The appropriate classification of the malignant lymphomas was a subject of contention since the first attempts to define distinct subtypes of lymphoma. From the original report by Thomas Hodgkin in 1832 through the early twentieth century, a multitude of clinical entities were named and described with variable and imprecise language, ranging from reticulum cell sarcoma to lymphosarcoma. The earliest attempts at systematic classification of the lymphomas emerged in the 1930s and 1940s, based on either morphology alone or in combination with clinicopathologic considerations. These efforts led in part to the Rappaport classification, which was the first system to incorporate prognosis in a lymphoma classification system.1

PATHOLOGY

Since that time, an expansion of understanding of immunology has led to a similar blossoming in number and variety of classification systems for the lymphomas, although the two that were the first to be widely adopted were the Kiel classification (generally favored in Europe) and the Lukes and Collins classification (more popular in North America). These systems coexisted and competed with other proposed modifications of the Rappaport classification, including Dorfman’s working classification and the British National Lymphoma Investigation classification. Driven by a desire to adopt a common language, in part to facilitate the conduct and comparison of clinical research, unification was attempted in 1982, when Rosenberg, DeVita, and Kaplan, under the auspices of the United States National Cancer Institute (NCI), brought together experts with the intent of identifying one of the extant classification systems as the most prognostically powerful. No single system emerged victorious, however, and instead an “international working formulation” (IWF) was put forward to allow clinicians to interpret findings reported within the context of classification systems with which they were potentially unfamiliar.2 The IWF soon was adopted in North America for classifying lymphomas, although the Kiel classification and subsequent modifications retained prominence in Europe.3 However, by the 1990s even the modifications to the Kiel classification were felt to have become outdated, and the most obvious flaw of the IWF—its strict emphasis on morphology and natural history at the expense of excluding the growing body of knowledge of lymphoma biology—made the need for a modern classification system all the more apparent. A second attempt at unification was attempted under the aegis of the International Lymphoma Study Group, an effort charged with incorporating all of the then-available understanding of morphology, genetics, and molecular science in creating a classification system that could be broadly adopted and allow for consistent language and reproducible diagnosis. The report of their efforts was published in 1994 as the Revised European-American Lymphoma (REAL) classification.4 The REAL was updated and refined with the World Health
Organization (WHO) classification, maintaining the structure of the REAL and sharing its focus on morphology and immunophenotype over clinical outcomes. The resulting WHO classification remains the currently accepted worldwide classification system for lymphoma.

Within the WHO classification, there exist 27 distinct types of lymphoma, not including acknowledged subtypes and subcategories that were also recognized. The major diagnostic entities are listed in Box 1. In addition to characteristic architectural morphology, different types of lymphoma often possess stereotypical immunophenotypic and molecular lesions that can aid in accurate classification (Table 1).

**EPIDEMIOLOGY**

In the WHO classification, the initial major distinction is the putative cell of origin: B cell, T cell, or natural killer (NK) cell. The lymphomas are next classified as derived from either precursor or mature lymphocytes. More than 30 types of lymphoma are recognized, with clinical behavior spanning from remarkably indolent to profoundly aggressive. In the United States in 2007, there are expected to have been 8200 new diagnoses of Hodgkin lymphoma (HL) and 63,200 new diagnoses of NHL. Distribution of the subtypes of Hodgkin lymphoma (HL) and 63,200 new diagnoses of NHL in the United States.6,7 In the United States, more than half of newly diagnosed NHL consists of either diffuse large B-cell lymphoma (DLBCL), an aggressive B-cell lymphoma, or follicular lymphoma (FL), an indolent B cell lymphoma, comprising 31% and 22%, respectively. Several other subtypes are relatively common (<5% of newly diagnosed NHL), including marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT), 5%; small lymphocytic lymphoma (chronic lymphocytic leukemia type), 6%; peripheral T-cell lymphoma, unspecified (PTCLu), 6%; and mantle cell lymphoma (MCL) 6%. The 12 most common subtypes of lymphoma (treating Burkitt and Burkitt-like lymphoma as a single disease entity, as in the WHO classification) account for 88% of new diagnoses of NHL in the United States.6,7

**DIAGNOSIS**

Appropriate management of lymphoma begins with an accurate and precise diagnosis. Traditionally, this has necessitated a surgical (either excisional or incisional) biopsy specimen to obtain adequate tissue. However, as discussed earlier, the WHO classification is built not only on morphologic criteria but also incorporates immunophenotypic and, in some instances, genetic data in establishing a diagnosis. To obtain tissue of greatest diagnostic quality, a new diagnosis of lymphoma will ideally be based on an excisional lymph node biopsy. Although fine needle aspiration (FNA) can be accurate and cost-effective in the diagnosis of certain types of lymphoma, and
is accurate in the setting of relapsed disease, excisional biopsy remains the standard of care for initial diagnosis and for clinical scenarios in which cellular morphology and nodal architecture are relevant to the diagnosis (eg, transformation of low-grade lymphoma, as is discussed later). The clinical staging of both HL and NHL derive form the Ann Arbor (AA) staging system originally developed for HL alone, as subsequently modified at the Cotswolds meeting in 1989.

**STAGING**

The modification retained the previous four-stage system, adding the modifier “X” for bulk, defined as greater than 10 cm in long axis or for a mediastinal mass as measuring greater than one third of the internal transverse thoracic diameter of a standard posteroanterior chest radiograph at the level of the fifth or sixth thoracic vertebral body. The staging system is based on the extent of involvement of nodal groups: stage I is a single lymph node group; stage II is multiple lymph node groups ipsilateral to the diaphragm; stage III is involvement of lymph node groups both above and below the diaphragm; and stage IV includes noncontiguous extranodal involvement (eg, lung nodules or involvement of bone marrow). The “E” modifier qualifies direct extension to an extranodal site or, for stage IE disease, isolated involvement of a single extranodal site without evidence of nodally based disease (eg, primary lymphoma of bone or thyroid). The “B” modifier refers to the presence of one or more of a set of symptoms associated with lymphoma that have been associated with more aggressive disease or worse prognosis: unexplained recurrent or persistent fever, drenching night sweats, or unexplained loss of 10% or more of body weight.
Staging is characterized as either clinical stage if it is based on physical examination, routine radiographic evaluation, including cross-sectional imaging of relevant anatomic regions and in select cases functional imaging such as $^{18}$F fluoro-2-deoxyglucose positron emission tomography (18-FDG PET) and bone marrow biopsy, or pathologic stage if confirmed by one or more additional surgical staging procedures, such as staging laparoscopy or gastrointestinal endoscopy. Many types of lymphoma, particularly the indolent B-cell NHLs, routinely involve marrow, resulting in clinical stage IV disease being the norm rather than the exception. However, marrow involvement has not been demonstrated to independently confer worse prognosis, and grouping by limited stage (Ann Arbor stage I/II) and advanced stage (AA stage III/IV) is more clinically relevant in NHL. Given the limited predictive power of AA stage for both HL and NHL, clinical prognostic models (incorporating characteristics of both the patient and the malignancy) have been developed to aid clinical trial interpretation and to assist clinicians in conveying prognostic information to patients. Several models have subsequently been developed for common lymphoma subtypes, including the Hodgkin Lymphoma International Prognostic Score (Table 3), the International Prognostic Index (IPI) for diffuse large B-cell lymphoma (Table 4), and the Follicular Lymphoma International Prognostic Index (FLIPI) for follicular lymphoma (Table 5).

