TABLE 49-3 STAGING EVALUATION FOR LYMPHOMAS

REQUIRED EVALUATION PROCEDURES
Biopsy of lesion with review by an experienced hematopathologist
History with attention to the presence or absence of B symptoms
Physical examination with attention to node-bearing areas (including Waldeyer's ring) and size of liver and spleen
Standard blood work:
Complete blood count
Lactate dehydrogenase and β_2-microglobulin
Evaluation of renal function
Liver function tests
Calcium, uric acid
Bone marrow aspirate and biopsy
Radiologic studies, including:
Chest radiograph (posteroanterior and lateral)
Chest, abdomen, and pelvic CT scans
PET scan (in Hodgkin's and intermediate- and high-grade lymphomas)
PROCEDURES REQUIRED UNDER CERTAIN CIRCUMSTANCES
Plain bone radiographs of symptomatic sites or abnormal areas on bone scan
Brain or spinal CT or MRI if neurologic signs or symptoms
Serum and urine protein electrophoresis
Lumbar puncture with cerebrospinal fluid cytology (Burkitt's and lymphoblastic lymphoma)

B symptoms, Fever, sweats, and weight loss >10% of body weight; CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography.

TABLE 49-4 LYMPHOMA STAGING SYSTEM

STAGE*	DESCRIPTION
I	Involvement of a single lymph node region or structure (I) or a single extralymphatic site (IE)
II	Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of a contiguous extralymphatic site and lymph node region (IIE)
III	Involvement of lymph node regions on both sides of the diaphragm (III), which may be accompanied by localized involvement of one extralymphatic site (IIIE) or spleen (IIIS) or both (IIISE)
IV	Diffuse or disseminated involvement of one or more extralymphatic organs with or without associated lymph node involvement

*Presence or absence of symptoms should be documented with each stage designation: A (asymptomatic) or B (fever, sweats, and weight loss >10% of body weight).

the extent of involvement, provides prognostic information, and may influence the choice of therapy. The modified Ann Arbor staging classification is used to stage patients with NHL and Hodgkin's disease (Table 49-4).

A variety of ancillary tests may be performed in specific situations. For example, a test for HTLV-1 or HIV should be performed if adult T-cell leukemia/lymphoma is suspected. Patients with a clinical history suggesting immunodeficiency or behavioral risk factors should be tested for HIV infection. A gastrointestinal series or endoscopic evaluation may be warranted for patients with gastrointestinal symptoms or patients at risk for gastrointestinal tract involvement (i.e., mantle cell lymphoma and other lymphomas involving Waldeyer's ring). The choice of therapy for NHLs is guided by stage, specific subtype, and clinical considerations such as age and the general medical condition of the patient.

Lymphoma Subtypes

Indolent Non-Hodgkin's Lymphomas

The common low-grade or indolent histologic conditions include follicular lymphoma, small lymphocytic lymphoma (which is identical to CLL and discussed later), and marginal zone lymphomas.

Follicular lymphoma accounts for one third of all lymphomas and is the most common indolent lymphoma. It is a mature clonal B-cell neoplasm that histologically retains nodular architecture in the lymph node, which is infiltrated by small, mature-appearing lymphocytes. The immunophenotype is positive for surface markers (CD10, CD19, CD20, CD21) and negative for CD5. Follicular lymphomas are characterized cytogenetically by the t(14;18) translocation that juxtaposes the immunoglobulin heavy chain *(IGH)* locus with the antiapoptotic B-cell CLL/lymphoma 2 gene *(BCL2)*; the BCL2 protein is uniformly overexpressed in follicular lymphomas, immortalizing affected cells.

Follicular lymphoma is a low-grade, indolent neoplasm with a long natural history (median survival approaches 10 years), but 80% to 90% of patients have advanced-stage (III/IV) disease at diagnosis, often with bone marrow involvement, and they cannot be cured with standard treatment modalities. For up to one half of patients with follicular NHL, the disease eventually transforms to a more aggressive lymphoma, characterized pathologically by a diffuse large cell infiltrate and clinically by rapidly expanding nodes or other tumor masses, rising lactate dehydrogenase (LDH) levels, and the onset of disease-related symptoms.

Management of follicular lymphomas is influenced by the stage. For the few patients with early-stage (I/some nonbulky II) disease after clinical staging, the appropriate treatment is radiation therapy. With the use of subtotal or total lymphoid irradiation, more than one half of patients with early-stage disease achieve a durable remission or cure.

For patients with advanced-stage disease, the management is more controversial. Although advanced-stage indolent NHL is responsive to a variety of treatment modalities, the incurability and the long natural history have led to the practice of deferring treatment until the patient develops symptoms. This strategy is referred to as the *watch and wait approach*. Indications for treatment include cosmetic or mechanical problems caused by enlarging lymph nodes, high tumor burden, constitutional symptoms, and evidence of marrow compromise.

Available treatment options include monoclonal antibody therapies, chemotherapeutic agents, and radiolabelled antibodies. For most patients, the appropriate treatment typically includes the chimeric anti–B-cell monoclonal antibody rituximab with or without systemic chemotherapy. The addition of rituximab to chemotherapy regimens has increased response rates, duration of remission, and in some studies, overall survival (level I evidence).

The choice of chemotherapy to employ in combination with rituximab may be influenced by the patient's age and medical condition. Multiple options are available, and no regimen has proved superior with regard to overall survival. The combination of bendamustine, a unique agent with properties similar to alkylating agents and purine analogues, plus rituximab appeared advantageous compared with the CHOP regimen