17
Reticuloendothelium Malignancy: Current Role of Imaging

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Key Points

- Imaging plays a vital role in the diagnosis and staging of lymphoma, thereby influencing patient management and outcome.
- Older modalities like lymphangiography have been superseded by newer cross-sectional imaging modalities.
- CT is probably the most widely used modality for this purpose.
- MRI is as useful as CT in the initial work-up of the patient.
- PET/CT has the ability to detect residual disease post-treatment, and is superior to both CT and MRI in this regard.

Introduction

The reticuloendothelial system (RES), also known as the mononuclear phagocytic system (MPS), is comprised of lymphoid organs including the bone marrow, liver, spleen, lymph nodes, thymus, microglia of the brain, tonsils as well as MALT (mucosa associated lymphoid tissue), BALT (bronchus-associated lymphoid tissue) and GALT (gut-associated lymphoid tissue). The T-lymphocytes make up 75 percent and the B-lymphocytes constitute 25 percent of the total lymphocytes. The spleen contains both B- and T-lymphocytes. Lymphoid tissue associated with mucosa, bronchus and gut are termed MALT, BALT and GALT, respectively. Tonsils respond to antigens by producing B-lymphocytes.

Since the basic tenets of imaging the reticuloendothelial system essentially remain the same, this chapter will be confined to imaging of the lymph nodes and spleen. Other organ systems (such as liver, thymus etc) will be dealt with elsewhere in this book.

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The merits and disadvantages of all imaging modalities will be discussed. Moreover, the increasingly important role of newer imaging techniques such as PET-CT will also be emphasized, especially in the evaluation of post-treatment residual disease.

Lymph Nodes and Spleen: Imaging *Armamentarium*

Sonography

Sonography is a straightforward and convenient technique to investigate lymphadenopathy [1]. Superficial lymphadenopathy is a common manifestation of lymphoma. The head and neck regions are the most common sites of involvement in lymphoma [2]. In clinical practice it is important to differentiate between lymphomatous and metastatic nodes. Lymphomatous nodes have a consistent pattern of involvement that provides a clue to their diagnosis. Submandibular, submental and deep cervical nodes are most commonly involved in lymphoma. Metastatic lymph nodes usually involve the submandibular and upper cervical regions. Posterior triangle involvement is infrequent in the metastatic disease process [3]. Two distinct features can be used to differentiate between lymphomatous and metastatic nodes [4]. The presence of distal enhancement in lymphoma is a significant and consistent differentiating feature from metastatic nodes. The second distinguishing feature is the presence of intranodal necrosis (both coagulation and cystic necrosis), which is more frequent in metastatic head and neck nodes, than in lymphomatous nodes [5]. Thus, sonography may prove to be a useful initial investigation [6]. However, the main disadvantages of sonography are the poor spatial resolution, its limited use in the thorax and deep retroperitoneum, and high operator dependency. These limitations may be overcome by Doppler sonography which offers functional imaging of the lymph node. Since feeding vessels determine tumor growth, color/power Doppler sonography (US) may be used to differentiate lymphoma from metastatic carcinoma [7-10].

Giovagnorio et al. [11] have described that vessels could be identified in all lymph nodes in patients with lymphoma. The majority of the lymph nodes demonstrated hilar vascularity because lymphoma arises within the lymph nodes and progresses in a centrifugal fashion.

Other studies have also reported a similar central perfusion pattern of lymphomatous nodes [12, 13]. In contrast, metastatic nodes show the presence of peripheral subcapsular vessels which access lymph nodes through afferent lymphatic vessels and invade marginal sinuses.

Recent reports suggest that intravenously administered microbubbles help the diagnosis of lymphadenopathy with accurate demonstration of vascular flow within a lymph node [14]. In a relatively small series of patients contrast-enhanced color power Doppler sonography with Levovist® was used to study the vascular patterns of lymph nodes with different types of lymphoma. The patterns of vessel distribution were classified as “central” when hilar vessels were seen with minimal or no rim vessels; a “peripheral” pattern was assigned when vessels were observed only

in the periphery; “capsular and central” when vessels were apparent in the parenchyma of the node, as well as in the periphery. B-cell lymphoma patients were noted to have a central vascular pattern in the lymph nodes. A peripheral vascular pattern was observed in the lymph nodes of T-cell lymphoma patients [15].

Sonography is a quick and noninvasive method for detecting splenic involvement in lymphoma [16]. Lymphomatous nodules and hematogenous metastases may have similar characteristics, appearing isoechoic or hypoechoic to normal spleen on unenhanced images [17, 18].

