The Management of Stage I-II Hodgkin's Disease With Irradiation Alone or Combined Modality Therapy: The Stanford Experience

By Richard T. Hoppe, C. Norman Coleman, Richard S. Cox, Saul A. Rosenberg, and Henry S. Kaplan

At Stanford University, between 1968 and 1978, 230 patients with pathologic stage I-II Hodgkin's disease were treated on prospective clinical trials with either irradiation alone or irradiation followed by 6 cycles of adjuvant combination chemotherapy. The actuarial survival at 10 yr was 84% for patients in either treatment group. Freedom from relapse at 10 yr was 77% among patients treated with irradiation alone and 84% after treatment with combined modality therapy \( p(Gehan) = 0.09 \). Freedom from second relapse at 10 yr was 89% and 94%, respectively \( p(Gehan) = 0.56 \). Several prognostic factors were evaluated in order to identify patients at high risk for relapse or with poor ultimate survival after initial treatment with irradiation alone. Systemic symptoms, histologic subtype, age, and limited extranodal involvement (E-lesions) did not affect the prognosis of patients and failed to identify patients whose survival could be improved by the routine use of combined modality therapy. Patients with large mediastinal masses (mediastinal mass ratio \( \geq 1/3 \) had a significantly poorer freedom from relapse when treated with irradiation alone than when treated initially with combined modality therapy (45% versus 81% at 10 yr, \( p(Gehan) = 0.03 \)). The 10-yr survival of these patients, however, was not significantly different (84% versus 74%). The implications of these observations on the management of patients with early stage Hodgkin's disease are discussed.

MATERIALS AND METHODS

Between July 1, 1968, and December 31, 1978, 253 patients with PS I-II Hodgkin's disease were treated on prospective clinical trials.
Table 1. Sequence of Stanford Studies for Patients With PS-I-II Hodgkin’s Disease

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>IA, IIA</td>
<td>H 1 (Favorable)</td>
<td>R 1</td>
<td>S 1</td>
</tr>
<tr>
<td>II EA</td>
<td>H 4 (Favorable)</td>
<td>R 1</td>
<td>S 2</td>
</tr>
<tr>
<td>IB, IIB</td>
<td>H 2</td>
<td>H 2</td>
<td>H 2</td>
</tr>
<tr>
<td>II EB</td>
<td>H 4</td>
<td>H 4</td>
<td>S 3</td>
</tr>
</tbody>
</table>

Favorable: lymphocyte predominant or nodular sclerosing Hodgkin’s disease without involvement of low left neck, left infraclavicular, left axillary, or paraortic regions.

at Stanford. Patients were eligible for inclusion in these trials if they were less than 66 yr old, in good general health with the exception of Hodgkin’s disease, lived within 300 miles of Stanford, had the permission of their referring physician, and were able to provide informed consent. The sequence of trials, therapy options, and numbers of patients are summarized in Tables 1 and 2. Excluded from this analysis were the 23 patients treated in clinical trials that employed limited (involved field, mantle, or inverted-Y field) irradiation alone (H1-A, R1-A). The diagnosis in each case was confirmed by the Division of Surgical Pathology at Stanford University using the Rye modification of the Lukes and Butler classification.17

All patients underwent thorough staging including complete physical exam, routine blood counts and serum chemistries, bipedal lymphography, and staging laparotomy with splenectomy. The stage of each patient was determined according to the Ann Arbor criteria.18 In addition, the extent of disease and other prognostic factors were evaluated by measuring the total number of lymphoid sites involved, the presence of constitutional symptoms, the presence of extranodal extension of disease, and the presence of subdiaphragmatic involvement.

For patients who had involvement of the mediastinum at presentation, the extent of involvement was assessed by calculating a "mediastinal mass ratio."16 This ratio was determined by dividing the maximum width of the mediastinal mass, excluding the hilum, by the maximum intrathoracic cage width as visualized on the pretreatment standing PA chest radiograph.10 Initial radiographs were available in 140/156 (90%) patients for determination of the mediastinal mass ratio. Based on other reports in the literature and a preliminary review of these data, a mediastinal mass ratio >½ was considered large, while one ≤½ was considered small.

