The non-Hodgkin’s lymphomas (NHLs) are a heterogeneous group of neoplasms with varied manifestations. Unlike Hodgkin’s disease, which typically has a predictable pattern of spread, NHL is less predictable in its behavior. It is not confined to nodal or extranodal lymphatic tissue, and it can involve organs without apparent lymphatic tissue (e.g., testes or brain). In general, the indolent lymphomas are frequently widely disseminated at diagnosis, whereas the aggressive lymphomas tend to be more localized, often affecting extranodal organs.

The staging of NHL has become both more complicated and more accurate with the advent of increasing numbers of noninvasive studies and increased sophistication of the tools available for testing. The goal of staging is to define the extent of the disease so that patients with similar disease staging can be clustered into groups with similar prognostic significance. Therefore, staging of lymphoma provides information about its natural history. In most cases, however, lymphoma is approached as a systemic disease, attesting to the potential systemic nature of disease involving an immune organ system that is spread throughout the body. In the rarer cases of true stage I or II disease (10 to 15%), the accuracy of staging may be of more importance to modification of treatment strategy.

Unlike many solid tumors, in which stage more accurately equates with prognosis, this is true less often with the lymphomas, using currently available staging systems. For example, most indolent lymphomas present with advanced-stage disease with involvement of the bone marrow. Although stage is important in the International Prognostic Index, particularly for the large cell lymphomas, its importance may lie more in its measure of tumor burden. For example, does a bulky stage I lymphoma carry the same prognosis as a more extensive but non-bulky lymphoma? The true benefit of thorough staging is to permit a comparison of results from various treatment studies and to allow for uniform treatment plans and study groups. The value of comparable groups lies in their ability to predict the likelihood of response and outcome to proposed treatment.

**STAGING SYSTEMS**

The Ann Arbor staging system (Table 4–1) was formulated in 1971, primarily as a staging system for Hodgkin’s disease. This system defined the distribution of lymphatic involvement and has been adapted for use in NHL, where dissemination may be more hematogenous than lymphatic and, therefore, non-contiguous. Despite its drawbacks and inaccuracies, this system remains the most widely used staging system. Examples of problems with the Ann Arbor staging system include the following: (1) B symptoms (fever, night sweats, or weight loss) may be of less importance in NHL than in Hodgkin’s disease; (2) bulky disease and kinetics of disease are not addressed; (3) stage IV disease may be of differing consequence whether it is secondary to bone marrow involvement or extranodal sites of disease; and (4) stage III versus stage IV disease has more prognostic implication in Hodgkin’s disease. Furthermore, Ann Arbor staging is of little use in lymphoblastic lymphoma or Burkitt’s lymphoma. In general, the TNM staging used for solid tumors is
not of use in NHL, although an endoscopically derived TNM system using ultrasonography has been recommended in the staging of gastric mucosa-associated lymphoid tissue (MALT) lymphomas.5

**PATHOLOGY CLASSIFICATIONS**

Ultimately, patients need a histologic diagnosis. This can help guide further staging studies and treatment based on the natural history of the specific histologic subtype of lymphoma. Several classifications are in use, and none are perfect. Initially in the United States, the Rappaport Classification experienced the greatest use among clinicians; it was based primarily upon histologic assessment of nodular and diffuse patterns of large and small cells. The Lukes and Butler Classification and the Kiel classification recognized the immunologic nature of lymphoproliferative disease. The Working Formulation6 was an attempt at synthesizing the salient features of the six most dominant classifications at the time, including Kiel, World Health Organization (WHO), Lukes/Butler, Rappaport, Dorfman, and British National Lymphoma Investigation (BNLI), and has been the most widely used system until recently. It categorized disease primarily by morphology and biologic aggressiveness, defining low, intermediate, and high grades; however, it did not distinguish B- and T-cell lineage or certain subtypes of lymphoma that now can be defined by cytogenetic, immunologic, or biologic markers. The REAL (Revised European American Lymphoma) classification proposed by the International Lymphoma Study Group7 has gained prominence as a means of combining the pathologic, immunologic, and genetic information in conjunction with clinical data and includes lymphoproliferative disorders not recognized in the Working Formulation. The proposed WHO classification will further define REAL categories by morphology, immunophenotype, cytogenetics, clinical features, and postulated normal cellular counterparts. A detailed description of preferred biopsy techniques, histology, and immunopathology is provided in other chapters of this text.

