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The Management of Hodgkin's Disease in Relapse after Primary Radiation Therapy

Richard T. Hoppe

Approximately 20–25% of patients with stage I–II Hodgkin's disease treated initially with irradiation alone will experience a relapse of disease. Restaging at the time of relapse provides a useful prognostic indicator and may help in the selection of salvage therapy. Systemic treatment is indicated in nearly all patients. In the Stanford experience, 109 patients who relapsed were treated with MOPP (or MOPP-like chemotherapy) with or without local irradiation. The actuarial 10-year survival and freedom from second relapse were both 57%. Important prognostic factors included 'relapse stage' (IA vs. II–IIIA vs. I–IIIB or IV) and type of salvage therapy (combined modality vs. chemotherapy alone). Important issues in management of these patients include the selection of chemotherapy agents, whether to incorporate localised irradiation, and the use of even more aggressive salvage treatment programs, such as autologous bone marrow transplantation, in selected patients with a very poor prognosis.
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INTRODUCTION

APPROXIMATELY 75–80% of patients with early stage Hodgkin's disease selected for treatment with irradiation alone, can expect to achieve long-term disease-free survival after treatment with that modality. The management of the 20–25% of patients who relapse poses a significant clinical challenge. Important issues to address include documentation of the initial relapse, an evaluation of the extent of disease at the time of relapses, and selection of the salvage treatment program. This manuscript will deal with each of these issues.

Approximately 75% of relapses after initial treatment with irradiation alone will occur within the first 3-year follow-up

Table 1. Hodgkin's disease—management of relapse after initial treatment with irradiation alone

Institution	Chemotherapy	No. of pts	Radiotherapy*	Survival (%) 5	Survival (%) 10-year	FF2R (%) 5	FF2R (%) 10-year
PMCI [11]	MOPP	133	—	76	71	65	62
CALGB [8]	CVPP, ABOS or CVPP/ABOS	113	—	60		49	
Stanford [6]	MOPP	109	43%	65	57	61	57
Yale [10]	MVVPP	61	100%	81	81	81	80
Milan [9]	ADM-Reg	63	37%	81†		73†	

*Percentage of patients receiving irradiation as a component of salvage therapy.
†Data at 7 years.
PMCI = Peter MacCallum Cancer Institute; CALGB = Cancer and Leukemia Group B; FF2R = Freedom from second relapse; MOPP = nitrogen mustard, vincristine, procarbazine and prednisone; CVPP = CCNU, vinblastine, procarbazine, and prednisone; ABOS = doxorubicin, bleomycin, vincristine and streptozotocin; MVVPP = nitrogen mustard, vincristine, vinblastine, procarbazine and prednisone; ADM-Reg = doxorubicin-containing regimens.

period. For this reason, the follow-up evaluation should be most intensive and frequent during that period of time. Occasional relapses will occur at an even later date, supporting the concept of continued surveillance in this patient population [1]. A relapse may be heralded by the onset of systemic symptoms including fevers, night sweats, or weight loss, or also pruritus or alcohol intolerance. There may be an evolution of abnormalities of laboratory parameters such as an elevation of the erythrocyte sedimentation rate [2], alkaline phosphatase, or serum copper, or the interim development of adenopathy or splenomegaly may be detected by either the patient or physician. Routine screening radiographs such as chest X-rays, abdominal X-rays (in patients who have had lymphograms) as well as computed tomographic (CT) scans or gallium imaging may pinpoint abnormalities indicative of relapse [37].

In general, whatever constellation of clinical findings is present, initial relapse should be documented by biopsy. It is not uncommon for reactive lymph nodes to become enlarged outside of the radiotherapy fields, for infections to cause transient elevation of serum markers, or for radiographs to become abnormal with benign aetiologies [4]. It is important to rule out these causes of lymph node enlargement. In other instances, other cancers, especially non-Hodgkins lymphomas, may mimic the clinical abnormalities of Hodgkin's disease and yet require much different therapy. In general, biopsy documentation of initial relapse will help to avoid any compromise of subsequent clinical management.

RESTAGING

A thorough restaging evaluation is helpful both for identifying appropriate therapy and anticipating prognosis. As in the initial staging evaluation, a thorough physical examination with careful attention to all of the lymph node groups, routine blood studies including blood counts and erythrocyte sedimentation rate, and PA (postero-anterior) and lateral chest radiographs should be obtained in all patients. Other helpful imaging studies include CT and magnetic resonance (MR) imaging (although both need not be done). In addition, if facilities are available to perform an adequate lymphogram or gallium scan, these studies may be helpful. A bone marrow biopsy is performed both to evaluate that site for involvement and to assess the marrow reserve.

Prognosis after relapse is potentially related to multiple factors including host characteristics such as age, sex, and treatment compliance; the type of initial treatment; the time from completion of treatment to relapse; the stage of disease at relapse, and the type of relapse therapy.

Based upon the distribution of disease at the time of relapse, a 'relapse stage' may be assigned, utilising the same criteria as for initial staging with the Ann Arbor system. As shown subsequently, relapse stage may be correlated with the outcome of therapy.

For patients who have relapsed after initial treatment with irradiation alone, salvage treatment programs almost always include a systemic component. Although it is tempting to consider treatment with limited field irradiation alone for patients who have limited nodal relapse outside of previous radiation treatment fields, analyses of outcome in this clinical setting reveal that only about 25% of these patients will achieve long-term disease-free survival [5].

