Non-Hodgkin lymphoma (NHL) may arise in nodal and extranodal sites. The term non-lymph node nodal lymphoma refers to certain lymphomas located in Waldeyer’s ring, the thymus, and the spleen. Extranodal lymphoma (ENL) may arise along the gastrointestinal tract (GIT), head and neck, orbit, central nervous system (CNS) and peripheral nervous system, lung and pleura, bone, skin, breast, testis, thyroid, and genitourinary tract (GUT) [1]. When lymphoma involves extranodal sites, it is of importance to determine whether the tumor originated in nonnodal tissue (primary ENL), whether it originated in nodal tissue and spread to adjacent nonnodal tissue, or whether it originated in nodal tissue and hematogenously spread to extranodal sites (secondary ENL) [2]. Accurate localization of disease is essential for appropriate treatment strategy, which may be related to organ-specific problems [1,3]. Moreover, extranodal involvement is among the well-established pretreatment prognostic factors in patients with lymphoma [4].

The incidence of NHL has increased over the past 2 decades and at a more significant pace for extranodal disease as compared with nodal disease [1,5]. Potential explanations for this epidemiologic phenomenon are the AIDS epidemic and other viral infections, an increase in the number of patients...
exposed to previous immunosuppressive treatment, and altered environmental conditions [1]. At least one quarter of NHLs arise primarily at extranodal sites. Summarizing the database on 91,306 patients with NHL, Glass and colleagues [2] reported extranodal NHL to form 28% of all cases and 15% in the case of low-grade histology. In another series on 318 patients with NHL, 46% had primary ENL. The stomach was the most common extranodal site, followed by the skin and head and neck region. Compared with nodal disease, primary ENLs tend to be localized and to have extranodal relapses more often [6]. Aggressive types of lymphoma, mainly diffuse large B-cell lymphoma (DLCL), predominate histologically in ENL, followed by follicular lymphomas. There are other subtypes of lymphoma, however, such as mucosa-associated lymphoid tissue (MALT) lymphomas and mantle cell lymphomas, which, overall, are less common lymphoma subtypes but are associated with a high incidence of extranodal involvement [7–9]. Being the third most frequent histologic subtype, MALT lymphoma, an ENL originating in marginal zone (MZ) cells, accounts for only 8% of all NHL cases but for almost half of primary gastric lymphomas [1]. The mantle cell subtype accounts for 5% to 10% of NHL cases, with an overall poor prognosis. Frequently, disease is disseminated, involving the lymph nodes, bone marrow, spleen, and extranodal sites. In a report on 121 patients with mantle cell lymphoma, 96 had bone marrow disease, 58 had splenic involvement, 21 had GIT disease, 15 had involvement of the liver, 14 had lymphoma in the head and neck, 9 had lymphoma in the pleura and/or lung, and 10 had involvement of other extranodal sites [10].

Hodgkin’s disease (HD) is usually confined to the lymph nodes. Extranodal involvement is much less common in HD compared with NHL. Extranodal involvement is more often attributable to direct extension from adjacent nodal disease. Hematogenous spread has been reported during the course of the disease in 5% to 10% of the patients, however. According to the Ann Arbor classification of lymphoma, “E” defines the involvement of a single extralymphatic site or a contiguous extranodal extension in proximity to a known nodal site. Disseminated involvement of one or more organs or tissues, with or without associated lymph node involvement, is termed stage IV disease and is associated with a less favorable outcome [11].

