG uptake is commonly seen in the lymphatic structures of the head and neck (Waldeyer ring, lymph nodes, and lymphatic channels), usually representing an accumulation of FDG within macrophages and lymphocytes. Often, the interpretation is not difficult, especially when the uptake is mild and symmetric without corresponding anatomic abnormalities (42). Other organs, such as the salivary glands, muscles, blood vessels, vocal cords, and thyroid gland, can demonstrate variable physiologic FDG avidity, and the corresponding CT portion of the FDG PET/CT study is essential for localization



5. 6a. 6b.

Figures 5, 6. **(5)** Large cell lymphoma in a patient who presented with a shallow ulcer in the hard palate. Axial fused PET/CT image shows a large focus of abnormally increased FDG uptake in the hard palate (arrow), a finding that is suggestive of squamous cell carcinoma. However, histologic analysis of a biopsy specimen demonstrated non-Hodgkin large cell lymphoma. **(6)** Primary T-cell lymphoma of the mandible in an immunocompromised (human immunodeficiency virus–positive) patient who presented with trismus and a left mandibular mass. Axial **(a)** and sagittal **(b)** fused PET/CT images show a large focus of FDG accumulation in the left mandibular angle and ramus (arrow).

and identification (43). Infection, or inflammation that may or may not be due to recent surgery, chemotherapy, or radiation therapy, can also result in FDG accumulation and should be taken into account in the interpretation of FDG-avid lesions in the head and neck (43).

Unsuspected nasopharyngeal involvement may be seen in up to 41% of patients with head and neck lymphoma (Fig 3). Lymphoma involving the nasopharynx tends to extend into the airways and tonsils, as opposed to carcinoma or sarcoma of the nasopharynx, which tend to extend cranially into the base of the skull. Extranodal natural-killer/T-cell lymphoma is a distinct clinical entity that accounts for 9% of all malignant lymphomas and 74% of lymphomas arising from the nasal cavity and paranasal sinuses. Nasal type natural-killer/T-cell lymphomas are highly aggressive and demonstrate frequent distant relapse. They are hypermetabolic tumors, and FDG PET can be successfully used for the detection of local and distant disease (44).

Primary NHL of the salivary glands is relatively uncommon and most often occurs in the parotid gland (Fig 4). The most common subtype is MALT MZL; this subtype typically arises in association with a benign lymphoepithelial lesion or myoepithelial sialadenitis, which is associated with Sjögren syndrome. Secondary involvement of the parotid gland is more commonly seen in diffuse large B-cell or follicular lymphomas. Primary extranodal NHL of the hard palate accounts for 6% of all primary extranodal lymphomas of the head and neck (45) and usually has B-cell histologic features (Fig 5). Lymphomatous involvement of the mandible is rare and can manifest as various NHL histologic subtypes (Fig 6). Because of the volume of medullary bone, the body of the mandible is the most common site of involvement (46).

Primary lymphoma of the thyroid gland is rare, with only about 2% of extranodal lymphomas arising within this gland. Thyroid lymphomas are typically NHL and of B-cell lineage, whereas Hodgkin disease of the thyroid gland is exceptionally rare. Nearly 80% of thyroid lymphomas are diffuse large B-cell lymphomas. FDG uptake is usually low to absent in the normal thyroid tissue (47). At FDG PET/CT, lymphoma of the thyroid gland may manifest as diffusely increased uptake or a focal lesion. However, both manifestations are nonspecific and can be attributed to other conditions. Focal thyroid FDG uptake has been associated more with primary thyroid malignancy. Papillary thyroid cancer is commonly seen in up to one-half of cases in which incidental focal thyroid FDG uptake has been identified (48). Furthermore, diffusely increased FDG accumulation in the thyroid gland is associated with chronic lymphocytic thyroiditis (Hashimoto disease) (49).

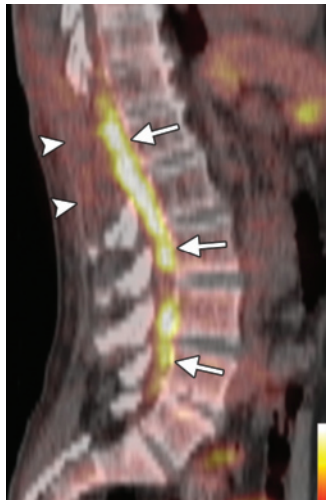


Figure 7. Relapsed-refractory diffuse large B-cell lymphoma in a patient who had undergone successful treatment for a spinal cord mass with external beam radiation therapy and decompressive laminectomy 2 years earlier. The patient presented with severe back pain and bilateral lower extremity weakness 50 days after undergoing miniautologous bone marrow transplantation. Initial MR imaging of the lumbar spine showed persistent unchanged thickening of the distal spinal cord and cauda equina. Sagittal fused PET/CT image shows intense FDG accumulation along the distal spinal cord and cauda equina (arrows), findings that are consistent with the recurrence of lymphoma. Arrowheads indicate the region of the decompressive laminectomy.

Ocular adnexal lymphoma represents 8% of all extranodal lymphomas. In a retrospective study of 11 patients with ocular adnexal lymphoma, FDG PET proved valuable in helping identify extranodal lymphomatous sites not detected at conventional imaging (50). Nevertheless, FDG PET was somewhat limited for assessing orbital lesions due to the small volume of the orbital deposits and the proximity of the lesions to physiologic background FDG activity in the brain and ocular muscles (50).

CNS Lymphoma

CNS lymphoma accounts for 1%–4% of all malignant brain tumors. The reported prevalence of CNS involvement in patients with nodal or extranodal lymphoma is less than 20%. Primary CNS lymphoma has become more common, representing 4%–7% of newly diagnosed primary CNS tumors (51). Because of the intense physiologic FDG uptake in the brain cortex, detection of intracranial lymphomatous involvement is difficult. Moreover, steroid therapy, which is given to most patients with suspected brain involvement, may interfere with the uptake of FDG and possibly lead to false-negative results (33). More often than not, intracranial lymphoma is evaluated with contrast-enhanced CT and magnetic resonance (MR) imaging (51). MR imaging is very useful in the primary diagnosis and therapy monitoring in patients with primary CNS lymphoma in the brain and spinal cord. Nevertheless, in the follow-up of patients with primary CNS lymphoma who have completed chemotherapy, MR imaging findings can be falsely positive. In such cases, FDG PET can provide additional information that helps correctly identify recurrence or exclude disease (Fig 7) (52). Systemic spread of primary CNS lymphoma, although rare, is important to identify because it can alter therapeutic management.

Lymphoma of the Chest Wall, Lung, and Pleura

Lymphoma in the thorax may involve the lung, pleura, chest wall, heart, thymus, and breast. Intrathoracic involvement is more common in Hodgkin disease than in NHL. Pulmonary involvement is more commonly seen in secondary than in primary lymphoma. Hodgkin disease of the lung parenchyma is relatively rare and is usually due to direct extension from mediastinal nodal disease (Fig 8). Secondary involvement due to direct hilar extension is also the most common type of pulmonary NHL involvement, and the diffuse large B-cell histologic subtype is the one most frequently seen. The CT appearance of pulmonary lymphoma can vary and may include direct extension from nodal disease, central ill-defined nodules, or rounded-segmental consolidation with air bronchogram (53). When FDG PET/CT is performed for staging, increased FDG uptake in lung lesions or extending from involved lymph nodes into the parenchyma can be interpreted as lymphomatous involvement, a benign condition (granulomatous disease), or, less likely, a second primary lesion. At post-therapy scanning, the presence of FDG uptake in the lung represents a challenge, since it may be related to concomitant benign conditions such as

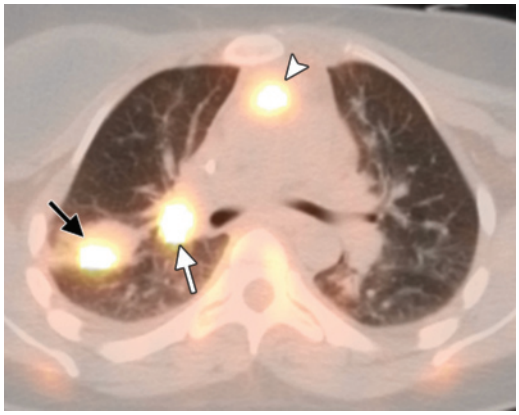


Figure 8. Mixed cellularity type Hodgkin disease with lung and mediastinal involvement. Axial fused PET/CT image shows foci of abnormal FDG uptake in a right lung mass along the major fissure (black arrow), the thymus (arrowhead), and enlarged right hilar lymph nodes (white arrow). In both Hodgkin disease and NHL, secondary lung involvement is more common than primary pulmonary disease and is characterized by lymphomatous extension from pathologic mediastinal nodes to the lung parenchyma.

pneumonia, chemotherapy-associated pneumonitis, radiation-induced changes, opportunistic infections, or bronchiolitis obliterans with organizing pneumonia (54). New lung nodules in patients with no pretherapy evidence of pulmonary lymphoma, having a size greater than 1.5 cm and FDG uptake higher than that of the mediastinal blood pool, should be considered suggestive of lymphoma (19). In the interim, if there is evidence of complete response in all the previously known disease sites, such nodules should be considered negative for lymphoma and as most likely representing infectious or inflammatory lesions (19). Chest wall involvement has been reported in 6% of patients with Hodgkin disease (33) and is usually due to direct extension from nodal anterior mediastinal disease. FDG PET/CT may improve the identification of chest wall invasion by allowing correct localization of an FDG-avid lesion on the CT scans.