The following discussion addresses specific features of eight common types of lymphoma, which collectively account for more than 80% of lymphoma diagnosed in Western countries.

### Table 1

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Immunophenotype</th>
<th>Molecular Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classical Hodgkin lymphoma (HL)</td>
<td>CD15+ CD30+</td>
<td>Variable</td>
</tr>
<tr>
<td>Nodular lymphocyte-predominant HL</td>
<td>CD20+ CD15- CD30-</td>
<td>Variable</td>
</tr>
<tr>
<td>Diffuse large B-cell</td>
<td>CD20+</td>
<td>BCL2, BCL6, CMYC</td>
</tr>
<tr>
<td>Follicular</td>
<td>CD20+ CD10+ CD5-</td>
<td>BCL2</td>
</tr>
<tr>
<td>Small B-cell (CLL type)</td>
<td>CD20+ CD5+ CD23+</td>
<td>V gene, p53, +12, 11q</td>
</tr>
<tr>
<td>Peripheral T-cell unspecified</td>
<td>CD20- CD3+</td>
<td>Variable</td>
</tr>
<tr>
<td>Mantle cell</td>
<td>CD20+ CD5+ CD23-</td>
<td>Cyclin D1</td>
</tr>
<tr>
<td>Marginal zone, MALT type</td>
<td>CD20+ CD5- CD23-</td>
<td>BCL10, MALT1</td>
</tr>
<tr>
<td>Primary mediastinal large B-cell</td>
<td>CD20+</td>
<td>Variable</td>
</tr>
<tr>
<td>Anaplastic large cell, T/null</td>
<td>CD20- CD3+ CD30+ CD15- EMA+</td>
<td>ALK</td>
</tr>
<tr>
<td>Lymphoblastic (T/B)</td>
<td>T cell: CD3+</td>
<td>TCL1-3</td>
</tr>
<tr>
<td></td>
<td>B cell: CD19+</td>
<td>Variable</td>
</tr>
<tr>
<td>Marginal zone, nodal type</td>
<td>CD20+ CD5- CD23-</td>
<td>+3, +18</td>
</tr>
<tr>
<td>Burkitt lymphoma</td>
<td>CD20+ CD10+ CD5-</td>
<td>CMYC</td>
</tr>
</tbody>
</table>

### HODGKIN LYMPHOMA

Approximately 8200 new cases of Hodgkin lymphoma (HL) will have been diagnosed in 2007 in the United States. There is a modest male predominance (1.4:1), and in Western countries there is a bimodal age distribution, with the first peak in the third decade of life and a second smaller and broader peak after age 50. Heritable characteristics may contribute to risk, as siblings have a two- to ninefold increased risk, and as first-degree relatives have a less striking but nonetheless greater risk than age-matched controls. Investigations have identified risk associations with certain HLA antigens, lending further support to a genetic contribution to risk. Infection with Epstein-Barr virus (EBV) resulting in infectious mononucleosis has been associated with an increased incidence of HL in a large Danish study, and evidence of EBV early RNA can frequently be detected in the classic Reed-Sternberg cells. Other contributors to risk of HL have not been fully elucidated. While an increased incidence of HL has been noted in patients infected by HIV, there is no evidence of virally mediated oncogenesis from HIV (unlike EBV), and the observation that rates of HL in HIV have increased despite the advent of highly active anti-retroviral therapy (HAART) offers circumstantial evidence against direct viral pathogenesis.

[Table 3](#), [Table 4](#), [Table 5](#)
### Table 2
Distribution of the major non-Hodgkin lymphoma subtypes by geographic region

<table>
<thead>
<tr>
<th>Major NHL Subtypes</th>
<th>Omaha (n = 200)</th>
<th>Vancouver (n = 200)</th>
<th>Capetown (n = 188)</th>
<th>London (n = 119)</th>
<th>Würzburg/Göttingen (n = 203)</th>
<th>Lyon (n = 192)</th>
<th>Locarno/Bellinzona (n = 79)</th>
<th>Hong Kong (n = 197)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small B-lymphocytic</td>
<td>7%</td>
<td>1%</td>
<td>8%</td>
<td>8%</td>
<td>11%</td>
<td>8%</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Mantle cell</td>
<td>7%</td>
<td>7%</td>
<td>1%</td>
<td>7%</td>
<td>8%</td>
<td>7%</td>
<td>14%</td>
<td>3%</td>
</tr>
<tr>
<td>Follicular</td>
<td>32%</td>
<td>31%</td>
<td>33%</td>
<td>28%</td>
<td>18%</td>
<td>17%</td>
<td>11%</td>
<td>8%</td>
</tr>
<tr>
<td>Marginal zone B-cell, MALT type</td>
<td>6%</td>
<td>7%</td>
<td>4%</td>
<td>3%</td>
<td>9%</td>
<td>13%</td>
<td>9%</td>
<td>10%</td>
</tr>
<tr>
<td>Diffuse large B-cell</td>
<td>28%</td>
<td>29%</td>
<td>28%</td>
<td>27%</td>
<td>30%</td>
<td>25%</td>
<td>36%</td>
<td>36%</td>
</tr>
<tr>
<td>Primary mediastinal large B-cell</td>
<td>0%</td>
<td>2%</td>
<td>3%</td>
<td>2%</td>
<td>0%</td>
<td>4%</td>
<td>9%</td>
<td>3%</td>
</tr>
<tr>
<td>Peripheral T-cell unspecified</td>
<td>3%</td>
<td>1%</td>
<td>8%</td>
<td>8%</td>
<td>4%</td>
<td>4%</td>
<td>6%</td>
<td>10%</td>
</tr>
<tr>
<td>Anaplastic large T/null cell</td>
<td>2%</td>
<td>3%</td>
<td>3%</td>
<td>2%</td>
<td>1%</td>
<td>3%</td>
<td>0%</td>
<td>3%</td>
</tr>
<tr>
<td>Angiocentric nasal T/NK cell</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>2%</td>
<td>0%</td>
<td>8%</td>
</tr>
<tr>
<td>Other</td>
<td>15%</td>
<td>19%</td>
<td>12%</td>
<td>15%</td>
<td>19%</td>
<td>17%</td>
<td>10%</td>
<td>16%</td>
</tr>
</tbody>
</table>

Historically, Hodgkin lymphoma was subdivided into five histologic variants: nodular sclerosis, mixed cellularity, lymphocyte-rich, lymphocyte-depleted, and nodular lymphocyte-predominant. With modern therapy the differences in prognosis between subtypes have largely vanished; as a result, nodular sclerosis, mixed cellularity, lymphocyte-rich, and lymphocyte-depleted HL have been collectively grouped under the unified diagnosis of "classical HL" in the WHO classification. Nodular lymphocyte-predominant HL (NLPHL) remains a clinically distinct entity, with different natural history and immunophenotype (see earlier).

