Introduction

Although there have been many advances in the treatment of Hodgkin's disease, diagnosis of the disease still rests on the identification of the Reed-Sternberg cell. This distinctive, though nonspecific, cell was first described by Sternberg in 1898 and further elucidated by Reed in 1902. In most biopsies, the Reed-Sternberg cell accounts for only 1% of the cells present, with the remainder consisting of lymphocytes, granulocytes, histiocytes, plasma cells, and fibroblasts [1].

Histologic Classification

In addition to recognition of the Reed-Sternberg cell, the background cells and their ratio to Reed-Sternberg cells are important in the classification of Hodgkin's disease [1]. The first such classification system, based on biologic characteristics, was developed by Lukes and Butler in 1963. That system was modified in 1966 at the Rye Conference. The Rye modification divides Hodgkin's disease into four histologic types, named according to their characteristic features: (1) lymphocyte-predominant, (2) nodular sclerosis, (3) mixed cellularity, and (4) lymphocyte-depleted. Two variants of lymphocyte-predominant disease (nodular and diffuse) have been identified based on different phenotypes and behavioral characteristics. Nodular lymphocyte-predominant Hodgkin's disease is now widely regarded as a B-cell lymphoma and is the only subtype for which the cell of origin is known, although some investigators contest this conclusion [6-8].
Nodular sclerosis Hodgkin's disease encompasses the lacunar cell variant of the Reed-Sternberg cell. Nodular sclerosis Hodgkin's disease may be difficult to distinguish from large-cell lymphoma, especially if there are many lacunar cells. MacLennan et al have divided nodular sclerosing Hodgkin's disease into grade-1 and grade-2 histology because they found differences in disease-free and overall survival rates between the two grades [9]. More recent investigations, however, have not demonstrated a correlation between a difference in grade and prognosis [10-13]. The third type of Hodgkin's disease, mixed cellularity, has much more variation in cell type, has rare Reed-Sternberg cells, and may be confused with other lymphomas, especially peripheral T-cell lymphoma. Finally, the lymphocyte-depleted form of Hodgkin's disease is rare, partly because many of the cases described in the early literature were mistaken for large-cell lymphoma. A patient with this diagnosis should undergo a thorough pathologic review to ensure that the proper diagnosis has been made [6,7].

**Epidemiology**

Hodgkin's disease is an uncommon disorder. Overall, 7,500 cases occur annually in the United States, accounting for 0.7% of all malignancies. The nodular sclerosing subtype has a female predominance, with the remaining subtypes occurring more commonly in men. Hodgkin's disease occurs more frequently in developed than in underdeveloped countries. The disease has a bimodal incidence pattern in both developed and underdeveloped countries, but for unknown reasons, the first peak occurs at an earlier age in patients in underdeveloped countries. Investigators have performed multiple studies examining possible risk factors associated with Hodgkin's disease, including small family size, single family dwellings, and high parental education. This series of factors may be explained by the delayed-infection hypothesis, which, although it may apply to young adults, may be less important in the pathogenesis of Hodgkin's disease in older patients. Epstein-Barr virus (EBV) has been implicated as a causative agent associated with the development of Hodgkin's disease, because cases of this malignancy have occurred following bouts of infectious mononucleosis, and the EBV genome can be found in many of the cells present in involved lymph nodes. Immunodeficiency, induced by the human immunodeficiency virus type 1, has also been associated with the development of Hodgkin's disease, especially the mixed-cellularity subtype. The significance of this association, however, remains unclear [6,14,15].

**Staging System**

Peters et al introduced the first clinically relevant system for staging this disease, based on results obtained with radiotherapy alone. Patients with stage-I disease had a single site of involvement, those with stage-II had two or more contiguous sites of involvement, and patients with stage-III disease had extensive nodal or visceral involvement. The concept of disseminated or stage-IV Hodgkin's disease was introduced at the Rye Conference. The Ann Arbor System used today is based on these reports (Table 1).

<table>
<thead>
<tr>
<th>Stage I</th>
<th>Involvement of a single lymph-node region (I) or a single extralymphatic organ or site (IE)</th>
</tr>
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<tbody>
<tr>
<td>Stage II</td>
<td>Involvement of two or more lymph-node regions on the same side of the diaphragm (II) or localized involvement of an extralymphatic organ or site (II E)</td>
</tr>
<tr>
<td>Stage III</td>
<td>Involvement of lymph-node regions on both sides of the diaphragm (III) or localized involvement of an extra-lymphatic organ or site (III E), spleen (III S), or both (III SE)</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Diffuse or disseminated involvement of one or more extralymphatic organs, with or without associated lymph-node involvement; (P) pulmonary, (O) osseous, or (H) hepatic</td>
</tr>
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</table>

At the Ann Arbor Staging Conference, the suffix letter “E” was introduced to designate patients with nodal involvement who had a limited degree of extension from diseased nodes into lung, bone,
pericardium, and skin. Important modifications of the Ann Arbor System were developed at the Cotswalds Conference in 1989. At this time, it was recommended that patients who had bulky disease, including masses larger than 10 cm in their greatest dimension or mediastinal masses greater than one-third the chest wall diameter, have a stage designated with the suffix “X,” and that patients achieving greater than 90% partial response with stable adenopathy be designated as having achieved “CR” (complete response uncertain). Because there is no clear prognostic difference in subsets of patients with or without residual radiographic abnormalities, there is little clinical utility in creating an unduly complex staging system [16].