Pleural effusion in patients with lymphoma may be either due to actual pleural disease or reactive in nature. At CT, pleural involvement can be seen as pleural effusion, plaques, discrete pleural nodules, or a combination thereof, and may not be fully appreciated. FDG PET/CT is instrumental in helping develop the differential diagnosis by aiding in identifying and localizing foci of disease activity, particularly with accurate anatomic correlation of the FDG-avid lesions.

Lymphoma of the Heart

Cardiac or epicardial-pericardial lymphomatous involvement is rare and can result from retrograde lymphatic spread, hematogenous spread, or direct extension from adjacent masses (53). Lymphomatous involvement of the heart can be mistaken for normal FDG-avid myocardium on a PET study; therefore, FDG PET scans coregistered with CT scans are very helpful in localizing an avid lesion in the myocardium. Documentation of cardiac NHL involvement mimicking ischemic heart disease at FDG PET has been reported in immunocompromised patients following heart transplantation (55). Although very rare, Hodgkin disease involvement of the heart and pericardium has also been demonstrated at FDG PET (56). Pericardial effusion in patients with large mediastinal masses can easily be depicted with CT; it is usually reactive in nature and resolves after chemotherapy. Lymphomatous pericardial effusion with high FDG uptake has also been described (57).

Lymphoma of the Thymus

In Hodgkin disease, thymic involvement does not alter disease staging, since the thymus is considered to be a "nodal organ." Thymic enlargement is common in patients with Hodgkin disease and is most often attributed to thymic hyperplasia, a benign, usually moderately FDG-avid condition that appears during or after chemotherapy and can be observed in children, young adults, and even 40-year-old patients (58). Thymic hyperplasia must be considered when evaluating FDG-avid anterior mediastinal lesions in patients treated for lymphoma, since this entity may be mistaken for disease recurrence. Thymic FDG uptake can be seen in up to 23% of patients with lymphoma (58). Thymic hyperplasia can demonstrate variable FDG avidity, depending on the time interval between chemotherapy and imaging. High thymic FDG avidity in lymphoma patients who have completed chemotherapy may decrease or disappear at repeat imaging performed several weeks later. Active disease in an

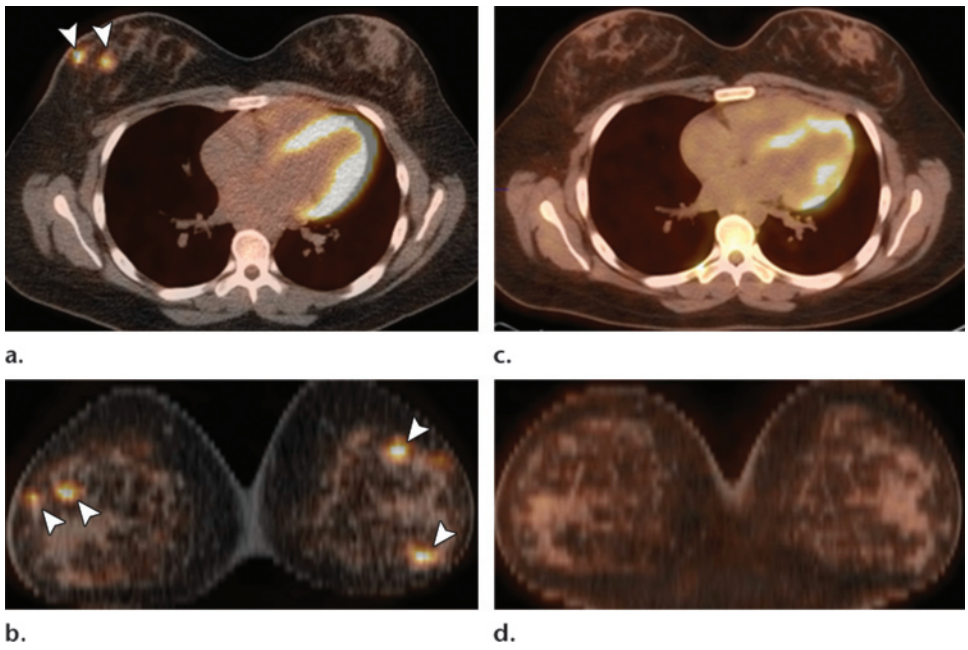


Figure 9. Burkitt lymphoma in a 20-year-old woman. **(a, b)** Pretreatment axial **(a)** and coronal **(b)** fused PET/CT images show multiple foci of abnormal FDG accumulation in both breasts (arrowheads). **(c, d)** End-of-treatment axial **(c)** and coronal **(d)** fused PET/CT images show resolution of the foci of abnormal FDG uptake.

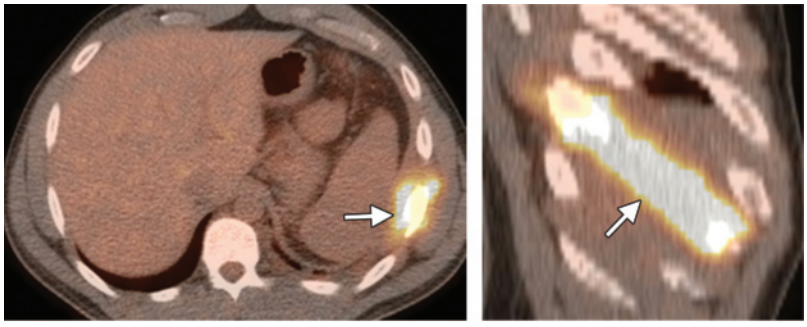
FDG-avid mediastinal mass cannot be entirely excluded (Fig 8); however, the time pattern of appearance, along with evidence or absence of disease at other sites, can be helpful. In uncertain cases, biopsy of the lesion is indicated.

Lymphoma of the Breast

Primary extranodal NHL in the breast is very rare, representing 0.5% of all breast malignancies. Bilateral primary breast lymphoma typically affects younger women and is associated with Burkitt lymphoma (Fig 9). Unilateral primary breast lymphoma manifests clinically like breast carcinoma, affects older women, and typically has B-cell histologic features. Secondary breast lymphomatous involvement in a patient with diffuse NHL is more common. Few case reports have described the FDG findings in extranodal lymphoma of the breast. Breast lymphomatous involvement is characterized by increased FDG uptake and may manifest as diffuse increased FDG accumulation in both breasts (mammographic and ultrasonographic [US] findings can be negative) (59); unilateral, ring-shaped FDG uptake in the breast tissues (60); or intense, round, homogeneous activity in a breast mass (61). FDG PET can be very useful in female patients with suspected lymphoma and dense breast tissues, since extranodal breast involvement may be missed at CT and mammography (62).