Classical Hodgkin Lymphoma

Classical Hodgkin lymphoma (HL) is pathologically defined by the presence of Reed-Sternberg cells and their variants that are seen against a background of nodular sclerosis, mixed cellularity, lymphocyte-depleted, or a lymphocyte-rich stroma. HL is a distinct entity both pathologically and clinically, with a unique natural history and disease-specific management strategies.
Clinical presentation

The most typical presentation of HL is painless, enlarged superficial lymphadenopathy that on investigation involves contiguous nodal chains in a predictable and orderly fashion as the disease progresses; only late in disease progression does vascular invasion occur, permitting hematogenous dissemination. Most patients will present with supradiaphragmatic disease; in most large series, isolated infradiaphragmatic disease occurs in only 3% to 7% of cases.\(^{35-37}\) Between 60% and 80% of patients will present with cervical and/or supravacular adenopathy, and approximately 30% with axillary disease. Mediastinal involvement is common at presentation (50%–60%), and frequently large masses can be found with routine radiography in the absence of symptoms. Infradiaphragmatic disease tends to develop after involvement of para-aortic lymph nodes, but involvement of abdominal viscera is an infrequent event. Indeed, only 10% to 15% of patients with HL will harbor extranodal disease, with the most frequent sites being bone, bone marrow, lung, and liver. Central nervous system (CNS) involvement is extremely rare, although extension into the epidural space from contiguous para-aortic adenopathy can lead to neurologic symptoms at time of presentation.

A significant proportion of patients with undiagnosed HL will develop one or more systemic symptoms before discovery of adenopathy. “B” symptoms are present in 25% of patients with newly diagnosed HL, although this proportion is greater in patients presenting with advanced disease, and the presence of these symptoms independently predicts a worse prognosis in both early- and advanced-stage disease. Other systemic symptoms that are often present with, or

| Table 3 | Hodgkin lymphoma international prognostic scoring system |
| Factors | |
| Serum albumin, <4 g/dL | |
| Hemoglobin, <10.5 g/dL | |
| Male gender | |
| Stage IV disease | |
| Age ≥ 45 years | |
| White blood cell count, ≥ 15,000/mm\(^3\) | |
| Lymphocyte count, <600/mm\(^3\) or <8% of white blood cells | |
|  |
| Rates of freedom from freedom from progression and overall survival by number of factors | |
| Number of Factors | 5-year Progression-Free Survival | 5-year Overall Survival |
| 0 | 84 | 89 |
| 1 | 77 | 90 |
| 2 | 67 | 81 |
| 3 | 60 | 78 |
| 4 | 51 | 61 |
| ≥ 5 | 42 | 56 |


| Table 4 | International Prognostic Index for aggressive lymphoma |
| Factor | Adverse Feature |
| Age | >60 years |
| Performance status | ≥ 3 (limited in self-care) |
| LDH | > upper limit normal |
| Extranodal disease | ≥ 2 sites |
| Stage (Ann Arbor) | III or IV |
| Risk Group | No. Adverse Factors | 5-year Disease-Free Survival, % | 5-year Overall Survival, % |
| Low | 0 or 1 | 70 | 73 |
| Low-intermediate | 2 | 50 | 51 |
| High-intermediate | 3 | 49 | 43 |
| High | 4 or 5 | 40 | 26 |

even antedate, the diagnosis of HL include pruritus, which can be severe, and alcohol-induced pain occurring minutes after ingestion and localizing to regions of involved adenopathy. While uncommon (reported in fewer than 10% of patients), it is felt to be pathognomonic for HL. Rare neurologic paraneoplastic syndromes, including cerebellar degeneration and the stiff-person syndrome, have been reported and interestingly can be present in early-stage disease, persist despite curative therapy, or even develop following curative therapy.

**Staging**

Clinical staging of HL according to the Cotswolds modification of the Ann Arbor staging system remains standard now almost 20 years after its introduction. Currently recommended approaches for determining clinical stage consist of routine physical examination, laboratory analysis including assessment of renal and hepatic function, chest x-ray; CT scans of the chest, abdomen, and pelvis; and bone marrow biopsy for any extent of disease beyond clinical stage (CS) IA. 18-FDG PET is included in the most recent National Comprehensive Cancer Network (NCCN) staging recommendations for pretreatment evaluation, particularly in the setting of equivocal CT scan results. However, given the near universal pretreatment FDG-avidity of HL, a baseline 18-FDG PET may not be necessary when CT imaging establishes minimal CS III disease. However, even in this scenario, 18-FDG PET can be beneficial for restaging, and response by PET criteria is emerging as a powerful prognostic tool.

**Management**

The advent first of effective radiotherapy and later of combined-modality therapy and chemotherapy-only regimens has made HL a highly curable malignancy. Management of HL is currently tailored according to the stage of disease, clinical features including prognostic factors, and considerations of potential long-term toxicities of therapy. Attempts to advance the management of early-stage HL (ESHL) have been driven by the observation that, despite variability in rates of disease control among different treatments, overall outcome is excellent even for patients who relapse, resulting in similar overall survival rates. Furthermore, treatment of HL, while effective, has significant short-term and long-term toxicity, and in long-term survivors, treatment-related toxicity surpasses HL as the greatest contributor to overall mortality (Box 3). Poor prognostic factors in ESHL were identified, including male sex, age greater than 40 years, “B” symptoms, erythrocyte sedimentation rate greater than 50, large mediastinal mass, extranodal disease, infradiaphragmatic disease, and involvement of three or four lymph node stations. Historically, good-risk ESHL was managed with extended field radiotherapy, whereas poor-risk ESHL received full-course combined-modality therapy (CMT) (chemotherapy and radiotherapy), but CMT has become standard for both groups on the basis of progression-free survival benefits seen in trials performed in Europe and the United States. The optimal multiagent chemotherapy program has also evolved over time, from alkylator-based therapy (MOPP) to anthracycline-based therapy (ABVD). Efforts in advancing the treatment of ESHL have focused on identifying strategies to improve outcomes in poor-risk patients and to reduce toxicity.

**Table 5**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Adverse Feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&gt;60 years</td>
</tr>
<tr>
<td>Hgb</td>
<td>&lt;12 g/dL</td>
</tr>
<tr>
<td>LDH</td>
<td>&gt;upper limit normal</td>
</tr>
<tr>
<td>Number of nodal sites</td>
<td>≥ 5</td>
</tr>
<tr>
<td>Stage (Ann Arbor)</td>
<td>III or IV</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>No. Factors</th>
<th>% Patients</th>
<th>5-year Overall Survival, %</th>
<th>10-year Overall Survival, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0 or 1</td>
<td>36</td>
<td>90.6</td>
<td>70.7</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2</td>
<td>37</td>
<td>77.6</td>
<td>50.9</td>
</tr>
<tr>
<td>High</td>
<td>3 to 5</td>
<td>27</td>
<td>52.5</td>
<td>35.5</td>
</tr>
</tbody>
</table>

on testing whether reduction of dose and volume of radiotherapy, decreasing the number of cycles of chemotherapy or eliminating bleomycin (and avoiding its well-characterized pulmonary toxicity), or even replacing CMT with chemotherapy-only programs. At the present time, however, CMT with four cycles of ABVD and subsequent radiation of involved fields (involved field radiation therapy [IFRT]) remains a standard of care in the treatment of ESHL in all patients except young women who would receive radiation to breast tissue. For such patients, chemotherapy-only programs that can spare the recognized increased risk of breast cancer are an important clinical consideration.

For advanced-stage HL (ASHL), treatment is also based in part on clinical features. The HL international prognostic scoring system identifies seven poor prognostic features: age older than 45 years, male gender, serum albumin less than 4, hemoglobin less than 10.5, white blood cell (WBC) count greater than 15,000, absolute lymphopenia (<600), and stage IV disease. Whereas the standard of care has been full-course ABVD, with treatment given every 2 weeks for 24 weeks, patients with high-risk disease, defined by the presence of four or more of these poor prognostic features, have unacceptably poor outcomes. Intensified treatment with the dose-intensified regimen escalated-BEACOPP and post-treatment radiation therapy to residual nodal masses of 2 cm or larger has been shown to improve survival when compared with a regimen clinically equivalent to standard ABVD.\textsuperscript{44} Investigation of a CMT regimen of an eight-drug weekly chemotherapy program (the Stanford V regimen) and more intensive radiotherapy for any nodal mass measuring larger than 5 cm before treatment has demonstrated excellent activity in single-institution experiences,\textsuperscript{45} and is currently being compared with ABVD in ASHL, but mature data are not yet available.