**DIAGNOSTIC AND STAGING EVALUATION**

An outline of various diagnostic tests and staging for NHL appears in Table 4–2.

**Blood Screening**

A complete blood count (CBC) and differential, renal, and liver function tests are essential initial laboratory studies for a patient diagnosed with NHL. Lactate dehydrogenase (LDH) should be assessed as a measure of kinetically active (or necrosing) disease, particularly among the more aggressive lymphomas. Correlation between peripheral blood counts and bone marrow involvement is poor. Circulating lymphoma cells are unusual by routine microscopic evaluation in most circumstances, particularly at presentation, although tissue culture and molecular techniques can detect histologically inapparent disease.8 Erythrocyte sedimentation rate (ESR), β2-microglobulin, iron studies, and other inflammatory markers of disease are nonspecific but may be helpful in serial follow-up of patients in whom the markers are elevated at presentation. Calcium may be elevated in certain T-cell lymphomas such as adult T-cell leukemia/lymphoma. Uric acid and PO4/Mg are helpful in monitoring tumor lysis that may accompany the treatment of lymphomas. Protein studies are most useful in the indolent lymphomas, particularly those with plasmacytic features, or in chronic lymphocytic leukemia (CLL).

Serology can be useful in some cases to distinguish an infectious etiology rather than lymphomatous disease as a cause of B symptoms. Furthermore,
some serologic associations have been made such as Epstein-Barr virus (EBV) and Burkitt’s lymphoma or post-transplant lymphomas, human T-lymphotropic virus 1 (HTLV-1) positivity, and adult T-cell leukemia/lymphoma, especially in association with hypercalcemia; Kaposi’s sarcoma–associated herpesvirus (human herpesvirus 8) is seen in conjunction with body cavity–based lymphomas in patients with human immunodeficiency virus (HIV); and hepatitis C infection is associated with clonal B-cell expansions and certain lymphomas.

**Bone Marrow Assessment**

Bone marrow assessment consists of an aspirate for histology and for special studies, such as flow cytometry or cytogenetics. However, aspiration alone is inadequate for assessment of involvement, and a trephine bone marrow biopsy must be obtained. In many cases, treatment decisions are independent of marrow involvement, and assessment of marrow involvement is not always critical. Certain histologies commonly involve the marrow (such as follicular center cell lymphoma), but the extent and pattern of involvement may be of importance. For example, the follicular lymphomas are characterized by paratrabecular aggregates. Bilateral iliac crest assessment will increase the diagnostic yield, as will molecular studies of involvement such as polymerase chain reaction (PCR) analysis, but this may have little impact upon initial therapy.

In large cell lymphoma, bone marrow involvement may be of more consequence since it correlates with an increased risk of central nervous system (CNS) disease and the need to provide prophylactic intrathecal therapy as part of treatment. Cytogenetics may be of use in confirming pathologic or clinical suspicion of the diagnosis, such as t(14;18) in follicular center cell lymphoma or t(8;14) in Burkitt’s lymphoma. Gallium scanning in large cell histologies and MRI scanning also can help identify bone marrow involvement, but they are less sensitive for minor marrow involvement than are histology and molecular techniques. Histochemical stains of the marrow may be particularly useful in the aggressive large cell lymphomas (REAL) such as terminal deoxynucleotidyl transferase (TdT) staining in lymphoblastic lymphoma.