Other recommendations made at the Cotswalds Conference included recognizing the importance of computed tomography in evaluating liver and spleen involvement and designating abdominal disease substages-III and -III. Patients with stage-III disease have splenic involvement or lymphadenopathy involving the splenic hilar, celiac, or portal nodes. Disease involving the para-aortic, iliac, or mesenteric nodes is designated III. On the basis of our treatment experience, we at M.D. Anderson Cancer Center have designated patients with iliac or inguinal nodal involvement as having stage-III disease [6,14].

**Patient Evaluation**

The initial evaluation of patients with Hodgkin’s disease has both prognostic and therapeutic significance. In addition to performing a hemogram, obtaining a chemical profile, measuring the beta-2-microglobulin level and erythrocyte sedimentation rate, and obtaining roentgenographic studies, other diagnostic procedures should be considered, depending upon the disease presentation and planned treatment (Table 2). Bilateral bone marrow biopsy should be routinely performed, although it is more likely to yield positive results in patients with B symptoms.

**Table 2. Recommended Procedures for Staging of Hodgkin’s Disease Patients**

- Identification of B symptoms
- Plain chest x-rays
- Computed tomography
- Computed tomography
- Bipedal lymphography
- Full blood count with differential
- Determination of erythrocyte sedimentation rate
- Bilateral bone marrow aspiration and biopsy
- Liver function tests
- Serum albumin, lactate dehydrogenase

**Procedure**

- Laparotomy
- Ultrasound scanning
- Magnetic resonance imaging
- Gallium scanning
- Technetium bone scan
- Liver-spleen scanning
Lymphangiography remains a valuable diagnostic tool, especially in the evaluation of disease in the abdomen. Lymphangiography will detect early nodal disease that might be missed with computed tomographic imaging. In addition, nodal status can easily be serially evaluated on routine x-ray films to assess response both during and after therapy. The radiotherapist may also use these results to delineate treatment fields, although lymphangiography may be less essential for patients treated with chemotherapy alone [7].

Staging by laparotomy remains a controversial subject. Various studies have examined clinical features predictive of abdominal involvement. Approximately 30% to 50% of patients with early-stage Hodgkin's disease will have microscopic abdominal involvement that is not detected by lymphangiography or computed tomography. For this reason, with few exceptions, all patients should be considered as having abdominal disease unless they have undergone a staging laparotomy that has shown otherwise.

Glatstein et al found that the presence of “B” symptoms (unexplained fever above 38ºC, night sweats, and unexplained weight loss exceeding 10% of body weight) was predictive of abdominal disease [17]. At M.D. Anderson, male gender, age greater than 40 years, the presence of B symptoms, and mixed cellularity disease were correlated with higher-than-average risks of abdominal disease [18]. Investigators elsewhere have identified other features predictive of abdominal disease, including the number of nodal sites in the upper torso. However, there is currently no way to predict with total accuracy the presence of abdominal disease in a patient whose lymphangiogram is negative, except in patients with stage-I disease above the cricoid cartilage, patients with lymphocyte-predominant stage-I disease, and women with nodular sclerosis stage-IA disease and a peripheral presentation [7].

Other radiologic studies are of limited benefit in the management of Hodgkin's disease. Some authors have proposed that gallium scans may be used to detect complete response vs partial response to therapy. Hagemeister et al retrospectively reviewed 240 gallium scans from 165 patients with Hodgkin's disease. In untreated Hodgkin's disease, the sensitivity of this test was only 64%, with a specificity of 95%. In untreated patients or those in whom disease had recurred, gallium uptake was predictive for disease in specific sites. Unfortunately, 95% of predicted relapses were not detected by this study during routine follow-up.

The usefulness of the gallium scan, therefore, may be limited to confirming the diagnosis of Hodgkin's disease in new patients and in treated patients who have new or residual lesions [19]. Magnetic resonance imaging has not yet superseded computed tomographic scanning of the abdomen and chest in the evaluation of Hodgkin's disease. Bone scans should be considered only in patients with symptoms. Ultrasound of the spleen may play a role in the detection of occult splenic involvement.

Treatment of Early Disease

Laparotomy Staged

Patients with laparotomy-staged supradiaphragmatic disease and no mass or a small mediastinal mass may be treated with radiotherapy alone. Initial investigations used low-dose involved-field radiation only. Patients responded well initially but had a high rate of disease relapse in a disseminated pattern, prompting investigation of higher doses of radiation, extended fields, and the use of prophylactic radiotherapy [7].

Largely because of results from early clinical trials by investigators at Stanford, prophylactic abdominal irradiation for both pathologically and clinically early-staged supradiaphragmatic disease was initially standard therapy in the United States [20-22]. Later, questions arose concerning whether wider radiation fields were necessary. Patients receiving extended-field radiotherapy for pathologically early-staged disease were found to have excellent 10-year survival rates of 82% and 83% for stages-I and -II disease, respectively, with no reported adverse prognostic features [23]. However, it is unclear whether there was real benefit from the abdominal irradiation or whether the patients were simply of a more favorable group.

In studies comparing mantle vs extended-field radiotherapy, other investigators found that the addition of radiotherapy to the upper abdomen was not necessary in patients whose disease was staged by laparotomy [24,25]. Of note, patients in these studies were only offered single-modality radiotherapy if they lacked adverse features (eg, B symptoms, large mediastinal masses, or advanced age).

Lee et al added low-dose radiation to the lungs and liver to extended-field radiotherapy being done in patients with pathologically early-staged disease. They found that the 5-year disease-free survival
rate was improved to 82%, compared with 58% in patients who received extended field radiation alone, with minimal or no added toxic effects [26].