Fluorine-18 fluorodeoxyglucose PET and PET/CT in extranodal lymphoma: overview

Before the fluorine-18 fluorodeoxyglucose (18F-FDG) PET era, staging of lymphoma was based on physical examination and morphologic imaging, mainly using CT. CT has a limited sensitivity in detecting lymphomatous involvement of normal-sized lymph nodes, bone marrow, and spleen, however. CT may show nonspecific findings suggestive of extranodal sites of disease; therefore, it often requires further validation [3]. In a recent meta-analysis of 20 publications that assessed the role of 18F-FDG PET in staging lymphoma, it was shown that PET upstaged disease in 8% to 17% of patients and downstaged disease in 2% to 23% of patients [12]. Several studies have specifically addressed the superiority of 18F-FDG PET over CT for assessment of extranodal involvement [13–16]. Moog and coworkers [13] reported that in 16% of the patients (43 with NHL and 38 with HD), PET modified staging as compared with CT by detecting unsuspected involvement of the spleen, liver, and bone or by excluding disease in false-positive CT lesions. Rodriguez and colleagues [17] reported detection of greater extension by PET compared with endoscopy and CT in patients with high-grade lymphoma of the stomach. In another study by Schaefer and coworkers [18] on 60 patients with lymphoma, PET/CT was found to be more sensitive than full-dose contrast-enhanced CT in identification of nodal and extranodal sites of disease. For extranodal involvement, the sensitivity and specificity were 88% and 100%, respectively, for PET/CT and 50% and 90%, respectively, for contrast-enhanced CT. In a recent report by Raanani and colleagues [16], the diagnostic accuracy of PET/CT and diagnostic CT were compared in 103 consecutive patients with newly diagnosed NHL and HD. Upstaging disease by PET/CT was observed mostly in patients in stages I and II, detecting involvement in small-sized lymph nodes as well as in the spleen, liver, thymus, cortical bone, bone marrow, lung, and pleura, sites that were overlooked when CT was interpreted alone.

18F-FDG avidity is a hallmark for the accurate staging of lymphoma using 18F-FDG PET/CT. High-grade lymphomas are usually 18F-FDG–avid, as are many cases of follicular type lymphomas. 18F-FDG avidity of marginal zone lymphomas (MZLs), the third most common lymphoma type in extranodal lesions, is a controversial issue, however.

Fluorine-18 fluorodeoxyglucose PET/CT in marginal zone lymphomas

The secondary B follicle found in the lymph nodes, spleen, and ENL tissue is composed of a follicle center and the mantle, which comprises the lymphocytic corona and the MZ. The MZ is developed in the spleen, Payer’s patches, and tonsils, which are secondary lymphoid organs, and is poorly developed in peripheral lymph nodes. There are three subtypes of lymphomas originating in the MZ:
nodal (monocytoid) MZ lymphoma, splenic MZ lymphoma, and extranodal MZ lymphoma (also referred as MALT lymphoma). Osaacson and Wright defined MALT lymphoma as a distinct entity in 1983 [7,8]. MALT lymphoma was originally identified in the GIT but was later identified in the lung and salivary and lacrimal duct mucosa as well and then in other sites normally devoid of MALT, where MALT is acquired in response to antigenic stimulation, such as Hashimoto’s thyroiditis, Sjögren’s syndrome, and gastric Helicobacter pylori. There is compelling evidence implicating H pylori in the pathogenesis of gastric lymphoma, which is the most common site of MALT lymphoma [1,7,8,19]. Nongastric MALT lymphoma may involve the skin, thyroid, breast, thymus, orbit, liver, kidney, prostate, urinary bladder, and gallbladder [7,8,19]. Disseminated disease is common in MALT lymphoma, where 25% of patients have involvement of multiple mucosal sites and/or involvement of nonmucosal sites, such as the bone marrow [20]. MALT lymphoma has generally been considered as non-18F-FDG–avid. In a preliminary study, Hoffman and colleagues [21] assessed the role of PET for the staging of MALT lymphoma in 21 patients and reported a difference in 18F-FDG avidity between nodal MZL, with PET-positive studies in 5 of 6 patients, as compared with negative studies in all patients with MALT lymphoma. The authors therefore suggested the potential use of 18F-FDG PET for differentiating nodal and extranodal MZL. Opposite conclusions were suggested recently by Beal and coworkers [22], who reported on 175 patients with biopsy-proven MALT lymphoma. Of 42 patients who underwent PET for initial staging, 34 (81%) had 18F-FDG–avid disease, 6 (14%) had non-18F-FDG–avid disease, and 2 (5%) showed indeterminate uptake. Based on PET assessment, regional nodal involvement was found in 21% of the patients with 18F-FDG–avid disease. In 4 patients, disease was upstaged based on unexpected PET findings. Follow-up PET was found to be accurate in differentiating complete response from active disease [22]. The authors thus concluded that 18F-FDG PET is a valuable imaging modality for staging and for monitoring response to therapy of MALT lymphoma. Other reports, mainly case studies, have described 18F-FDG–avid MALT lymphomas. MALT lymphoma of the lung, for example, was reported to present occasionally as a solitary 18F-FDG–avid lesion, and the authors thus suggested the inclusion of this entity in the differential diagnosis of indeterminate lung lesions showing increased tracer uptake [23].