The different sonographic patterns observed in Hodgkin’s Lymphoma are: diffuse involvement, focal small nodular lesions, focal large nodular lesions and bulky disease. High-grade lymphoma is usually manifested as large nodular or small nodular lesions. The diffuse pattern is seen predominantly in low-grade lymphoma [19]. Different morphological patterns are also seen in Non-Hodgkin’s Lymphoma (NHL) with sonography. Diffuse infiltration is more common in NHL [20]. On sonography, lymphoma may appear anechoic, thus mimicking a cyst. The shape, echogenicity of the lesion and mode of posterior echo are not specific enough characteristics to differentiate between splenic lymphomas and splenic cysts. However, the boundaries of the lesions are indistinct in splenic lymphomas and distinct in splenic cysts. Blood flow signals and vascular penetration are also seen exclusively in splenic lymphoma [21].

Lymphomatous lesions in the spleen appear as clear hypoechoic defects after contrast medium injection. Regularly deposited vessels may be first seen encircling and then entering the nodule, especially during the early phase of opacification. The tumor tissue usually shows a lesser degree of enhancement, compared to the surrounding normal splenic parenchyma [22].

Computed Tomography

The potentially curative chemotherapeutic agents used for the treatment of lymphoma require accurate staging for maximal efficacy. Computed tomography (CT) has been the primary imaging technique used for staging and follow-up of patients with lymphoma for many years. In many institutions CT examination is the standard to map disease sites and estimate tumor burden.

Common CT criteria to assess Hodgkin’s and Non-Hodgkin’s Lymphoma in the lymph nodes and spleen are organomegaly, abnormal contrast enhancement, or presence of an abnormal mass. Enlarged nodes are the most common finding on CT of lymphoma (Fig. 17.1). Although absolute numbers are difficult to define, cervical, thoracic and pelvic lymph nodes are generally considered to be enlarged if they are greater than 10 mm in size. Abdominal lymph nodes are considered to be abnormal if they are greater than 5 mm, and inguinal lymph nodes are enlarged if they are greater than 15 mm in size. The sensitivity of CT in evaluating nodal and extranodal disease ranges between 60 percent and 90 percent [23]. The anterior mediastinal, pretracheal and hilar nodal chains are the most common nodal chains involving

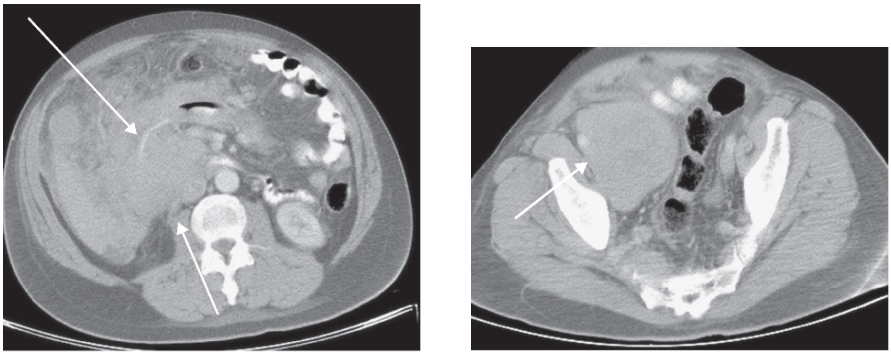

Fig. 17.1 Axial CT images of a 56-year-old patient with a known diagnosis of non-Hodgkin's lymphoma. (**a**) The lymphadenopathy has conglomerated to form a soft tissue mass compressing part of the small bowel with infiltration of the bowel wall. (**b**) This image shows a large soft tissue mass in the pelvis that represents enlarged lymph nodes. This mass displaces the bowel and the right external iliac artery

lymphoma in the chest [24]. In the thorax, Hodgkin's disease tends to spread to contiguous nodal groups. The subcarinal, peridiaphragmatic, periesophageal and internal mammary nodes are involved in decreasing order of frequency. Isolated hilar lymph node enlargement is a relatively unusual finding in the setting of lymphoma. The presence of large mediastinal adenopathy has a higher risk of relapse, and a dual treatment strategy with chemotherapy and radiation therapy is warranted regardless of tumor grade [25]. In most cases the enlarged lymphomatous nodes are homogeneous, although necrotic nodes are not uncommon. Hopper, et al. [26] have observed that the presence of necrosis has no significant effect on the patient's clinical response to treatment or ultimate survival. Necrotic nodes, when present, are most commonly associated with nodular sclerosing Hodgkin's disease. However, nodal necrosis can be identified subsequent to chemotherapy or radiation therapy. Enhancing nodes may be observed, though infrequently in NHL. Lymph node calcification before treatment is fairly rare, but can be associated with aggressive Hodgkin's or Non-Hodgkin's Lymphoma [27]. In lymphoma patients irregular or eggshell calcifications are seen in lymph nodes post-treatment [28].