Most of the patients (210/230) were sensitized with 500 μg (0.5%) 2,4-dinitrochlorobenzene (DNCB) followed by a challenge dose of 100 μg (0.1%) DNCB applied 10 days to 3 wk later in order to assess delayed hypersensitivity response.19 The appearance of erythema and palpable induration within 48 hr was considered a positive response.

One-hundred-nine patients were randomized to treatment with irradiation alone (Table 2). Until 1970, nearly all these patients were treated with total lymphoid irradiation (TLI) (mantle and inverted-Y).21 Since 1970, only patients with B symptoms or subdiaphragmatic involvement have been treated with TLI, while asymptomatic patients treated with irradiation alone have received subtotal lymphoid irradiation (mantle and spade) that spares treatment to the pelvis.23

The details of our irradiation technique have been described previously.21 The standard dose employed was 4000–5000 rad in 4–6 wk by opposed fields to each region treated. Important characteristics of our mantle treatment included irradiation of the pulmonary hilar regions to full dose even when clinically uninvolved; the use of a “shrinking field” and split course technique in the treatment of patients with large mediastinal masses; prophylactic irradiation (1650 rad) to the ipsilateral lung whenever the pulmonary hilum was clinically involved by Hodgkin’s disease; the treatment of all extranodal sites of involvement to full tumoricidal dose; and the use of appropriate blocks to shield the larynx, spinal cord, humeral heads, and heart. In patients with high cervical lymph node involvement, the preauricular region was treated by means of an opposed lateral small “Waldeyer’s” field to a dose of 3600–4400 rad in 4–6 wk. The mantle and subdiaphragmatic fields were treated sequentially with a break averaging 2 wk between treatment to the two regions. Patients with subdiaphragmatic presentations were treated to the subdiaphragmatic field first.

One-hundred twenty-one patients were randomized to receive adjuvant chemotherapy for 6 cycles beginning 4–6 wk after completion of irradiation (Table 2). In 114 instances, the planned adjuvant was MOP(P), and in the remaining 7 it was procarbazine, 1-phenylalanine mustard, and vinblastine (PAVe).20 A prior review of our experience has indicated that MOP and MOPP have equivalent efficacy.21 Prospective randomized clinical trials have demonstrated that MOP (P) and PAVe are also equally effective adjuvants.20 Depending on initial stage, patients randomized to combined modality therapy received either involved field (I-IIA),22 subtotal lymphoid (I-IIA, IIAE), or total lymphoid irradiation (I-IB, IIEB).23 Irradiation techniques employed in this group of patients were similar to those treated with irradiation alone except that prophylactic irradiation of the preauricular region and lungs was not employed routinely.

All patients were followed regularly in the conjoint lymphoma clinic at Stanford. A physical examination was performed and routine blood studies, PA and lateral chest film, and abdominal x-ray were obtained at each visit. Most patients underwent repeat bipedal lymphography if there was inadequate contrast remaining.
for follow up examination of unirradiated retroperitoneal and pelvic lymph nodes for 2-3 yr following initial therapy. In most instances, first recurrences were documented pathologically.

Survival, freedom from relapse, and freedom from second relapse were calculated from the date of first visit to Stanford according to the actuarial technique of Kaplan and Meier. The generalized Wilcoxon test of Gehan was used to assess significance of differences between actuarial curves. The prognostic significance of selected covariates was also evaluated using the multivariate regression technique of Cox.

RESULTS

Patient Characteristics

Table 3 lists the characteristics of the two different treatment groups. The extent of disease as measured by pathologic stage or the presence of constitutional symptoms was similar in both groups. The distribution of histologic subtypes, age and sex distributions, sites of lymphoid involvement, and immunocompetence as reflected by ability to respond to initial challenge with DNCB after primary sensitization were also similar. A larger proportion of patients treated with combined modality therapy had E-lesions, a reflection of treatment protocols in use between 1974 and 1980, in which all such patients were treated with combined modality therapy (Tables 1 and 2).

Protocol Compliance

Only two patients failed to complete their initial course of irradiation. Both refused further therapy after completion of mantle irradiation. Four patients refused treatment with adjuvant chemotherapy and two additional patients had an extension of their Hodgkin’s disease to unirradiated sites after completion of irradiation but prior to the initiation of chemotherapy. Among the 115 patients who received adjuvant chemotherapy as planned, 88% received at least 5 cycles of drugs. The mean number of drug cycles completed was 5.4. The average dose of alkylating agent received (nitrogen mustard or 1-phenylalanine mustard) was 65.7% of the calculated dose. The average procarbazine received was 57.3% of the calculated dose.