It is not clear why some cases of MALT lymphoma would show increased uptake of 18F-FDG, whereas others would not. MZLs display a broad morphologically heterogeneous composite of cells that include small B cells (centrocyte-like cells, monocytoid cells, and small lymphocytes), large B cells, and plasma cells [8]. This heterogeneity of the cellular composition may be the potential cause for differences in 18F-FDG avidity. It should be noted that in previous publications on MALT lymphoma, PET was usually the technology performed rather than PET/CT. It is therefore yet to be determined whether the use PET/CT may improve the diagnostic accuracy of 18F-FDG PET in detecting MALT lymphomas, particularly in tissue in which uptake may be found physiologically, such as the GIT (Fig. 1).

Lymphoma of the gastrointestinal tract and abdominal and pelvic organs

The GIT is the most common extranodal site in NHL, accounting for approximately 10% to 15% of all NHLs and 30% to 40% of all extranodal cases [1]. Any region along the GIT, from the oral cavity to the anus, may be involved by lymphoma, with the stomach and small intestine being the most common sites. Lymphoma of the stomach comprises 1% to 10% of all gastric malignancies. It may be limited disease localized to the stomach and perigastric lymph nodes or advanced disease (Fig. 2) [1,23–25]. Small intestinal lymphoma represents 36% to 54% of all GIT lymphomas and 18% to 24% of all small bowel malignancies. Lymphoma types involving the small intestine are usually DLCL and MALT lymphoma [25–27]. Patients with celiac disease have an increased risk of developing enteropathy-associated T-cell lymphoma [1]. Involvement of the GIT by HD is uncommon. When the GIT is involved, it is usually by extension from adjacent lymph nodes [11].

Encouraging results have been reported by Kumar and colleagues [26] when PET was used to differentiate residual or recurrent disease and non-active masses in patients with GIT lymphomas, with a positive predictive value (PPV) of 100% and a negative predictive value (NPV) of 92%. Physiologic uptake of 18F-FDG along the GIT may lead to false-positive and false-negative interpretations of PET in patients with GIT lymphoma, however, particularly in the presence of minimal disease [13]. PET/CT may improve the differentiation between physiologic 18F-FDG uptake from uptake in lymphoma, as was illustrated in a pictorial assay on PET/CT in ENL cases [28]. Oral administration of contrast media seems to be beneficial in patients with GIT lymphoma, allowing for better delineation of the stomach or bowel wall on the CT part of the PET/CT study (see Fig. 2; Fig. 3) [29].
Assessment of splenic involvement has been a clinical and imaging challenge. Staging laparotomy, which is not a rare procedure in patients with HD, revealed splenic involvement in 30% to 40% of cases at presentation [1, 30]. The spleen is involved in approximately one fifth of the patients with NHL. Organ size is a poor predictor of lymphomatous involvement. The spleen may be enlarged without being involved, or it may be of normal size despite tumor infiltration. Spleen enlargement has a sensitivity of 38% and a specificity of 61% for the diagnosis of lymphomatous involvement [13]. The pattern of splenic involvement may be diffuse, more common in HD, or with the appearance of single or multiple small nodules. Involved spleen may appear normal on ultrasound (US) or CT. The reported accuracy of CT for identifying splenic involvement in patients with HD ranges from 37% to 91% when different criteria to suggest splenic involvement have been applied. On MRI, nodular involvement may appear as hypo- or isointense on T1-weighted images and as hyperintense on T2-weighted images and may demonstrate reduced enhancement after administration of gadolinium compared with normal spleen. Splenic involvement may be overlooked in cases in which normal and lymphomatous tissue has similar signal intensity [26, 31, 32]. On 18F-FDG PET/CT, lymphomatous involvement of the spleen may appear as diffusely increased splenic uptake (although this pattern is not specific and may also