**Central Nervous System Assessment**

Assessment of the CNS is accomplished by imaging studies (see below) and cerebrospinal fluid (CSF) examination. In addition to diagnosis of primary CNS lymphomas, accurate assessment of the CNS is necessary to evaluate neurologic symptoms and to

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**Table 4–2. DIAGNOSTIC TESTS AND USES FOR STAGING NHL**

<table>
<thead>
<tr>
<th>Study</th>
<th>Essential</th>
<th>Special Circumstances</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory tests</td>
<td>cbc, differential, LFTs including LDH</td>
<td>Protein studies, ESR, β₂-microglobulin, calcium, uric acid, serology, cytogenetics</td>
</tr>
<tr>
<td>CT scan</td>
<td>Chest, abdomen, pelvis</td>
<td>Head and neck</td>
</tr>
<tr>
<td>MRI</td>
<td>—</td>
<td>CNS involvement</td>
</tr>
<tr>
<td>Ultrasonography</td>
<td>—</td>
<td>Bone lesions</td>
</tr>
<tr>
<td>Nuclear scans</td>
<td>Aggressive histologies</td>
<td>GU involvement</td>
</tr>
<tr>
<td>Gallium</td>
<td></td>
<td>Biliary tract involvement</td>
</tr>
<tr>
<td>PET</td>
<td></td>
<td></td>
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<tr>
<td>Bone scan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone marrow assessment</td>
<td>Aggressive histologies</td>
<td>Role yet to be determined</td>
</tr>
<tr>
<td>CNS assessment</td>
<td>Large cell involvement of bone marrow</td>
<td>Bony sites of involvement</td>
</tr>
<tr>
<td>Phenotyping</td>
<td>Lymph node biopsy</td>
<td>Effusions</td>
</tr>
<tr>
<td></td>
<td>Bone marrow</td>
<td></td>
</tr>
</tbody>
</table>

cbc = complete blood count; LFT = liver function test; ESR = erythrocyte sedimentation rate; CT = computed tomography; MRI = magnetic resonance imaging; CNS = central nervous system; GU = genitourinary; PET = positron emission tomography.

*Considered routine but may not impact on treatment.
assess histologies in which there is a predilection for CNS involvement, such as Burkitt’s or lymphoblastic lymphoma and HIV-related NHL. Certain extranodal sites of disease, including bone marrow, testis, paranasal sinus, and nasopharynx, also have an increased incidence of CNS involvement, thereby warranting assessment and prophylaxis. Studies of CSF should include cell count and differential by cytocentrifuge spin, chemistries, cultures and stains, and, most importantly, cytology. In certain circumstances, phenotyping may also be of value in documenting involvement.

**Effusions**

On occasion, effusions of the pleura, pericardium, and peritoneum require evaluation to determine whether they represent a transudative or exudative process. A chylous effusion without malignant cells does not change the stage of disease and occurs commonly in situations of bulky low-grade disease in which lymphatic flow is interrupted. In addition to standard cytologic analysis, phenotyping can be useful in helping to elucidate involvement. A pleural effusion of any etiology has been considered by some to be an ominous prognostic sign, but this may be more a reflection of bulk (primary disease compressing vasculature or lymphatics, or increased volume of disease due to pleural implants) than an independent poor prognostic feature.

**Specialized Testing**

Certain sites of involvement might warrant specialized testing. Extranodal presentation is more common in the aggressive lymphomas and may involve skin, CNS, bone, lung, gastrointestinal tract, and kidney. Elevation of alkaline phosphatase might signal bony involvement. Liver, lung, or renal involvement warrants assessment of function at these sites and potentially biopsy to substantiate involvement. Certain lymphomas have recognized patterns of spread warranting specific assessment. For example, testicular lymphoma has a predilection for the contralateral testis and CNS involvement. Likewise, the presence of preauricular node involvement is associated with disease in Waldeyer’s ring. Large cell lymphomas of Waldeyer’s ring often spread to the gastric region, necessitating radiographic or endoscopic evaluation of this site. In contrast, MALT lymphomas at these sites generally remain true to the site of origin and are less likely to spread along these pathways.

**Molecular Techniques**

Immunoglobulin gene or T-cell receptor rearrangements, expression of oncogene translocation, cytogenetics, and molecular studies of proto-oncogenes and tumor suppressor genes may have implications in the staging and treatment of lymphomas in the future. Whereas bcl-2 expression is common in the follicular lymphomas, no single genetic marker has been observed in the large cell histologies. Bcl-6 gene rearrangement may have import in the large cell histologies, predicting a more favorable outcome. Polymerase chain reaction can assess tumor involvement at the molecular level and detect minimal residual disease. Also, PCR can reliably detect one cancer cell in 1,000,000 normal cells. This may be of more concern in protocol studies, particularly in assessing response or persistence of minimal residual disease, rather than guiding primary therapy.

