Stage I–II Hodgkin’s Disease: Current Therapeutic Options and Recommendations

By Richard T. Hoppe

ADVANCES in the pathology, staging, and treatment of Hodgkin’s disease during the past 3 decades have provided for a dramatic improvement in the prognosis of all patients with this disease.1 A number of institutions and collaborative groups report 5-yr survivals of 90% or better for patients who present with early stage disease. Standard policies in the evaluation and treatment of these patients, however, have evolved in slightly different directions at different institutions. The purpose of this review will be to summarize the similarities and differences of these treatment approaches and to review the current Stanford policies in the management of early stage Hodgkin’s disease. For the purposes of this discussion, early stage Hodgkin’s disease is defined to include all presentations of stage I–II, with or without extralymphatic extension (E-lesions) and with or without systemic (B) symptoms.2 Only selected major issues will be addressed. Management programs affected by consideration of patient age,3,4 and unusual but important clinical presentations, such as lymphocyte-predominant Hodgkin’s disease restricted to the high neck5 or Hodgkin’s disease limited to intrathoracic sites,6 will not be considered.

Table 1 summarizes some of the major reports of the past few years relating the outcome of treatment for early stage Hodgkin’s disease.7–13 Together, these series report on the outcome of more than 1,500 patients treated during the past 15 yr. This list is by no means complete. Series were selected on the basis of the numbers of patients included and variation in staging and treatment policies.

These reports share a number of features, including excellent 5-yr survival rates of 88%–98%. Careful review shows other similarities. In every instance, careful clinical staging criteria are specified. Policies in effect at each of these institutions called for thorough radiographic evaluation, including radiographs of the chest, mediastinal and full lung tomography, or CT scanning when indicated, and bipedal lymphography. Patient management programs were developed by a multidisciplinary team that included pathologists, radiation oncologists, medical oncologists, and, when appropriate, surgical oncologists. The large number of patients treated in each instance permitted the development of substantial expertise by the investigators in the intricacies of staging and treatment—experience essential in providing for the best possible outcome. All patients were treated with irradiation, although the extent of the fields irradiated ranged from involved field to total lymphoid. Treatment was with megavoltage equipment, and the doses utilized were always tumoricidal (3,500–4,400 rad to involved fields and 3,000–4,400 rad to uninvolved fields).

While the ultimate survival of patients in these different series was similar, substantial differences in the staging and treatment policies are evident. The major staging difference relates to the use of laparotomy and splenectomy, and the major treatment variable relates to the use of systemic chemotherapy. These two issues are closely related. Staging laparotomy and splenectomy were utilized routinely in four of the reports,7–12 selectively in one,8 in a randomized fashion in one series,13 and not at all in another.7 When combined modality therapy was utilized, the chemotherapy combination was most commonly MOPP14 or similar combinations,15 but in one series, patients were treated with single-agent vinblastine or procarbazine.13

In several of these reports,9–12 laparotomy with splenectomy was utilized in the staging evaluation of all patients. Previous data have shown that this procedure results in the identification of subdiaphragmatic disease, primarily in the spleen, in approximately 30% of patients with clinical stage I–II disease presenting above the diaphragm.1 Treatment policies utilized in these same reports included irradiation alone (usually extended field, i.e., subtotal lymphoid irradiation) and combined modality treatment with involved field, mantle, or extended field irradiation followed by six cycles of MOPP (or similar) chemotherapy. In those series in which the treatment was assigned by randomization, combined modality therapy provided for superior 5-yr freedom-from-relapse rates compared to

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Table 1. Staging-II Hodgkin’s Disease: Contemporary Series

