Controversies in the Management of Early Stage Hodgkin’s Disease

By Peter M. Mauch

OVER THE LAST 25 YEARS, there has been great success in the treatment of early stage Hodgkin’s disease (HD; defined as stage I-II for this review). Yet considerable controversy exists in both the staging and treatment of patients as the late complications of treatment such as the development of second malignant neoplasms have become more evident. New treatments that aim to maintain a high freedom from relapse while reducing long-term adverse effects are being studied, yet it may be many years before their effectiveness is known. This review discusses the current controversies in the staging and treatment of early stage HD. It examines the role of radiation field size, use of chemotherapy in early HD, influence of prognostic factors on treatment, indications for staging laparotomy, factors for development of late complications, and details of ongoing clinical trials.

HISTORICAL PERSPECTIVE

In his historic paper entitled, “On Some Morbid Anomalies of the Exorbant Glands and Spleen” to the Medical Chirurgical Society in London January 10, 1832, Thomas Hodgkin briefly described the clinical history and postmortem findings of massive enlargement of lymph nodes and spleen in six patients and added the description of a seventh who had been seen by Carswell in 1828.1 For the next 70 years, most of the advances in HD were descriptive. Between 1865 and 1902, Wilks, Pel, Ebstein, and others contributed clinical information,2,3 and Greenfield, Sternberg, and Reed provided definition of the microscopic appearance of HD.5,7

The early treatment of HD with crude x-rays in 1901 followed the discovery of x-rays by Roentgen, radioactivity by Becquerel, and radium by the Curies in the late 1800s. Before this, serum and other biologic preparations, arsenic, iodine, and surgery were all used in the treatment of HD with dismal results. The first reports of x-ray treatments that would dramatically shrink enlarged lymph nodes produced great excitement and premature predictions for the curability of HD.8,9

The development of modern radiation therapy techniques for the treatment of HD began with the work of Gilbert, a Swiss radiotherapist, in 1925.10 One of the first physicians to point out certain clinical patterns in the behavior of HD, he also attempted to adapt his radiotherapy techniques to these patterns. Gilbert began to advocate irradiation to apparently uninvolved adjacent lymph node chains that might contain suspected microscopic disease, as well as to the evident sites of lymph node involvement. This technique was also adapted by Peters at the Princess Margaret Hospital in the late 1930s and early 1940s. In her historic report published in the American Journal of Roentgenology in 1950, Peters observed that patients with limited HD could be cured with aggressive radiation therapy that covered involved nodal sites as well as adjacent sites.11

Despite these studies, the concept that early stage HD might be curable with higher dose and larger field radiation therapy (RT) was slow to be accepted: before the 1960s most patients with limited HD were not treated at all, or only with small doses of radiation. When in 1963 Eason and Russell published their report, “The Cure of Hodgkin’s Disease,” physicians were closer to accepting the effectiveness of radical treatment for this once fatal illness than they were in 1950, the year Peters published her report.12 The development of the linear accelerator, which allowed for higher doses and larger radiation fields to be used, the proposal of new classification systems for histologic subtyping13 and staging,14 the pioneering of methods for more precise radiographic and surgical staging (bipedal lymphangiography and staging laparotomy),15,16 and the development of an effective multi-agent chemotherapy regimen17 all contributed to the development of curative treatment for early HD. Because of these advances, the philosophy and practice of managing early stage HD changed dramatically by the late 1960s from no treatment to extensive staging and radiation therapy with wide-fields and high doses.

RANDOMIZED CLINICAL TRIALS

Studies of radiation field size. Significant advances in the treatment of early stage HD were made with information obtained from clinical trials first organized in the 1960s. Both Stanford University Medical School and the European Organization for the Research and Treatment of Cancer (EORTC), along with other groups, made significant contributions. Results from prospective randomized trials that systematically evaluated the role of limited radiation therapy versus extensive radiation therapy are shown in Table 1. Representative trials that have reported large numbers of patients and long follow-up (greater than 5 years) are emphasized in Table 1.

Two trials have noted significant differences in the freedom from progression in disease-free survival favoring treatment with wide-field versus limited field radiation therapy. At Stanford University, laparotomy staged (pathologic staged [PS]) IA-IIB patients treated with subtotal nodal irradiation (STLI; including treatment of upper abdominal nodes) or total nodal irradiation (TNI) had an 83% freedom from progression versus a 32% freedom from progression for patients treated with involved field (IF) irradiation.18 Significant differences were also noted in PS I-II patients and clinically staged (CS) I-II patients in the Collaborative Clinical Trial favoring STLI over IF irradiation.
The role of prophylactic abdominal irradiation in early stage HD, the EORTC H-5 trial studied the use of mantle and paraaortic-splenic pedicle irradiation (MPA) versus mantle irradiation (M) alone in patients with favorable early stage HD. This study, in contrast to the BNLI trial, included only patients with nodular sclerosis (NS) or lymphocyte predominance (LP) histology, age 40 years or younger. PS I or PS II without mediastinal adenopathy, and an erythrocyte sedimentation rate (ESR) of less than 70. No differences were seen in disease-free survival between the two treatment groups. This select subgroup of patients treated with mantle irradiation alone had only an 11% risk of relapsing below the diaphragm. Other retrospective studies have demonstrated high relapse rates for unselected patients with CS I-II HD treated with mantle irradiation alone, but improved results for patients who have a negative staging laparotomy and have favorable prognostic features such as disease limited to a single lymph node region without "B" symptoms.