The range of follow-up is 10 mo to 11 yr, with a median follow-up interval of 6 yr. Figure 1 displays the survival and freedom from relapse of the entire group of 230 patients. The 10-yr survival is 84% for treatment with either irradiation alone or combined modality therapy (p = 0.39). Freedom from relapse figures at 10 yr are 77% and 84% respectively (p = 0.09).

Figure 2 displays the freedom from second relapse. This function takes into account the effects of salvage treatment. Patients are not scored as treatment failures in this analysis unless they have failed to enter a complete remission, have failed to enter a second complete remission after relapse, or have relapsed after a second complete remission. Freedom from second relapse at 10 yr is 89% among patients treated initially with irradiation alone, and 94% among patients treated initially with combined modality therapy (p = 0.56).

Exclusion from analysis of patients who either
refused to complete therapy or who relapsed after completion of irradiation but prior to the institution of chemotherapy has little effect on these overall results. Ten-year survival and freedom from second relapse figures are altered by ≤1%. Freedom from relapse in the combined modality group, however, is improved by 3% at 10 yr, and the difference compared to treatment with irradiation alone then becomes statistically significant (p = 0.03).

Effect of Systemic Symptoms

Figure 3 shows the influence of systemic symptoms in the two different treatment groups. It is apparent that systemic symptoms are not an important prognostic variable in our experience. In fact, in the irradiation alone group, patients with systemic symptoms had a slightly better 10-yr freedom from relapse than those without symptoms (83% versus 75%). The addition of chemotherapy as an adjuvant improved the freedom from relapse of asymptomatic patients (85% versus 75% at 10 yr, p = 0.07), however, provided no improvement in results among symptomatic patients.

The Effect of Histologic Subtype

So-called “favorable” histologic subtypes (nodular sclerosing or lymphocyte predominant) were present in 86% of the patients. The remaining 14% had mixed cellularity disease. Figure 4 demonstrates that histologic subtype had little influence on freedom from relapse within each of the two different categories. Patients with mixed cellularity type Hodgkin’s disease had a slightly better freedom from relapse than those with nodular sclerosing or lymphocyte predominance, although the differences were not significant. Slight improvement in freedom from relapse after the addition of adjuvant chemotherapy was noted in both histologic categories.
The Influence of Limited Extranodal Involvement (E-Lesions)

Limited extranodal involvement was identified in 55 locations among 40 patients. These included lung—28, pleura—2, pericardium—13, bone—6, soft tissue—5, and myocardium—1 patient. Figure 5 demonstrates the influence of extranodal involvement on freedom from relapse. This was not an important prognostic variable within either treatment group and failed to identify a subgroup of patients in whom even freedom from relapse could be significantly improved by the use of adjuvant chemotherapy ($p = 0.31$).

The Influence of Mediastinal Mass Size

The likelihood of relapse after treatment with irradiation alone was much greater for patients with extensive mediastinal disease than minimal mediastinal involvement (7/14 versus 10/49). For patients with large mediastinal masses, although there was a suggestion of increasingly worse prognosis as the mediastinal mass ratio increased, there were too few patients to draw any firm conclusions. The relapse rate after treatment with irradiation alone was 4/9 for mass ratios greater than 0.33 but less than 0.4 and 3/5 for ratios of 0.4 or greater.

Figure 6 displays freedom from relapse as a function of the mediastinal mass ratio and initial therapy. Among patients with small mediastinal masses (mass ratio $< 0.3$), there was no benefit derived from the addition of adjuvant chemotherapy. Among patients with large mediastinal masses, however, the improvement in freedom from relapse by the addition of adjuvant chemotherapy was quite marked (45% versus 81% at 10 yr, $p = 0.03$). The long-term survival of these patients, however, was not improved by the addition of adjuvant chemotherapy (84% versus 74% at 10 yr, $p = 0.09$).