Fig. 1. Esophageal MALT lymphoma. At diagnosis, fused PET/CT images show increased uptake in the esophagus (arrow in B) with corresponding wall thickening on CT (arrow in A). (C) After successful treatment, fused PET/CT images show a normal appearance of the esophagus on CT and PET (arrow).

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Fig. 2. Gastric lymphoma. CT (A) and fused PET/CT (B) images show increased 18F-FDG uptake in a primary lymphoma in the stomach (arrows in B) and in involved perigastric lymph nodes (arrowhead in B). Oral contrast on the CT part of the study allows better delineation of the stomach walls.
be found in nonmalignant “reactive” spleen) and/or focal increased accumulation of the tracer with or without corresponding hypodense lesions on the CT part of the PET/CT study. Comparing the assessment of splenic involvement by $^{18}$F-FDG PET and CT in 7 patients with lymphoma, $^{18}$F-FDG PET correctly identified or excluded splenic involvement in all patients (accuracy of 100%) as opposed to CT, which was correct for only 4 of the patients (accuracy of 57%) [33]. At times, a splenic mass may be the presenting finding of lymphoma. Metser and coworkers [34] performed PET/CT in 20 patients without a known malignancy who were referred for $^{18}$F-FDG PET/CT in 20 patients without a known malignancy who were referred for $^{18}$F-FDG PET/CT for characterization of splenic masses. In 10 patients (50%), the lesions were $^{18}$F-FDG--avid, and 7 of these patients were diagnosed as having lymphoma. In 5 of these 7 patients, PET also identified nodal disease, whereas 2 patients had lymphoma limited to the spleen, consistent with primary splenic lymphoma.

Liver involvement in lymphoma may present as diffuse disease, as patchy infiltrates originating in the portal areas, as miliary with multiple small lesions, or, less commonly, as large focal lesions [11,35]. The gallbladder, pancreas, peritoneum, adrenal glands, kidneys, female genital organs, and testis are other sites of ENL in the abdomen and pelvis (Fig. 4). Involvement of the gallbladder and pancreas is almost always secondary to adjacent nodal disease. Because the pancreas has no definable capsule, it may be difficult to distinguish adjacent lymph node disease from pancreatic infiltration. Accurate detection of lymphoma in the pancreas or gallbladder is possible with PET/CT, especially when a mass is detected on the CT part of PET/CT corresponding to PET findings. Involvement of the peritoneum or omentum is found exclusively in NHL, resembling peritoneal involvement by other malignancies, with focal $^{18}$F-FDG accumulation in nodules and, often, ascites. Secondary involvement of the adrenal with NHL has been reported to occur in up to 25% of patients during the course of the disease, whereas primary NHL arising from endocrine glands represents only 3% of ENLs. Primary adrenal lymphoma (PAL) is extremely rare. Approximately 70 cases have been reported in the English literature. Because adrenal thickening or an adrenal mass is not an uncommon incidental abnormality on CT, $^{18}$F-FDG has been suggested for differentiating...
benign incidentaloma from tumoral adrenal involvement [36,37].