Staging of lymphoma is as follows: Single-station nodal disease is defined as stage 1; multiple nodes restricted to one body area are defined as stage 2, and disease on both sides of the diaphragm is defined as stage 3. Visceral involvement is regarded as stage 4 (Fig. 17.2). Accurate description of the extent of disease is important for radiation therapy planning [29]. The extrapleural space can be involved by nodal disease, especially in patients with NHL [29]. Obstruction of the pleural lymphatics by the tumor is often associated with pleural effusion. Extranodal involvement is more commonly observed in NHL [30]. In Hodgkin's disease, extranodal invasion of adjacent tissue is seen in up to 15 percent of cases [3].

Another important role of CT in patients with lymphoma is to assess response to therapy, evaluate recurrence and monitor patients before and after treatment [32].

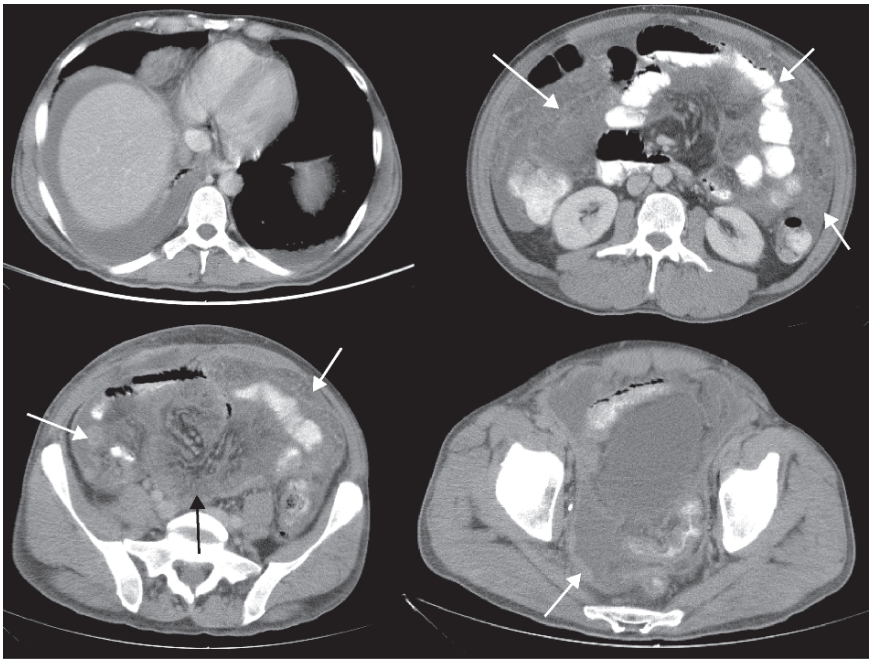

Fig. 17.2 Axial CT images of a 32-year-old patient with a known diagnosis of non-Hodgkin's lymphoma. The image shows nodular and infiltrative involvement of the lymphoma throughout the mesentery

Disease recurrence is common in the pericardial and internal mammary lymph nodes, since these are usually not included in the radiation field.

CT of the chest, abdomen and pelvis has also been shown to be valuable in the follow-up of lymphoma. Neumann, et al. have reported that CT enabled detection of unsuspected active disease in 43 percent of patients with NHL thought to be in remission [33]. Primary splenic lymphoma is rare. The spleen represents a "nodal organ" in Hodgkin's disease and an extranodal organ in NHL [31]. However, most of the primary splenic lymphomas tend to be NHLs (marginal zone cell lymphoma). Splenic involvement is usually secondary to generalized lymphoma. The most common finding is splenomegaly, but it may be absent in up to 30 percent of lymphoma patients. However, if the spleen is markedly enlarged in the presence of involvement of other sites, splenic lymphoma is more likely [34]. Staging laparotomy has shown that the spleen is infiltrated in about 30 percent to 40 percent of patients at presentation [35]. Splenic lesions in lymphoma could present as diffuse splenic enlargement, or a solitary mass and multifocal lesions (Figs. 17.3 and 17.4), with diffuse infiltration being the most common manifestation. If nodules are noted, they demonstrate low attenuation with reduced contrast material enhancement, compared with normal splenic tissue, and are infrequently larger than 1 cm in diameter [36]. However, caution should be exercised in interpreting CT scans obtained during the early phase of a bolus injection of contrast material, due to the