Miscellaneous Prognostic Factors

Table 4 summarizes 5-yr survival and freedom from relapse according to initial treatment and a number of other potential prognostic variables.

Initial Sites of Relapses

Table 5 details the initial sites of relapse in the two different treatment groups. The most common site of relapse among patients treated with irradiation alone was in previously treated lymphoid regions, usually initially involved mediastinal or axillary lymph nodes. However, 4/53 patients (8%) treated with subtotal lymphoid irradiation had their initial relapse limited to untreated pelvic nodes. The addition of adjuvant chemotherapy decreased the likelihood of relapse in all regions about equally.

Complications of Treatment

The possible complications of treatment are noted in Table 6. Radiation pericarditis was most frequent among patients with large mediastinal masses in whom inadequate protection of the heart and pericardium could be provided during the course of irradiation. There were two cases of fatal posttreatment sepsis and one fatal case of herpes encephalitis. Subsequent malignancies were identified in five patients. The leukemia, melanoma, and sarcoma were all fatal.

Current Patient Status

Table 7 summarizes the current patient status. Overall, 87% of the patients are alive without evidence of disease. Most of the patients (7/10) who died after initial treatment with irradiation alone died with active Hodgkin's disease. The three intercurrent deaths in this group were due to myocardial infarction, cerebrovascular accident, and probable sepsis. There were five deaths due to Hodgkin's disease among patients treated initially with combined modality therapy. The eight intercurrent deaths included three instances of second malignancies, two cases of sepsis, and one case each of idiopathic pneumonitis and probable pancarditis.
Fig. 6. The influence of mediastinal mass size on survival (left) and freedom from relapse (right) of 140 patients with PS I–II Hodgkin's disease with involvement of the mediastinum treated at Stanford University with either irradiation alone (XRT) or irradiation followed by adjuvant chemotherapy (XRT + CHX).
Table 4. A Detailed Analysis of Clinical Characteristics, Prognostic Factors, and Their Influence on 5-yr Survival and Freedom From Relapse Among 230 Patients With PS I-II Hodgkin’s Disease

<table>
<thead>
<tr>
<th>Subgroup</th>
<th># Patients</th>
<th>XRT</th>
<th>XRT + CHX</th>
<th>p(Gehan)</th>
<th>XRT</th>
<th>XRT + CHX</th>
<th>p(Gehan)</th>
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<td>92</td>
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<td>83</td>
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<td>.52</td>
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<td>.47</td>
<td>78</td>
<td>88</td>
<td>.08</td>
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<td>Subdiaphragmatic</td>
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<td>88</td>
<td>.24</td>
<td>100</td>
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<td>Non-E</td>
<td>190</td>
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<td>93</td>
<td>.75</td>
<td>79</td>
<td>86</td>
<td>.18</td>
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<td>100</td>
<td>88</td>
<td>.24</td>
<td>78</td>
<td>90</td>
<td>.33</td>
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<td>Mediastinum involved</td>
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<td>91</td>
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<td>.87</td>
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<td>87</td>
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<td>100</td>
<td>97</td>
<td>.26</td>
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<td>85</td>
<td>.76</td>
</tr>
<tr>
<td>DNCB negative</td>
<td>130</td>
<td>92</td>
<td>90</td>
<td>.97</td>
<td>73</td>
<td>86</td>
<td>.08</td>
</tr>
</tbody>
</table>

*LP, lymphocyte predominance; NS, nodular sclerosis; MC, mixed cellularity; UN, unclassified HD.
The p (Gehan) value compares survival or freedom from relapse for treatment with irradiation alone (XRT) versus irradiation followed by adjuvant chemotherapy (XRT + CHX).