Studies of chemotherapy in early stage HD. Since the development of effective multi-agent chemotherapy regimens for HD, chemotherapy has been used for early stage HD. Twenty-two randomized trials of radiation therapy alone versus combined radiation therapy and chemotherapy (CMT) have been performed worldwide. Many of these trials have been published with a number showing relapse-free survival advantages favoring CMT. However, none of the trials have demonstrated an overall survival difference between the two treatment approaches. Representative trials with large numbers of patients and/or long follow-up are shown in Table 2.

The EORTC H1 trial was one of the first studies to evaluate the role of chemotherapy in the treatment of early stage HD. Clinically staged I-II patients were randomized to receive mantle irradiation alone or combined with velban chemotherapy. Results were better in patients receiving both mantle irradiation and velban chemotherapy. However, relapse rates were high in both groups, suggesting that mantle irradiation alone was not adequate treatment for patients with CS I-II HD and that velban was only partially effective in eliminating recurrences, many of which occurred below the diaphragm. Clinically staged I-II patients with mixed cellularity (MC) histology had a particularly high abdominal recurrence rate of 40%.

Table 2 lists one additional study in CS I-II patients and five studies in PS I-II patients comparing MOPP (nitrogen mustard, vincristine, procarbazine, prednisone) or MVPP (vinblastine substituted for vincristine) chemotherapy and radiation (to involved, mantle, or STLI/TLI fields) versus M, STLI, or TLI without chemotherapy. Although numerical differences in the freedom from relapse (FFR) are seen in all studies favoring MOPP and RT versus RT alone, these differences reach statistical significance in only two of the five reports of PS patients. The variation in field sizes in these studies does not provide data to determine whether significant field size reduction can be achieved in early stage HD patients receiving CMT. This may be an important issue as there appears to be some association with the use of large radiation fields and the development of long-term complications such as second malignancies. However, two studies have suggested that involved field or mantle irradiation without subdiaphragmatic irradiation may be sufficient for CS I-II patients receiving combined modality therapy with standard chemotherapy.

None of the trials for CS or PS patients shown in Tables 1 or 2 demonstrate an overall survival advantage favoring either the use of wide-field irradiation versus more limited radiation, or combined chemotherapy and radiation therapy versus RT alone, even when significant disease-free survival differences are present. One explanation includes the possibility that these studies have not reached the very long follow-up (10 to 15 years) needed to see survival differences in HD. Alternatively, the effectiveness of salvage chemotherapy for relapse after radiation therapy alone may minimize the impact of any increase in relapse on survival and may be balanced by an increased mortality from other complica-
tions (cardiac, second tumors) often seen patients receiving more intensive initial treatment. A third alternative is that there are not enough patients in any single study to show a small significance difference; megatrails or overviews may be needed to determine whether differences in relapse-free survival will result in smaller but significant differences in overall survival. Such trials are in progress.

**PROGNOSTIC FACTORS DEVELOPED FROM EARLY TRIALS**

*Implications for treatment of PS I-II patients.* Prognostic factors have been used to identify subgroups stage I-II HD patients who have a potentially higher risk of relapse or worse survival; these factors help individualize treatment to the extent of disease. Table 3 lists results from three studies that identify independent prognostic factors in PS I-II patients.38-40 The first two studies evaluate PS IA-IIA patients treated with STLI/TLI alone. Both report large mediastinal adenopathy (LMA), defined as a mass greater than one-third the maximum thoracic diameter on a standing chest radiograph, as the major factor predicting an increased risk of relapse.38,39 In neither study did LMA predict for a lower relapse rate; however, age 40 years or older and MC/LD histology were felt to be adverse prognostic factors for survival in the Harvard Joint Center for Radiation Therapy (JCRT). study.38 The third study from the Danish National Study Group analyzed PS I-A-IIIB patients treated with either RT or CMT. Patients with a high tumor burden, treated with RT alone, or of male sex had an increased relapse risk. Patients age 40 years or older or with an increased tumor burden had a decreased survival.40 The presence of B symptoms was not an independent adverse factor in this study. A fourth study from the Manchester Lymphoma Study Group of PS I-II patients treated with RT or CMT identified low lymphocyte counts, low serum albumin, and treatment with RT alone as independent adverse prognostic factors for relapse.41 The significance of these identified factors in the staging and treatment of patients is discussed in more detail below.