<table>
<thead>
<tr>
<th>Series</th>
<th>No. Patients</th>
<th>Years</th>
<th>Staging Laparotomy</th>
<th>Stages Included</th>
<th>Treatment</th>
<th>5-Year (%)</th>
<th>Comments</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>Andrieu et al. Hopital</td>
<td>166</td>
<td>1972–1976</td>
<td>No</td>
<td>I–II A</td>
<td>MOPP x 3 + modified IF</td>
<td>93.5</td>
<td>89.9</td>
<td>92.9</td>
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<tr>
<td>Saint-Louis 1980</td>
<td></td>
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<tr>
<td>Bergsagel et al. Princess Margaret Hospital</td>
<td>220</td>
<td>1973–1977</td>
<td>Selected (12%)</td>
<td>I–II (All)</td>
<td>EF (STLI) Combined modality for MCHD and LDHD</td>
<td>93</td>
<td>75</td>
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<td>Hospital 1982</td>
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<tr>
<td>Hagemeister et al. M.D. Anderson 1982</td>
<td>196</td>
<td>1970–1980</td>
<td>Yes</td>
<td>I–II (All)</td>
<td>IF or mantle (n = 90)</td>
<td>94</td>
<td>72</td>
<td>88</td>
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<tr>
<td>Hellman and Mauch 1982</td>
<td>233</td>
<td>1969–1979</td>
<td>Yes</td>
<td>I–II A</td>
<td>STLI</td>
<td>96</td>
<td>84</td>
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<td>Harvard–Joint Center 1982</td>
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<td>Hoppe et al. Stanford 1982</td>
<td>230</td>
<td>1968–1978</td>
<td>Yes</td>
<td>I–II (All)</td>
<td>STLI or TLI (n = 105)</td>
<td>96</td>
<td>79</td>
<td>89</td>
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<td>1982</td>
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<td>IF, STLI, or TLI + MOPP x 6 (n = 105)</td>
<td>92</td>
<td>87</td>
<td>94</td>
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<tr>
<td>Nissen and Nordenfelt Danish National Study</td>
<td>261</td>
<td>1971–1980</td>
<td>Yes</td>
<td>I–II (All)</td>
<td>STLI or TLI (n = 128)</td>
<td>93</td>
<td>72</td>
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<td>Group 1982</td>
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<td>Mantle + MOPP x 6 (n = 133)</td>
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<td>Tubiana et al. EORTC</td>
<td>300</td>
<td>1972–1976</td>
<td>Yes</td>
<td>I–II (n = 144)</td>
<td>STLI or TLI (n = 94)</td>
<td>88</td>
<td>74</td>
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<td>1981</td>
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<td>MCHD or LDHD</td>
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<td>STLI + VLB (n = 20) or STLI + PCB (n = 30)</td>
<td>90</td>
<td>68</td>
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MOPP, nitrogen mustard, vincristine, procarbazine, and prednisone. VLB, vinblastine. PCB, procarbazine. IF, involved field irradiation (limited to sites clinically involved.) EF, extended field irradiation (involved sites plus next echelon of lymphatics, which in these series always included mantle plus paraaortic-splenic pedicle field for supradiaphragmatic presentations). STLI, subtotal lymphoid irradiation (mantle plus paraaortic-splenic pedicle field). TLI, total lymphoid irradiation (mantle plus inverted-Y field, which includes pelvic lymph nodes).
treatment with irradiation alone (87%-92% versus 66%-79%). However, because of the efficacy of salvage chemotherapy in patients who relapse after treatment with irradiation alone, 5-yr survivals utilizing either combined modality therapy or irradiation as initial treatment are identical (92%-98% versus 93%-96%). Similarly, freedom from second relapse, when reported, is the same for patients treated with each approach. 

When irradiation alone was utilized, prophylactic treatment to the paraaortic lymph nodes and splenic pedicle region was usually a part of the treatment program, even after a negative staging laparotomy. This policy is justified partially by the randomized trial conducted at Stanford University between 1967 and 1971 in which patients were treated with either involved field irradiation or subtotal-total lymphoid fields. The 5-yr freedom-from-relapse rates were 32% and 82%, respectively, for the two different irradiation groups. Retrospective analysis of data from other institutions also has supported prophylactic subdiaphragmatic treatment. Prophylactic treatment to the paraaortic node-splenic pedicle region does increase the length of treatment by an additional 4-5 wk. However, in view of the absence of significant additional morbidity and the excellent results that have been reported with this treatment policy, most centers continue to incorporate subdiaphragmatic treatment as a standard component of therapy for stages I-II Hodgkin's disease.

In one series, supradiaphragmatic irradiation alone (involved field or mantle) was utilized in surgically staged patients. There was no significant difference in survival or freedom-from-relapse compared to patients who were treated with extended (subtotal) fields. However, in this series, assignment of patients to the two different radiotherapeutic approaches was by randomization only during the first 2 yr of the 10-yr period during which patients were accrued. Unequal distribution of patients with certain clinical characteristics in the two different treatment groups may account for the inability to demonstrate a difference in outcome. For example, 78% of patients treated with involved field or mantle irradiation had stage I disease compared to only 58% in the extended field group. Furthermore, the 5-yr freedom-from-relapse utilizing extended field treatment at this institution was somewhat inferior to that reported in the other series (66% versus 72%-84%).

The important question of the necessity for staging laparotomy in patients being treated with irradiation alone cannot be answered definitively by these studies. In the report by Bergsagel et al., although staging laparotomy was not performed routinely, it was done selectively in 12% of patients. The criteria for selection of patients for laparotomy were not defined clearly. Furthermore, two major treatment policies were employed—irradiation alone or combined modality therapy—and the results of treatment for the two different approaches are combined in the analysis. A comparison of outcome for patients treated with irradiation alone as a function of whether or not an initial staging laparotomy was performed is not provided. Unfortunately, even if it was provided, the comparison would not be valid since laparotomy was performed selectively, not randomly.

Even the EORTC trial reported by Tubiana et al. fails to answer the question of the necessity for staging laparotomy. Although laparotomy was performed in a prospectively randomized fashion, only two-thirds of the patients were treated with irradiation alone and the remainder were treated with combined modality therapy. One of the primary arguments for laparotomy and splenectomy is to avoid the use of combined modality therapy. Again, the outcome of patients treated in either way is compared and does not permit conclusions regarding the utility of staging laparotomy for patients being treated with irradiation alone.