Extensive Mediastinal Disease
A detailed analysis of patients with extensive mediastinal involvement (mediastinal mass ratio > 1/3) revealed that relapse occurred in 7 of 14 patients (50%) treated initially with irradiation alone and 5 of 27 patients (19%) treated initially with combined modality therapy. Recurrent intrathoracic disease was a component of the initial relapse in 7 of the 12 patients (5/7 treated with irradiation alone, 2/5 treated with combined modality therapy). Both patients with large mediastinal masses who were treated with irradiation alone and subsequently died had active Hodgkin’s...
in addition to the mantle field, is adequate.\textsuperscript{1,22,32} While these treatment fields are sufficient in most instances, pelvic nodal extensions of disease will subsequently occur in some cases. Among our 27 PS IA–IIA patients with supradiaphragmatic presentations who were treated with total lymphoid irradiation, no subsequent failure was observed in pelvic lymph nodes. Among patients treated with subtotal fields, however, disease extension to pelvic lymph nodes as the only manifestation of recurrent disease was noted in 4 of 53 patients (8%). Although this pattern of disease recurrence accounted for 4 of 14 (29%) treatment failures in this group, the Gehan test does not show a significant difference in either freedom from relapse ($p = 0.3$) or survival ($p = 0.3$) when compared with the total lymphoid group. A multivariate analysis of patient characteristics in this series does indicate, however, that patients treated with the more limited fields are at significantly greater risk for relapse ($p = 0.04$) (Table 8). In view of the added morbidity associated with pelvic treatment—including the additional hematologic toxicity, prolonged duration of therapy, and higher gonadal irradiation dose—we are reluctant to irradiate the pelvic nodes routinely in all these patients. It may, however, be reasonable to institute a program of lower dose prophylactic irradiation (2500–3500 rad) to the pelvic lymph nodes, especially in cases where subsequent fertility is not a significant consideration.

This study confirms the observation that histologic subtyping in Hodgkin’s disease has little influence on prognosis when careful staging and treatment are employed. Furthermore, the occasional difficulties that pathologists encounter in subclassifying cases of Hodgkin’s disease makes any subclassification of limited value.\textsuperscript{33}

The influence of extranodal involvement on prognosis in Hodgkin’s disease is a controversial issue. The initial data of Musshoff\textsuperscript{34} suggested that extranodal

\textbf{Table 8. Multivariate Analysis of Clinical Factors and Their Influence on Freedom From Relapse in 109 Patients Treated With Irradiation Alone for PS I–II Hodgkin’s Disease at Stanford University}

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Relative Risk*</th>
<th>$p$(Cox)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mediastinal mass ratio ($&gt;1/3/\leq1/3$)</td>
<td>4.0</td>
<td>0.002</td>
</tr>
<tr>
<td>Treatment (subtotal/total lymphoid)</td>
<td>2.5</td>
<td>0.04</td>
</tr>
<tr>
<td>Total number of sites ($\geq4/&lt;4$)</td>
<td>2.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Extralymphatic extension (E/non-E)</td>
<td>1.1</td>
<td>0.9</td>
</tr>
</tbody>
</table>

*Relative risk represents the relapse risk for patients with condition X relative to the relapse risk for patients with condition Y (X/Y), and the $p$ value is given for each variable after adjusting for all others.
extension of Hodgkin's disease did not confer a worse prognosis on patients who received appropriate irradiation, and the concept of the "E-lesion" was therefore incorporated into the Ann Arbor staging classification system. The validity of this decision has been challenged by Levi and Wiernik in a review of patients from the Baltimore Cancer Research Center. They reported on a group of 11 patients with limited extranodal involvement who were treated with irradiation alone. In all 11 cases, extranodal disease involved the pulmonary parenchyma. In 7 of the 11 cases there was, in conjunction with pulmonary parenchymal disease, a large mediastinal mass. All 7 patients with large mediastinal masses and parenchymal disease and 2 of the 4 patients with small mediastinal masses with parenchymal disease relapsed. Eight of these 9 recurrences were in the lung. Salvage therapy was ineffective and both survival and freedom from relapse were significantly better in a group of patients with extranodal lesions treated initially with combined modality therapy.

Our experience in this study with patients who had extranodal involvement was much more favorable. Nine patients with extranodal disease were treated with irradiation alone. Six of these 9 had pulmonary parenchymal involvement and 3 of these had massive mediastinal disease. Only one of the six patients with pulmonary parenchymal disease relapsed. He presented initially with a huge mediastinal mass (mediastinal mass ratio 0.46), pulmonary parenchymal involvement, and a pericardial effusion. He relapsed in the pulmonary parenchyma but was successfully salvaged with MOP chemotherapy and is alive without evidence of disease 8 yr after completion of chemotherapy. The remaining 5 patients who had pulmonary parenchymal involvement, two of whom had large mediastinal masses (mediastinal mass ratios 0.35 and 0.40), have been continuously free of disease. In view of these results in the treatment of patients with limited extranodal Hodgkin's disease, it is possible that the unfavorable course identified in the patients of Levi and Wiernik was due not to the presence of limited extranodal disease in the lung but to extensive mediastinal involvement. A better statistical tool for evaluation of the relative importance of these covariates is a multivariate regression model that is able to account for correlations among them. Table 8 shows such an analysis for relapse in our patients treated with irradiation alone. It demonstrates that mediastinal mass size is the most significant prognostic variable, whereas extranodal involvement adds nothing to the predictive power of the model.