Although the incidence of kidney involvement at presentation is only 3%, the kidney is a more common site of recurrence later in the course of NHL. Physiologic $^{18}$F-FDG uptake in the renal collecting system may cause false-positive and false-negative PET interpretation of renal involvement in patients with NHL. PET/CT allows for more accurate interpretation, however. Extranodal involvement of the kidney may appear on $^{18}$F-FDG PET/CT as multiple focal sites of increased uptake located in the renal cortex, occasionally with corresponding lesions on CT that appear slightly hyperdense on unenhanced and hypodense on contrast-enhanced images; as a contiguous extension from adjacent nodal disease; or, less commonly, in the form of a single mass or diffuse infiltration with organ enlargement [38]. Involvement of HD is rather by invasion of the perirenal space without renal parenchymal involvement [11,35].

Primary lymphomas arising in the female genital organs are rare. They seem to be more common secondary to nodal or extranodal disease (Fig. 5). Based on a report by Kosari and colleagues [39] on 186 patients with lymphoma involving the female genital tract, it seems that the adnexa is the most commonly involved site, followed by the uterine body and cervix, and that the vagina and vulva are the least common sites. The most frequent lymphoma type in the genital tract is DLCL in 45% of cases, followed by Burkitt’s lymphoma in 19% of patients. In premenopausal patients, physiologic $^{18}$F-FDG uptake may be seen in the ovaries and endometrium during menstruation or in the ovulatory phase of the cycle. It has also been found in association with anticancer therapy–related oligomenorrhea. It is thus important to obtain a full menstrual history when increased $^{18}$F-FDG uptake is seen in the genital organs [40]. Lymphoma of the testis accounts for 5% of all testicular malignancies and 1% of all lymphomas. It is the most common testicular malignancy in patients older than 60 years of age, however. Involvement of other mainly extranodal sites at presentation is common, especially such extranodal sites as the contralateral testicle, CNS, skin, and Waldeyer’s ring. A high incidence of relapse ranging from 50% to 80% has often been reported in extranodal sites, with the CNS being the relapse site in up to a third of patients. Occasionally, the CNS is the only site of recurrence in patients with testicular lymphoma [41,42]. Although physiologic $^{18}$F-FDG uptake is found in the brain cortex and scrotum, disease

Fig. 5. Burkitt’s lymphoma involving the breast and cervix. $^{18}$F-FDG PET (maximum intensity projection) (A) and fused PET/CT (B) images at the level of the thorax demonstrate extensive involvement of the right breast and a smaller site of disease in the left breast (arrows in B) as well as involvement of a small right internal mammary lymph node (arrowhead in B). (C) Fused PET/CT image of the pelvis indicates involvement of the cervix.
involvement may occasionally be identified by the detection of focal sites of a higher intensity compared with that of the background.

**Lymphoma of the head and neck**

The head and neck region is the second most common site of NHL. Primary ENL of the head and neck may originate in the tonsils, nasopharynx, mandible and/or gingiva, hard palate, parotis, nasal cavity, hypopharynx and larynx, thyroid, ocular adnexa, and paranasal sinuses. Primary head and neck lymphoma accounts for 10% to 20% of all cases of NHL and for 5% of the malignancies in the head and neck region. Most NHLs of the head and neck arise from Waldeyer’s ring, including the adenoids and the lymphoid tissue of the nasopharynx and around the pharyngeal opening of the Eustachian tube as well as the oropharynx, involving the palatine tonsils, the lymphoid tissue of the soft palate, and the posterior third or base of the tongue (Fig. 6). Waldeyer’s ring is the primary site of NHL in more than 30% of all extranodal sites, most commonly involving the tonsils, followed by the nasopharynx. The tonsil resembles MALT but also has characteristics of peripheral lymph nodes, and the classification of Waldeyer’s ring as nodal or extranodal is thus controversial. Lymphoma of the head and neck may be asymptomatic and unsuspected clinically. The nasopharynx was found to be involved in up to 41% of patients when a routine biopsy was performed [43,44].