In studies done at M.D. Anderson and elsewhere for which favorable patients were not selected, the inclusion of abdominal irradiation did not decrease the low rate of abdominal relapse following single-modality radiotherapy for laparotomy-staged early disease in the upper torso [27-29]. At M.D. Anderson, a series of patients with pathologic early-stage Hodgkin’s disease were treated with involved-field (including the mantle, if indicated), extended-field radiation, or involved-field radiation followed by six cycles of mechlorethamine (Mustargen), vincristine (Oncovin), procarbazine (Matulane), and prednisone (MOPP) chemotherapy [27]. Overall, the 5-year disease-free survival rate for those patients treated with involved-field radiation including the mantle was 72%, compared with 66% for patients treated with extended-field radiation. Importantly, in studies of treatment options for pathologically staged early disease, including those mentioned above, several adverse prognostic features were identified that predicted for relapse if only radiotherapy was used. These included the presence of a mediastinal mass greater than 7.5 cm or greater than one-third the diameter of the chest, hilar lymphadenopathy, B symptoms, advanced age, extension of disease into pulmonary parenchyma, mixed cellularity histology, stage-II disease, and increased number of nodal sites [25-33]. The major point to emerge from these trials was that the disease-free survival of patients with poor prognostic factors significantly improved with the use of combined modality chemotherapy and radiotherapy.

To compare chemotherapy alone with radiotherapy, Cimino et al treated patients who had pathologic stage-I to -IIA disease with extended-field radiotherapy or six cycles of MOPP [34]. The disease-free survival rates were 73% for patients treated with MOPP and 74% for those treated with radiotherapy. At 8-year follow-up, the radiotherapy arm had a significantly higher overall survival rate of 93%, compared with 56% for the chemotherapy arm. The respective rates of relapse-free survival were similar, at 70% and 71%. Lack of response to salvage treatment on the chemotherapy arm was thought to be the primary reason for the discordant survival rates. Adverse features for those treated with chemotherapy included bulky disease. The authors suggested that patients with early bulky disease be treated with combined-modality therapy [34,35]. In contrast, investigators at the National Cancer Institute reported improved overall and disease-free survival rates with MOPP chemotherapy vs extended-field radiation [36]. The discrepancy is likely accounted for by the fact that the American trial included patients with stages-IIIB and -IIIA disease, which have been shown to fare worse with single-modality radiotherapy, and excluded patients with peripheral stage-IA disease.

As survival improved during the evolution of treatment methods, a new focus of therapy was the possibility that less intense or less toxic treatment could give equivalent results with decreased long- and short-term complications. A program was designed at M.D. Anderson to treat patients with poor-prognosis laparotomy-staged early disease with only two cycles of MOPP chemotherapy followed by radiotherapy [37]. The 4-year disease-free survival rate was 79% compared with 78% for patients who had favorable presentations and were treated with radiation alone. Toxic effects, including sterility and secondary malignancies, were reduced. Horning et al treated patients with favorable pathologic stage-IA, -IIA, or -IIIA disease with a combination of radiotherapy and a novel chemotherapy regimen of six cycles of vinblastine, bleomycin (Blenoxane), and methotrexate to avoid the toxic effects of MOPP chemotherapy [38]. The patients were randomized to either subtotal or total lymphoid irradiation or to involved-field radiation with vincristine, bleomycin, and methotrexate. The 5-year rates for freedom from disease progression were 70% for those treated with radiotherapy alone and 95% for those who received the combined-modality regimen. The outcome was comparable with reported results from studies of adjuvant MOPP treatments, and there was little adverse effect on fertility, although some reduction in pulmonary function was seen in patients who received irradiation plus bleomycin.

In summary, patients with laparotomy-staged early disease without large mediastinal masses can be treated with either involved or extended-field radiotherapy with equivalent results. The presence of B symptoms, bulky mediastinal disease, hilar involvement, extension into pulmonary parenchyma, or advanced age, especially in males, necessitates combined-modality radiotherapy and chemotherapy for optimal control of both local and abdominal recurrence, since there is a 10% to 15% risk of the latter even with the addition of splenic pedicle and para-aortic irradiation when radiotherapy is used alone. If adverse prognostic features are identified and the treatment approach instead focuses on combined modality therapy, staging by laparotomy becomes unnecessary.

**Clinically Staged**

The optimal therapy for patients with clinically staged I or II Hodgkin’s disease remains controversial.
Most centers recommend combined modality therapy. However, radiotherapy or chemotherapy alone may suffice in appropriate situations. One of the most challenging tasks in the treatment of clinically staged Hodgkin's disease is the identification of prognostic risk factors that will allow a therapeutic regimen to be tailored to any particular patient for maximum efficacy and minimal immediate and delayed toxic effects.

Sutcliffe et al. investigated a large series of patients who had clinically staged I or II Hodgkin's disease. Based on the relapse rates following radiotherapy alone, the authors were able to define three groups. Group 1 consisted of patients who had disease above the cricoid cartilage. Group 2 comprised those patients who had stage-IA disease below the cricoid cartilage or stage-IIB lymphocyte-predominant or nodular sclerosis disease. Patients with early-stage disease and unfavorable histology or B symptoms were classified as group 3. Based upon disease relapse rates, the authors recommended that group 1 patients receive involved-field radiotherapy, that group 2 patients receive extended-field radiotherapy, and that group 3 patients receive combined-modality therapy (radiotherapy plus chemotherapy) [39].