Extensive mediastinal disease has been reported by several authors to adversely affect the prognosis of patients with Hodgkin's disease treated with irradiation alone, however, the data reported are inadequate to conclude that their prognosis can be significantly improved by the addition of adjuvant chemotherapy. Nevertheless, the recommendation for routine adjuvant chemotherapy has been made for these patients. Our study clearly shows that the freedom from relapse of patients with large mediastinal masses can be significantly improved by the use of routine adjuvant chemotherapy (45% versus 81% at 10 yr, \( p = 0.03 \)). Despite the marked improvement in freedom from relapse, however, a survival benefit is not apparent (10-yr survival 84% versus 74%, \( p = 0.9 \)). The lack of a survival benefit results from two factors. First of all, even with large mediastinal disease, the majority of patients who fail initial radiation treatment were salvaged with subsequent MOP therapy and are currently without evidence of disease. Secondly, intercurrent deaths were more frequent in the group of patients with large mediastinal disease treated with combined modality therapy and, in fact, accounted for both deaths in that group.

There are several possible reasons why patients with large mediastinal masses are at high risk for relapse after treatment with irradiation alone. Large mediastinal masses may have poorly vascularized and hypoxic regions that may be less radiosensitive. If this is the case, then large masses elsewhere should also prove resistant to control with irradiation alone. Massive disease in regions other than the mediastinum is not commonly observed in Hodgkin's disease; however, Thar et al. have noted a poor local control rate with irradiation in Hodgkin's disease when nodal masses at any site exceed 6 cm in diameter.

Intrathoracic recurrence in patients with large mediastinal masses may result from disease extension beyond the margins of the field. This may reflect an initial inadequate assessment of the extent of mediastinal disease, even when full lung and mediastinal tomography was employed. Thoracic computerized tomographic scans may provide more precise delineation of intrathoracic tumor and also assist in designing both the initial fields and those employed after tumor "shrinkage."

The fact that patients with large mediastinal masses also have a higher frequency of relapse in extrathoracic sites suggests that the biologic behavior of their disease may be different. Five of the seven patients with large mediastinal masses who relapsed after treatment with irradiation alone had initial relapse sites that included extrathoracic regions. The disease in these patients may have been intrinsically more aggressive and required more intensive therapy.

In view of our overall experience, we intend to
continue surgical staging followed by treatment with irradiation alone in patients with stage I–II Hodgkin's disease, including those with systemic symptoms and those with limited extranodal extension. Our standard treatment will be either subtotal of total lymphoid irradiation. We plan to continue intensive clinical staging, including mediastinal and full lung tomography and thoracic CT scans, in patients with large mediastinal masses. After partial completion of a carefully planned course of mantle irradiation, most of these patients will be able to undergo lymphography, and many will have adequate reduction of the mediastinal mass size to permit laparotomy and splenectomy. Others may require a full course of mantle therapy before completion of their staging. If the response of the mediastinal disease to treatment has been good, we will manage these patients with irradiation alone.

Some patients may show an inadequate response to mantle irradiation, be poor candidates for laparotomy, and require chemotherapy early in the course of their management. However, the increased incidence in complications and failure to observe a survival benefit in patients with large mediastinal masses treated routinely with adjuvant chemotherapy makes it impossible to recommend combined modality therapy for all patients with large mediastinal masses.

Finally, in new clinical trials we plan to investigate new therapeutic programs for patients with large mediastinal masses, some of which eliminate staging laparotomy and employ chemotherapy at an earlier point in the combined modality program. We hope thereby to continue to improve upon our results of treatment in this challenging subgroup of patients.

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