**Imaging Techniques**

Multiple imaging modalities are used in the staging of NHL. These include plain films (most commonly, chest radiographs, as well as films of any symptomatic bones), computed tomography, sonography, magnetic resonance imaging, and radionuclide imaging (predominantly gallium scanning and positron emission tomography). Lymphangiography, although historically important in the staging of lymphoma, is rarely performed at present. Other imaging modalities, including gastrointestinal series, urography, and mammography, also may be used when there is suspicion of lymphomatous involvement in these specific regions.

**Plain Films**

*Chest radiographs*. The conventional chest radiograph is the initial radiologic study in the detection,
diagnosis, and staging of intrathoracic lymphoma (Figure 4–1). Chest radiography is fairly sensitive in the detection of most thoracic sites of lymphoma, including lymph nodes, lung parenchyma, pleura, pericardium, and chest wall. However, subcarinal and internal mammary lymph nodes often are poorly imaged, and posterior mediastinal and anterior diaphragmatic lymphadenopathy often are not visible.15,16 Unlike in Hodgkin’s disease, in which superior mediastinal lymphadenopathy is typically present (84% of cases), in NHL, mediastinal involvement may be isolated to the posterior mediastinal and paracardial nodal regions.17 Even with bulky adenopathy, it is uncommon to find airway compromise, superior vena cava syndrome, dysphagia, or other symptomatic evidence of adjacent organ compromise as lymphoma more commonly displaces than encases adjacent mediastinal structures.18

Pulmonary involvement may occur without associated mediastinal or hilar lymphadenopathy. The most common presentation is that of an ill-defined pulmonary nodule (Figure 4–2). However, nodules may be solitary or multiple, tend to involve the lower lobes and perihilar areas, and may contain air bronchograms. The latter is a characteristic not commonly seen with other metastatic nodules. Bronchovascular (or lymphangitic) spread along the perivascular and peribronchial bundles causes coarse reticular or patchy opacities, typically due to direct spread from lymph nodes, and is more commonly seen with Hodgkin’s disease19 (Figure 4–3). The pneumonic (or alveolar) form is the least common radiographic presentation of pulmonary lymphoma and is indistinguishable from an infectious process17 (Figure 4–4).

**Bone radiographs.** Conventional radiographs are obtained in patients with symptoms referable to the bones, most commonly revealing permeative osteolytic lesions (Figure 4–5). Sclerotic lesions and periosteal reaction are rare. Primary bone lymphoma is uncommon, occurring in younger individuals (11 to 40 years old) and involving the metaphyseal region of the appendicular skeleton. Secondary involvement is much more common and indicates stage IV disease, with the most frequent sites of involvement being the spine, pelvis, and skull20 (Figure 4–6). A primary bone lesion indicates stage IE disease, with associated nodal involvement at two or more sites on the same side of the diaphragm indicating stage IIE disease, and nodes on both sides of the diaphragm indicating stage IIIE disease. In a recent review of 422 patients with osseous lym-

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**Figure 4–1.** Posteroanterior (A) and lateral (B) chest radiographs in a 33-year-old male with large cell lymphoma presenting as a large anterior mediastinal mass (arrows).
phoma, staging was the most important prognostic variable, with 5- and 10-year survival rates of over 50 percent with primary disease and 12 to 20 percent to survival rates in patients with both osseous and extraosseous involvement. Therefore, bone scintigraphy, chest radiography, and abdominopelvic computed tomography (CT) are indicated in patients with suspected primary osseous lymphoma. Bone lymphomas are usually aggressive, predominantly large cell lymphomas. Low-grade lymphomas

![Figure 4-2](image2.png)

**Figure 4-2.** Posteroanterior (*A*) and lateral (*B*) chest radiographs in a 69-year-old female with non-Hodgkin’s lymphoma manifesting as an ill-defined solitary mass in the left lower lobe (*arrows*).