In addition to the above trials, a number of retrospective studies have identified LMA as an adverse prognostic factor for relapse in PS IA-IIIB patients treated with radiation therapy alone.36,41-48 The majority of relapses in these patients have been in lymph nodes above the diaphragm or in thoracic extranodal sites, including the pleura, chest wall, or pulmonary parenchyma.36,41,43-47 The routine use of thoracic computed axial tomographic scanning and gallium scanning has aided in determination of initial treatment of patients with LMA.36,40-56 These studies suggest that patients with pericardial nodes, extensive pericardial involvement, bulky axillary disease, or significant involvement of the pleural or lung are probably not suitable for RT alone because of the high risk of relapse and the potential toxicity associated with the large radiation volumes needed to treat such extensive HD. These patients can be quite successfully treated with 6 cycles of combination chemotherapy followed by regional or mantle irradiation without the need for staging laparotomy or abdominal irradiation.46

### Table 2. Combined Chemotherapy and Radiation Therapy Versus Wide-Field Radiation Therapy Alone

<table>
<thead>
<tr>
<th>Study</th>
<th>Stage</th>
<th>Design (no. of patients)</th>
<th>FFR (yr)</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard University</td>
<td>PS IA-IIA</td>
<td>IF + MOPP (35) v STLI/TLI (35)</td>
<td>83% v 66% (9)</td>
<td>84% v 91%</td>
</tr>
<tr>
<td>Stanford University</td>
<td>PS IB-IIIA</td>
<td>TLI + MOPP (35) v TLI (28)</td>
<td>76% v 73% (15)</td>
<td>78% v 79%</td>
</tr>
<tr>
<td>Danish National Study</td>
<td>PS I-II</td>
<td>M + MOPP (133) v STLI/TLI (128)</td>
<td>90% v 67% (7)*</td>
<td>92% v 93%</td>
</tr>
<tr>
<td>SWOG</td>
<td>PS I-II</td>
<td>IF + MOPP (120) v STLI (115)</td>
<td>82% v 71% (8)*</td>
<td>82% v 86%</td>
</tr>
<tr>
<td>Manchester Lymphoma Group</td>
<td>PS I-II</td>
<td>M + MOPP (59) v M (56)</td>
<td>91% v 67% (10)*</td>
<td>95% v 90%</td>
</tr>
<tr>
<td>EORTC HS Trial</td>
<td>CS I-II</td>
<td>MOPP + STLI/TLI (152) v TLI (144)</td>
<td>83% v 66% (9)*</td>
<td>88% v 73%</td>
</tr>
<tr>
<td>EORTC H1 Trial</td>
<td>CS I-II</td>
<td>M (Y) + Velban (136) v M (Y) (152)</td>
<td>60% v 38% (15)*</td>
<td>65% v 58%</td>
</tr>
</tbody>
</table>

Abbreviations: regional, involved field irradiation plus the immediate adjacent nodal site; FFR, freedom from relapse, also freedom from progression, or disease-free survival in some studies; Y, inverted Y irradiation (abdominal-pelvic nodes); Velban, Velban.

* Statistically significant differences; none of the trials show significant differences in actuarial survival rates.
† Numbers estimated from survival curves.
§ Patients dying of intercurrent causes were censored from the survival curves.

### Table 3. Prognostic Factors in PS I-II Patients (P Values Adjusted for Other Factors)

<table>
<thead>
<tr>
<th>Study</th>
<th>Stage</th>
<th>Adverse Factor</th>
<th>FFR</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stanford University</td>
<td>PS IA-IIA</td>
<td>LMA</td>
<td>&lt;.0001</td>
<td>NS</td>
</tr>
<tr>
<td>(109 patients, RT alone)</td>
<td></td>
<td>STLI (v TLI)</td>
<td>.04</td>
<td>NS</td>
</tr>
<tr>
<td>Harvard University</td>
<td>PS IA-IIA</td>
<td>LMA</td>
<td>&lt;.0001</td>
<td>NS</td>
</tr>
<tr>
<td>(JCRT)</td>
<td></td>
<td>Age &gt;40 yr</td>
<td>.008</td>
<td>NS</td>
</tr>
<tr>
<td>(315 patients, RT alone)</td>
<td></td>
<td>No. of sites ≥4</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Danish National Study</td>
<td>PS I-II</td>
<td>Tumor burden</td>
<td>&lt;.0001</td>
<td>.001</td>
</tr>
<tr>
<td>(Study Group)</td>
<td></td>
<td>Age &gt;40 yr</td>
<td>.04</td>
<td>NS</td>
</tr>
<tr>
<td>(290 patients, RT or CMT)</td>
<td></td>
<td>RT alone</td>
<td>&lt;.0001</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MC/LD histology —</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td></td>
<td></td>
<td>B symptoms</td>
<td>NS</td>
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<td></td>
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<td>Male sex</td>
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<td></td>
<td></td>
<td>ESR &gt;40</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No. of sites</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviations: FFR, freedom from relapse, also freedom from progression, or disease-free survival in some studies; LMA, large mediastinal adenopathy; LD, lymphocyte depletion histology; NS, no significant difference.
Patients age 40 years or older appear to have a worse survival (but not a worse FFR) both because they may not be as successfully treated at relapse as younger patients and because they may have a greater absolute excess risk of developing long-term complications such as second tumors and/or cardiac disease. This argues for the continued use of surgical staging (at least for patients under 60 years of age) and radiation therapy alone in this group of patients, with the goal of maintaining a high disease-free survival while minimizing the initial extent of treatment.

The identification of MC histology as an adverse factor for survival but not for FFR in PS IA-IIA patients in the JCRT study has not been universally accepted. The investigators initially determined that PS IA-IIA patients with MC histology were more likely to relapse below the diaphragm, often with bulky nodal disease, and suggested that this might have accounted for less success with salvage chemotherapy. In a subsequent study, PS IA-IIIB patients with MC histology who relapsed after initial radiation therapy had lower second CR rate, lower freedom from second relapse, and decreased survival after salvage chemotherapy compared with patients with NS or LD histology. This was independent of bulk of disease at relapse. In contrast, others have failed to identify histology at relapse as a prognostic factor.