Subsequently, Gospodarowicz et al. expanded on this report with a larger number of patients treated at the same institution and identified subsets of patients who had favorable, intermediate, and unfavorable prognoses. Favorable prognosis included presentation of disease in the “high upper neck” that was nodular sclerosing stage-IA disease in females, disease that had a lymphocyte-predominant histology, and disease that presented in the groin [40]. Patients with favorable features should achieve excellent disease-free survival rates with extended-field or even involved-field radiotherapy, because the likelihood of abdominal disease in these patients is low [41]. Other investigators have studied the use of chemotherapy with or without radiotherapy. Pavlovsky et al. treated patients who had clinically staged I and II Hodgkin's disease with cyclophosphamide (Cytoxan, Neosar), vincristine, procarbazine, and prednisone (CVPP) or CVPP plus radiotherapy. Patients with higher-risk features—age greater than 45 years, involvement of more than two nodal areas, a mediastinal mass larger than 10 cm in its greatest dimension, or peripheral lymphadenopathy greater than 5 cm—had freedom-from-progression rates of 34% with CVPP alone and 75% with combined-modality therapy. In the absence of these factors, patients had freedom-from-progression rates of 77% with CVPP and 70% with combined-modality therapy. The authors suggested that patients with adverse features receive combined-modality therapy [42]. Although most investigators recommend combined-modality therapy in early clinically staged Hodgkin's disease, programs vary with respect to the amount of chemotherapy and radiotherapy delivered. Carde et al. examined patients who had clinically staged I and II Hodgkin's disease with favorable or unfavorable characteristics. Those patients of advanced age, or with mediastinal involvement, unfavorable histologies, or bulky disease after laparotomy were included in the unfavorable group. The purpose of the study was to compare the efficacy of total lymphoid or subtotal lymphoid irradiation with that of combined-modality therapy consisting of six cycles of MOPP followed by mantle irradiation. Overall, the relapse-free survival rates were better for those treated with combined-modality therapy, although overall survival rates were identical because of salvage therapy [24].

Zittoun et al. studied patients who had clinically staged I and IIIA Hodgkin's disease treated with MOPP and radiotherapy. Those patients with favorable presentations received three courses of MOPP followed by involved-field or extended-field radiotherapy. Those patients with unfavorable characteristics received six courses of MOPP followed by radiotherapy. Most patients had a good outcome. However, patients with mixed-cellularity disease, men, and patients over 40 years old had a worse outcome. The investigators concluded that patients having unfavorable presentations should receive six courses of MOPP followed by involved-field radiotherapy [43]. Nonetheless, in a study of 166 patients with clinically-staged I to II A disease, Andrieu et al. examined the efficacy of three cycles of MOPP followed by radiotherapy to varying fields, depending on the extent of disease. They reported a 5-year survival rate of 93% and a disease-free survival rate of 90% for patients who achieved a complete remission. Disease did not recur in the mediastinum among patients with mediastinal disease, and disease recurred in the abdomen among only a small percentage of patients, even without prophylaxis to this area. These authors thus concluded that a minimum of three courses of MOPP would be sufficient to prevent relapse in the mediastinum and abdomen [44].

Another significant investigation was conducted by Ferme et al. [45]. In that study, patients with clinically staged IB to III disease received three or six cycles of MOPP before radiotherapy. Complete responses were obtained in 96% of these patients after three cycles of MOPP and in 94% following six cycles [45]. This study was important because it illustrated the efficacy of three cycles of MOPP.
The presence of a large mediastinal mass has also been confirmed in other studies as an adverse prognostic feature in patients treated with radiotherapy or chemotherapy alone or with combined-modality therapy [46,47].

**Infradiaphragmatic Presentation**

Hodgkin's disease that presents initially in the abdomen is unusual. Some investigators have recommended chemotherapy based on the presence of B symptoms and bulky disease. However, patients with pathologic stage-I A disease may receive “inverted Y” radiotherapy that includes the splenic pedicle. Patients with stage-II A disease should receive total lymphoid irradiation, and patients with stage-II B disease should receive combined-modality therapy [48].

At M.D. Anderson, 60 patients with pathologic or clinical stage-I to -II Hodgkin's disease received radiotherapy with or without MOPP. The disease-free survival rate of the patients who received radiotherapy alone was 50%, compared with 92% for those who received combined-modality therapy. Radiotherapy alone may be adequate, however, in patients evaluated with lymphangiography who have pelvic, inguinal, or femoral involvement [49].

**Treatment of Stage-III Disease**

The optimal therapy for stage-III Hodgkin's disease remains controversial. As with the other stages, treatment depends primarily on the extent of disease. Several studies have examined the role of certain factors that influence the outcome of treatment in stage-III A Hodgkin's disease. Patients with stage-III A disease have been observed to have improved overall and disease-free survival rates, compared with patients who have stage-III A disease. Patients with stage-III A and -III B disease treated with radiotherapy alone had disease-free survival rates of 64% and 32%, respectively. The investigators noted that these patients showed a marked improvement in survival rates if they received combined-modality therapy and concluded that patients with extensive disease should receive such therapy [50].

Hoppe et al examined the significance of the number of splenic nodules in patients receiving radiotherapy alone [51]. Patients with fewer than five nodules had a 5-year disease-free survival rate of 90%, whereas patients with more than five nodules had a 5-year disease-free survival rate of only 30% [51]. Mazza et al also found that such patients with small lymphadenopathy had better disease-free survival rates than did those with larger nodes [52]. However, prognostic factors for these patients are different when the treatment is combined-modality therapy.

At M.D. Anderson, 102 patients with stage-III A Hodgkin's disease received two cycles of MOPP followed by radiotherapy. A total of 73 patients received pelvic radiotherapy and 29 did not; the 10-year survival rates for these patient groups were 89% and 93%, respectively. Five-year survival and freedom-from-progression rates for the patients who did not receive pelvic radiotherapy were 93% and 85%, respectively. Twenty-three patients with stage-III A disease were treated with two courses of MOPP and radiotherapy to involved sites. Five-year survival and freedom-from-progression rates were 85% and 79%, respectively. Twenty patients with stage-III A disease treated with combined-modality therapy had 5-year-survival and freedom-from-progression rates of 82% and 85%, respectively. The results of this study indicated that the extent of abdominal involvement did not affect survival [53].