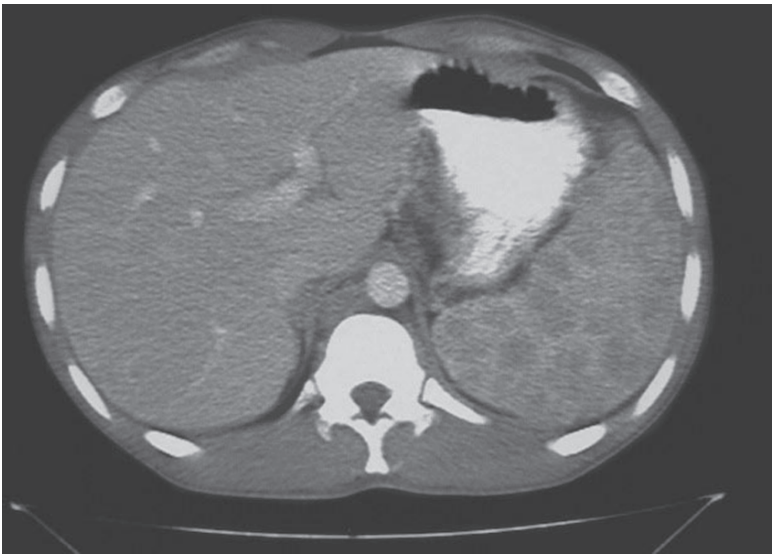

Fig. 17.3 CT image of a 42-year-old male patient with non-Hodgkin's lymphoma. There are multiple low attenuation lesions within the spleen

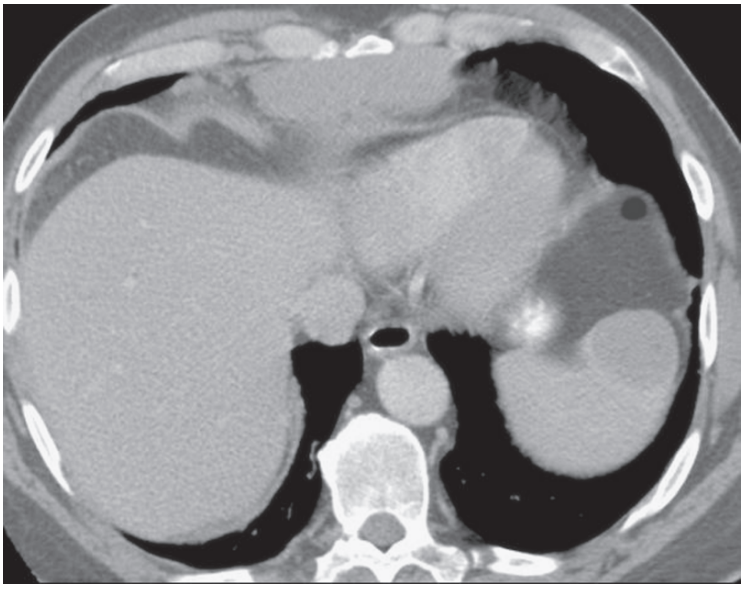

Fig. 17.4 Axial CT image in a 30-year-old patient showing a solitary hypodense mass in the spleen. This proved to be a Hodgkin's lymphoma

heterogeneous enhancement of the spleen that mimics tumor infiltration. Diffuse involvement of the spleen in Hodgkin's disease could be nonspecific, and splenomegaly may be present in the absence of lymphoma, or the spleen could be normal in size in spite of tumor infiltration [37-39].

The near isotropic images produced by multi–detector row spiral computed tomography (CT) also enables determination of splenic volume, accurate depiction of polar arteries, the presence, number and size of all accessory spleens, and of focal parenchymal lesions [40]. Despite advances in CT technology, CT has its limitations. It may not depict tumor activity within a post-therapy residual mass. Inability to detect disease in normal-sized lymph nodes could be a cause for false negatives. Moreover, splenic and bone marrow infiltration are not well depicted on CT [41]. CT assessment of lymphoma is frequently based only on size criteria. For example, lymph nodes less than 1 cm in diameter are not considered abnormal by most current criteria. In addition, CT may not be able to differentiate between residual tumor masses and fibrosis on post-treatment follow-up imaging [42].