The Danish National Study Group analysis did not identify B symptoms as an independent adverse prognostic factor. A large retrospective study combining data of PS IB-IIB patients treated at Stanford University and the JCRT suggested that patients with night sweats without other B symptoms treated with RT alone had a prognosis similar to patients with PS IA-IIA disease. However, the presence of fevers, weight loss, LMA, or age 40 or older all independently predicted for an increased risk of relapse, and survival was impaired in patients who had the presence of both fevers and weight loss. Treatment with CMT was suggested for patients with adverse prognostic factors.

Implications for treatment of CS I-II patients. Table 4 lists representative studies that have evaluated adjusted prognostic factors in clinically staged patients. Two of the three studies evaluate patients treated with either RT or CMT, and the third uses data from patients treated with chemotherapy (CT) or CMT. Adverse factors for relapse include male sex (in 1 of 2 studies), large number of sites involved (in 2 of 3 studies), age (in 2 of 3 studies), high ESR (in 2 of 2 studies), MC/LD histology (in 1 of 2 studies), involved field RT (in 1 of 1 study), and LMA (in 1 of 1 study). Other studies have also identified these adverse prognostic factors. Many of the factors, including B symptoms (similar to ESR), male sex, number of sites of involvement, and, to a lesser extent, age, have predicted for an increased risk of occult abdominal involvement in CS I-II patients and may explain in part why these factors are identified for CS patients but usually not for PS patients. Prognostic factors for survival in Table 4 include age in all three studies, and male sex, high ESR, MC/LD histology, number of sites of involvement, and large mediastinal involvement in one of three studies. Identification of adverse prognostic factors is essential for determining treatment of CS I-II patients in centers that do not routinely use staging laparotomy and splenectomy. Some of the ways in which these factors help determine treatment for CS I-II patients are presented at the end of the next section.

STAGING LAPAROTOMY AND SPLENECTOMY: IMPACT ON TREATMENT

Staging laparotomy remains the most precise way to determine the presence and extent of abdominal involvement in patients presenting with supradiaphragmatic HD. Twenty to 30% of CS I-IIA and 35% of CS IB-IIB patients with HD will have occult splenic or upper abdominal nodal involvement not detected by biperid lymphangiography, computed axial tomography, magnetic resonance imaging, or gallium imaging. These radiographic studies have not been successful at visualizing HD in the spleen and often miss lymph node involvement in the upper abdomen. A number of studies have evaluated the ability of selected prognostic factors to predict for occult abdominal involvement in CS I-II patients. Selected subgroups of CS I-II patients, including CS IA females, CS IIA females 26 years old or younger, and CS IA males with lymphocyte predominant histology, appear to be at lowest risk for occult abdominal involvement (6% to 9%). The remainder of CS IIA and all CS IB-IIB patients, who make up about 75% to 80% of all CS I-II patients, remain at substantial risk for HD in the spleen or abdominal nodes (24% to 36%).

There have been a number of arguments for and against the routine use of diagnostic staging laparotomy and splenectomy in the management of patients with HD. Arguments for the use of surgical staging are that it (1) improves staging accuracy over the use of clinical prognostic factors, allowing treatment to be tailored to the extent of disease. Surgical staging allows for selection of early stage patients to receive radiation therapy alone and reduces the overall need for chemotherapy.
for chemotherapy.21 (2) Laparotomy and splenectomy allow for the use of smaller radiation fields with less risk to the heart, lungs, and kidneys. If treatment with STLI is needed, the volume of abdominal tissue irradiated is significantly reduced with the prior removal of the spleen. In patients with early HD, a negative laparotomy may allow treatment with mantle field radiation alone.33,24,76,77 This approach requires only 4 to 5 weeks of treatment and is quite successful in selected PSIA-IIIA patients, but is too risky for most patients who do not undergo surgical staging.33,34

Arguments against the routine use of staging laparotomy and splenectomy are that it (1) delays initial treatment by 2 to 3 weeks, requires 5 to 7 days in the hospital, and is associated with potential morbidity and mortality. In centers that routinely perform surgical staging, the mortality risk should be well under 0.5%.70,71 We have seen only a 3% risk of major morbidity from wound abscess, subphrenic abscess, and small bowel obstruction.71 However, others have reported higher major complication rates.78-81 (2) After splenectomy, patients are at increased risk for bacterial sepsis. The risk depends on intensity of treatment; it is very low in patients receiving radiation therapy alone (1%), but is increased by as much as 10-fold in patients treated with extensive radiation therapy (ie, TNI) and chemotherapy.82 Vaccination against meningococcus and pneumococcus or administration of prophylactic antibiotics reduces the risk of sepsis in some patients.83 (3) Patients may have a small (approximately 2-fold) increased risk of leukemia after splenectomy. This is in contrast to the 60- to 120-fold relative risk conferred by exposure to MOPP-like chemotherapy. This increased risk after splenectomy is not seen in all studies, is complicated by confounding variables, and is difficult to explain epidemiologically, suggesting that further evaluation is needed.84-86