While most patients with HL are cured with chemotherapy, radiation therapy, or CMT, patients who relapse after achieving complete remission or demonstrate refractory disease have poor outcomes. However, for those patients who demonstrate chemotherapy-sensitive disease when treated with second-line systemic therapy, consolidation of second-line therapy with high-dose chemotherapy and autologous stem cell rescue (HDT/ASCR) has been shown to achieve durable remission in between 45\% and 60\% of patients.\textsuperscript{46–52} The role of allogeneic stem-cell transplantation, particularly nonmyeloablative transplantation of HLA-identical siblings, in the treatment of patients not cured with second-line therapy and consolidative HDT/ASCR is a subject of ongoing investigation and is a clinical consideration in select cases.\textsuperscript{53,54}

### Nodular Lymphocyte-Predominant Hodgkin Lymphoma

The epidemiology of NLPHL differs from that of HL, with a bimodal age distribution peaking in childhood and the fourth decade of life, and with a 3:1 male predominance.\textsuperscript{55,56} It is an uncommon disease, with only approximately 500 newly diagnosed cases annually in the United States.

---

**Box 3**

**Toxicities associated with treatment of Hodgkin lymphoma**

**Acute toxicity**
- Alopecia
- Anemia
- Antabuse-like reaction to alcohol (procarbazine)
- Leukopenia
- Mucositis
- Nausea/vomiting
- Neuropathy
- Pneumonitis (bleomycin)
- Thrombocytopenia

**Second primary malignancy**
- Acute myelogenous leukemia (chemotherapy)
- Acute lymphoblastic leukemia (chemotherapy)
- Breast (radiotherapy)
- Gastric
- Lung (radiotherapy)
- Melanoma
- Non-Hodgkin lymphoma
- Sarcoma (radiotherapy)
- Thyroid (radiotherapy)

**Late cardiovascular toxicity**
- Accelerated atherosclerosis
- Non-ischemic cardiomyopathy
- Pericardial fibrosis (radiotherapy)

**Endocrine toxicities**
- Hypothyroidism (radiotherapy)
- Premature ovarian failure (chemotherapy)
- Azoospermia (chemotherapy)
Evidence now exists to implicate the germinal center lymphocyte as the putative cell of origin of the characteristic lymphocytic and histiocytic (L&H) cell of NLPHL. The natural history of NLPHL is often quite distinct from that of HL. More than 75% of patients will present with early-stage (clinical stage I or II) disease, and both extranodal disease and systemic symptoms are rare. Staging of NLPHL routinely includes physical examination, laboratory analyses, and CT of the chest, abdomen, and pelvis; bone marrow biopsy is of limited yield. The utility of 18-FDG PET in staging of NLPHL has yet to be fully elucidated; the theoretic ability to upstage disease is of questionable clinical benefit in NLPHL, and the specificity of 18-FDG-PET in NLPHL has been called into question, as the disease can coexist with a benign disease of lymph nodes, progressive transformation of germinal centers (PTGC), which can also be 18-FDG avid.

Historically, NLPHL was treated in a fashion identical to HL, and many of the largest clinical trials in the management of HL have included small subsets of NLPHL. However, the natural history of NLPHL is quite distinct from HL; whereas HL is typically an aggressive disease that, when not cured, will lead to significantly shorter survival, NLPHL is responsive to many therapies but tends to follow a relapsing pattern more similar to indolent B-cell NHL. Accordingly, aggressive treatment programs such as combination chemotherapy or CMT have in many cases been replaced by more conservative management strategies.

For limited stage disease that is considered amenable to radiation (disease within a single reasonable involved field radiation port), IFRT is often favored in patients and disease locations amenable to such therapy. Systemic chemotherapy for limited disease is now typically reserved for patients who are not suitable for radiation therapy (RT) and for whom observation would be inappropriate due to clinical features. For advanced stage (stages III/IV) disease, treatment has largely consisted of regimens with activity in HL, including anthracycline-based regimens such as ABVD. Unlike early-stage NLPHL, it is not clear that advanced stage NLPHL has a natural history drastically different from HL.

Given that NLPHL is generally recognized as an incurable malignancy, and one with which patients can live for many years, concerns about cumulative toxicity of therapy are particularly relevant. In modern cohorts, cause of death for patients with NLPHL has been more likely to be due to second primary malignancies (including secondary leukemia), cardiac disease, or other conditions than due to the lymphoma itself. Given concerns about the cumulative toxicity of chemotherapy, there is significant interest in the potential use of rituximab, a monoclonal antibody against CD20
that was first approved by the Food and Drug Administration (FDA) in 1997 and has become a component of the treatment of many B cell lymphomas. Experience using rituximab in the treatment of NLPHL continues to develop, but its optimal role in the management of the disease, both alone and in combination, has yet to be firmly established. 62,63

NON-HODGKIN LYMPHOMA
Diffuse Large B-Cell Lymphoma

Diffuse large B cell lymphoma (DLBCL) is a clinically aggressive non-Hodgkin lymphoma (NHL) and is the single most common type of lymphoma in Western countries, accounting for over 30% of new diagnoses. 6 Although a pathologically heterogeneous set of disorders, the diagnosis DLBCL is understood to include routine centroblastic large B-cell lymphoma, immunoblastic lymphoma, T-cell/histocyte-rich B-cell lymphoma, and B-cell anaplastic large cell lymphoma.

Some insight into the clinical significance of the pathologic heterogeneity of DLBCL has been shed by profiling of differential gene expression. Using DNA microarrays, individual cases of lymphoma can be classified based on gene expression patterns into one of three categories of putative cell of origin: germinal-center B-cell-like (GCB, favorable), activated B-cell-like (ABC, unfavorable), and type 3 (also unfavorable). 64–66 Others have attempted to simplify the full DNA microarray classification to either assessment of expression of a small group of genes or, even more practical, commonly available immunohistochemistry. 67,68 The determination of gene expression pattern was found to be strongly predictive of outcome with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy, leading some to begin to approach these subsets as clinically distinct entities. However, it is unclear if the gene expression pattern continues to offer important prognostic information, as there are conflicting data regarding the prognostic impact of cell of origin for patients treated with CHOP and rituximab, as has become standard (see later in this article). 69–73

Clinical presentation

The most typical presenting complaint in newly diagnosed DLBCL is a symptomatic enlarging nodal mass, either centrally or peripherally located. Approximately 20% of patients will present with stage I or stage IE disease, and approximately 40% of patients will present with disease limited to one side of the diaphragm (stage II). 74 An additional 20% of patients will present with nodal involvement above and below the diaphragm, and 40% of patients have disseminated disease with extranodal involvement at presentation. Common sites of extranodal dissemination include liver, kidney, bone, lung, and bone marrow. This stands in contrast to common primary extranodal sites of origin of DLBCL (representing approximately 30% of all DLBCL), which include the gastrointestinal tract, thyroid, bone, brain, testis, soft tissue, kidney, liver, breast, and skin. 75 When extranodal disease is present with no or minimal nodal involvement, the disease is typically considered primary extranodal DLBCL, whereas when both nodal and extranodal disease are present, the disease is typically considered nodal lymphoma. Symptomatically, in addition to those symptoms directly referable to locally invasive or extranodal disease, patients will often experience systemic symptoms before diagnosis. Approximately 30% of patients will report “B” symptoms, whereas less specific symptoms of malaise and fatigue are more common yet.