PET/PET-CT

As discussed earlier, CT has inherent limitations in the detection and follow-up of lymphoma. PET with ^{18}F-FDG can provide functional information based on the increased metabolic demands of tumor cells requiring adenosine triphosphate generated by glycolysis [43]. In addition to detection of tumor foci in the lymph nodes and spleen, PET imaging has the ability to differentiate between aggressive and low-grade lymphomas. Aggressive lymphomas tend to have a higher ^{18}F-FDG uptake with an SUV of more than 10 [44, 45]. The median sensitivity and specificity reported for PET is 90.3 percent and 91.1 percent, respectively. The maximum joint sensitivity and specificity was 87.8 percent [46-49]. ^{18}FDG PET is very useful in the identification of patients with and without splenic disease and is superior to CT for this purpose. Splenic lymphoma, either diffuse or focal, tends to have an ^{18}FDG uptake greater than hepatic uptake [18]. Reported accuracies of ^{18}FDG PET and CT for evaluating the spleen are 100 percent and 57 percent, respectively [50]. In newly diagnosed Hodgkin's disease, FDG can identify splenic involvement precisely and is significantly more sensitive and accurate than Ga-67 for this purpose [51]. However, PET imaging has numerous limitations such as absence of precise anatomic landmarks for accurate localization of lesions, inherent lack of specificity since ^{18}F-FDG can be taken up by lymphomatous nodes and sites of active inflammation and physiologically by some organs and low-grade lymphomas may not demonstrate uptake or have a low ^{18}FDG uptake [52, 53].

The advent of PET-CT has remarkably improved the accuracy in the diagnostic work-up of patients with lymphoma. PET-CT provides dual modality imaging, which combines the functional information provided by PET and the excellent anatomic resolution offered by CT. Several studies [54, 55] have noted the role of PET/CT in the staging of lymphoma. PET/CT can aid in the differentiation between

tumoral and physiologic or inflammatory pathologic uptake, thereby overcoming false positives resulting from using PET alone in the diagnosis of lymphoma. PET/CT plays an important role in the staging of lymphoma since it can identify pathologic lymphadenopathy accurately [54, 56-58]. In a prospective study PET/CT proved to be superior compared with CT and PET alone in nodal evaluation and detection of extranodal disease [59]. There were some previous issues indicating that the use of oral and intravenous contrast for the CT part of PET-CT caused problems in CT-based attenuation correction [60, 61]. However, recent studies have demonstrated that intravenous contrast material, when used at normal concentrations, does not interfere with CT-based attenuation correction [62, 63]. However, the optimal protocol of PET/CT is not yet determined, and controversy remains regarding the acquisition of a full diagnostic CT with oral and intravenous contrast [55].

A major drawback of PET/CT is the concern regarding the radiation dose incurred by the patient. Whole-body mean effective dose from FDG is approximately 10.73 mSv [64]. A whole-body diagnostic CT scan significantly increases the effective dose to 19.262 mSv for a whole-body PET/CT scan. Hence, protocol optimization is vital for the evaluation of lymphoma with PET/CT, and must be tailored according to the patient in question.

Magnetic Resonance Imaging

The introduction of fast MR imaging techniques has reduced imaging time substantially without compromising the quality of MR images. MR imaging is considered to be as diagnostic as CT for staging Hodgkin's disease. The excellent soft tissue contrast and the lack of exposure to ionizing radiation are formidable advantages offered by MR imaging.

Lymphoma is usually hypointense or nearly isointense on T1-weighted images, and hyperintense on T2-weighted images. Injection of contrast medium may improve detection of splenic lymphoma [65]. Lymphomatous tissue has an increased water content that returns a high signal on the STIR sequence, enabling detection [66, 67]. Detection of splenic lymphoma at MR imaging is difficult because normal splenic parenchyma and lymphomatous tissue may have similar signal intensity [37]. Lymphomatous nodules are hypo- or isointense on T1-weighted MR images, and hyperintense on T2-weighted images. These nodules do not enhance as much as the normal spleen after administration of gadopentetate dimeglumine. MRI has a good capability in distinguishing nodal and extranodal involvement, both in Hodgkin's Lymphoma and in NHLs [68]. Detection of nodal involvement in normal sized lymph nodes and residual tumor activity after therapy are some issues that need consideration. However, newly developed lymphotropic contrast agents for MR imaging might be helpful to answer these questions in the future [69]. Detection of splenic involvement can alter management. Lymphomatous deposits have T1 and T2 signal intensities similar to those of normal splenic parenchyma. Gadolinium-enhanced sequences are more sensitive for the evaluation of splenic lymphoma.