Patients are candidates for diagnostic staging laparotomy and splenectomy only if the outcome influences treatment. This approach continues to be used by some centers in the United States and is based on the philosophy that aggressive staging minimizes the treatment needed. Patients with extensive mediastinal involvement, multiple “B” symptoms, or obvious CS III disease require chemotherapy as part of their management and should not undergo surgical staging. For patients at very low risk for abdominal involvement (CS IA females and CS IA males with lymphocyte predominant histology), options include STLI and splenic irradiation without a staging laparotomy or mantle irradiation alone after a negative laparotomy. For the remainder of CS I-II patients, recurrence rates are low after a negative laparotomy and treatment with extended field irradiation (or mantle irradiation alone in selected patients). This staging and treatment approach can be supported even for patients with mixed cellularity histology, age 40 years or older, or with 4 sites or greater above the diaphragm. These patients have a long-term FFR of 75% to 82% after a negative laparotomy and treatment with MPA.

An alternative approach favored in many of the recent clinical trials uses prognostic factors in clinically staged patients without a staging laparotomy (common in Europe, Canada, and South America). Treatment is determined by the presence of adverse prognostic factors that predict for likelihood of occult disease in the abdomen and for the effectiveness of treatment (usually radiation therapy alone) to prevent relapse (see previous discussion). Based on the number of adverse factors, patients are placed into favorable or unfavorable prognostic groups. The most favorable patients are treated with mantle or extended field irradiation alone.33,65,76 Patients with a less favorable prognosis receive chemotherapy combined with involved or regional field irradiation. The type of chemotherapy and the number of cycles delivered (often as part of ongoing clinical trials) is also determined by the presence of adverse factors. Two recent EORTC trials illustrate this approach. In the EORTC H-6 trial, CS I-II patients with favorable prognostic features (number of sites = 1 or 2, and ESR <50 without B symptoms or <30 with B symptoms) were randomized to receive either STLI without a laparotomy or a staging laparotomy followed by mantle irradiation (for NS or LP histology, lap negative), STLI (for MC histology, lap negative), or combined CT and RT (lap positive). As longer follow-up data become available, this trial should help determine the influence of staging laparotomy on outcome in favorable CS I-II patients whose treatment is modified by the findings at surgery.23,87 In the ongoing EORTC H-7 trial, CS I-II patients are divided into very favorable, favorable, or unfavorable groups. None of the patients is to receive a staging laparotomy. Mantle alone is the treatment for the very favorable group (only about 6% of the total group), which is restricted to CS IIA women with NS or LP histology and an ESR less than 50. Patients in the favorable group are randomized to receive either six cycles of modified chemotherapy (EBVP; epirubicin, bleomycin, vinblastine, and prednisone) followed by involved field irradiation or subtotal lymph node and splenic irradiation. Patients in the unfavorable group are randomized to receive either six cycles of MOPP/ABV followed by involved field irradiation or 6 cycles of EBVP and involved field irradiation. This trial was started in 1988 and is discussed in more detail later in this review.

LONG-TERM OUTCOME OF TREATMENT FOR EARLY STAGE HD

Much of the long-term follow-up data for early stage HD is derived from the treatment of patients with radiation therapy alone. Large, single institutional studies show greater than an 80% actuarial 10- to 15-year freedom from relapse and less than a 10% mortality from HD after STLI for PS IA-IIIA patients.38,39,90 These results have been achieved through careful delineation of extent of involvement (including staging laparotomy and splenectomy), adherence to the precise use of radiation therapy (including treatment simulation, individually contoured divergent blocks, equal doses from front and back, and machine generated verification films),91,92 and the successful treatment of patients who relapse with multiagent chemotherapy.58,59

The treatment of early stage HD has become so successful that at 15 to 20 years the overall mortality from causes other than tumor mortality may approach that seen from HD itself.93-95 A Stanford University Medical School study pro-
vides some of the most detailed information. The report evaluates 5107 patients treated on clinical trials either with radiation therapy alone or with CMT. A total of 107 of 326 patients who died at the time of the study. Causes of death included 41% from HD, 26% from second cancers, and 16% from cardiovascular events. These three causes of death are discussed in detail below.

The most common cause of death in patients after treatment for HD is tumor-related mortality. Its relative frequency is greater in patients with more advanced stage disease, and there is a correlation between increased relapse frequency and decreased survival. The absolute excess risk of mortality in 5-year intervals over the first 20 years after treatment for HD is constant with early mortality caused by HD and later mortality caused by second malignant tumors or myocardial infarction.

Patients who develop recurrent HD are more likely to be cured with chemotherapy if their initial treatment was RT versus CT or CMT. The 10-year actuarial survival of patients initially treated with radiation therapy alone after relapse and treatment with multi-agent chemotherapy is 57% to 62%. Results are significantly worse for patients with HD who relapse after initial CT or CMT. Treatment with similar or alternative non-cross-resistant CT regimens yields 5-year actuarial disease-free survival rates of only 22% to 38% for these patients. Patients who have a disease-free interval of 12 months or longer before relapse, or who relapse exclusively in nodal sites, appear to have a greater likelihood of survival than those who have a shorter time to relapse or recur in extranodal sites. Because of the poor overall prognosis of patients who relapse after initial chemotherapy, many are now considered candidates for high-dose chemotherapy and autologous bone marrow rescue. Although the results of such treatment are still preliminary, the 3-year disease-free survival, which has ranged from 27% to 45%, suggests that this approach may be no better than second-line combination chemotherapy. It appears that salvage of patients who developed recurrent HD after initial CT may be no better than for patients initially treated with CT for advanced disease. The results of salvage of patients relapsing after treatment with RT and modified CT regimens (modified drugs or reduced number of cycles of treatment) remains to be determined. All these data suggest that, when CT or CMT are used as initial treatment for patients with HD, treatment should be designed in a manner so as to minimize relapse.