Mauch et al identified a group of patients with stage-III A disease (those with fewer than five splenic nodules) that can be adequately treated with total lymphoid irradiation alone. They recommended combined-modality therapy, however, for all other patients with stage-III A Hodgkin's disease [54]. Most investigators recommend chemotherapy with or without radiotherapy for stage IIIB Hodgkin's disease. Factors that might influence survival include advanced age, histologic tumor subtype, and tumor burden [7]. At M.D. Anderson, patients with stage-IIIB Hodgkin's disease were treated with two courses of MOPP and radiotherapy. In this study, patients who had stage-IIIB or -IIIB disease had similar good outcomes, but patients with stage-IIIB disease had inferior results. Therefore, patients with stage-IIIB disease should be treated more intensively [55,56].

In another study, Bonadonna et al randomized patients with stage-IIIB, -III, or -IV Hodgkin's disease to receive MOPP or doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) followed by radiotherapy. Radiotherapy increased the complete response rate of patients treated with ABVD from 69% to 94%, and for those treated with MOPP, from 66% to 95%. Freedom-from-progression rates were 81% for the ABVD group and 63% for the MOPP group [57]. Other studies utilizing different chemotherapeutic regimens and radiotherapy sequences have yielded similar results. Therefore, stage-IIIB disease should be treated with combined-modality therapy, although the extent of disease may play a role in the number of cycles of chemotherapy needed to achieve good results.
Treatment of Stage-IV Disease

Multiple prognostic factors for treatment outcome in stage-IV Hodgkin's disease have been studied. Investigators at M.D. Anderson, the National Cancer Institute, and other centers have identified B symptoms, dose of vincristine administered, extent of extranodal lesions, mechlorethamine dose, bone marrow involvement, anemia, elevated erythrocyte sedimentation rate, and advanced age as factors that influence prognosis [58-60].

Longo et al examined 158 patients with stage-IV Hodgkin's disease, 84% of whom achieved a complete response and 45% of whom were alive without disease at 9-year follow-up. Factors influencing complete response were lack of B symptoms and vincristine dose intensity. Factors noted to affect duration of remission were B symptoms, pleural disease, advanced age, and increased number of extranodal sites [58].

At M.D. Anderson, among 53 patients treated with MOPP, the complete response rate was influenced by the number of extranodal sites. Of patients with one extranodal site, 75% entered complete remission compared with 25% of those with two or more extranodal sites. Overall survival was also influenced by this factor. Patients who received more than 80% of the planned dose of mechlorethamine also had higher disease-free and overall survival rates [60].

Alternative treatments for advanced Hodgkin's disease have also been proposed (Table 3).

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Dose (mg/m²)</th>
<th>Route</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOPP</td>
<td></td>
<td></td>
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<tr>
<td>Mechlorethamine</td>
<td>6</td>
<td>IV</td>
<td>1</td>
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<tr>
<td>Vincristine</td>
<td>1.4</td>
<td>IV</td>
<td>1</td>
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<td>Procarbazine</td>
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<td>PO</td>
<td>1</td>
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<tr>
<td>Prednisone</td>
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<td>PO</td>
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<td>MVPP</td>
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<td>Vinblastine</td>
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<td>Bleomycin</td>
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<tr>
<td>MOPP/ABVD</td>
<td>Alternating months of MOPP and ABVD</td>
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</table>
The ABVD regimen was examined as first-line therapy for advanced Hodgkin's disease by Bonadonna et al. [61]. They showed that ABVD was equivalent to MOPP in achieving a complete response rate but that disease-free survival rates appeared to be superior with ABVD [61]. The Cancer and Leukemia Group B (CALGB) also investigated MOPP vs ABVD and noted a complete response rate of 47% for the MOPP group and 83% for the ABVD group. The disease-free survival rate was also better with ABVD [62]. Bonadonna et al also examined the efficacy of MOPP-ABVD in stage-IV Hodgkin's disease and found that the complete response rate was better for MOPP-ABVD than for MOPP alone [61]. However, only 44% of patients in the MOPP group received more than 80% of the planned dose, whereas 64% of patients in the MOPP-ABVD group received more than 80% of the planned dose, and, as previously stated, the amount of drug delivered may affect outcome. In a three-armed study, CALGB treated 38 patients with MOPP-ABVD, ABVD, or MOPP alone. Patients in the MOPP-ABVD and ABVD groups had better overall survival rates as well as better complete response rates than did those in the MOPP group [62]. Connors and Klimo modified the MOPP-ABVD regimen. They gave patients a regimen of MOPP plus a combination of doxorubicin, bleomycin, and vinblastine, with patients receiving all seven drugs each month, and showed that this regimen yielded similar results to MOPP-ABVD [53].

The use of combined modality therapy in stage-IV Hodgkin's disease remains controversial. Studies at the National Cancer Institute revealed that patients treated with adjuvant radiotherapy after MOPP therapy had no significant improvement in overall survival [7]. At Memorial Sloan-Kettering Cancer Center, Yahalom et al examined the effect of adjuvant radiotherapy in patients with advanced-stage Hodgkin's disease treated with combined chemotherapy. They found that the majority of relapses occurred in previously unirradiated sites and, therefore, concluded that radiotherapy in combination with chemotherapy could improve survival and decrease relapse in patients with advanced Hodgkin's disease [64].