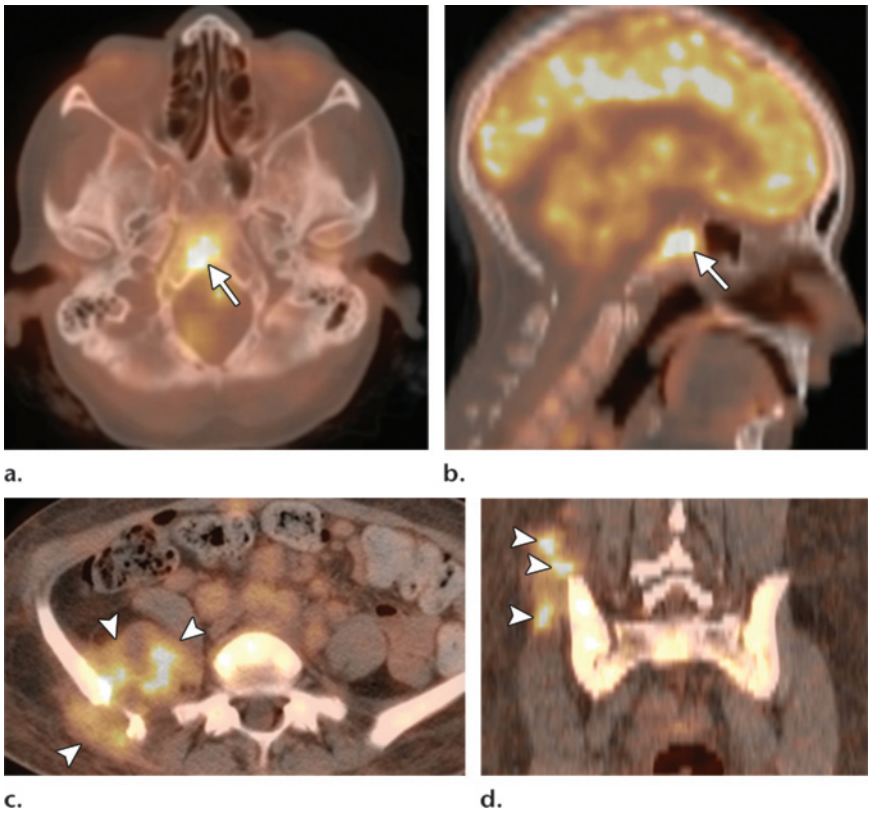
Lymphoma of the Bone

Primary lymphoma of the bone accounts for less than 5% of all bone malignancies. A lesion originating solely from the bone is considered a stage I NHL, whereas a lesion associated with disease at other sites is considered stage IV, with an entirely different prognosis. The most common osseous lymphoma, whether primary or secondary, is diffuse large B-cell lymphoma. Primary osseous NHL lymphoma arises from the appendicular skeleton or from flat bones of the axial skeleton, whereas secondary osseous disease usually involves the axial skeleton (skull, spine, ribs, and pelvis) (Fig 10). Primary Hodgkin disease of the bone is very rare, whereas secondary osseous involvement is found in 10%–25% of patients with Hodgkin disease (Fig 11) (33). The imaging features of osseous lymphoma at conventional radiography, CT, and MR imaging are nonspecific, usually reflecting an aggressive pattern of bone destruction. Identifying osteoblastic or metabolic activity can be more helpful in determining the nature of bone disease. FDG PET has proved to



a. b.

Figure 10. Primary diffuse large B-cell lymphoma of the rib in a 19-year-old male athlete who presented with posttraumatic chest wall pain after falling while playing soccer. Chest radiography showed a destructive left rib lesion. Axial **(a)** and sagittal **(b)** fused PET/CT images show intense FDG accumulation along a destructive mass of the left 10th rib (arrow). Biopsy results were compatible with diffuse large B-cell lymphoma.



a. b. c. d.

Figure 11. Nodular sclerosis type Hodgkin disease (stage IV). **(a, b)** Axial **(a)** and sagittal **(b)** fused PET/CT images show an uncommon focus of intense FDG activity in the clivus (arrow), a finding that is consistent with lymphomatous involvement. **(c, d)** Axial **(c)** and coronal **(d)** fused PET/CT images show a destructive mass arising from the right iliac crest and containing multifocal areas of high FDG accumulation (arrowheads).

be more specific and sensitive than conventional bone scintigraphy in identifying osseous involvement by malignant lymphoma (63).

Lymphoma of the Bone Marrow

Bone marrow disease is present at the time of diagnosis in approximately 50%–80% of patients with low-grade NHL, 25%–40% of those with high-grade NHL, and 5%–14% of those with Hodgkin disease (33,64). Evaluation of bone marrow involvement is essential in the management of NHL and Hodgkin disease (Fig 12). Bone marrow biopsy is considered the standard of reference for detecting bone marrow disease

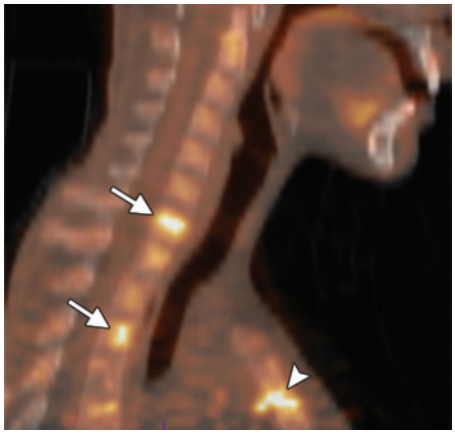


Figure 12. Nodular sclerosis type Hodgkin disease. Sagittal fused PET/CT image shows focal areas of abnormal FDG accumulation in vertebral bodies (arrows) and the sternum (arrowhead), findings that are consistent with bone marrow involvement. The diagnosis was confirmed at bone marrow biopsy.

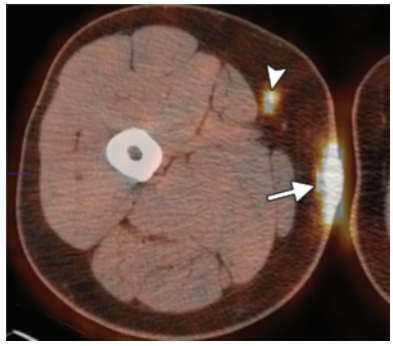


Figure 13. Primary cutaneous T-cell lymphoma. Axial fused PET/CT image shows two foci of abnormally high FDG uptake, in a thickened portion of the skin in the middle aspect of the right thigh (arrow) and in a small intradermal lymph node (arrowhead). T-cell lymphoma is the most common histologic type of primary cutaneous lymphoma and can be confined to the skin or spread to extracutaneous organs such as the lymph nodes. PET/CT is an important tool for detecting extracutaneous sites and documenting disease extent.

but can be limited due to technical issues or different patterns of bone marrow involvement at presentation. MR imaging can be very sensitive in detecting bone marrow involvement but is usually time consuming, anatomically limited, and not cost effective (33). FDG PET has been shown to be highly sensitive in the early detection of bone marrow disease (17,65). Whole-body FDG PET has additional value relative to bone marrow biopsy in detecting bone marrow disease and can also be used to guide biopsy (22,66).

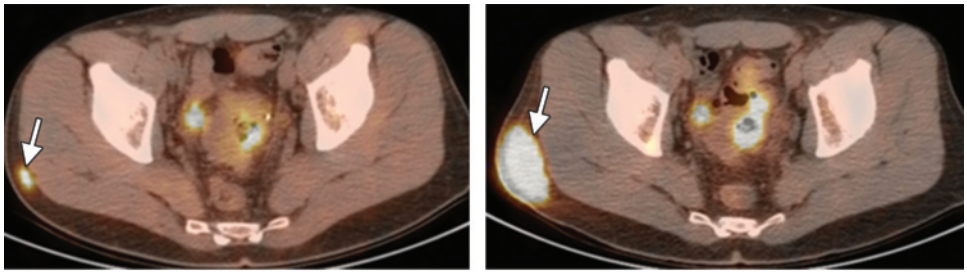
Two different patterns of bone marrow involvement have been reported (64):

1. Diffuse bone marrow disease, in which all of the bone marrow demonstrates increased abnormal FDG accumulation. This pattern can easily be confused with increased FDG uptake due to colony-stimulating factors, anemia, erythropoietin administration, or β-thalassemia.

2. Focal mono- or polyostotic bone marrow disease, in which FDG PET shows foci of increased uptake outside the dorsal iliac crest biopsy site, which could result in negative bone marrow biopsy results. In this setting, there is a high probability of bone marrow involvement, and a subsequent bone marrow biopsy should be guided appropriately. FDG PET is a complement to, not a substitute for, biopsy in evaluating bone marrow disease (64). However, FDG PET can improve diagnosis and staging and may be used to direct biopsy to foci outside the routine iliac bone marrow sampling sites (64).

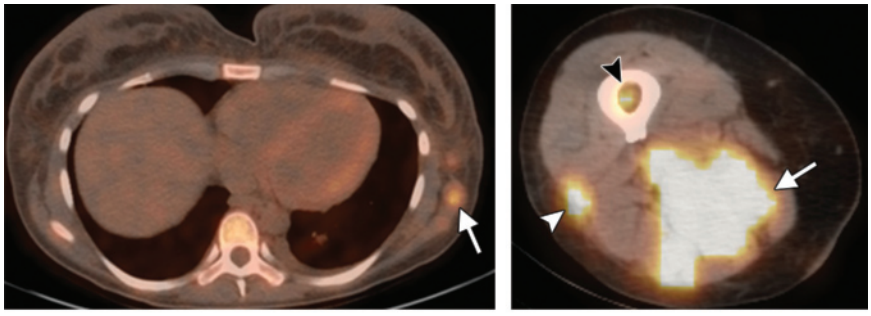
Cutaneous Lymphoma

Cutaneous lymphomas may manifest either as primary tumors or as secondary to disseminated disease. Primary cutaneous lymphoma is the second most prominent group of NHLs (67), whereas primary or secondary skin involvement is very rare in patients with Hodgkin disease. Almost 65% of primary cutaneous lymphomas are T-cell lymphomas (Fig 13), with the remainder being B-cell lymphomas. About 25% of primary cutaneous lymphomas demonstrate extracutaneous involvement at the time of diagnosis. The presence of extracutaneous disease in primary cutaneous lymphoma is important in treatment planning and in predicting prognosis at initial staging and posttherapy restaging. Cutaneous lymphoma is a heterogeneous group of diseases. It has many subtypes with variable clinical behavior, prognosis, and FDG avidity (68). FDG PET/CT can provide good metabolic and anatomic information concerning a variety of cutaneous T-cell lymphomas and may be useful in staging and in monitoring response to therapy (Fig 14) (69). In a study of patients with various subtypes of peripheral T-cell lymphoma, the sensitivity and specificity of FDG PET in detecting nodal and



a. b.