Many years after chemotherapy and/or radiotherapy, HD patients have an increased risk of developing acute nonlymphoblastic leukemia (ANLL), non-Hodgkin’s lymphoma (NHL), and second solid tumors. This increased risk is probably multifactorial, resulting in part from the immunologic deficits associated with HD and/or its treatment and partly from the carcinogenic effects of radiation therapy or chemotherapy. Certain chemotherapeutic agents, especially those contained in the MOPP and CHLPP (chlorambucil, vincristine, procarbazine, and prednisone) regimens, are associated with a marked increase in risk of developing ANLL. There does not appear to be an increased risk of developing ANLL after radiation therapy alone. The observed to expected ratio of developing acute nonlymphocytic leukemia after treatment with chemotherapy has ranged between 100 to 1 to approximately 200 to 1 in three large studies. Despite this high observed to expected ratio, the low background incidence of leukemia results in an overall risk of developing leukemia within 10 years of initial chemotherapy of as low as 2% in some studies to 5% to 6% in others. The excess risk of developing ANLL appears to be confined to the first 10 years after treatment.

Nearly all cases of NHL occurring after HD are of intermediate-grade or high-grade histology. The histologies represented are similar to lymphomas seen in patients with immunodeficiency diseases or under chronic immunosuppression for organ transplantation or autoimmune disorders. From several large studies, the observed to expected ratios for developing NHL vary between 8 to 1 and 31 to 1. The Tucker et al. and Abrahamsen et al. studies, the observed to expected ratios were the same for the patients who received radiation alone or radiation with adjuvant chemotherapy. In the van Leeuwen et al. study, the observed to expected ratio for developing NHL was lower after radiation alone than with combined radiation and chemotherapy. In all three series there continues to be an increased observed to expected risk 10 years after treatment and beyond.

The increased observed to expected ratios for developing second primary cancers are of much lower magnitude than for ANLL or NHL. However, because the overall background risk of developing a solid tumor is high, the absolute excess risk of developing a solid tumor is greater than the absolute excess risk of developing leukemia after HD. Solid tumors constitute 55% of the second malignancies in the Tucker et al. study, and 64% in the van Leeuwen et al. study. As seen with HNL, the observed to expected ratios for developing a second malignant tumor continues to be elevated beyond 10 years after treatment. The observed to expected ratios for developing a solid tumor in the Tucker et al. study with time from treatment increased from 1.9 to 1 within the first 5 years, to 4.9 to 1 in the second 5 years, to 6.3 to 1 in patients out 10 years or more. Although additional numbers are needed, the risk of developing a solid tumor after treatment for HD has been primarily reported in patients treated with initial radiation therapy or combined RT and CT. Few cases have been reported with CT alone; however, there remains little data on the follow-up of patients treated with chemotherapy alone who are at risk 15 years or beyond. Very little is known of the association between radiation volume or dose and development of a second solid tumor. In some studies, the combination of radiation therapy and chemotherapy may result in a higher risk than with radiation therapy alone. In other studies, this does not appear to be the case. The observed to expected ratios for developing a solid malignancy in two large studies varies between 2.5 to 1 and 2.8 to 1. In these two studies, the highest observed to expected ratios were for lung cancer (between 4.9 to 1 and 7.7 to 1); however, there were also modest increases in the risk of stomach cancer, in melanoma, and in tumors of the bone and connective tissue. More recently, an age-dependent
at treatment increased risk of breast cancer has been noted, with the highest risk being in patients under 20 at the time of treatment.18 Young females may be at particularly high risk for other second malignant neoplasms as well.19

Complications related to cardiac irradiation (arrhythmias, myocardial infarction and coronary artery disease, pericarditis, myocarditis, pericardial effusion, and tamponade) have been carefully documented after radiation therapy to the mediastinum.59,61,94,130-138 In many of the earlier studies these complications were related to treatment techniques that resulted in a high radiation dose to the anterior mediastinum and heart (lower energy machinery, anterior weighted fields, doses per fraction of greater than 200 cGy, and treatment with one field per day). Current practice, which restricts the dose to the whole heart, blocks the subcarinal region partway into treatment, delivers treatments equally from front and back, and uses radiation dose and volume by the use of preradiation chemotherapy in patients with LMA, has yielded more satisfactory results. In the Stanford study, despite 16% of the deaths occurring from cardiac disease, no observed to expected increase in cardiac death was seen.64 In contrast, a recent report by Boivin et al124 demonstrated a small age-adjusted significantly increased risk of death from myocardial infarction (RR, 2.56; CI, 1.11 to 5.93) after mediastinal irradiation. This risk did not differ by age at treatment or by time from treatment, but, when analyzed by year of diagnosis of HD the risk was much greater for patients treated 1966 or earlier (RR, 6.33; CI, 1.73 to 23.16) compared with 1967 or later (RR, 1.97; CI, 0.75 to 5.17), suggesting an important role for modern treatment techniques in reducing the risk of complications.