Salvage Therapy

The optimal selection of salvage therapy for relapsed Hodgkin's disease depends primarily on the initial therapy. Patients in whom disease recurs after radiotherapy for early-stage Hodgkin's disease may receive any chemotherapeutic regimen with an 80% to 90% chance of achieving complete remission [7]. Patients in whom disease recurs after achieving complete response with chemotherapy may be treated again with another regimen (Table 4).

<table>
<thead>
<tr>
<th>Table 4. Conventional Dose Salvage Combination Chemotherapy Regimens for Relapsed Resistant Hodgkin’s Disease</th>
<th>Regimen</th>
<th>Dose (mg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VABCD</strong></td>
<td>Vinblastine, 6 mg/m² IV every 3 wk</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Doxorubicin, 40 mg/m² IV every 3 wk</td>
<td>8 (45)</td>
</tr>
<tr>
<td></td>
<td>Dacarbazine, 800 mg/m² IV every 3 wk</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Lomustine, 80 mg/m² PO every 6 wk</td>
<td>(35)</td>
</tr>
<tr>
<td></td>
<td>Bleomycin, 15 U IV once a week</td>
<td>47</td>
</tr>
<tr>
<td><strong>ABDIC</strong></td>
<td>Doxorubicin, 45 mg/m² IV on day 1</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>Bleomycin, 5 U/m² IV on days 1 and 5</td>
<td>(35)</td>
</tr>
<tr>
<td></td>
<td>Dacarbazine, 200 mg/m² IV on days 1 through 5</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Lomustine, 50 mg/m² PO on day 1</td>
<td>(45)</td>
</tr>
<tr>
<td></td>
<td>Prednisone, 40 mg/m² PO on days 1 through 5</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Repeat every 28 days</td>
<td>8</td>
</tr>
</tbody>
</table>

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**CBVD**

- Lomustine, 120 mg/m² PO on day 1
- Bleomycin, 15 U IV on days 1 and 22
- Vinblastine, 6 mg/m² IV on days 1 and 22
- Dexamethasone, 3 mg/m² PO on days 1 through 21

Repeat every 6 wk

**PCVP**

- Vinblastine, 3 mg/m² IV every 2 wk
- Procarbazine, 70 mg/m² PO every other day
- Cyclophosphamide, 70 mg/m² PO every other day
- Prednisone, 8 mg/m² PO every other day

Repeat for 1 yr

**CEP**

- Lomustine, 80 mg/m² PO on day 1
- Etoposide, 100 mg/m² PO on days 1 through 5
- Prednimustine, 60 mg/m² PO on days 1 through 5

**CEP/ABVD**

**CEP (as above)**

**EVA**

- Etoposide, 200 mg/m² PO on days 1 through 5
- Vincristine, 2 mg IV on day 1
- Doxorubicin, 50 mg/m² IV on day 1

**LVB**

- Lomustine
- Vindesine
- Bleomycin

**MIME**

- Methyl GAG, 500 mg/m² IV on days 1 through 14
- Ifosfamide, 1 g/m² IV on days 1 through 5
- Methotrexate, 30 mg/m² IV on day 3
- Etoposide, 100 mg/m² IV on days 1 through 3 every 3 wk

**MTX-CHOP**

- Methotrexate, 30 mg/m² IV every 6 h for 4 days, beginning on days 1 and 8, with rescue
- Cyclophosphamide, 750 mg/m² IV on day 15
- Vincristine, 1 mg/m² IV on days 15 and 22
- Prednisone, 100 mg/m² PO on days 22 through 26
- Doxorubicin, 50 mg/m² IV on day 15 every 4 wk

**CEM**

- Lomustine, 100 mg/m² PO on day 1
Etoposide, 100 mg/m² PO on days 1 through 3 and 21 through 23
Methotrexate, 30 mg/m² PO on days 1, 8, 21, and 28 every 6 wk

**CEVD**
- Lomustine, 80 mg/m² PO on day 1
- Etoposide, 120 mg/m² PO on days 1 through 5 and 22 through 26
- Vindesine, 3 mg/m² IV on days 1 and 22
- Dexamethasone, 3 mg/m² PO on days 1 through 8, followed by 1.5 mg/m² PO on days 9 through 26 every 6 wk

**MOPLACE**
- Cyclophosphamide, 750 mg/m² IV on day 1
- Etoposide, 80 mg/m² IV on days 1 through 3
- Prednisone, 60 mg/m² PO on days 1 through 14
- Methotrexate, 120 mg/m² IV on days 15 and 22, with rescue
- Cytarabine, 300 mg/m² IV on days 15 and 22
- Vincristine, 2 mg IV on days 15 and 22 every 4 wk

**CAVP**
- Lomustine, 90 mg/m² PO on day 1
- Melphalan, 7.5 mg/m² PO on days 1 through 5
- Etoposide, 100 mg/m² PO on days 6 through 10
- Prednisone, 40 mg/m² PO on days 1 through 10 every 6 wk

**EVAP**
- Etoposide, 120 mg/m² IV on days 1, 8, and 15
- Vinblastine, 4 mg/m² IV on days 1, 8, and 15
- Cytarabine, 30 mg/m² IV on days 1, 8, and 15
- Cisplatin, 40 mg/m² IV on days 1, 8, and 15, every 4 wk

Fisher et al studied a series of patients whose disease recurred after treatment with MOPP. Patients whose disease recurred 1 year or more after they had achieved complete remission had a greater than 90% chance of achieving a second complete remission. Those patients in whom MOPP treatment failed to induce a complete remission had a poor prognosis. Patients whose disease recurs less than 1 year after they achieve a complete remission may be retreated with a second regimen, but results may vary depending on prognostic features. Patients may also be considered for high-dose chemotherapy followed by autologous or allogeneic bone marrow transplantation [65,66].