![Figure 4-3](image3.png)

**Figure 4-3.** Radiograph in a 47-year-old female with bronchovascular extension of large cell lymphoma from the anterior mediastinum and hila (*arrows*).
uncommonly affect bone, but they frequently infiltrate the bone marrow.\textsuperscript{19}

**Computed Tomography**

**Chest.** The use of CT for evaluation of thoracic involvement by NHL is somewhat controversial. Several studies have shown that CT is more sensitive in the detection of intrathoracic disease than plain chest radiography and may increase the stage of disease.\textsuperscript{15,16} However, the importance of CT with regard to staging and management is disputed. Khoury and colleagues, in a study of 48 patients with NHL, concluded that chest CT is useful for initial staging in two groups of patients: those patients with stage I or II disease and questionably abnormal or normal chest radiographs and those patients with definitely abnormal chest radiographs and no evidence of extrathoracic disease. The additional information from CT is felt to be useful for staging in the former case and for defining radiation portals in the latter case.\textsuperscript{22} Castellino and colleagues concluded that chest CT is not indicated in the initial staging of any patient with NHL as the information does not affect initial therapy at all, given the near-universal use of chemotherapy for aggressive lymphomas and in the majority of patients with low-grade neoplasms.\textsuperscript{16} However, others argue that chest CT does play a role in initial staging as it gives the most thorough baseline evaluation and is useful for follow-up assessment of disease.

**Abdomen.** Computed tomography has replaced lymphangiography (LAG) as the staging procedure of choice for evaluation of intra-abdominal and pelvic lymphadenopathy. Reported sensitivities and accuracies for LAG are 100 percent versus 86 percent and for CT are 91 percent versus 82 percent, respectively, with equal specificities of 75 percent.\textsuperscript{23} Lymphangiography offers the advantage of evaluating internal nodal architecture, thus detecting tumor defects in small nodes that would not appear abnormal with CT. Also, LAG can be useful in follow-up and for radiation planning, and it is relatively inex-

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**Figure 4–4.** Radiograph in a 25-year-old male with alveolar form of large cell NHL presenting as dense consolidation with air bronchograms in the right lower lobe.

**Figure 4–5.** Radiograph of an osteolytic lesion in the tibial metaphysis (arrows) of a 42-year-old male; the lesion is compatible with biopsy-proven NHL.
pensive. However, disadvantages include the limitation of opacification to the mesenteric, upper retroperitoneal, porta hepatis, and peripancreatic lymph nodes and the inability to image other potential abdominopelvic sites of involvement (Figure 4–7). In addition, LAG requires considerable expertise to perform and interpret, but it is no longer routinely taught in diagnostic radiology residency programs. At some institutions, both CT and LAG are used to complement one another.23 Recent studies indicate no significant contributions by LAG in the staging of lymphoma.24,25 Thus, CT has become the examination of choice for staging of NHL in the abdomen to determine the presence or absence of nodal disease and to define the extranodal extraluminal extension of NHL.26 The latter includes ill-defined stranding within the mesentery, without discrete mesenteric nodal masses but typically with associated retroperitoneal lymphadenopathy.

The detection of hepatic or splenic disease is dependent upon the size of tumor deposits (Figure 4–8). Unless there is marked organomegaly (Figure 4–9), the use of size criteria alone as predictors of disease in the liver and spleen is inaccurate. Lymphomatous involvement may be too small to detect by cross-sectional imaging studies. Alternatively, diffuse splenic infiltration may go undetected. However, the latter would typically be accompanied by subdiaphragmatic lymphadenopathy, so staging and management would not commonly be affected.18

The gastrointestinal tract can be involved by direct extension from adjacent nodal masses or by intrinsic lymphoma (Figure 4–10). This represents the most common extranodal site of NHL, with the stomach being most frequently involved, followed by small intestine and colon. In children, gastrointestinal lymphoma is nearly always seen in males, involves the ileocecal region, and is often of Burkitt-type histol-

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Figure 4–6. Radiograph of a large lytic lesion involving the right acetabulum (arrows) in this 38-year-old male with large cell lymphoma.