Reviewing a series of 100 consecutive patients presenting with NHL in the head and neck, Morton and coworkers [45] have reported that otolaryngologic examination performed in patients with cervical nodal disease may reveal unsuspected extranodal disease in Waldeyer’s ring in one third of the patients. Lymphoma involving the nasopharynx tends to extend into the airways and tonsils as opposed to carcinoma or sarcoma of the nasopharynx, which tends to extend up into the skull base [44]. Regional nodal involvement, mainly of cervical nodes, is found at presentation or later during the course of the disease in most patients with extranodal involvement of the head and neck [44]. Primary nasal cavity lymphoma is a distinct clinical entity common in Asia, which extends locally into the maxillary and ethmoid sinuses. Lymphoma originating in the paranasal sinuses is aggressive, with frequent distant relapse and early mortality, therefore often warranting CNS prophylaxis.

$^{18}$F-FDG uptake in the buccal region, nasopharynx, tonsils, and nasal cavity may be physiologic. Even when asymmetric or of high intensity, $^{18}$F-FDG uptake does not necessarily indicate the presence of lymphoma and may be related to physiologic tracer activity or associated with upper respiratory tract infection (URI). Corresponding CT abnormalities, such as the presence of a soft tissue mass extending into the airways, may assist in the diagnosis of lymphoma on PET/CT, whereas a clinical history of recent URI may help to exclude malignancy as the cause of increased $^{18}$F-FDG uptake in this region. In a recent publication by Brianzoni and coworkers [46], the role of PET/CT in radiotherapy planning was assessed in 28 patients, including 4 patients with lymphoma of the head and neck region. PET/CT modified radiotherapy planning in 44% of the study population.

Lymphoma involving the thyroid may present on $^{18}$F-FDG PET/CT as a focal abnormality or diffusely increased uptake. Both presentations are, however,
nonspecific and may also be seen in goiter, thyroid adenoma, thyroid cancer, or thyroiditis [47]. The most common type of ocular-adnexal lymphoma is MALT lymphoma. Ocular-adnexa lymphoma refers to lymphoma arising in the extraocular orbital space involving the conjunctiva, eyelids, lacrimal gland, and orbital soft tissue [48]. The ability to identify lymphoma in this region on PET/CT may be hampered by the small size of these structures and the physiologic 18F-FDG uptake seen in the ocular muscles and nearby brain cortex. When a distinct mass is identified on the CT part of the PET/CT study, its 18F-FDG avidity can be more easily determined.

**Lymphoma in the region of the thorax**

In the thorax, ENL may involve the lung, pleura, chest wall, myocardium and pericardium, thymus, and breast. In the presence of direct extension from nodal mediastinal disease into the lung or chest wall, HD is staged according to the nodal disease with an associated extranodal (E) designation. These patients have a better prognosis compared with patients with stage IV disease. Pulmonary involvement without nodal disease is more commonly seen in recurrent disease than at presentation. On CT, lymphoma involving the lungs may show variable characteristics. The most common pattern is that of direct extension from nodal disease, whereas other appearances include central ill-defined nodules, rounded or segmental consolidation with an air bronchogram, or nodules or strikes extending peribronchially from the hilum [11,35]. Increased 18F-FDG uptake extending from involved lymph nodes into the lung or in separate pulmonary lesions should lead to the differential diagnosis of lymphomatous lung involvement versus a synchronous primary lung malignancy or a benign condition, such as active granulomatous disease. On PET/CT studies performed after therapy, the presence of 18F-FDG–avid lung abnormalities represents a more difficult diagnostic dilemma, because increased tracer uptake may be related to benign conditions, such as chemotherapy-induced pneumonitis, radiation, opportunistic infections, or bronchiolitis obliterans with organizing pneumonia (BOOP) [3]. Occasionally, the pattern of CT abnormality may be suggestive of infection or treatment-induced abnormalities.

Pleural and pericardial effusions are not uncommon in newly diagnosed lymphoma. Pericardial effusion may be associated mainly with large mediastinal masses. These effusions represent involvement of the pleura or pericardium by lymphoma or may be of a reactive etiology. Pleural involvement may manifest as plaques, discrete nodules, or a combination of the two, or it may be underappreciated on CT when interpreted alone but may be identified on fused 18F-FDG PET/CT images when corresponding in location to PET abnormalities (Fig. 7) [49].