**Complications of Treatment**

The treatment of Hodgkin's disease may predispose patients to secondary malignancies. The use of chemotherapeutic agents, especially alkylating agents, is associated with an increased incidence of hematologic malignancies, whereas radiotherapy has been associated with an increased incidence of solid tumors. Patients with Hodgkin's disease may also experience endocrine dysfunction, cardiopulmonary complications, and musculoskeletal abnormalities as a result of treatment (Table 5).
<table>
<thead>
<tr>
<th>Complication</th>
<th>Etiology/Medical Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune dysfunction</td>
<td></td>
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<tr>
<td>Herpes zoster/varicella</td>
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<tr>
<td>Pneumococcal sepsis</td>
<td>Splenic dysfunction</td>
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<tr>
<td>Nonlymphocytic leukemia</td>
<td>Treatment; age above 40</td>
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<tr>
<td>Myelodysplastic syndromes</td>
<td>Treatment; age above 40</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td></td>
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<tr>
<td>Solid tumors</td>
<td></td>
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<tr>
<td>Thymic hyperplasia</td>
<td></td>
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<tr>
<td>Hypothyroidism</td>
<td></td>
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<td>Thyroid cancer</td>
<td></td>
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<td>Male infertility</td>
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<td>Male impotence</td>
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<td>Female infertility</td>
<td></td>
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<tr>
<td>Female impotence</td>
<td></td>
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<tr>
<td>Pericarditis, acute</td>
<td>Mediastinal radiotherapy; chemotherapy recall post-irradiation</td>
</tr>
<tr>
<td>Pericarditis, chronic</td>
<td>Mediastinal radiotherapy; pericardiectomy</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td></td>
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</tbody>
</table>
Secondary Malignancies
Almost any type of malignancy may occur after chemotherapy for Hodgkin's disease. The most common are acute nonlymphocytic leukemia, myelodysplastic syndrome, non-Hodgkin's lymphoma, and solid tumors. The overall risk of occurrence of acute nonlymphocytic leukemia is 0.5% to 2.0% per year. The cumulative risk is 10% to 15% [67].
Risk factors associated with the development of acute nonlymphocytic leukemia include prolonged exposure to alkylating agents and advanced patient age. Diffuse non-Hodgkin's lymphoma is the next most common secondary malignancy, with a cumulative 10-year risk of 4% to 5% [68]. Although most secondary malignancies are thought to be related to therapy, the incidence of non-Hodgkin's lymphoma may also be increased in untreated patients [69]. Unlike the hematologic malignancies, the occurrence of solid tumors in patients with Hodgkin's disease appears to be related to radiotherapy. The incidence of secondary solid tumors is highest approximately 7 years after treatment [70]. The cumulative incidence of solid tumors is 9% at 10 years [71]. Solid tumors that show an increased incidence include carcinoma of the head and neck, melanoma, and female breast cancer [72-77].

Endocrine Complications
Patients treated for Hodgkin's disease may experience endocrine abnormalities that are primarily limited to thyroid and gonadal dysfunction. Patients may develop thyroid hyperplasia, which may need to be distinguished from malignancy [78]. Clinical hypothyroidism occurs in 6% to 25% of patients treated with mantle or cervical radiotherapy. Chemotherapy has little or no role in the development of thyroid dysfunction. Thyroid malignancy may develop in patients treated for Hodgkin's disease, especially those who receive partial thyroid ablation with radiation, thereby causing excessive stimulation of residual thyroid tissue by thyroid-stimulating hormone [79,80]. Because some patients with Hodgkin's disease attain prolonged disease-free survival, the issue of fertility has become important. Approximately 30% to 50% of men have suboptimal semen analyses before therapy [71]. Radiotherapy or its scatter may affect testicular function. Recovery of that function and the length of time to optimal recovery are related to radiation dose. Testicular shielding will reduce exposure [76,81].
Alkylating agents are the most important agents affecting male fertility. These agents include cyclophosphamide, chlorambucil (Leukeran), mechlorethamine, and procarbazine [82]. MOPP therapy results in prolonged testicular dysfunction in 80% of patients. Only 10% of patients will show partial recovery within 1 to 7 years of treatment. Patients who receive less than four cycles of MOPP have a more rapid recovery [83]. Studies of ABVD have shown that 54% of men have impaired spermatogenesis but that all patients recover adequate function within 2 years [84]. Women are also affected by chemotherapy. Menopausal symptoms may develop several years after chemotherapy. Ovarian dysfunction may be heralded by irregular or anovulatory cycles. However, even with preexisting ovarian damage, pregnancy can occur and, thus, should not be considered a sign of adequate ovarian function [71,85].
As with the testis, the ovary appears to be more affected by alkylating agents. In general, the ovary tolerates radiotherapy better than the testis does. Patients nearer to menopause will experience primary amenorrhea at lower radiotherapy doses than will other patients [71]. Ovarian shielding and oophoropexy may be useful for preventing an excessive radiation dose to the ovary. Of all women treated for Hodgkin's disease, 80% will have some ovarian dysfunction and 20% to 30% will have permanent amenorrhea. Patients who receive combined modality therapy and radiotherapy have a higher incidence of dysfunction [86]. Ovarian failure has been correlated to the age of the patient during the period of treatment. Eighty to 100% of patients over 25 years old will experience ovarian failure compared with 25% to 30% of women under 25 [71].