Diffuse involvement may be seen as large irregularly enhancing regions. Multifocal disease is also common and can be seen as multiple focal lesions that are hypointense relative to the enhancing splenic parenchyma [70, 71].

Lymphangiography

Lymphangiography was used in the past to investigate lymphadenopathy and the staging of lymphoma. However, these indications are now evaluated using CT, PET/CT or MRI. Technologic advances leading to state-of-the-art CT and PET/CT scanning, coupled with the development of more effective chemotherapeutic regimens and the potential adverse effects of lymphangiography, have further led to its fallout in current clinical practice as a staging tool in patients with lymphoma. A study to determine the current value of lymphography in previously untreated patients with Hodgkin's and Non-Hodgkin's Lymphoma concluded that lymphographic findings did not significantly contribute to staging in these patients [72]. Detection of subtle nodal changes is no longer needed since the advent of potent chemotherapy and radiation therapy.

Interventional Radiology in Lymphoma

Image-guided biopsy of abdominal or thoracic lymphoma plays an important role in patient management and can be performed either by sonographic or CT guidance. Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) is feasible even in very small foci, when CT- or US-guided biopsy is not successful [73]. Fine needles (16 to 18 G) are just as likely as larger needles (20 to 24 G) to enable both determinations of tumor grade and treatment [74]. Flow cytometry is valuable in assessing immunophenotypic criteria that are helpful in the diagnosis of T-cell neoplasms. Features attributable for malignancy include loss or markedly dim expression of CD45; complete loss of one or more pan-T antigens and CD4/CD8 dual-positive or dual-negative expression [75].

Post-Treatment Follow-up Imaging

The treatment of lymphoma usually involves the administration of chemotherapy until a complete clinical remission is attained. Approximately 85 percent of patients will respond satisfactorily to their primary chemotherapy [76]. It is important to identify patients early in the course of chemotherapy who do not attain complete remission to modify treatment strategies either with high-dose chemotherapy or adjuvant radiotherapy.

Cheson's criteria [77] are most commonly employed to follow up residual disease with CT scanning. The maximum short-axis dimension is most commonly

used to measure residual disease following treatment [78]. However, a clear consensus has not been achieved regarding response criteria. The glaring limitation of using Cheson's criteria is that disease involvement is based solely on size criteria. Shape, longitudinal/transverse diameter ratios and enhancement patterns are not used in this assessment. The growing role of tumor volumetrics to monitor tumor response following treatment promises to address the limitations posed by using size as the only criteria to measure residual disease [79].

The inability of CT to differentiate active lymphoma from necrosis and fibrosis is a significant limitation in the follow-up for residual disease or relapse post-treatment. 67-Gallium scintigraphy is a metabolic imaging technique to detect active tumor tissue; however, low spatial resolution and difficulty identifying residual abdominal masses are serious limitations [80]. MRI demonstrates high accuracy in the assessment of residual disease post-treatment if performed at least six months after the end of therapy, reaching the highest sensitivity and specificity values at 12-month follow-up. MRI can help in distinguishing fibrous from active residual masses in treated Hodgkin's disease. Low signal intensity and low contrast enhancement are generally signs of inactive residues; homogeneous high signal intensity and high contrast enhancement are suggestive of active residual disease; heterogeneous signal intensity and heterogeneous contrast enhancement are indicative of partial remission or necrotic/inflammatory processes [81].

^{18}F-FDG PET can distinguish between post-treatment fibrosis and viable tumor. FDG-PET/CT can improve re-staging in lymphoma leading to improved patient therapy and survival [82]. Hypermetabolic brown fat can lead to false positives in the assessment of tumoral activity of residual masses [83].

Summary and Conclusion

Imaging has an important role in the diagnosis and staging of patients with lymphoma, with a major influence on both patient management and outcome. CT is probably the most widely used modality in patients with lymphoma bur MRI is probably as useful as CT in the initial work-up of the patient. Finally, PET/CT can detect residual disease in patients post-treatment better than both CT and MRI and is playing an increasing role in the imaging of patients with lymphoma.

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