Figure 14. Large cell lymphoma in an immunocompromised patient. Axial fused PET/CT images obtained before **(a)** and 6 weeks after **(b)** EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) chemotherapy show interval worsening of a right gluteal subcutaneous soft-tissue mass with an increase in FDG uptake (arrow).



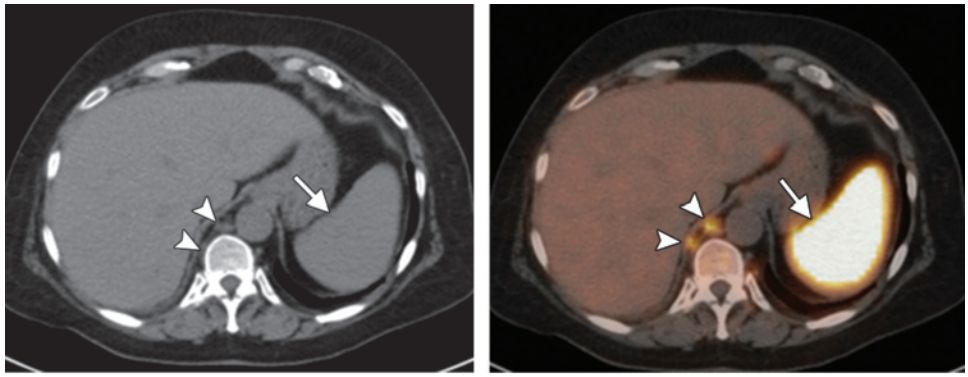
a. b.

Figure 15. Muscular involvement by lymphoma. **(a)** Lymphocyte predominance type Hodgkin disease. Axial fused PET/CT image shows a focus of mild FDG accumulation in the lateral aspect of the left latissimus dorsi muscle (arrow), a finding that was suspicious for lymphoma. Biopsy results confirmed lymphomatous involvement of the muscle. **(b)** Primary T-cell lymphoma. Axial fused PET/CT image shows a large focus of abnormal FDG accumulation in the muscles of the posterior compartment of the right thigh (arrow) and a second focus in the lateral compartment (white arrowhead). Bone marrow involvement is also noted (black arrowhead). Biopsy results confirmed lymphomatous involvement of the muscles.

noncutaneous extranodal systemic disease were 95% and 100%, respectively (70). In the same study, the sensitivity for detecting involvement at cutaneous sites in patients with early-stage (1A) peripheral T-cell lymphoma was very poor. This finding could be related to the small volume and early stage of the tumor. FDG PET may also be useful in detecting metastatic cutaneous anaplastic large cell lymphoma (71) and has proved to be more accurate than CT in detecting distant metastases from primary cutaneous lymphoma (68).

Lymphoma of the Muscle

Primary skeletal muscle lymphoma is very rare, accounting for approximately 0.3% of cases of Hodgkin disease and 1.5% of NHLs. In a 15-year series, only eight patients had primary skeletal muscle NHL, three of whom had no nodal or adjacent bone involvement (72). Primary lymphoma of the muscle has been associated with a poor prognosis and usually has diffuse large cell histologic features. However, the majority of cases of lymphomatous involvement of the muscle develop secondarily by means of hematogenous dissemination from nodal disease. Again, FDG PET is very useful in depicting lymphomatous muscle involvement and can also assist in making the correct diagnosis by guiding the radiologist to an FDG-avid biopsy site (Fig 15). A single asymmetric focus or multiple foci of abnormally increased FDG accumulation in a given muscle should raise suspicion for lymphomatous involvement, even though the muscles can accumulate variable degrees of FDG in a physiologic state.



a. b.

Figure 16. Splenic involvement by NHL. **(a)** Axial CT scan shows small retrocrural nodes (arrowheads) and a normal-sized spleen (arrow), findings that were not suspicious for lymphomatous involvement according to CT criteria. **(b)** Axial fused PET/CT image shows increased FDG activity in the spleen (arrow) and nodes (arrowheads). Note the absence of bone marrow activation. These findings are consistent with lymphoma and were confirmed at splenectomy.

Lymphoma of the Adrenal Glands

Up to 25% of patients with NHL will develop secondary involvement of the adrenal gland (33). Primary adrenal lymphoma is a very rare extranodal lymphoma, with only 70 cases having been reported in the English medical literature (73). Bilateral adrenal involvement was seen in 56 of these cases, with the most common histologic subtype being diffuse large B-cell lymphoma (73). The standard procedure for diagnosis is percutaneous biopsy, although findings at CT, MR imaging, and US may suggest involvement. FDG PET was performed for staging in a patient with biopsy-proved bilateral adrenal B-cell lymphoma and showed bilateral increased adrenal uptake, whereas the remainder of the study was negative (73). Findings at posttherapy follow-up FDG PET were also negative. Thus, the authors suggested that FDG PET may be a valuable noninvasive imaging method for diagnosis, staging, and treatment response evaluation in primary adrenal lymphoma.

Lymphoma of the Spleen and Liver

The spleen is considered an extranodal region in NHL and appears to be affected in 20% of patients. The most common histologic subtype is large cell lymphoma. In Hodgkin disease, the spleen is referred to as a nodal organ and is involved in 30%–40% of cases at presentation.

Primary splenic lymphoma is rare and has the histologic features of NHL in most cases. Organ size should not be used to assess splenic involvement in patients with lymphoma, since the spleen can be normal in size despite tumor infiltration, or may be enlarged without neoplastic involvement (33). The superiority of PET/CT over CT in detecting extranodal lymphoma in the spleen and liver remains uncontested (74,75). FDG PET/CT has an accuracy of almost 100% in diagnosing primary splenic involvement during initial staging, whereas CT alone has an overall accuracy of 57% (76). However, in the posttherapy setting, the evaluation of secondary splenic involvement is limited in some cases due to splenic activation. At FDG PET/CT, the patterns of splenic activity that help differentiate involvement from posttherapy splenic activation include *(a)* diffusely increased FDG uptake greater than that in the liver and bone marrow, and *(b)* multiple areas of intense radiotracer accumulation with or without corresponding CT lesions (Fig 16). FDG-avid splenic lesions may require biopsy or splenectomy to confirm results.

Teaching Point

Primary lymphoma of the liver is very rare, accounting for only 0.016% of all cases of NHL and even fewer cases of Hodgkin disease. The predominant histologic subtype is diffuse large B-cell lymphoma (77). Secondary hepatic involvement in lymphoma is more common and manifests at cross-sectional imaging as small lesions rather than large masses, along with con-

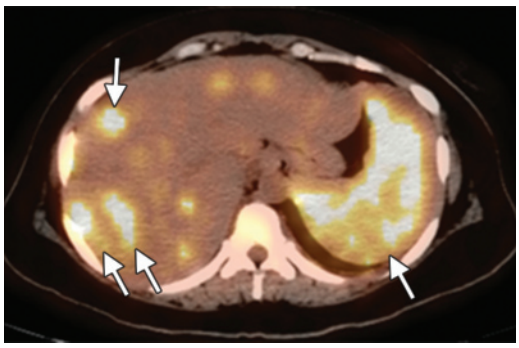
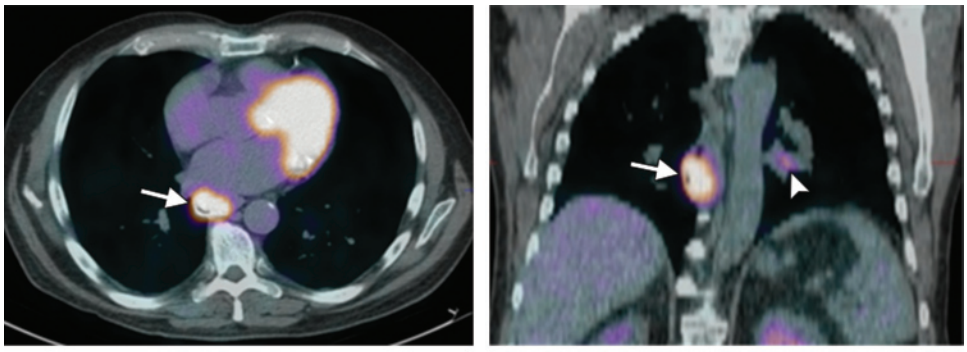


Figure 17. Nodular sclerosis type Hodgkin disease. Axial fused PET/CT image shows multiple foci of abnormal FDG uptake in the liver and spleen (arrows), findings that are consistent with lymphomatous involvement. Secondary hepatic involvement is usually accompanied by splenic disease.



a. b.

Figure 18. Diffuse large B-cell lymphoma of the esophagus. Axial **(a)** and coronal **(b)** fused PET/CT images show a large focus of FDG accumulation in an intraluminal esophageal mass (arrow) and a smaller focus in the left hilar nodes (arrowhead in **b**). Primary esophageal lymphoma is rare and is commonly mistaken for esophageal carcinoma. Biopsy provides the final diagnosis.

glomerates of lymph nodes in the porta hepatis and retroperitoneum (78). At PET/CT, it manifests as patchy foci of FDG uptake originating in the portal areas, with higher SUVs than those of the surrounding parenchyma. In most cases of secondary hepatic involvement, the spleen is also infiltrated by lymphoma (Fig 17). In contrast, hepatic metastases from solid tumors usually appear as large and heterogeneous masses with no splenic involvement.