OUTCOME OF TREATMENT

The Stanford experience in the management of patients who have relapsed after initial treatment with radiation alone has been published in detail by Roach *et al.* [6]. A summary of that experience is presented.

109 patients were analysed, receiving initial treatment between 1968 and 1982 for pathological stage I–II A/B or IIIA disease with subtotal lymphoid irradiation or total lymphoid irradiation. The majority of patients (83%) initially had stage II disease. Nearly all patients had biopsy documentation of relapse, and clinical restaging studies were performed as described above. The median time to relapse was slightly more than 18 months. The relapse stage (RS) distribution included: I (or IE)A 24%; II–III (or II–IIIE)A 31%; I–II (or I–IIE)B 13%; and IIIB–IV 32%. Common sites of relapse included the lung, axillary lymph nodes, iliac lymph nodes (especially in patients whose pelvic lymph nodes were not irradiated), mediastinal lymph nodes,

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and cervical/supraclavicular lymph nodes. A smaller proportion of patients relapsed in bone, pulmonary hilus, paraortic lymph nodes, or bone marrow. Included in this analysis were a number of patients with large mediastinal masses who were treated initially with radiation therapy alone. Their pattern of relapse, with a prominent intrathoracic component, has been described previously [7]. By current standards, most of these patients with large mediastinal adenopathy would have been treated initially with combined modality therapy.

At the discretion of the treating physicians, patients were treated either with chemotherapy alone (57%) or combined modality therapy (43%). The chemotherapy employed was nearly always MOPP (93%), with the prednisone deleted if there was prior mediastinal irradiation. When combined modality therapy was utilised, radiation doses were generally 36–44 Gy to previously unirradiated lymphoid regions and 15–25 Gy to previously irradiated sites. Extralymphatic sites were generally treated to doses of 15–25 Gy, depending upon organ tolerance.

The duration of follow-up after relapse was 1–20 years (median 8 years). The actuarial survival (including all causes of death) and freedom from second relapse are both 57% at 10 years.

Prognosis following relapse was related to the extent of disease at relapse (relapse stage). For patients with RS I (or IE)A, the 10-year freedom from second relapse was 90%. For those with RS II–III (or II–IIIE)A, the 10-year freedom from relapse was 60%. For patients with RS I–IIIB or IV the 10-year freedom from second relapse was only 30%.

For patients with RS I (or IE)A, the outcome of salvage treatment was excellent, whether chemotherapy alone or combined modality therapy was utilised. The remaining patients, with RS II–IV, were analysed with respect to the impact of salvage treatment type. The 10-year freedom from second relapse was 62% after treatment with combined modality therapy vs. 37% after treatment with chemotherapy alone ($P = 0.04$). Furthermore, a multivariate analysis among patients with RS II–IV disease showed that the relapse treatment type was the most important predictor of outcome. Relapse stage (II–IIIA vs. I–IIIB and IV) and age (as a continuous variable) were the other predictors of prognosis in the multivariate analysis.

DISCUSSION

Table 1 summarises recent reports of outcome of treatment for patients who have had a relapse after initial treatment with radiation therapy for early stage Hodgkin's disease. In most instances, the chemotherapy utilised was MOPP (or MOPP-like) with the exception of some patients on the Cancer and Leukemia Group B (CALGB) trial [8] and more than half of the patients treated at the Tumor Institute in Milan [9]. Irradiation was added to the treatment program either selectively [6, 9], in all patients [10], or not at all [8, 11]. 5-year survivals ranged from 60% to 81% and 10-year survivals (when reported) from 57% to 81%. 5-year freedom from second relapse ranged from 49% to 81% and at 10 years from 57% to 80%. In each of these series, prognostic factor analyses were performed to identify patients who were at the highest risk for second relapse. Common factors included B symptoms at relapse [6, 9, 11], relapse stage IV [6, 10, 11], and age greater than 40 or 50 [6, 8, 10]. Other factors, identified in one or more analyses, included specific extranodal sites of relapse (such as lung or pleura), mixed cellularity histology, and initial disease free interval less than 1 year.

A comparison of each of these series is difficult because of different selection criteria, treatments employed, etc. However, it is encouraging that prognostic variables for patients at the time of relapse are somewhat similar from one series to another and may assist in the development of standard treatment approaches. Despite the overall excellent outcome, important clinical questions remain for these patients. The issue of optimal chemotherapy type is unresolved. If data derived from primary treatment programs continue to indicate a superiority of ABVD or MOPP–ABVD compared to MOPP alone [12], utilisation of these combinations may provide for an important increment in outcome for these patients as well.

The role of combined modality therapy, compared to chemotherapy alone for these patients, is also unresolved. In the Stanford analysis, a favourable subgroup could be identified which did so well after treatment with chemotherapy alone that irradiation provided no added benefit. On the other hand, the less favourable group of patients had a significantly improved outcome by the addition of irradiation.

A final question is whether there are very poor prognostic groups of patients who would benefit from more aggressive salvage treatment programs, such as high-dose chemotherapy and autologous bone marrow transplantation [13]. With the refinement of primary treatment programs for Hodgkin's disease, attention should now be directed at these groups of patients in prospective clinical trials.

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