The range of clinical presentations of DLBCL is made all the more diverse when transformation of low-grade lymphoma is considered. Low-grade B-cell lymphomas, including follicular lymphoma, small lymphocytic lymphoma, marginal zone lymphoma, and lymphoplasamocytic lymphoma can all develop high-grade transformation of disease into DLBCL, an event believed to be typically triggered by acquisition and accumulation of additional transforming mutations. 76 Transformation of low-grade lymphoma is a common event, occurring at a rate of 3% per year in patients with FL with a cumulative risk of approximately 50% after 15 years. 77–79 It can occur in patients without a known clinical history of the original indolent disease (de novo transformation), or at any point during the clinical course of illness, although patients without transformation after living with a low-grade B cell lymphoma for more than 15 years are unlikely to ever experience transformation. 77 Staging and management of transformed low-grade lymphoma mirrors that of DLBCL, with the exception of post-treatment follow-up, as the nontransformed component of the low-grade lymphoma will continue to follow its own natural history, “unaware” that transformation had occurred.

Staging

In addition to the routine application of body imaging with CT and 18-FDG PET and bone marrow biopsy, lumbar puncture for both diagnostic and therapeutic purposes (with administration into the cerebrospinal fluid [CSF] of chemotherapy, either methotrexate or cytarabine) is indicated in select cases. Analyses of patterns of failure in DLBCL...
have shown a predilection for CNS recurrence when the original disease arises in the testis, paranasal sinuses, or when disease involves the bone marrow or epidural space.\textsuperscript{80,81} Primary breast DLBCL may also present an increased risk of CNS recurrence, prompting consideration of CNS prophylaxis, although data are conflicting.\textsuperscript{82–84} Accordingly, such patients must undergo diagnostic lumbar puncture to rule out primary leptomeningeal disease, and when involvement of the CSF is not present, are believed to benefit from CNS prophylaxis, as the typical chemotherapeutic programs for DLBCL have poor CNS penetrance.

**Management**

Patients with newly diagnosed DLBCL are treated with curative intent. Indeed, many patients can achieve a long-term disease-free status with aggressive combination chemotherapy or CMT. Treatment with CHOP emerged as the preferred chemotherapeutic regimen when compared with even more intensive chemotherapy regimens in the National High-Priority Lymphoma Study.\textsuperscript{85} The addition of rituximab to CHOP (R-CHOP) has been shown to further improve survival regardless of age, stage, or IPI score based on the results of 4 randomized clinical studies.\textsuperscript{86–89} For patients presenting with favorable early-stage, nonbulky disease, shortened chemotherapy with only three to four cycles of R-CHOP and consolidative IFRT is associated with excellent outcomes, as is a full six cycles of R-CHOP without radiation therapy.\textsuperscript{87,90} Bulky early-stage disease is often treated in a manner similar to advanced-stage disease, with treatment consisting of six cycles of R-CHOP chemotherapy, although there is no well-established standard of care, and one study did find an aggressive chemotherapy regimen without radiation to be superior to three cycles of CHOP and RT.\textsuperscript{91}

Recurrent or refractory disease, however, continues to represent a clinical challenge. Ongoing research to improve first-line therapy has focused on shortening time intervals between cycles, administering medicines by continuous infusion, or including sequential non–cross-reactive regimens.\textsuperscript{72,86,92} Following relapse, or in the face of disease that persists despite first-line chemotherapy, optimal management involves administration of second-line chemotherapy to attempt to achieve remission, followed by stem cell mobilization and administration of high-dose therapy, either chemotherapy alone or CMT, with administration of banked stem-cells to rescue the patient from supralethal therapy. High-dose therapy and autologous stem cell rescue (HDT/ASCR), or “autologous bone marrow transplantation,” for patients responding to second-line therapy, offers the potential of cure in a substantial fraction of patients.\textsuperscript{93} Patients ineligible for HDT/ASCR or whose disease is not chemotherapy sensitive have poor outcomes.

Two clinical variants of DLBCL merit brief discussion, given differences in natural history and outcomes from typical DLBCL: Primary mediastinal large B cell lymphoma and intravascular large B cell lymphoma.

**Primary mediastinal large B-cell lymphoma**

Primary mediastinal large B cell lymphoma (PMLBCL) is a distinct clinicopathological entity that has been shown by gene expression profiling studies to share more genetic features with HL than with DLBCL.\textsuperscript{94,95} Unlike DLBCL, PMLBCL is typically diagnosed in the fourth decade of life and shows a mild female predominance. It will most often present with a locally advanced anterior mediastinal mass, and patients will show clinically overt signs of superior vena cava (SVC) syndrome in more than 50% of cases and radiographic evidence of SVC compromise in as many as 80% of cases.\textsuperscript{96} Management typically consists of full-course anthracycline-based chemotherapy (eg, R-CHOP) and consolidative IFRT or with more aggressive sequential chemotherapy programs.\textsuperscript{97–99}

**Intravascular large B-cell lymphoma**

Intravascular large B-cell lymphoma (IVLBCL) is an uncommon variant of DLBCL, presenting with systemic complaints and end-organ dysfunction due to vascular insufficiency. Organ infiltration can be seen, but nodal disease is the exception. It appears that there are two clinical variants of this disease, with the European form frequently presenting with neurologic symptoms and CNS involvement, while the Asian form more frequently presents with marrow failure, “B” symptoms, and hemophagocytosis. Although the rarity of IVLBCL makes it difficult to draw conclusions regarding optimal management, long-term remission seems achievable with timely initiation of anthracycline-based chemotherapy such as R-CHOP.\textsuperscript{100,101}

**Follicular Lymphoma**

Follicular lymphoma (FL) is the most common indolent B-cell NHL, and is defined as a lymphoma of follicle center cells (centrocytes and centroblasts) with a partially or completely follicular morphologic pattern. There is significant morphologic variability among cases of FL, with the presence of large-cell centroblasts varying from minimal with grade 1 FL to significant with grade 3 FL.
Clinical presentation
FL has a median age of diagnosis of approximately 60 years, and a slight male predominance exists; the disease is more common among Caucasians than those of African descent, and FL is rare in Asia (but less so in the descendants of Asian immigrants to Western countries).30 The most typical clinical presentation is that of subacute or chronic asymptomatic peripheral adenopathy, sometimes having persisted or waxed and waned for years. Abdominal, pelvic, or retroperitoneal adenopathy can often be bulky without leading to gastrointestinal or genitourinary symptoms, and nodal masses tend not to be locally invasive or destructive. There tends not to be an orderly progression of lymph node station involvement, and early hematogenous dissemination is common. When sensitive assays are applied, blood or bone marrow involvement by FL can be detected in 80% of patients, but other sites of extranodal disease are uncommon at presentation. “B” symptoms are also uncommon, seen in fewer than 20% of patients presenting with FL, and should prompt consideration of transformed lymphoma (see earlier in this article).