Lymphoma of the Gastrointestinal Tract

Hodgkin disease rarely involves the organs of the gastrointestinal tract; when there is involvement, however, only a single site is affected, and the patient usually has a poor prognosis (79). On the other hand, lymphomatous involvement of the gastrointestinal tract occurs in up to 10%–30% of all patients with NHL. The most commonly involved organs (in decreasing order of frequency) are the stomach, small bowel, large bowel, and esophagus.

Lymphoma of the Esophagus.—Primary Hodgkin disease and NHL of the esophagus are extremely rare (79). Most cases of esophageal involvement are secondary and arise by extension from pathologic mediastinal lymph nodes (80). Again, the most common subtype of NHL involving the esophagus is diffuse large B-cell lymphoma. At FDG PET/CT, lymphoma of the esophagus manifests as circumferential thickening of the esophageal wall with diffusely increased FDG uptake (Fig 18). The most important possibility in the differential diagnosis is carcinoma of the esophagus, which can be excluded only with biopsy.

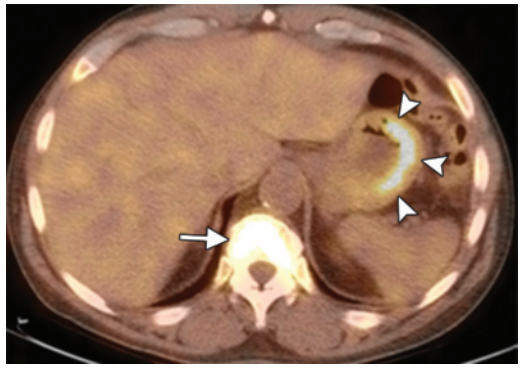


Figure 19. MALT of the stomach. Axial fused PET/CT image shows a circumferential focus of FDG accumulation in the stomach (arrowheads) and diffuse bone marrow activity (arrow). Diffuse FDG activity in the stomach has a broad differential diagnosis, including physiologic uptake, gastritis, and primary gastric carcinoma. Biopsy is necessary to confirm the diagnosis.

Lymphoma of the Stomach.—As mentioned earlier, the stomach is the most common site of gastrointestinal tract lymphoma (~50% of cases). However, gastric lymphoma is much less common than gastric adenocarcinoma or gastrointestinal stromal tumor, accounting for only 3%–5% of all primary gastric malignancies. Primary gastric lymphoma is rare in Hodgkin disease and occurs 10 times less frequently than in NHL. The most common histologic subtypes are *Helicobacter pylori*–associated low-grade MALT lymphoma (50%–70% of cases) and high-grade diffuse large B-cell lymphoma. Secondary gastric involvement is more common. At PET/CT, the FDG uptake pattern in gastric lymphoma is variable, is usually diffuse, and can involve all portions of the stomach with no predilection for any one site (Fig 19). The uptake is higher than liver uptake in the majority of cases, with maximum SUVs in FDG-avid primary gastric lymphoma as high as 15 (±11) (81). The most common diagnoses in the differential diagnosis of gastric FDG uptake are normal physiologic activity, gastritis, and gastric adenocarcinoma.

It should be understood that in patients with primary gastric lymphoma, regional or distant lymph nodes as well as other extranodal sites (eg, lungs, liver, splenic subcutaneous nodes, and bone) can be affected. Extragastric involvement is found in 61% of cases of primary gastric lymphoma, mostly with a diffuse large B-cell histologic subtype (81). Regional nodal stations (perigastric, mesenteric, and retroperitoneal lymph nodes) are involved in 47% of cases, whereas distant nodal sites (supraclavicular, infraclavicular, mediastinal, pelvic, and inguinal lymph nodes) are found in 10% of cases (81). The capacity of PET/CT to help detect extragastric sites of involvement may represent a good indication for its use in initial staging, even when the histologic subtype is indolent, as in MALT lymphoma.

Lymphoma of the Small Bowel.—In the small bowel, Hodgkin disease and NHL are usually the result of direct extension from involved mesenteric lymph nodes. Among the organs of the gastrointestinal tract, the small bowel is the second most commonly affected by NHL (after the stomach), with the distal ileum being the most frequently affected area (82). Mantle cell lymphoma appears to be the predominant histologic subtype in small bowel involvement (83). A classic feature of NHL involvement of the small bowel is the lack of desmoplastic reaction, thus making intestinal obstruction unlikely. At FDG PET/CT, this feature can manifest as multiple foci of intense radiotracer activity arranged in a curvilinear pattern that corresponds to the appearance and location of small bowel loops in the abdomen. The pitfalls of evaluating possible lymphomatous involvement of the small intestine include normal peristaltic activity, normal gastrointestinal lymphoid tissue, and granulomatous or inflammatory conditions (eg, Crohn disease, tuberculosis).

Lymphoma of the Large Bowel.—In a study of gastrointestinal tract lymphoma by Phongkitkarun et al (84), large bowel involvement was discovered in up to 36% of cases, with the colon and rectum being the most commonly affected sites. FDG PET shows a characteristic pattern of uptake consisting of focal, nodular, or diffuse

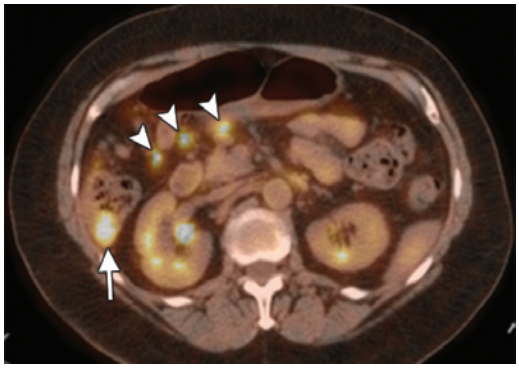


Figure 20. Recurrent mantle cell lymphoma involving the colon. Axial fused PET/CT image shows a focus of abnormal FDG uptake in the ascending colon at the hepatic flexure (arrow) and in multiple subcentimeter mesenteric lymph nodes (arrowheads). Secondary colonic involvement should be suspected if adjacent pathologic mesenteric nodes are present. Findings at colonoscopy-guided biopsy confirmed the diagnosis of lymphomatous involvement.

hypermetabolic activity (especially compared with background activity in high-grade lymphomas) (Fig 20). The limitations of FDG PET/CT for large bowel evaluation are similar to those for small bowel evaluation, but pitfalls include other common FDG-avid benign lesions such as hemorrhoids and diverticulitis.

The vermiform appendix can be affected by NHL on rare occasions, with a prevalence as low as 0.015% in appendectomy specimens (85). The most common histologic subtypes are Burkitt lymphoma (in children) and large B-cell lymphomas (in adults). FDG PET/CT can demonstrate abnormal intense radiotracer uptake in the region of the vermiform appendix.

Lymphoma of the Pancreas

Pancreatic involvement in Hodgkin disease is extremely rare, and almost all cases are secondary to contiguous lymph node disease due to the absence of a pancreatic capsule (33). The pancreas is involved in 0.6% of cases of gastrointestinal tract NHL (86). In a study of 1212 patients with NHL, only five (0.4%) had primary pancreatic lymphoma (87). Regarding sites of recurrence in NHL, one study demonstrated that the pancreas was affected in only five of 400 patients (1.25%) (88). The characteristic imaging pattern at FDG PET/CT is focal or diffuse increased uptake in the pancreatic tissue. A circumscribed mass or diffuse enlargement can be seen at the nondiagnostic CT portion of the study. When lymphoma diffusely infiltrates the pancreas, the imaging appearance can be mistaken for pancreatitis. The differential diagnosis also includes adenocarcinoma of the pancreas, which in some cases will manifest as atrophy of the gland distal to the tumor. Again, the final diagnosis can be made only at biopsy.

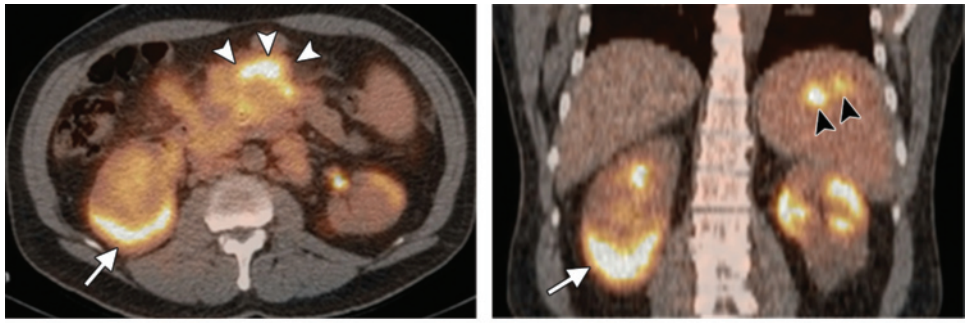
Lymphoma of the Peritoneum

Peritoneal lymphomatosis is a rare clinical presentation that is often associated with high-grade primary gastrointestinal NHL. It can manifest as discrete nodules, a large infiltrative mass, or ascites. At PET/CT, ascites in peritoneal lymphomatosis has high attenuation due to its increased proteinaceous content, mildly diffuse FDG activity, and, possibly, higher uptake in the discrete peritoneal nodules. An additional imaging feature is the large stellate appearance of the mesentery caused by diffuse lymphomatous infiltrative masses in the peritoneum, which fixates the small bowel loops.