Figure 4–7. Computed tomographic image in a 68-year-old male with follicular lymphoma causing bulky retroperitoneal and mesenteric lymphadenopathy.

Figure 4–8. Computed tomographic image in a 29-year-old female with radiographically apparent hepatic and splenic involvement by large cell lymphoma.
Staging of Non-Hodgkin’s Lymphoma

Stage of disease is the most important prognostic factor with gastrointestinal NHL. Endoscopy and gastrointestinal radiography often will reveal an abnormality, but the findings are nonspecific. One helpful characteristic in differentiating gastric lymphoma from carcinoma is the persistence of gastric pliability, which is not typically seen in carcinomas, in which the stomach becomes rigid.

Renal lymphoma has been reported to occur in 4.9 percent of patients at presentation but has been seen in 30 to 50 percent at autopsy. It typically is due to direct extension from adjacent nodes or perirenal involvement and less commonly is due to an intrinsic mass or masses (Figure 4–11).

The use of intravenous contrast for CT is an area of controversy. There is no question that the presence of intravenous contrast can increase the visibility of abnormal structures and intraparenchymal lesions (eg, within liver, spleen, or kidneys), thus increasing sensitivity for their detection. Some radiologists argue that a knowledge of anatomy is sufficient and that abnormal structures should be detected without the assistance of intravenous contrast. Although intravenous contrast does enhance lesion detection in the liver and spleen, imaging techniques cannot be relied upon to accurately predict splenic involvement, and isolated hepatic involvement at presentation is uncommon.

Brain. Primary CNS disease is less common than is secondary involvement by NHL. The latter typically is associated with widespread disease and occurs in 5 to 29 percent of patients with systemic lymphoma. The diagnosis of intracranial lymphoma should be considered in high-risk groups, specifically immunocompromised patients, patients with testicular or epidural NHL, and those patients with high-grade histology (regardless of primary site). Primary CNS lymphoma typically lacks evidence of systemic dissemination and has a high inci-

Figure 4–9. Massive splenomegaly seen in a computed tomographic image in a 54-year-old male with mantle cell lymphoma.

Figure 4–10. A, Computed tomographic images. A 61-year-old male with follicular lymphoma and large mesenteric mass (white arrows) engulfing/invading adjacent colon (black arrows). B, Marked thickening of the stomach wall in this 53-year-old female with primary gastric lymphoma.
ence of local failure. This has led to the incorrect conclusion that extensive radiologic imaging is not necessary for staging. However, small studies have noted the importance of complete staging in primary CNS lymphoma as 4 to 12 percent of patients may have systemic disease.29,30

The CT appearance of an intraparenchymal brain lesion is that of an isodense or hyperdense homogeneous enhancing mass in the periventricular or subarachnoid space, with or without peritumoral edema26,31 (Figure 4–12). Epidural, subdural, and leptomeningeal spread along the brain and spinal cord are much better evaluated with magnetic resonance imaging (MRI).

**Head and Neck.** The head and neck (specifically, Waldeyer’s ring) is the second most common site of extranodal lymphoma. Systemic disease is present in approximately 40 to 60 percent of patients presenting with head and neck disease. Several patterns of disease have been described, including nodal only, extranodal only, nodal and extranodal, or multifocal. Extranodal disease is the most common pattern, with Waldeyer’s ring being the most common site.32 In these patients, CT scanning is most useful as findings associated with extranodal-extralymphatic disease are typically more suggestive of NHL. In patients with NHL, lymph nodes may be small but numerous, or enlarged, but are typically not necrotic. Therefore, the usefulness of CT in the staging of lymphoma in the head and neck is debated.
**Bone.** Although conventional radiographs are adequate to identify bone lymphoma in the appendicular skeleton, CT scanning is important in the evaluation of those lesions involving the axial skeleton (Figure 4–13).