Retrospective studies of selected patients with early stage Hodgkin's disease have reported excellent results utilizing subtotal lymphoid irradiation, including the spleen, in patients who have not undergone staging laparotomy and splenectomy. However, longer term follow-up of these stage IIA patients shows a significantly worse freedom-from-relapse compared to patients treated after staging laparotomy and splenectomy (55% versus 80% at 10 yr), and the authors now recommend that staging laparotomy be performed.

In a single series, staging laparotomy was never utilized. In the report by Andrieu et al., patients with very limited clinical stage disease (only one or two lymphoid regions involved) were treated with three cycles of MOPP followed by modified involved field irradiation. Although patients were spared the complications of staging laparotomy and splenectomy and the irradiation fields could be minimized, they were exposed to the hazards of three cycles of combination chemotherapy, and the ultimate survival of these patients proved no better than that obtained with radiotherapy alone at the other institutions.

Which is the appropriate management program for patients with early stage Hodgkin's disease? These series cannot be strictly compared to answer this question. There are inestimable influences related to patient selection factors (age, participation in trials, etc.), differences in staging criteria, period of patient

*Taylor E: Personal communication.
acrrual, exclusion of patients with "unfavorable characteristics," such as systemic symptoms, extralymphatic extension, or certain sites of disease, etc. Nevertheless, if one looks only at the survival statistics, no single approach stands out as clearly superior. One must examine not only survival but also the complications of therapy. Unfortunately, complication data are not always reported as compulsively as outcome data, and few clinical trials include prospective assessment of toxicity in their study design. Furthermore, the types of complications that may be associated with one management approach may be very difficult to compare with another.

Staging laparotomy and splenectomy, even in the hands of the best surgeons, may be associated with a small risk of perioperative morbidity, including infection, fever, ileus, and phlebitis. Rare fatalities have been reported secondary to the procedure, and this is clearly related to the skill and experience of the surgeons involved. At Stanford University, in a series of more than 1,000 consecutive staging laparotomies, there have been no postoperative deaths.1 Irradiation may be responsible for complications, including hypothyroidism, pneumonitis, pericarditis, and sterility. As these complications have been identified, modifications of technique that limit the does of radiation to sensitive structures have permitted a reduction or elimination of most of these complications.1

The primary complications of MOPP (or similar) chemotherapy include the acute toxicities of nausea, vomiting, neuropathy, leukopenia, and the significant long-term complications of sterility (in virtually all men) and risk of acute myelogenous leukemia. Newer combinations of chemotherapy, such as adriamycin, bleomycin, vinblastine, and DTIC (ABVD), may avoid some of the toxicities, such as sterility and leukemia induction.20 However, other long-term complications (especially cardiac and pulmonary) from these newer combinations may yet be identified.

At Stanford University, the general philosophy in the management of patients with early stage Hodgkin's disease is to maximize staging in order to minimize therapy and thereby minimize significant long-term complications. In the absence of medical contraindications, nearly all patients undergo thorough staging, including lymphography and staging laparotomy with splenectomy. Approximately one-third of these patients will have either subdiaphragmatic lymph node disease or minimal splenic involvement identified, necessitating extension of the subdiaphragmatic irradiation portals to include the pelvic lymph nodes or liver.21 In approximately one-third of those patients with subdiaphragmatic disease, extensive splenic involvement will require the use of combined modality therapy.22

Attempts have been made to identify patients with poor prognostic characteristics in stage I–II. Although histologic subtype has been suggested by some to be of importance, the Stanford data fail to support this contention for patients with equivalent stage disease treated with modern therapy.11,23 Likewise, the presence of systemic (B) symptoms or the presence of extralymphatic disease (E-lesion) has not indicated the need to utilize systemic treatment.11 A number of investigators have reported on the adverse prognostic influence of a large mediastinal mass in early stage Hodgkin's disease.11,24,25 However, although the proportion of these patients who relapse after treatment with irradiation alone is more than twice as great as after combined modality therapy, there is no survival difference between the two different treatment approaches.11,24 We therefore individualize treatment in this subgroup of patients, delivering a dose of 1,500–2,000 rad to the mantle field and assessing response to that treatment before deciding whether to proceed with a staging laparotomy and possible treatment with irradiation alone or, if the response is poor, to utilize combined modality therapy.

Whichever general approach is used in the management of patients with early stage Hodgkin's disease, every patient deserves the opportunity to be treated at a facility where there is adequate collaboration among pathologists, medical oncologists, radiation oncologists, and surgical oncologists. The treatment team must have adequate experience in all aspects of the management of this disease and potential treatment complications in order to provide the patient with the best probability of cure with the least long-term toxicity.

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REFERENCES