A frequently occurring pathologic condition in the differential diagnosis is tuberculous peritonitis, which can produce FDG-avid loculated high-attenuation ascites, making it quite difficult to distinguish from peritoneal lymphomatosis.

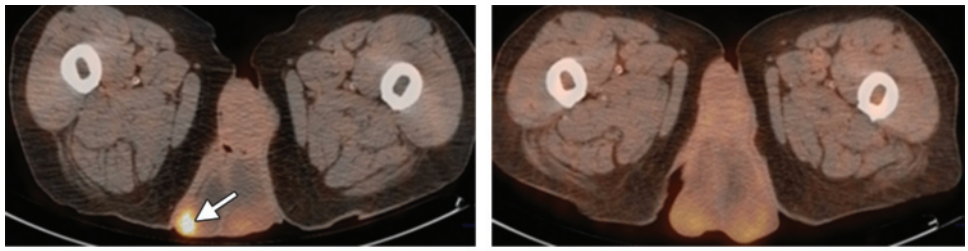
Lymphoma of the Kidneys

Renal lymphoma is most commonly seen in aggressive forms of NHL such as intermediate and high-grade B-cell lymphomas. Burkitt lymphoma is the predominant subtype. Because FDG is excreted by the kidneys, a number of false-positive and false-negative PET interpretations can occur in patients with lymphoma. At fused FDG PET/CT, renal involvement in NHL can appear as multiple focal areas of increased uptake in the renal cortex with or without corresponding lesions on nondiagnostic CT scans, together with abnormally increased uptake in bulky coalescent lymph nodes (Fig 21). PET/CT should always be followed with US-guided percutaneous biopsy if a confirmed diagnosis is required. Other possible explanations for the FDG uptake in the kidneys are normal renal



a. b.

Figure 21. Grade 1 follicular lymphoma. **(a)** Axial fused PET/CT image shows abnormal FDG uptake in the posterior aspect of the inferior pole of the right kidney (arrow) and in a large mesenteric mass (arrowheads). **(b)** Coronal fused PET/CT image shows foci of abnormal FDG uptake in the spleen (arrowheads) and right kidney (arrow). The asymmetry of the right renal finding was suggestive of lymphomatous involvement, which was confirmed at biopsy.



a. b.

Figure 22. Diffuse large B-cell lymphoma with right testicular involvement. Axial fused PET/CT images acquired before **(a)** and 6 weeks after **(b)** R-CHOP (rituximab, cyclophosphamide, vincristine, doxorubicin, and prednisone) chemotherapy show interval resolution of a focus of abnormal FDG uptake in the right testicle (arrow in **a**).

cortical activity, renal cell carcinoma, transitional cell carcinoma, and pyelonephritis.

Lymphoma of the Genital Organs

Of the female genital organs, the adnexa is the most commonly involved by NHL, followed by the uterine body and cervix and, less commonly, the vulva and vagina. The most frequently seen histologic subtype is diffuse large B-cell lymphoma (45% of cases), mainly centroblastic type, followed by Burkitt lymphoma (19%). At FDG PET/CT, lymphomatous involvement may appear as multifocal abnormally increased uptake in the adnexa and uterus. However, physiologic asymmetric uptake may also be seen in the ovaries and endometrium during menstruation, which can lead to false-positive interpretation.

Primary testicular lymphoma is a rare entity, representing 5% of all testicular tumors and less than 2% of all NHLs. In men over 60 years of age, it is the most common type of testicular tumor. Testicular lymphoma is a highly aggressive disease with a high rate of relapse in the CNS (both meningeal and parenchymal) and in other organs such as the contralateral testicle, skin, and Waldeyer ring, with an overall 5-year survival rate ranging from 16% to 50% (89). Secondary testicular involvement is also a rare phenomenon and is usually seen in patients with extensive disease. Most cases of testicular lymphoma have diffuse large B-cell histologic features, and the diagnosis is commonly made with orchiectomy, which is also therapeutic, providing local tumor control. At FDG PET/CT, testicular lymphoma appears as a focus of abnormally increased asymmetric uptake in the affected testicle (Fig 22). Inguinal and retroperitoneal lymph nodes, particularly at the level of the renal hilum, can also demonstrate abnormal FDG accumulation. A common pitfall is physiologic FDG accumulation in the testes; this accumulation can vary significantly and may also be asymmetric.

Conclusions

The prevalence of lymphoma is increasing, so that more extranodal forms are being seen in routine clinical practice. As discussed in this article, PET/CT has become the technique of choice for staging and follow-up in patients with extranodal involvement in Hodgkin disease and in most cases of NHL. At any stage during the course of the disease, the potential presence of extranodal involvement should be considered when interpreting FDG PET/CT studies. Awareness of the increasing frequency of the appearance of unusual single extranodal sites of involvement in NHL and Hodgkin disease is important, since their presence may change treatment strategy and overall prognosis. Although extranodal lymphomatous involvement may be suspected at PET/CT, the diagnosis can be confirmed only with biopsy. Finally, adherence to a standardized PET/CT protocol and correct timing of end-of-treatment scanning are essential for adequate diagnostic accuracy.

References

1. American Cancer Society. Cancer Facts & Figures 2008. Available at: http://www.cancer.org/downloads/STT/2008CAFFfinalsecured.pdf. Accessed March 11, 2009.
2. Zucca E, Conconi A, Cavalli F. Treatment of extranodal lymphomas. Best Pract Res Clin Haematol 2002;15:533–547.
3. Gurney KA, Cartwright RA. Increasing incidence and descriptive epidemiology of extranodal non-Hodgkin lymphoma in parts of England and Wales. Hematol J 2002;3:95–104.
4. Groves FD, Linet MS, Travis LB, Devesa SS. Cancer surveillance series: non-Hodgkin's lymphoma incidence by histologic subtype in the United States from 1978 through 1995. J Natl Cancer Inst 2000;92:1240–1251.
5. Glass AG, Karnell LH, Menck HR. The National Cancer Data Base report on non-Hodgkin's lymphoma. Cancer 1997;80:2311–2320.
6. Kostakoglu L, Goldsmith SJ. Fluorine-18 fluorodeoxyglucose positron emission tomography in the staging and follow-up of lymphoma: is it time to shift gears? Eur J Nucl Med 2000;27:1564–1578.
7. Seam P, Juweid ME, Cheson BD. The role of FDG PET scans in patients with lymphoma. Blood 2007;110:3507–3516.
8. Fougère C, Hundt W, Brockel N, et al. Value of PET/CT versus PET and CT performed as separate investigations in patients with Hodgkin's disease and non-Hodgkin's lymphoma. Eur J Nucl Med Mol Imaging 2006;33:1417–1425.
9. Terasawa T, Nihashi T, Hotta T, Nagai H. 18F-FDG PET for posttherapy assessment of Hodgkin's disease and aggressive Non-Hodgkin's lymphoma: a systematic review. J Nucl Med 2007;49:13–21.
10. Freudenberg LS, Antoch G, Schutt P, et al. FDG PET/CT in re-staging of patients with lymphoma. Eur J Nucl Med Mol Imaging 2004;31:325–329.
11. Raanani P, Shasha Y, Perry C, et al. Is CT scan still necessary for staging in Hodgkin and non-Hodgkin lymphoma patients in the PET/CT era? Ann Oncol 2005;17:117–122.
12. Kwee TC, Kwee RM, Nievelstein RA. Imaging in staging of malignant lymphoma: a systematic review. Blood 2008;111:504–516.
13. Isasi CR, Lu P, Blaufox MD. A metaanalysis of 18F-2-deoxy-2-fluoro-D-glucose positron emission tomography in the staging and restaging of patients with lymphoma. Cancer 2005;104:1066–1074.
14. Zijlstra JM, Lindauer-van der Werf G, Hoekstra OS, Hooft L, Riphagen II, Huijgens PC. 18F-fluorodeoxyglucose positron emission tomography for post-treatment evaluation of malignant lymphoma: a systematic review. Haematologica 2006;91:522–529.
15. Schaefer NG, Hany TF, Taverna C, et al. Non-Hodgkin lymphoma and Hodgkin disease: coregistered FDG PET and CT at staging and restaging—do we need contrast-enhanced CT? Radiology 2004;232:823–829.
16. Pelosi E, Pregno P, Penna D, et al. Role of whole-body [18F] fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) and conventional techniques in the staging of patients with Hodgkin and aggressive non Hodgkin lymphoma. Radiol Med (Torino) 2008;113:578–590.
17. Moog F, Bangerter M, Diederichs CG, et al. Extranodal malignant lymphoma: detection with FDG PET versus CT. Radiology 1998;206:475–481.
18. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J Clin Oncol 2007;25:579–586.
19. Juweid ME, Stroobants S, Hoekstra OS, et al. Use of positron emission tomography for response assessment of lymphoma: consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma. J Clin Oncol 2007;25:571–578.
20. Schoder H, Moskowitz C. PET imaging for response assessment in lymphoma: potential and limitations [viii.]. Radiol Clin North Am 2008;46:225–241.
21. Schoder H, Noy A, Gonen M, et al. Intensity of 18fluorodeoxyglucose uptake in positron emission tomography distinguishes between indolent and aggressive non-Hodgkin's lymphoma. J Clin Oncol 2005;23:4643–4651.
22. Elstrom R, Guan L, Baker G, et al. Utility of FDG PET scanning in lymphoma by WHO classification. Blood 2003;101:3875–3876.
23. Kako S, Izutsu K, Ota Y, et al. FDG PET in T-cell and NK-cell neoplasms. Ann Oncol 2007;18:1685–1690.
24. Allen-Auerbach M, de Vos S, Czernin J. The impact of fluorodeoxyglucose-positron emission tomography in primary staging and patient management in lymphoma patients [vii.]. Radiol Clin North Am 2008;46:199–211.
25. Hutchings M, Loft A, Hansen M, Ralfkiaer E, Specht L. Different histopathological subtypes of Hodgkin lymphoma show significantly different levels of FDG uptake. Hematol Oncol 2006;24:146–150.