**Sonography**

**Genitourinary tract.** One of the most accepted uses of sonography in the staging of lymphoma is to evaluate the genitourinary (GU) system. Although direct invasion of the GU system by adjacent nodal masses is visualized adequately with CT, sonography is used occasionally for the detection of intrinsic renal masses. One must be aware of the sonographic appearance of renal lymphoma and the potential for a homogeneously hypoechoic or anechoic mass to be misinterpreted as a cyst.33

Sonography is the modality of choice in the evaluation of the testis (Figure 4–14). The testicle is the most commonly involved organ among GU tract presentations of lymphoma.27 Testicular lymphoma occurs in older males (over 50 years of age). It is bilateral in 10 to 23 percent of cases,26 thus necessitating sonographic evaluation of the symptomatic and the contralateral testes. Testicular lymphoma has a propensity for extension to the periaortic lymph nodes, as well as spread to the lung, CNS, and Waldeyer’s ring. Staging therefore includes imaging evaluation of these areas.27,34,35

**Miscellaneous.** Sonography is used occasionally to further characterize lesions detected with CT. For example, it may be useful in distinguishing a small intrahepatic cyst or hemangioma from a solid focus of lymphoma, or it may be used in evaluating the adnexa, for which CT is suboptimal. Sonography also is used as an adjunct to mammography in the evaluation of breast lesions (Figure 4–15). In special circumstances (eg, pregnancy), sonography may be used in the evaluation of cervical, intrathoracic, and intra-abdominal disease. However, its limited field of view and high operator dependency limit its widespread use in the staging evaluation of NHL.

**Magnetic Resonance Imaging**

**Cerebrospinal.** Leptomeningeal spread of lymphoma cells or extradural masses that cause compression are more typical manifestations of secondary CNS lymphoma than is intrinsic involvement of the brain and spinal cord.18 Magnetic resonance imaging is more sensitive in its detection than is CT and is therefore the imaging modality of choice for the evaluation of cerebrospinal involvement by lymphoma (Figure 4–16).

**Chest.** For initial staging of intrathoracic lymphoma, MRI has not been shown to be significantly

![Figure 4–13. Axial computed tomographic image in a 23-year-old male with primary bone lymphoma revealing a large left iliac expansile soft tissue mass with bony destruction.](image)

![Figure 4–14. Right testicular sonogram in a 65-year-old male with bilateral testicular masses revealing two well-defined hypoechoic masses (arrows). Pathology revealed large cell lymphoma.](image)
MALIGNANT LYMPHOMAS

better than CT to justify its expense and time. However, there are a few specific situations in which MRI is superior to CT due to its multiplanar and angiographic capabilities. These include the evaluation of suspected chest wall invasion (Figure 4–17) or pericardial involvement and vascular assessment in patients with suspected venous compression or occlusion from enlarged nodal masses\textsuperscript{36–38} (Figure 4–18). The use of MRI in differentiating residual disease from fibrosis in residual mediastinal masses following treatment has been evaluated;\textsuperscript{39,40} however, gallium scintigraphy remains the gold standard.

**Abdomen.** Magnetic resonance imaging and CT are fairly equivalent in the detection of nodal involvement.\textsuperscript{41} Possibly, MRI has a potential role in the diagnosis of splenic lymphoma, using a superparamagnetic contrast agent.\textsuperscript{42} However, given its cost and the time involved, MRI has no standard role in the evaluation of abdominal disease.

**Bone.** Magnetic resonance imaging can be used in the evaluation of bone lesions (Figure 4–19). Advantages over bone scintigraphy and conventional radiographs are its increased sensitivity and ability to image in the sagittal and coronal planes. In addition, MRI can detect lymphomatous involvement of bone marrow.
Figure 4–17. Axial magnetic resonance image revealing chest wall invasion (arrow) from an anterior mediastinal large cell lymphoma (arrowheads) in a 54-year-old female.