Staging
Staging of FL routinely consists of physical examination; routine laboratory evaluation including a serum lactate dehydrogenase (LDH); and CT imaging of the chest, abdomen, and pelvis. Bone marrow biopsy is required before initiation of therapy to complete staging as well as to determine whether repeat bone marrow biopsy (to evaluate response to therapy) will subsequently be required. 18-FDG PET scanning is useful in select cases, particularly either to confirm a clinical impression of early-stage disease amenable to RT with curative intent or to help guide diagnostic evaluation for possible transformation to large cell lymphoma (see earlier in this article).

Management
Many of the basic principles of management of FL apply, at least in part, to the other types of indolent B-cell NHL discussed later in this article. Appropriate staging of FL includes physical examination; routine laboratory analyses; and CT imaging of the chest, abdomen, and pelvis. While not universally necessary at time of diagnosis, bone marrow biopsy and aspiration are required in the evaluation of cytopenias and of completion of staging before initiation of therapy. 18-FDG PET is a useful adjunct to CT and physical examination, and is of particular utility when there is a clinical suspicion of transformed lymphoma; when feasible, diagnostic surgical biopsy of the most 18-FDG-avid site of disease should be performed in such instances.

When the results of a complete staging evaluation for newly diagnosed FL determine that the disease is localized (stage I or II within a single radiation port), IFRT has the potential of eradicating the disease. Long-term follow-up of patients receiving radiation for early stage FL have reported that between 20% and 60% of patients remain free of recurrence 10 or more years following treatment.103–105 Although the vast majority of relapses occur outside the radiation field, more extensive nodal radiation has not been associated with improved overall survival. Similarly, the addition of chemotherapy to radiation therapy in the treatment of early-stage irradiable FL does not appear to improve overall survival, although this question has not been readdressed during the rituximab era.104

In the setting of advanced-stage disease, the goals of treatment are considered palliative in nature, as routine therapies are not expected to be curative; indeed, only allogeneic stem-cell transplantation has been consistently associated with long-term disease-free survival for patients with advanced stage disease. Furthermore, treatment of low-bulk asymptomatic patients with systemic therapy has not been associated with a firm survival advantage. A widely accepted set of criteria for treatment (Box 4) emphasizes the principle of treating only patients who have symptomatic or progressive disease. Thus, many patients can be

| Box 4 |
| Criteria for initiation of therapy for advanced stage indolent lymphoma |

- Involvement of ≥3 nodal sites, each with a diameter (long axis) of ≥3 cm
- Any nodal or extranodal tumor mass with a diameter (long axis) of ≥7 cm
- B symptoms
- Symptomatic splenomegaly
- Pleural effusions or abdominal ascites
- Cytopenias (leukocytes <1 × 10^9/L and/or platelets <100 × 10^9/L)
- Leukemic phase (>5 × 10^9/L malignant cells in peripheral blood)
- Patient insistence

observed following initial diagnosis, with a median time from initial diagnosis to requiring systemic therapy of 2 to 3 years.\textsuperscript{106} When treatment is required, the most frequently used regimens combine immunotherapy (such as rituximab) and chemotherapy, with alkylating agents, anthracyclines, and purine analogs the most frequently used and the best studied in the disease. Radiation therapy is reserved for locoregional palliation, although the radiolabeled anti-CD20 antibodies 90-Y-ibritumomab tiuxetan and 131-I-tositumomab are administered systemically and deliver radiation to microscopic sites of disease. Autologous stem cell transplantation can be considered to consolidate responses in relapsed disease, and allogeneic stem cell transplantation is associated with a long-term disease-free survival in patients with multiply relapsed FL of between 40% and 50%.\textsuperscript{107,108}

\section*{Marginal Zone Lymphomas}

Marginal zone lymphoma (MZL) consists of three clinically and genetically distinct subtypes: extranodal MALT of mucosa-associated lymphoid tissue (MALT), splenic MZL, and nodal MZL. They are uncommon diseases, both individually and collectively. MALT lymphoma comprises approximately 5% of new diagnoses of NHL, and collectively the MZLs account for fewer than 10% of new diagnoses.\textsuperscript{6} Although each is considered an indolent B-cell NHL, there is little clinical overlap among the three diseases despite shared morphologic and immunophenotypic characteristics.\textsuperscript{109}

\section*{Clinical presentation}

MALT lymphoma is the most common of the three MZLs, and accounts for 5% of newly diagnosed lymphomas. Common sites of MALT lymphoma include stomach, lung, and the ocular-adnexa; although less common in other sites, MALT is the most common low-grade lymphoma of the breast, thyroid, bowel, skin and soft tissue, and dura. No strong age or gender predominance exists in MALT lymphoma. In the case of gastric MALT lymphoma, the predominant force behind lymphomagenesis is felt to be chronic stimulation of activated T cells by \textit{Helicobacter pylori}. Associations with other infections, including \textit{Chlamydia psittaci} in ocular-adnexal MALT lymphoma and chronic infection with hepatitis C virus and MALT lymphoma of various sites, are more controversial. Dissemination to other sites typical of MALT can occur, and approximately one third of patients have evidence of bone marrow involvement at time of initial presentation.\textsuperscript{110} Presenting signs and symptoms relate to the site or sites of involvement; here as well, “B” symptoms are rare and should raise the clinical consideration of transformed lymphoma.

Nodal MZL has significant clinical overlap with FL (see earlier in this article) and small lymphocytic lymphoma of chronic lymphocytic leukemia-type (SLL/CLL) (see later in this article). Its immunophenotype readily distinguishes it from these entities, as it does not express the germinal center antigen CD10 seen in FL or CD5 or CD23, antigens typically present in SLL/CLL.

Splenic MZL is largely a disease of the elderly, with a median age at diagnosis of 65 to 70 and with few diagnoses made in patients before the sixth decade of life. The most typical presentation is an older patient with significant or even massive splenomegaly, potentially resulting in symptomatic early satiety or cytopenias due to hypersplenism. Adenopathy tends to be minimal and involvement of the bone marrow by disease is the norm, seen in greater than 90% of patients when sensitive assays are applied.\textsuperscript{111,112} An association with chronic hepatitis C virus (HCV) infection has been reported, although there appears to be geographic variability in the interaction between HCV and lymphomagenesis, and may be due more to associated cryoglobulinemia than to viral infection itself.\textsuperscript{14,113–116}

\section*{Staging}

The appropriate pretreatment evaluation of each type of MZL follows from its unique natural history. For extranodal MZL, evaluation will routinely include endoscopic evaluation of the gastrointestinal tract for gastrointestinal MALT lymphoma (or bronchial mucosa–associated lymphoid tissue [BALT] lymphoma, which is frequently associated with gastrointestinal involvement), pulmonary function testing for BALT lymphoma, or imaging of other relevant anatomic regions (eg, MR imaging of orbits for ocular-adnexal MALT lymphoma). For nodal MZL, added to this is evaluation of relevant regional extranodal sites that could be the subclinical site of dissemination of the nodal disease (eg, gastrointestinal tract for abdominal adenopathy, lungs for hilar or mediastinal adenopathy, thyroid and ocular adnexa for neck adenopathy). For splenic MZL, routine physical examination; laboratory analyses; CT of the chest, abdomen, and pelvis; and bone marrow biopsy complete the requisite evaluation. 18-FDG PET scan will be positive in between 65% and 80% of patients with MALT lymphoma, but may be more sensitive in splenic and nodal MZL.\textsuperscript{117–119}

\section*{Management}

While in many circumstances the management of the marginal zone lymphomas is substantively
similar to that of FL, there are specific clinical scenarios where management diverges significantly. For early-stage gastric MALT lymphoma, eradication of *H. pylori* in patients with favorable cytogenetics leads to regression or remission in 50% to 80% of patients. Patients with limited disease for whom *H. pylori* eradication is ineffective are still frequently cured, with a 70% to 90% long-term disease-free survival with definitive radiotherapy. Another important divergence from routine management of FL exists for splenic MZL. For patients with symptomatic splenomegaly and associated cytopenias, surgical splenectomy can lead to normalization of peripheral blood counts, and also can help achieve disease stabilization or regression systemically; splenectomy in MZL is perhaps the only setting in the management of the lymphoma in which “surgical debulking” is a routine consideration.