26. Perry C, Herishanu Y, Metzer U, et al. Diagnostic accuracy of PET/CT in patients with extranodal marginal zone MALT lymphoma. Eur J Haematol 2007;79:205–209.
27. Rousseau C, Bourbouloux E, Campion L, et al. Brown fat in breast cancer patients: analysis of serial (18)F-FDG PET/CT scans. Eur J Nucl Med Mol Imaging 2006;33:785–791.
28. Christensen CR, Clark PB, Morton KA. Reversal of hypermetabolic brown adipose tissue in F-18 FDG PET imaging. Clin Nucl Med 2006;31:193–196.
29. Garcia CA, Van Nostrand D, Atkins F, et al. Reduction of brown fat 2-deoxy-2-[F-18]fluoro-D-glucose uptake by controlling environmental temperature prior to positron emission tomography scan. Mol Imaging Biol 2006;8:24–29.
30. Williams G, Kolodny GM. Method for decreasing uptake of 18F-FDG by hypermetabolic brown adipose tissue on PET. AJR Am J Roentgenol 2008;190:1406–1409.
31. Gelfand MJ, O'Hara SM, Curtwright LA, Maclean JR. Pre-medication to block [(18)F]FDG uptake in the brown adipose tissue of pediatric and adolescent patients. Pediatr Radiol 2005;35:984–990.
32. Parysow O, Mollerach AM, Jager V, Racioppi S, San Roman J, Gerbaudo VH. Low-dose oral propranolol could reduce brown adipose tissue F-18 FDG uptake in patients undergoing PET scans. Clin Nucl Med 2007;32:351–357.
33. Even-Sapir E, Lievshitz G, Perry C, Herishanu Y, Lerman H, Metser U. Fluorine-18 fluorodeoxyglucose PET/CT patterns of extranodal involvement in patients with non-Hodgkin lymphoma and Hodgkin's disease [vii.]. Radiol Clin North Am 2007;45:697–709.
34. Cook GJ. Pitfalls in PET/CT interpretation. Q J Nucl Med Mol Imaging 2007;51:235–243.
35. Lin C, Itti E, Haioun C, et al. Early 18F-FDG PET for prediction of prognosis in patients with diffuse large B-cell lymphoma: SUV-based assessment versus visual analysis. J Nucl Med 2007;48:1626–1632.
36. Wahl RL, Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: evolving considerations for PET response criteria in solid tumors. J Nucl Med 2009;50:122S–150S.
37. Boellaard R, Oyen WJ, Hoekstra CJ, et al. The Netherlands protocol for standardisation and quantification of FDG whole body PET studies in multicentre trials. Eur J Nucl Med Mol Imaging 2008;35:2320–2333.
38. Byun BH, Na II, Cheon GJ, et al. Clinical significance of 18F-FDG uptake by primary sites in patients with diffuse large B cell lymphoma in the head and neck: a pilot study. Ann Nucl Med 2008;22:645–651.
39. Zucca E, Roggero E, Bertoni F, Conconi A, Cavalli F. Primary extranodal non-Hodgkin's lymphomas. II. Head and neck, central nervous system and other less common sites. Ann Oncol 1999;10:1023–1033.
40. Mok TS, Steinberg J, Chan AT, et al. Application of the international prognostic index in a study of Chinese patients with non-Hodgkin's lymphoma and a high incidence of primary extranodal lymphoma. Cancer 1998;82:2439–2448.
41. Lopez-Guillermo A, Colomo L, Jimenez M, et al. Diffuse large B-cell lymphoma: clinical and biological characterization and outcome according to the nodal or extranodal primary origin. J Clin Oncol 2004;23:2797–2804.
42. Blodgett TM, Fukui MB, Snyderman CH, et al. Combined PET-CT in the head and neck. I. Physiologic, altered physiologic, and artifactual FDG uptake. RadioGraphics 2005;25:897–912.
43. Fukui MB, Blodgett TM, Snyderman CH, et al. Combined PET-CT in the head and neck. II. Diagnostic uses and pitfalls of oncologic imaging. RadioGraphics 2005;25:913–930.
44. Karantanis D, Subramaniam RM, Peller PJ, et al. The value of [(18)F]fluorodeoxyglucose positron emission tomography/computed tomography in extranodal natural killer/T-cell lymphoma. Clin Lymphoma Myeloma 2008;8:94–99.
45. Economopoulos T, Fountzilas G, Kostourou A, et al. Primary extranodal non-Hodgkin's lymphoma of the head and neck in adults: a clinicopathological comparison between tonsillar and non-tonsillar lymphomas (Hellenic co-Operative Oncology Group). Anticancer Res 1998;18:4655–4660.
46. Rosado MF, Morgensztern D, Peleg M, Lossos IS. Primary diffuse large cell lymphoma of the mandible. Leuk Lymphoma 2004;45:1049–1053.
47. Nakamoto Y, Tatsumi M, Hammoud D, Cohade C, Osman MM, Wahl RL. Normal FDG distribution patterns in the head and neck: PET/CT evaluation. Radiology 2005;234:879–885.
48. Choi JY, Lee KS, Kim HJ, et al. Focal thyroid lesions incidentally identified by integrated 18F-FDG PET/CT: clinical significance and improved characterization. J Nucl Med 2006;47:609–615.
49. Karantanis D, Bogsrud TV, Wiseman GA, et al. Clinical significance of diffusely increased 18F-FDG uptake in the thyroid gland. J Nucl Med 2007;48:896–901.
50. Valenzuela AA, Allen C, Grimes D, Wong D, Sullivan TJ. Positron emission tomography in the detection and staging of ocular adnexal lymphoproliferative disease. Ophthalmology 2006;113:2331–2337.
51. Haque S, Law M, Abrey LE, Young RJ. Imaging of lymphoma of the central nervous system, spine, and orbit [ix]. Radiol Clin North Am 2008;46:339–361.
52. Palmedo H, Urbach H, Bender H, et al. FDG PET in immunocompetent patients with primary central nervous system lymphoma: correlation with MRI and clinical follow-up. Eur J Nucl Med Mol Imaging 2006;33:164–168.
53. Guermazi A, Brice P, de Kerviler EE, et al. Extranodal Hodgkin disease: spectrum of disease. RadioGraphics 2001;21:161–179.
54. Nieuwenhuizen L, Verzijlbergen FJ, Wiltink E, Grutters JC, Biesma DH. A possible role of 18F-FDG positron-emission tomography scanning in the early detection of rituximab-induced pneumonitis in patients with non-Hodgkin's lymphoma. Haematologica 2008;93:1267–1269.