REDUCTION OF STAGING OR TREATMENT: ONGOING AND COMPLETED STUDIES

Over the past decade, there has been increasing concern for the long-term consequences of treatment, with many patients surviving long periods of time after treatment for early stage HD. This has prompted some investigators to reexamine the aggressive approaches developed for the staging and treatment of early stage HD in the 1960s and 1970s. A number of studies have been developed in an attempt to reduce the long-term complications of treatment without increasing mortality from HD. These include studies that evaluate (1) treatment with chemotherapy alone, (2) the reduction of radiation field sizes, (3) elimination of staging laparotomy and splenectomy, and (4) use of modified chemotherapy or shorter courses of standard chemotherapy combined with radiation therapy. Representative studies are listed below.

Most studies have relatively short follow-up and would not be expected to demonstrate survival differences. High relapse rates (ie, greater than 30% to 40%) or significant acute toxicity are used to measure adverse outcome.

Standard chemotherapy alone versus MPA (PS I-I). Two randomized studies have evaluated treatment with radiation therapy alone versus MOPP chemotherapy alone, both with median follow-up times of 7.5 to 8 years (Table 5). In the NCI study, patients with PS IIA, IIB, and IIIA HD were randomized to 6 months of MOPP or radiation therapy (M, MPA, or TNI). Recognizing that patients with massive mediastinal involvement or PS IIIA disease were not optimal candidates for RT alone, the randomization criteria were changed while the study was ongoing. When these patients are removed from the analysis, no differences in disease-free or overall survival are seen.29 In the Italian Prospective Randomized Study, PS IA-IIA patients were randomized to receive either 6 months of MOPP or STLI.100 There are no differences in freedom from progression. However, survival was significantly higher in patients treated with STLI (93%) compared with those treated with MOPP (56%). The difference in survival was attributed to the inability to salvage patients relapsing after MOPP chemotherapy, a situation similar to patients relapsing after combination chemotherapy for advanced HD. Both studies demonstrated greater acute toxicities in patients receiving MOPP chemotherapy. In the Longo et al125 study, more than 50% of patients receiving MOPP had at least one hospital admission for fever and neutropenia. Several small retrospective studies have also reported high relapse rates130,131 and poor survival131 after treatment with MOPP alone.

Mantle irradiation alone (PS IIA-IIB). The use of mantle irradiation alone for early stage HD is attractive because all treatment is completed within 5 weeks, patients avoid the long-term risks of radiation to the upper abdomen (second tumors and small bowel obstruction), and the potential for salvage with combination chemotherapy is not compromised. Results with mantle alone in selected CS I-II patients are disappointing, with the FFR at 10 to 15 years ranging from 38% to 54%.23,76 and a survival of only 58% at 15 years.23 Improved results with 10- to 15-year FFR of 58% to 81% were seen in selected patients with CS IIA disease.24,76 The EORTC H-7 trial is studying treatment with mantle irradiation alone in CS I A female patients with NS or LP histology, age less than 40 years, and a low ESR. These patients would be expected to have a risk of occult abdominal involvement of less than 10%.

The role of prophylactic abdominal irradiation in selected PS I-II patients (stage I disease, or stage IIA disease without mediastinal involvement, NS or LP histology, an ESR <70, and age <40 years) was studied in the randomized EORTC H-5 trial. Disease-free and overall survivals were identical for patients treated with mantle or MPA irradiation.22,23 These excellent results with mantle irradiation alone have been corroborated in other retrospective studies.24,77 At the Harvard Longwood area hospitals we are prospectively studying the treatment of mantle radiation alone in PS I-IIA patients with NS or LP histology. Patients with PS IIIA disease with mediastinal involvement limited to above the carina are included in the study. Patients with MC histology, with B symptoms, or with more extensive mediastinal involvement are not eligible for this treatment. Preliminary analysis suggest results similar to treatment with MPA.122 Because of the increased risk of abdominal relapse after mantle irradiation alone, a negative staging laparotomy and splenectomy and careful radiographic follow-up with monitoring of the abdominal-pelvic nodes after treatment are essential components of the trial.

Six cycles of modified chemotherapy and regional radiation therapy versus subtotal nodal and splenic irradiation.
With the objective of reducing the acute toxicity and chronic morbidity (sterility and increased risk of leukemia), Horning et al.\(^{133}\) developed a relatively "nontoxic" chemotherapy regimen, VBM (vinblastine, methotrexate, bleomycin), which was tested in a randomized trial of PS IA-IIB and PS IIIA patients comparing STLI/TLI versus VBM and IF irradiation. The freedom from progression data at 5 years favored IF + VBM (95%) versus STLI (70%) \((P = .09)\). No differences were seen in overall survival. Based on these favorable results, a follow-up Stanford University trial is underway. Patients with CS IA-IIA HD (staging laparotomy and splenectomy were eliminated) are being treated either with STLI (and splenic irradiation) or with 6 cycles of VBM and regional irradiation. This ongoing program is one of a number of studies developed to test less toxic chemotherapy for CS IA-IIA patients and define whether modified CT is sufficient treatment for the 25% of patients who statistically will have occult abdominal involvement.