Small Lymphocytic Lymphoma of Chronic Lymphocytic Leukemia Type

Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma of CLL type (SLL/CLL) are felt to represent one underlying pathophysiologic process with a spectrum of phenotypic presentation ranging from purely bone marrow and blood disease (CLL) to almost completely extramedullary disease (SLL). The distinction between leukemia and lymphoma is more semantic than pathophysiologic in nature, although the presence of adenopathy can in certain cases influence management decisions.

Clinical presentation

While CLL is a relatively common disease, only 10% of patients with the disease present as predominantly nodal disease; as such, SLL accounts for fewer than 5% of new diagnoses of NHL in the United States. Furthermore, even when presenting as a nodal disease, the majority of patients will go on to have clinically detectible marrow involvement during the course of their illness. SLL is an aging-associated disease, with no apparent plateau in adjusted incidence rates by age, and in the United States is more common in Caucasians than in individuals of African descent or Hispanic ethnicity. Common presenting signs and symptoms include painless peripheral adenopathy, often chronic in nature, asymptomatic lymphocytosis with persistence of absolute lymphocyte counts greater than (and at times markedly greater than) 5,000 cells/mm³, or symptoms attributable to cytopenias due either to bone marrow infiltration or autoimmune processes associated with the disease. A monoclonal antibody can be detected in 20% of cases, and hypogammaglobulinemia with recurrent infections may be present in up to 40% of cases. This stands in contrast to lymphoplasmacytic lymphoma (LPL), in which the malignant lymphocytes share morphologic characteristics with mature plasma cells, and the immunophenotype is more consistent with MZL. When a significant IgM paraprotein is detectable with an underlying LPL, the disease is typically referred to as Waldenström’s macroglobulinemia; such patients can present with coronary, cerebral, or ophthalmic insufficiency due to hyperviscosity caused by marked elevation in circulating IgM. Either SLL or LPL can present with cryoglobulinemia, often also in the context of coinfection with hepatitis C. Richter’s transformation, the transformation of small lymphocytic lymphoma to DLBCL that was the first description of transformed lymphoma, occurs less frequently than transformation of the other indolent lymphomas, with lifetime risk estimates for patients with SLL between 2% and 8%, and is typically heralded by rapidly progressive signs and symptomatology.

Staging

Routine evaluation before initiation of treatment for SLL includes routine physical examination; laboratory analyses; CT scan of the chest, abdomen, and pelvis; and bone marrow biopsy and aspiration. 18-FDG PET is useful in select situations, including patients presenting for treatment with a clinical suspicion of Richter’s transformation, as standard uptake velocities (SUVs) can help inform the clinician on which site of disease to which a biopsy should be directed to rule out transformation, as sites of transformed lymphoma tend to have SUVs greater than sites without transformation. It should be emphasized that although measurement of SUVs can be useful for the clinician, they cannot replace a surgical biopsy in treatment planning.

The extremely variable natural history of patients with SLL (and CLL), even within given Rai stages, has prompted investigators to attempt to delineate predictors of more aggressive disease. Certain karyotypic abnormalities have been found to be associated with shorter survival, including deletion of chromosome 17p (the locus of the p53 tumor suppressor gene) and deletion of chromosome 11q (the locus of the *ATM* gene), whereas in patients who have a deletion of chromosome 13q as the only cytogenetic abnormality, survival has been reported to be superior to those patients without detectable mutations. Of additional prognostic importance is whether the malignant clone has undergone somatic mutation of the immunoglobulin VH (Ig VH) gene, an event in the maturation of the lymphocyte when it is exposed to
a germinal center. Prognosis for patients with SLL that has not undergone Ig VH somatic mutation is significantly worse, independent of other cytogenetic features of the disease; patients with unmutated Ig VH have a median survival from the time of diagnosis of 117 months, compared with 293 months for patients with mutated Ig VH.126

**Management**

Treatment paradigms for SLL (and LPL) reflect the chronic, remitting, and relapsing nature of these diseases. However, the natural history of SLL is extremely heterogeneous, with subsets of patients stratified by cytogenetic and molecular features having median survivals despite treatment ranging from 32 months to 310 months.125–127 When indicated, initial therapy often consists of a combination of rituximab and purine analog-based chemotherapy, with reservation of anthracycline or anthrancenedione for use in the event of clinical transformation or resistant/refractory disease. The presence of high-risk cytogenetic abnormalities, particularly loss of the tumor suppressor p53 from a 17p deletion, predicts a worse response to purine analog-based therapy, however, and although no standard of care for such patients yet exists, alternative strategies that incorporate alemtuzumab, a monoclonal antibody targeting CD52, are an evolving consideration, particularly in patients without bulky nodal disease. Allogeneic stem cell transplantation has traditionally been reserved for relapsed or refractory high-risk disease, and (as in other indolent B-cell NHL) can potentially be curative therapy.

**Mantle Cell Lymphoma**

Mantle cell lymphoma (MCL) comprises approximately 7% of new diagnoses of NHL. It is a mature B-cell lymphoma that historically has been considered an indolent B-cell NHL, although its clinical behavior often tends to be more aggressive. It can be difficult to distinguish morphologically from SLL, and the distinction is made on the basis of differences in genetic and immunophenotype findings (see Table 1).

**Clinical presentation**

MCL has a median age at diagnosis of approximately 65, and between 70% and 90% of patients will present with detectable stage IV disease. Involvement of the bone marrow is frequently observed, and a leukemic phase is seen in as frequently as 75% of cases in some series.128 Gastrointestinal involvement is frequently identified, and can present along a spectrum from diffuse lymphomatous polyposis to a normal lumen with microscopic disease detected on blind biopsy. Other sites of common involvement include the spleen and Waldeyer’s ring. In 20% to 30% of patients, MCL will at some time during the course of illness undergo transformation to a blastic variant, an event associated with rapid progression of disease, resistance to therapy, and a median survival of 4 months.129,130

**Staging**

Stemming from this understanding of the clinical presentation of MCL, appropriate pretreatment evaluation includes routine physical examination and laboratory analyses; CT imaging of the chest, abdomen, and pelvis; bone marrow biopsy; and upper and lower endoscopy with, if no evident abnormalities, blind luminal biopsies. 18-FDG PET is not recommended as routine, although it does have utility in evaluation response to therapy, which itself can help guide management (see the following section). Sites of original disease involvement are routinely reevaluated during or after completion of therapy to evaluate the degree of response to the prescribed regimen.