55. Chang CY, Tsai CS, Peng YJ, Huang WS. Large B-cell lymphoma mimicking ischemic heart disease demonstrated by F-18 fluorodeoxyglucose PET/CT in a heart transplant patient. J Nucl Cardiol 2007; 14:754–757.
56. Buchmann I, Wandt H, Wahl A, Reske SN. FDG PET for imaging pericardial manifestations of Hodgkin lymphoma. Clin Nucl Med 2003;28:760–761.
57. Weijs LE, Arsos G, Baarslag HJ, Wittebol S, de Klerk JM. Pericardial involvement in a non-Hodgkin lymphoma patient: coregistered FDG PET and CT imaging. Eur Heart J 2007;28:2698.
58. Jerusalem G, Beguin Y, Fassotte MF, et al. Early detection of relapse by whole-body positron emission tomography in the follow-up of patients with Hodgkin's disease. Ann Oncol 2003;14:123–130.
59. Kyoung Jung H, Kim EK, Yun M, Jung Kim M, Young Kwak J. Bilateral breast involvement in Burkitt's lymphoma detected only by FDG PET. Clin Imaging 2006;30:57–59.
60. Bakheet SM, Bakheet R, Ezzat A, Tulbah A, Durakovic A, Hussain S. F-18 FDG positron emission tomography in primary breast non-Hodgkin's lymphoma. Clin Nucl Med 2001;26:299–301.
61. Nihashi T, Hayasaka K, Itou T, et al. Findings of fluorine-18-FDG PET in extranodal origin lymphoma in three cases of diffuse large B cell type lymphoma. Ann Nucl Med 2006;20:689–693.
62. Kumar R, Xiu Y, Dhurairaj T, Yu JQ, Alavi A, Zhuang H. F-18 FDG positron emission tomography in non-Hodgkin lymphoma of the breast. Clin Nucl Med 2005;30:246–248.
63. Moog F, Kotzerke J, Reske SN. FDG PET can replace bone scintigraphy in primary staging of malignant lymphoma. J Nucl Med 1999;40:1407–1413.
64. Pelosi E, Penna D, Deandreis D, et al. FDG PET in the detection of bone marrow disease in Hodgkin's disease and aggressive non-Hodgkin's lymphoma and its impact on clinical management. Q J Nucl Med Mol Imaging 2008;52:9–16.
65. Even-Sapir E. Imaging of malignant bone involvement by morphologic, scintigraphic, and hybrid modalities. J Nucl Med 2005;46:1356–1367.
66. Pakos EE, Fotopoulos AD, Ioannidis JP. 18F-FDG PET for evaluation of bone marrow infiltration in staging of lymphoma: a meta-analysis. J Nucl Med 2005;46:958–963.
67. Willemze R, Jaffe ES, Burg G, et al. WHO-EORTC classification for cutaneous lymphomas. Blood 2005; 105:3768–3785.
68. Kumar R, Xiu Y, Zhuang HM, Alavi A. 18F-fluorodeoxyglucose-positron emission tomography in evaluation of primary cutaneous lymphoma. Br J Dermatol 2006;155:357–363.
69. Kuo PH, McClennan BL, Carlson K, et al. FDG PET/CT in the evaluation of cutaneous T-cell lymphoma. Mol Imaging Biol 2008;10:74–81.
70. Bishu S, Quigley JM, Schmitz J, et al. F-18-fluorodeoxy-glucose positron emission tomography in the assessment of peripheral T-cell lymphomas. Leuk Lymphoma 2007;48:1531–1538.
71. Watanabe N, Kato H, Murakami J, et al. FDG PET imaging in cutaneous anaplastic large cell lymphoma. Clin Nucl Med 2006;31:564–565.
72. Samuel LM, White J, Lessells AM, Roddie H, Matheson LM. Primary non-Hodgkins lymphoma of muscle. Clin Oncol (R Coll Radiol) 1999;11:49–51.
73. Kumar R, Xiu Y, Mavi A, El-Haddad G, Zhuang H, Alavi A. FDG PET imaging in primary bilateral adrenal lymphoma: a case report and review of the literature. Clin Nucl Med 2005;30:222–230.
74. Metser U, Goor O, Lerman H, Naparstek E, Even-Sapir E. PET-CT of extranodal lymphoma. AJR Am J Roentgenol 2004;182:1579–1586.
75. de Jong PA, van Ufford HM, Baarslag HJ, et al. CT and 18F-FDG PET for noninvasive detection of splenic involvement in patients with malignant lymphoma. AJR Am J Roentgenol 2009;192:745–753.
76. Rini JN, Leonidas JC, Tomas MB, Palestro CJ. 18F-FDG PET versus CT for evaluating the spleen during initial staging of lymphoma. J Nucl Med 2003; 44:1072–1074.
77. Noronha V, Shafi NQ, Obando JA, Kummar S. Primary non-Hodgkin's lymphoma of the liver. Crit Rev Oncol Hematol 2005;53:199–207.
78. Fishman EK, Kuhlman JE, Jones RJ. CT of lymphoma: spectrum of disease. RadioGraphics 1991; 11:647–669.
79. Dodd GD. Lymphoma of the hollow abdominal viscera. Radiol Clin North Am 1990;28:771–783.
80. Taal BG, Burgers JM, van Heerde P, Hart AA, Somers R. The clinical spectrum and treatment of primary non-Hodgkin's lymphoma of the stomach. Ann Oncol 1993;4:839–846.
81. Radan L, Fischer D, Bar-Shalom R, et al. FDG avidity and PET/CT patterns in primary gastric lymphoma. Eur J Nucl Med Mol Imaging 2008;35: 1424–1430.
82. Levine MS, Rubesin SE, Pantongrag-Brown L, Buck JL, Herlinger H. Non-Hodgkin's lymphoma of the gastrointestinal tract: radiographic findings. AJR Am J Roentgenol 1997;168:165–172.
83. Sam JW, Levine MS, Farner MC, Schuster SJ, Alavi A. Detection of small bowel involvement by mantle cell lymphoma on F-18 FDG positron emission tomography. Clin Nucl Med 2002;27:330–333.
84. Phongkitkarun S, Varavithya V, Kazama T, et al. Lymphomatous involvement of gastrointestinal tract: evaluation by positron emission tomography with (18)F-fluorodeoxyglucose. World J Gastroenterol 2005;11:7284–7289.
85. Souza FF, Israel DA. PET/CT appearance of non-Hodgkin lymphoma of the vermiform appendix. Clin Nucl Med 2008;33:694–696.
86. Freeman C. Occurrence and prognosis of extranodal lymphomas. Cancer 1972;29:252–260.
87. Ezzat A, Jamshed A, Khafaga Y, et al. Primary pancreatic non-Hodgkin's lymphomas. J Clin Gastroenterol 1996;23:109–112.
88. Glazer HS, Lee JK, Balfe DM, Mauro MA, Griffith R, Sagel SS. Non-Hodgkin lymphoma: computed tomographic demonstration of unusual extranodal involvement. Radiology 1983;149:211–217.
89. Fonseca R, Habermann TM, Colgan JP, et al. Testicular lymphoma is associated with a high incidence of extranodal recurrence. Cancer 2000;88:154–161.

This article meets the criteria for 1.0 credit hour in category 1 of the AMA Physician's Recognition Award. To obtain credit, see accompanying test at http://www.rsna.org/education/rg_cme.html.

RadioGraphics

FDG PET/CT of Extranodal Involvement in Non-Hodgkin Lymphoma and Hodgkin Disease

Fabio M. Paes, MD, et al

RadioGraphics 2010; 30:253–267 • **Published online** 10.1148/rg.301095092 • **Content Code:** GI

Page 271
The current revised response criteria suggest the following indications for PET in lymphoma:
1. PET is routinely recommended for the staging of patients with FDG-avid, potentially curable lymphomas (eg, diffuse large B-cell lymphoma and Hodgkin disease) to more accurately delineate disease extent.
2. PET is not routinely recommended prior to treatment for incurable, non-FDG-avid or indolent histologic subtypes (eg, grade 1 follicular lymphoma and mantle cell lymphoma) or for most lymphomas with variable FDG activity, unless the medical oncologist is seeking to assess response to chemotherapy regimens or newer experimental drugs.
3. Midtreatment PET should be performed only as a part of clinical trials.

Page 272
The intensity of FDG uptake in lymphoma is determined by many factors, including histologic features (Hodgkin disease versus NHL), grade (indolent versus aggressive NHL), viable tumor cell fraction, tumor cell proliferation, upregulation of glucose metabolism, salvage pathways and tumor-specific pathways, local perfusion (which determines substrate delivery to the cancer cell), and the presence of hypoxia. Because FDG uptake is a multifactorial process, it should not be surprising that there is (sometimes considerable) heterogeneity between lesions of the same histologic subtype and overlap between tumor grades.

Page 274
In those rare instances in which correct metabolic-anatomic correlation remains difficult, misinterpretation as nodal and extranodal uptake may persist, leading to false-positive results. In such cases, brown fat uptake can be misidentified as adjacent soft-issue, thymic, lung, or muscular involvement by lymphoma. The presence of brown fat can also decrease tumor uptake by decreasing the pool of FDG available for the tumor tissues.

Page 275
The recommended timing for performing end-of-therapy PET varies with the treatment modality. Posttherapy PET should be performed at least 4–6 weeks after surgery or chemotherapy and 8–12 weeks after external beam radiation therapy or radioimmunotherapy.

Page 284
FDG PET/CT has an accuracy of almost 100% in diagnosing primary splenic involvement during initial staging, whereas CT alone has an overall accuracy of 57%. However, in the posttherapy setting, the evaluation of secondary splenic involvement is limited in some cases due to splenic activation. At FDG PET/CT, the patterns of splenic activity that help differentiate involvement from posttherapy splenic activation include (a) diffusely increased FDG uptake greater than that in the liver and bone marrow, and (b) multiple areas of intense radiotracer accumulation with or without corresponding CT lesions.