**Cardiovascular Complications**

Both radiotherapy and chemotherapy may have deleterious effects on the heart. Pericarditis resulting from mantle irradiation is the most common cardiovascular side effect of radiotherapy; its incidence is related to the dose, rate, and anatomic volume treated. Use of anterior-posterior ports contributed significantly to cardiac toxicity in early trials. The highest incidence of pericarditis occurs 5 to 9 months after completion of radiotherapy [87,88]. Most patients with pericarditis are asymptomatic, but others may present with cardiomegaly, friction rub, effusion, tamponade, fever, electrocardiographic changes, and pleuritic pain.

Multiple modes of therapy for acute pericarditis exist, depending upon symptomatology. For symptomatic relief, nonsteroidal agents, digoxin, and diuretics have been used. For patients with hemodynamic compromise, pericardiocentesis and pericardiectomy may be utilized. Pericardial effusions develop in 25% to 30% of patients. This usually occurs within 2 years of therapy, but may arise later [89]. Chronic pericarditis occurs 53 to 124 months after therapy [90]. These patients usually present with dyspnea on exertion. This form of pericarditis is usually constrictive and is treated with pericardiectomy.

Myocardial damage may also be experienced after radiotherapy. Brosius et al conducted a postmortem study of 16 patients who received greater than 3,500 cGy to the heart. Fifteen of these patients had signs of myocardial damage [91]. Utilizing radionuclide ventriculography, Burns et al examined ventricular function after radiotherapy in 12 of 21 asymptomatic patients and 10 historical controls. Right-ventricular ejection fraction dysfunction was the most common finding. The authors concluded that the right ventricle may experience more damage because of its location [92].

Other studies utilizing patients who underwent radiotherapy with various cardiac-shielding techniques showed objective evidence of myocardial damage in the absence of clinical symptoms, suggesting that newer techniques may decrease the severity of myocardial damage. Valvular abnormalities have also been seen in patients with Hodgkin's disease after radiotherapy. These abnormalities include aortic regurgitation and mitral regurgitation, both of which occur in the setting of myocardial fibrosis [71,93]. Accelerated atherosclerosis has resulted in myocardial infarction in otherwise healthy patients [94].

Various chemotherapeutic agents have been implicated in cardiac toxicity. The most important agent in the treatment of Hodgkin's disease is doxorubicin. At cumulative doses below 400 mg/m², the incidence of cardiomyopathy is less than 2% [95]. In addition to the chronic effects of doxorubicin, patients may experience severe acute side effects such as carditis and arrhythmias [96]. The mortality rate from doxorubicin-induced cardiomyopathy is 50%. Sequential endocardial biopsy may be helpful in predicting whether patients can continue to receive doxorubicin [71].

Previous studies have identified factors associated with cardiomyopathy. Advanced patient age, uncontrolled hypertension, and previous radiotherapy have all been shown to increase the incidence of cardiomyopathy in doxorubicin-treated patients [95-97]. The combination of radiotherapy with doxorubicin has been associated with “radiation recall,” which is an inflammatory endothelial reaction. In addition, mitomycin (Mutamycin) and cyclophosphamide may act synergistically with doxorubicin to produce cardiac damage [98,99].

**Pulmonary Complications**

The pulmonary system is also subject to the side effects of treatment of Hodgkin's disease. The effects secondary to radiotherapy can be categorized into acute and chronic changes. Acute radiation pneumonitis is the most common side effect. This phenomenon is related to the total radiation dose, dose rate, and volume of lung treated [100]. Two groups of patients are prone to this side effect: (1) those with mediastinal disease and (2) those who receive total body irradiation for bone marrow transplantation. Acute radiation pneumonitis may present with shortness of breath, cough, fever, pain, and wheezing. Chest x-ray films will most often show paramediastinal densities and interstitial pneumonitis. Pleural effusions may occur.

Some patients require little or no therapy, whereas others may need treatment with corticosteroids.
Rapid discontinuation of corticosteroids after MOPP therapy may precipitate acute radiation pneumonitis [101]. There may be synergy of radiotherapy with certain drugs, such as bleomycin, cyclophosphamide, and methotrexate, in producing acute radiation pneumonitis. Doxorubicin, bleomycin, and dactinomycin (Cosmegen) have been implicated in a “radiation recall” phenomenon, characterized by clinical signs and symptoms of chronic restrictive fibrosis occurring 9 to 12 months after the completion of therapy, chest x-ray findings consistent with chronic fibrosis, and evidence of restrictive airways disease upon spirometry [71].

Chemotherapeutic agents associated with pulmonary toxicity include bleomycin and carmustine (BCNU). Bleomycin toxicity most commonly presents as interstitial pneumonitis; a biopsy may be required to eliminate other causes [71]. Pulmonary fibrosis has been associated with carmustine [102] and hypersensitivity pneumonitis with procarbazine [103]. Increased pulmonary toxicity has also been associated with multiple-agent regimens [104].

Miscellaneous Complications

Patients with Hodgkin's disease may experience musculoskeletal complications, such as avascular necrosis of bone. The incidence is increased with radiotherapy to bone [105]. Children who receive radiotherapy to bone may experience growth asymmetry secondary to premature closure of the epiphyseal plates [71]. This risk may warrant adjusting or lowering the dose of radiotherapy given. Patients who receive radiation to soft tissue may develop fibrosis with edema, venous thrombosis, and nerve entrapment. Patients treated with mantle or cervical radiotherapy may experience transient or permanent xerostomia, with increased risk of dental caries [88].

Conclusions

Hodgkin's disease remains one of the human malignancies most amenable to treatment. A wide range of therapeutic modalities is available, including chemotherapy, radiotherapy, and combinations of the two. Controversies exist among different centers as to the appropriate treatment of this disorder at different stages, but this debate may be resolved with future studies. Finally, the improved outcome of patients with Hodgkin's disease makes it imperative to consider the acute and long-term side effects of treatment and to ameliorate them when possible.

References:


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