Figure 4–18. Coronal gradient echo magnetic resonance image in a 35-year-old female with mediastinal large cell lymphoma revealing compression of the distal superior vena cava, as well as compression and encasement of the left subclavian and brachiocephalic veins.
Radionuclide Imaging

**Gallium-67 and thallium-201 scintigraphy.** Gallium scintigraphy is dependent on the binding of gallium 67 citrate to transferrin receptors in the tumor. The clinical impact of gallium-67 imaging for NHL remains somewhat controversial. However, if performed with the administration of 10 mCi of gallium 67 citrate and subsequent acquisition of both planar and SPECT (single-photon emission computed tomography) images at 72 hours, gallium-67 scanning remains the “gold standard” for radionuclide imaging of lymphoma. Aggressive NHLs are typically gallium avid, although low-grade or follicular lymphomas are often not gallium avid (or have very low gallium avidity). Thallium-201 scintigraphy may be useful in these low-grade lymphomas (Figure 4–20). One small study revealed 100 percent sensitivity with thallium-201 imaging and only 56 percent sensitivity with

![Figure 4–19. Proton-density coronal magnetic resonance image of the right knee in a 49-year-old female with distal femoral and proximal tibial non-Hodgkin's lymphoma (arrows).](image)

![Figure 4–20. A. Gallium-67 scintigraphy revealing no abnormal uptake in this 50-year-old male with follicular lymphoma. B. Thallium-201 scintigraphy revealing activity in enlarged axillary, mediastinal, and cervical lymph nodes.](image)
gallium-67 scintigraphy in low-grade disease. Although the mechanism of thallium-201 uptake in lymphoma is unclear, several mechanisms have been postulated including blood flow, tumor viability, the adenosine triphosphate sodium-potassium pump, a co-transport system, and calcium-channel mechanisms. Gallium scintigraphy is also useful in predicting clinical outcome in aggressive NHL. Persistent gallium-avid disease during therapy is a poor prognostic indicator, with a high risk of subsequent relapse. Following therapy, residual soft tissue masses often can be seen on CT, and gallium scintigraphy plays a major role in differentiating residual viable disease from fibrosis (Figure 4–21).

**Positron emission tomography.** Positron emission tomography (PET) is the newest radionuclide imaging modality to be used in the staging of lymphoma (Figure 4–22). Radiolabeled fluorodeoxyglucose is taken up and metabolized by malignant cells, which then emit positrons, thereby permitting imaging of sites of uptake. Multiple studies have shown at least equal sensitivity and increased specificity of PET when compared to CT or MRI. However, the latter studies are more accurate for measuring disease and determining its exact anatomic location. Adequate prospective studies comparing PET to gallium imaging (with SPECT and appropriate radiopharmaceutical dose and time interval) have not yet been performed. Positron emission tomography may be useful

![Figure 4–21. A, Axial computed tomographic (CT) image in a 31-year-old male, following completion of chemotherapy for large cell lymphoma, revealing residual ill-defined anterior mediastinal soft tissue (arrow). B, Sagittal images from gallium-67 SPECT (single-photon emission computed tomography) revealing gallium avidity in the anterior mediastinum (arrows), corresponding with the CT finding shown in A and indicating residual lymphoma.](image-url)
in detecting splenic involvement, in contrast to gallium scintigraphy, which is of limited value below the diaphragm due to normal splenic uptake and bowel excretion. A limitation of PET is the uptake of radioisotope within muscles of the neck, which can be unilateral and focal (eg, at head of sternocleidomastoid muscle) and may be mistaken for lymphomatous involvement in supraclavicular and pectoral lymph nodes. Also, PET is not useful in imaging MALT-type lymphomas. Studies of PET, though encouraging, are inconclusive. Large prospective well-designed studies must be undertaken before its role in the staging of lymphoma can be defined.

**Technetium-99m bone scintigraphy.** Bone scanning typically is not employed in the routine staging evaluation of NHL. A specific situation in which it is indicated is the patient with suspected primary bone lymphoma; bone scintigraphy is used to determine if disease is mono- or polyostotic.

**CONCLUSION**

The NHLs are a heterogeneous group of diseases that are increasing in frequency. The tools available for staging them at diagnosis and for guiding their further management through and after treatment also have greatly increased in number and accuracy, and have the ability to detect minimal residual disease. With this increasing sophistication, more accurate initial staging and earlier detection of relapsed disease are possible, allowing for effective and successful intervention.

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