The most common type of chest wall involvement is by direct extension from nodal disease in the anterior mediastinum. Chest wall involvement has been documented in 6% of patients with HD. Detection of chest wall invasion is of clinical relevance because it is associated with higher relapse rates and requires more aggressive therapy [11]. The fused PET/CT data allow for improved identification of chest wall invasion by precise localization of the extent of the mediastinal PET abnormality. In patients with HD, the thymus is considered “nodal,” and thymic involvement thus does not change the stage of the disease. Up to half of the patients with thoracic HD may show an enlarged thymus, which may be persistent after successful treatment as a result of rebound thymic hyperplasia or the development of thymic cysts. Active disease and benign thymic hyperplasia may be associated with 18F-FDG accumulation. The timing relative to

![Fig. 7. Lymphoma involving the pleura. CT (A) and fused PET/CT (B) images show increased 18F-FDG uptake in a pleural plaque (arrow in B), suggesting the malignant etiology of the pleural effusion.](image-url)
therapy and evidence or absence of active disease elsewhere in the body may assist in differentiating the two conditions. When the etiology is uncertain, a biopsy may be indicated [50].

Primary lymphoma of the breast is rare, accounting for less than 2% of ENLs and 0.38% to 0.7% of all cases of NHL. Breast NHL represents 0.14% of all female breast malignancies [1]. Secondary breast lymphoma is also rare but represents the largest group of metastatic mammary tumors [51]. The most common type of unilateral breast lymphoma is DLCL, accounting for 45% to 79% of the cases. Less common is Burkitt’s lymphoma, which may present as rapidly disseminating bilateral diffuse disease mainly affecting puerperal women (see Fig. 5). MALT lymphoma of the breast is a subgroup with a relatively frequency of 0% to 75% [1,51]. The radiographic and mammographic features of breast lymphoma are nonspecific. Breast density, which poses difficulties in interpretation of mammography, does not seem to affect the accuracy of PET in identifying lesions in the breast [52]. In addition, the whole-body imaging capability of PET enables detection of unexpected involvement of the breast, because mammography is not performed routinely in lymphoma staging and CT is not accurate for assessment of breast pathologic findings.

**Lymphoma involving the bone marrow and cortical bone**

Involvement of the bone marrow is found in approximately 50% to 80% of low-grade NHL, 25% to 40% of high-grade NHL, and 5% to 14% of HD at diagnosis, with a further increase in incidence later in the course of the disease. Bone marrow involvement signifies advanced-stage disease and may affect treatment and prognosis. Pakos and colleagues [53] performed a meta-analysis of the literature on the issue of the ability of 18F-FDG PET to evaluate bone marrow infiltration in the staging of lymphoma. Thirteen studies with a total of 587 patients were analyzed. Bone marrow biopsy (BMB) had a sensitivity and specificity of 51% and 91%, respectively, when compared with PET. In some patients, however, PET results that were considered to be false-positive findings initially because of negative BMB marrow turned out to be true-positive findings when involvement was confirmed on repeat biopsy to sites guided by PET findings (Fig. 8). PET had a better sensitivity in HD and in aggressive types of NHL compared with less aggressive NHL. Before therapy, a pattern of patchy increased marrow uptake is suggestive of lymphomatous involvement, whereas diffuse uptake, mainly in HD, may be associated with reactive hematopoietic changes within the marrow or myeloid hyperplasia [54]. Because neither bone marrow biopsy nor 18F-FDG PET imaging or MRI is highly reliable as a single technique, Kostakoglu and coworkers [3] suggested their complementary use for assessment of marrow involvement in lymphoma.

After treatment, mainly chemotherapy, or after granulocyte colony-stimulating factor (G-CSF), increased reactive 18F-FDG bone marrow uptake is often detected and is difficult to differentiate from active marrow disease [55]. Increased splenic 18F-FDG uptake, which often accompanies skeletal uptake after G-CSF therapy, was suggested to represent a “clue” for correct diagnosis [56].