**Management**

No single standard of care exists for the initial therapeutic approach to a patient with newly diagnosed MCL. For patients with early-stage MCL, careful evaluation of bone marrow and both upper and lower gastrointestinal tracts for evidence of subclinical involvement by lymphoma are required before administering radiation therapy with curative intent. For patients with distinct evidence of having experienced an indolent course or with low-bulk and low-risk disease, initial observation can be appropriate. However, most patients will require treatment at time of presentation. Historically, outcomes with first-line treatment with alkylator, purine analog, or anthracycline-based regimens with or without rituximab were disappointing; for instance, R-CHOP alone leads to infrequent complete responses (<50%) and a brief duration of treatment benefit (<2 years).131 More aggressive treatment programs have been associated with improved outcomes in previously untreated MCL. Regimens including either alternating or sequential non-crossreactive chemotherapy regimens have led to complete remission rates in excess of 90%. Consolidation of such treatment with high-dose chemotherapy and autologous stem cell transplantation is associated with 5-year disease-free survival rates of between 40% and 65%.132,133 Management of relapsed disease frequently will incorporate previously unused classes of cytotoxic chemotherapy and novel agents such as bortezomib, an inhibitor of the
cellular proteosome that has been approved by the Food and Drug Administration for the treatment of relapsed MCL. Selected patients may be considered for consolidative allogeneic stem cell transplantation in second or later remission, or in first remission of blastoid MCL.

**Burkitt Lymphoma**

BL is a highly aggressive mature B-cell NHL characterized by a stereotypical morphology, an extremely high rate of cellular proliferation, with mitotic indices approaching 100%, and dysregulation of the c-myc due to translocations of chromosome 8. It is a rare form of lymphoma, with fewer than 1% of newly diagnosed NHL in Western countries diagnosed as BL, and demonstrates a strong male preponderance of disease. Nonetheless, its unique clinical features make BL an important disease entity.

**Clinical presentation**

There are three forms of BL with distinct clinical and epidemiologic features: endemic (African), sporadic (American), and immunodeficiency-related. Endemic BL classically presents in children as a tumor of the jaw or facial bones, and tends to disseminate hematogenously early in the course of illness to extranodal sites, including testis or ovary, kidney, CNS, and meninges. Sporadic BL typically presents as bulky abdominal disease involving cecum, small bowel, or stomach, with associated ascites. Renal, testicular or ovarian, and CNS or meningeal involvement is common as well. Immunodeficiency-related BL more frequently presents as nodally based disease, although it can involve bone marrow, CNS, or meninges, and rarely may present with a leukemic phase. Interestingly, although patients with HIV infection are at increased risk of developing BL, patients affected typically have adequate CD4+ T-cell reserves and frequently have no history of opportunistic infection. Each form shares the typical presentation of rapidly growing disease, elevated lactate dehydrogenase (LDH), and both systemic symptoms as well as symptoms directly attributable to disease infiltration.

**Staging**

Routine pretreatment evaluation of patients with BL includes routine physical examination; laboratory analyses (including the LDH); and CT scan of the chest, abdomen, and pelvis. BL tends to be markedly 18-FDG avid on PET scan, making 18-FDG PET a potentially useful modality in following response to therapy. Given the propensity for early hematogenous spread and early involvement of the CNS, bone marrow biopsy and diagnostic lumbar puncture are routine elements in the pretreatment evaluation.

**Management**

The treatment of BL is based on rapid institution of intensive combination chemotherapy, frequently adapting regimens developed for the treatment of pediatric acute lymphoblastic leukemia. These regimens incorporate agents with known CNS penetration, and additional multi-agent intrathecal prophylaxis is considered obligatory given otherwise high risks of CNS recurrence. These intensive regimens are associated with complete remission rates of approximately 80% to 90% and 5-year disease-free survival rates of 50% to 75%. Although some data suggest that HIV infection confers a worse prognosis in the treatment of BL, selection of chemotherapy does not differ by HIV status. For patients with relapsed or refractory BL, outcomes are poor, although one third of patients with chemosensitive relapsed disease may enjoy long-term disease-free survival with consolidation of a second remission with high-dose therapy and autologous stem cell rescue.

**Peripheral T-Cell Lymphoma**

The peripheral T-cell lymphomas (PTCLs) are a heterogeneous group of diseases that collectively comprise between 5% and 10% of newly diagnosed NHL in the United States, although they are more common in other regions. These diseases differ morphologically, immunophenotypically, and clinically, spanning the spectrum from indolent mild disease to moderately aggressive (and frequently curable) to aggressive and incurable. And while some subtypes are now managed in a tailored fashion, our ability to treat many of these diseases in a specific and evidence-based fashion remains limited.

The PTCLs can be broadly classified as diseases with predominantly leukemic, nodal, or extranodal distributions. A subset of the peripheral T-cell lymphomas frequently presents with a leukemic phase, including T-cell prolymphocytic leukemia, T-cell large granular lymphocytic (LGL), natural killer/T (NK/T)-cell leukemia, and adult T-cell leukemia/lymphoma (ATLL). A second set of T-cell lymphomas typically present with adenopathy, including angioimmunoblastic T-cell lymphoma (AITL), systemic anaplastic large cell lymphoma (ALCL), and peripheral T-cell lymphoma, unspecified (PTCLu).

The extranodal PTCLs include mycosis fungoides (MF) and cutaneous ALCL; these can have a chronic and indolent natural history, enjoying long remissions, and patients with early stage
and nonprogressive disease have actuarial life expectancies that do not differ from the general population.139–144 Sézary syndrome represents a leukemic progression of MF, presenting with abnormal circulating lymphocytes (Sézary cells), adenopathy, and erythrodermia, and carries a worse prognosis.145 Extranodal NK/T-cell lymphoma, nasal type (nasal NK/T lymphoma) is an aggressive lymphoma that is the most common cause of the “lethal midline granuloma” syndrome. Pathophysiologically, it is strongly associated with EBV infection, and although rare in the United States is seen more frequently in East Asia and among indigenous peoples in Peru. It can affect children or adults, and typically presents as a locally invasive disease presenting with nasal obstruction and destruction of nasal passages, hard palate, and sinuses.

For many types of PTCL, there exists no consensus approach to treatment. Indolent cutaneous T-cell lymphomas, including early-stage MF and cutaneous ALCL, can often be observed or treated with skin-directed therapies (topical medications, ultraviolet or electron radiation, or involved-field radiotherapy) or mild systemic treatments such as retinoids. 18-FDG PET scanning can be useful in selected cases, and can be particularly relevant in the evaluation of a patient with cutaneous T-cell lymphoma, as identification of extracutaneous disease can fundamentally alter both prognosis and therapeutic approach. For the aggressive PTCLs, multi-agent chemotherapy is often attempted, such as CHOP, although with the exception of Alk-1–positive ALCL, it is frequently associated with brief progression-free durations. For nasal NK/T lymphoma, early incorporation of radiation therapy into a combined modality therapy program has been shown to improve outcomes.146–150 The roles of autologous and allogeneic stem cell transplantation continue to be explored in the settings of consolidation of therapy or consolidative high-dose therapy with either autologous or allogeneic stem cell transplantation. An understanding of the principles of lymphoma, including the importance of a thorough diagnostic evaluation and the relevance of staging to treatment planning, and an appreciation of the unique elements of the natural history of specific types of lymphoma, are prerequisites to the appropriate management of patients with these challenging diseases.

REFERENCES


Overview of Lymphoma Diagnosis and Management


72. Moskowitz C, Hamlin PA, Horwitz SM, et al. Phase II Trial of Dose-Dense R-CHOP Followed by Risk-Adapted Consolidation with Either ICE or ICE and ASCT, Based upon the Results of Biopsy Confirmed Abnormal Interim Restaging PET Scan, Improves Outcome in Patients with Advanced Stage DLBCL. Blood 2006;108(11):532A.