Preliminary results in CS I-II patients with unfavorable characteristics (having at least one of the following features: age \(\geq 50\) years, \(\geq 4\) nodal regions involved, large mediastinal adenopathy, or a combination of B symptoms and elevated ESR) in the EORTC H7 trial raise concern for the routine use of non-MOPP or non-ABVD chemotherapy regimens in the management of patients with poor prognosis, early stage HD. Patients randomized to receive 6 cycles of EBVP and involved field irradiation had a significantly lower freedom from relapse than patients treated with 6 cycles of MOPP/ABV and involved field irradiation (73% vs 91%, respectively; \(P = .0003\)), causing this portion of the H7 trial to be discontinued.\(^{134}\) Further information is needed to determine which subgroups of CS I-II patients are suitable for modified chemotherapy and radiation therapy approaches.

**Shortened courses of chemotherapy and radiation therapy.** The M.D. Anderson Hospital tested the role of two cycles of adjuvant MOPP, and mantle with low-dose lung irradiation in patients with "unfavorable" PS IA-IIB HD.\(^{135}\) The study is prospective and nonrandomized. The early results are promising, but the median follow-up is only 26 months. A similar trial by the Cancer and Leukemia Group B (CALGB) testing three cycles of VP-16, adriamycin, and velban (EVA) and mantle or MPA irradiation in CS and PS IA-IIB and in PS IIIA patients has just been completed.

Straus et al.\(^{136}\) reported a randomized trial comparing 4 cycles of MOPP and mantle RT versus 4 cycles of thiotepa, bleomycin, and vinblastine (TBV) and mantle RT for patients with CS IA-IIA disease. With a median follow-up time of 64 months, the 5-year freedom from progression was 89% for MOPP and RT versus 81% for TBV and RT. Similarly, the Southwest Oncology Group and the CALGB have initiated a randomized trial evaluating the role of 3 cycles of adjuvant Doxorubicin and Vinblastine to subtotal nodal and splenic irradiation in CS IA-IIA HD patients. All these trials should help to determine the continued role of staging laparotomy and limited radiation therapy in selected early stage patients. Studies using radiation therapy and modifications in chemotherapy should also help to determine whether a reduced number of cycles of standard or modified chemotherapy can effectively substitute for staging laparotomy or abdominal irradiation.

**RECOMMENDATIONS**

The treatment of HD has become more complicated over the past 10 years. The development of standards for both radiation therapy and chemotherapy have made it more feasible to treat HD in community practice settings. Yet, initial treatment decisions may have profound long-term effects on patients who are young and likely to have a long survival. Whenever possible, routine cases should be treated along guidelines of standard accepted practice, and physicians should refer to major centers for the management of more complicated cases. There is hope that less toxic chemotherapy will be effective in curing occult microscopic disease, perhaps eventually obviating the need for staging laparotomy and splenectomy. Yet, for now, there are little long-term data defining specifics of treatment or the long-term efficacy or toxicity of such regimens. Thus, at present, the management of patients with HD in ways that do not adhere to standard practice, such as modifying standard radiation therapy or chemotherapy, should be strongly discouraged outside of controlled clinical trials.

Diagnostic staging laparotomy and splenectomy is not routinely performed outside the continental United States, Academic centers in Canada, Great Britain, Europe, and South America have identified prognostic factors to aid in determining treatment for clinically staged patients. Patients with favorable characteristics receive RT alone with RT and CT used for the remainder of patients. However, on average, without the information obtained at staging laparotomy, patients require more treatment, either with larger radiation fields or with the more frequent use of chemotherapy.

In many parts of the United States there is still a general acceptance of staging laparotomy and splenectomy as a means to aggressively stage patients to minimize treatment. Patients who are likely to need chemotherapy because of a high risk of relapse (LMA or extensive B symptoms) or high risk for having abdominal involvement (more than one positive abdominal radiographic test) should not undergo a staging laparotomy. In addition, there may be special cir-

**Table 5. CT Alone Versus Wide-Field RT (STLI/TLI)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Stage</th>
<th>Design (no. of patients)</th>
<th>FFR (yr)</th>
<th>Survival (yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Cancer Institute</td>
<td>PS IB, IIA, IIB</td>
<td>MOPP (41) v STLI (41)</td>
<td>82% v 74% (8)*</td>
<td>90% v 85% (8)</td>
</tr>
<tr>
<td>Italian Pros Randomized</td>
<td>PS IA-IIB</td>
<td>MOPP (44) v STLI (45)</td>
<td>64% v 76% (8)</td>
<td>56% v 93% (8)</td>
</tr>
</tbody>
</table>

* Numbers estimated from survival curves.  
† Statistically significant differences, \(P < .001\).
cumstances in which chemotherapy and limited field irradiation is preferred (ie, for pediatric patients). For the remainder of patients surgical staging should still be considered in the routine management of early stage HD. The majority of patients with PS IA-IIA HD will be cured with RT alone, thus sparing the toxicity of combined CT and RT and preserving the effectiveness of CT in case of relapse.

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[see comments]

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