Primary bone involvement occurs in 3% to 5% of patients with NHL, and 25% of patients with NHL have secondary bone involvement. Primary bone involvement is rare in HD (1%–4% at presentation). Secondary bone involvement occurs in 5% to 20% of patients with HD during the course of the disease, however [11,57]. Moog and coworkers [58] have reported 18F-FDG PET to be more sensitive and specific than 99mTc-methylene diphosphonate (MDP) bone scintigraphy for the detection of osseous involvement of lymphoma. Detection of malignant bone involvement on CT depends on the presence of a considerable amount of bone destruction. Early lymphomatous bone involvement may thus show positive lesions on PET that have a normal CT appearance [11].

**Lymphoma involving the nervous system**

Lymphoma of the CNS is confined to the cranial-spinal axis, including the brain, eye, leptomeninges,
and spinal cord, and accounts for 1% to 4% of malignant brain tumors and 2% to 4% of ENLs [1]. The incidence of CNS lymphoma is increasing in immunocompromised and immunocompetent patients [59]. The brain and meninges are the most commonly affected sites, followed by deep structures of the brain, including the periventricular areas, corpus callosum, basal ganglia, brain stem, and cerebellum. Most CNS lymphomas in immunocompetent patients are of the DLCL subtype. Patients with lymphoblastic or Burkitt’s lymphoma carry a 25% risk of CNS relapse. A high incidence of CNS relapse was also reported in association with high-grade lymphomas located in the testicles and paranasal sinuses [60,61].

Spinal cord compression may be the initial manifestation of lymphoma caused by localized ENL, or more commonly, by an epidural mass developing as an extension from involved nodes through the intervertebral neural foramina [62]. A valuable contribution of the CT portion of the PET/CT study in lymphoma is its capacity to identify the presence of the increased uptake in epidural masses and neural foramen invasion that may accompany vertebral or paravertebral disease (Fig. 9) [63].

Detection of lymphoma of the brain cortex may be hampered by the presence of physiologic 18F-FDG uptake. The latter may be less of a burden for detection of lesions in deeper brain structures. Palmedo and coworkers [59] compared the role of 18F-FDG PET with MRI in immunocompetent patients with biopsy-proven CNS lymphoma. PET identified lymphomatous lesions in six of seven patients and missed a 4-mm lesion in a single patient. During follow-up, PET accurately identified recurrence in three patients and excluded disease in five patients, with three of these patients having false-positive findings on an MRI study. A negative PET scan early during therapy was a reliable predictor of complete remission. It should be mentioned that steroid therapy, which is often initiated when brain involvement is suspected, may cause a reduction in 18F-FDG accumulation and lead to false-negative findings.

Peripheral neuropathy in patients with lymphoma may be caused by drug neurotoxicity, infection, nerve root compression, postradiation neuropathy, vasculitis, or infiltration of the peripheral nerve system (neurolymphomatosis). Two recently published case reports illustrated the benefit of 18F-FDG PET/CT imaging in the detection (sometimes the first modality to suggest the diagnosis) and monitoring response to therapy of neurolymphomatosis [64,65].

**Summary**

Lymphoma may originate in extranodal sites. ENL may also be secondary to and accompany nodal disease. ENL is probably more common than previously thought, with an incidence of approximately 25% in the overall population of patients with lymphoma, which may be even higher in some specific subtypes, such as MALT. 18F-FDG imaging has an
essential role in the staging of lymphoma, in monitoring the response to therapy, and in detection of recurrence. The introduction of 18F-FDG PET/CT hybrid imaging allows for accurate localization of disease and may be specifically beneficial for the detection of unexpected extranodal sites of disease or exclusion of disease in the presence of nonspecific extranodal CT findings. Accurate staging and localization often dictate the appropriate treatment strategy in patients with lymphoma. Therefore, at any stage in the course of the disease, the potential presence of extranodal disease should be considered when interpreting 18F-FDG PET/CT studies in patients with NHL and HD.

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