with advanced-stage disease. For patients who do require treatment, single-agent chlorambucil or cyclophosphamide or combination chemotherapy with CVP or CHOP is most frequently used. With adequate treatment, 50–75% of patients will achieve a complete remission. Although most patients relapse (median response duration is ~2 years), at least 20% of complete responders will remain in remission for >10 years. For the rare patients (15%) with localized follicular lymphoma, involved-field radiotherapy produces long-term disease-free survival in the majority.

A number of therapies have been shown to be active in the treatment of patients with follicular lymphoma. These include cytotoxic agents such as fludarabine, biologic agents such as interferon α, monoclonal antibodies with or without radionuclides, and lymphoma vaccines. In patients treated with a doxorubicin-containing combination chemotherapy regimen, interferon α given to patients in complete remission seems to prolong survival, but interferon toxicities can affect quality of life. The monoclonal antibody rituximab can cause objective responses in 35–50% of patients with relapsed follicular lymphoma, and radiolabeled antibodies appear to have response rates well in excess of 50%. The addition of rituximab to CHOP and other effective combination chemotherapy programs achieves prolonged overall survival and a decreased risk of histologic progression. Complete remissions can be noted in 85% or more of patients treated with R-CHOP, and median remission durations can exceed 6 or 7 years. Maintenance intermittent rituximab therapy can prolong remissions even further, although it is not completely clear that overall survival is prolonged. Some trials with tumor vaccines have been encouraging. Both autologous and allogeneic hematopoietic stem cell transplantations yield high complete response rates in patients with relapsed follicular lymphoma, and long-term remissions can occur in 40% or more of patients.

Patients with follicular lymphoma with a predominance of large cells have a shorter survival when treated with single-agent chemotherapy but seem to benefit from receiving an anthracycline-containing combination chemotherapy regimen plus rituximab. When their disease is treated aggressively, the overall survival for such patients is no lower than for patients with other follicular lymphomas, and the failure-free survival is superior.

Patients with follicular lymphoma have a high rate of histologic transformation to diffuse large B-cell lymphoma (5–7% per year). This is recognized ~40% of the time during the course of the illness by repeat biopsy and is present in almost all patients at autopsy. This transformation is usually heralded by rapid growth of lymph nodes—often localized—and the development of systemic symptoms such as fevers, sweats, and weight loss. Although these patients have a poor prognosis, aggressive combination chemotherapy regimens can sometimes cause a complete remission in the diffuse large B-cell lymphoma, at times leaving the patient with persisting follicular lymphoma. With more frequent use of R-CHOP to treat follicular lymphoma at diagnosis, it appears that the rate of histologic progression is decreasing. R-CHOP or bendamustine plus rituximab with intermittent rituximab maintenance for 2 years are the most commonly used treatment approaches.

Diffuse Large B-Cell Lymphoma Diffuse large B-cell lymphoma is the most common type of non-Hodgkin's lymphoma, representing approximately one-third of all cases. This lymphoma makes up the majority of cases in previous clinical trials of "aggressive" or "intermediate-grade" lymphoma. Table 134-10 shows the clinical characteristics of diffuse large B-cell lymphoma.

The diagnosis of diffuse large B-cell lymphoma can be made accurately by an expert hematopathologist (Fig. 134-8). Cytogenetic and molecular genetic studies are not necessary for diagnosis, but some evidence has accumulated that patients whose tumors overexpress the BCL-2 protein might be more likely to relapse than others. A subset of patients have tumors with mutations in *BCL6* and translocations involving *MYC*; these are called "double-hit" lymphomas and typically have more aggressive growth and are more poorly responsive to treatment than other diffuse large B-cell lymphomas. Patients with prominent mediastinal involvement are sometimes diagnosed as a separate subgroup having primary mediastinal diffuse large B-cell lymphoma. This latter group of patients has a younger median age (i.e., 37 years) and a female predominance (66%). Subtypes of diffuse large B-cell lymphoma, including those with an immunoblastic subtype and tumors with extensive fibrosis, are recognized by pathologists but do not appear to have important independent prognostic significance.

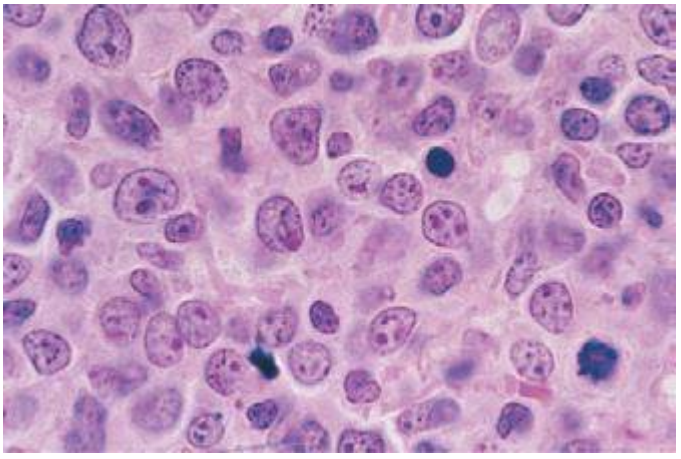

FIGURE 134-8 Diffuse large B-cell lymphoma. The neoplastic cells are heterogeneous but predominantly large cells with vesicular chromatin and prominent nucleoli.

Diffuse large B-cell lymphoma can present as either primary lymph node disease or at extranodal sites. More than 50% of patients will have some site of extranodal involvement at diagnosis, with the most common sites being the gastrointestinal tract and bone marrow, each being involved in 15–20% of patients. Essentially any organ can be involved, making a diagnostic biopsy imperative. For example, diffuse large B-cell lymphoma of the pancreas has a much better prognosis than pancreatic carcinoma but would be missed without biopsy. Primary diffuse large B-cell lymphoma of the brain is being diagnosed with increasing frequency. Other unusual subtypes of diffuse large B-cell lymphoma such as pleural effusion lymphoma and intravascular lymphoma have been difficult to diagnose and associated with a very poor prognosis.

Table 134-11 shows the initial evaluation of patients with diffuse large B-cell lymphoma. After a careful staging evaluation, ~50% of patients will be found to have stage I or II disease, and ~50% will have widely disseminated lymphoma. Bone marrow biopsy shows involvement by lymphoma in ~15% of cases, with marrow involvement by small cells more frequent than by large cells.

TREATMENT DIFFUSE LARGE B-CELL LYMPHOMA

The initial treatment of all patients with diffuse large B-cell lymphoma should be with a combination chemotherapy regimen. The most popular regimen in the United States is CHOP plus rituximab, although a variety of other anthracycline-containing combination chemotherapy regimens appear to be equally efficacious. Patients with stage I or nonbulky stage II disease can be effectively treated with three to four cycles of combination chemotherapy with or without subsequent involved-field radiotherapy. The need for radiation therapy is unclear. Cure rates of 70–80% in stage II disease and 85–90% in stage I disease can be expected.

For patients with bulky stage II, stage III, or stage IV disease, six to eight cycles of CHOP plus rituximab are usually administered. A large randomized trial showed the superiority of CHOP combined with rituximab over CHOP alone in elderly patients. A frequent approach would be to administer four cycles of therapy and then reevaluate. If the patient has achieved a complete remission after four cycles, two more cycles of treatment might be given and then therapy discontinued. Using this approach, 70–80% of patients can