Review

Management of early stage Hodgkin’s disease: The role of radiation therapy and/or chemotherapy

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Summary

Clinical trials in early stage Hodgkin’s disease comparing radiation therapy (RT) alone versus chemotherapy (CMT) have indicated fewer relapses in the CMT groups. However, none of the trials have demonstrated an overall survival difference. Risk factors for relapse in early stages include large mediastinal adenopathy, fevers, and weight loss. Ongoing clinical trials might prove less toxic CMT effective in curing occult microscopic disease, perhaps eventually obviating the need for staging laparotomy and splenectomy.

Key words: early stages, Hodgkin’s disease, radiation therapy, prognostic factors, splenectomy

Introduction

Over the last 25 years, there has been great success in the treatment of early stage Hodgkin’s disease (HD). Yet considerable controversy exists in both the staging and treatment of early stage patients, as the late sequelae of treatment have become more evident. New treatments that aim to maintain a high freedom from relapse while reducing adverse long-term effects are being studied. Yet it may be many years before the impact of these new treatments are known. This article discusses the current approaches to the staging and treatment of early stage HD. It examines the role of radiation field size, use of chemotherapy, influence of prognostic factors on treatment, indications for staging laparotomy, factors for development of late complications, and details of ongoing clinical trials.

The development of modern radiation therapy techniques for the treatment of HD began with the work of Dr. Rene Gilbert, a Swiss radiotherapist in 1925 [18]. 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 adapted by Dr. Vera Peters and Dr. Gordan Richards at the Ontario Institute of Radiology in the 1930's and early 1940's. In her historic paper published in the American Journal of Roentgenology in 1950, Dr. Peters observed that patients with limited HD could be cured with aggressive radiation therapy that covered involved nodal sites as well as adjacent sites [44].

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. Prior to the 1960's most patients with limited HD were not treated at all, or only with small doses of radiation. Only when Drs. Easson and Russell published their paper, 'The cure of Hodgkin's disease', in 1963, were physicians closer to accepting the effectiveness of radical radiation therapy for this once fatal illness [13].

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 1960’s. Both Stanford University Medical School and the European Organization for the Research and Treatment of Cancer (EORTC), along with other groups, made significant contributions. Three trials that have reported large numbers of patients and long follow-up are worth noting. At Stanford University laparotomy staged (pathological staged, PS) IA–IIA patients treated with subtotal nodal irradiation (STLI, including treatment of upper abdominal nodes) or total nodal irradiation (TLI) had an 83% freedom from recurrence (FFR) versus a 32% FFR for patients treated with involved field (IF) irradiation [47]. Significant differences were also noted in FFR in PS I–II patients and in clinically staged (CS) I–II patients in the Collaborative Clinical Trial favoring STLI over IF irradiation [15]. In contrast, differences favoring large field irradiation were not seen for PS or CS patients in the British National Lymphoma Investiga-
Early stage Hodgkin's disease defined from prognostic factors developed from clinical trials

Prognostic factors in PS I–II patients

Prognostic factors have been used to identify sub-groups 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. Results from studies that identify independent prognostic factors in PS I–II patients are listed below. Two studies that evaluate PS IA–IIB patients treated with STLI/TLI alone, report large mediastinal adenopathy (LMA), defined as a mass greater than one-third the maximum thoracic diameter on a standing chest radiograph [36], as the major factor predicting for an increased risk of relapse [27, 37]. In neither study did LMA predict for a lower survival rate, however, age 40 years or older was felt to be an adverse prognostic factor for survival in the Harvard Joint Center for Radiation Therapy (JCRT) study [37]; A third study from the Danish National Study Group analyzed PS IA–IIB patients treated with either RT or CMT. Male patients, patients treated with RT alone, and patients with a high tumor burden had an increased risk of relapse. Patients age 40 or older or with an increased tumor burden had a decreased survival [51]. 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 [1].

In addition to the above trials, a number of retrospective studies have identified LMA as an adverse prognostic factor for relapse in PS IA–IIB patients treated with radiation therapy alone [16, 30, 35, 36, 45, 49, 58, 60]. These studies suggest that patients with pericardial nodes, extensive pericardial involvement, bulky axillary disease, or significant involvement of the pleura 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 IF or mantle irradiation without the need for staging laparotomy or abdominal irradiation [32].

Patients aged 40 or older appear to have a worse survival (but not a worse FFR) both because they may bot be as successfully treated at relapse as younger patients [7, 22, 46] and because they may have a greater absolute excess risk of developing long-term complications such as second tumors and/or cardiac disease [23, 40, 43, 54]. This argues for the continued use of surgical staging for patients under 60 years of age and treatment with radiation therapy alone, with the goal of maintaining a high disease-free survival while minimizing initial treatment.

Studies of chemotherapy and radiation therapy in early stage Hodgkin's disease

Since their development, effective multi-agent chemotherapy (CT) regimens have been used for early stage HD. More than 20 randomized trials of radiation therapy (RT) alone versus combined radiation therapy and chemotherapy (CMT) have been carried out worldwide [52]. Many of these trials have been published showing FFR advantages favoring CMT. However, none of the trials have demonstrated an overall survival difference between the two treatment approaches [1, 4, 5, 11, 12, 21, 28, 29, 41, 47, 55, 57, 59]. This has been confirmed in a recent meta-analysis [50]. These trials did not address whether significant field size reductions could be achieved in early stage HD patients receiving CMT. This is an important issue as there appears to be some association with the use of large radiation fields and the development of the long-term complications of cardiac disease and second malignant tumors. This is being studied in ongoing clinical trials.

None of the trials for CS or PS patients described above 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 many of these studies have not reached the very long follow-up (10–15 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 complications (cardiac, second tumors, infection) often seen patients receiving more intensive initial treatment. The third alternative, that there are not enough patients in any single study to show a small significance difference, has been answered in the recent meta-analyses; differences in relapse free survival do not appear to result in significant differences in overall survival in early stage HD.
The Danish National Study Group analysis did not identify B-symptoms as an independent adverse prognostic factor [51]. A large retrospective study combining data of PS IB–IIIB patients treated at Stanford University and the JCRF suggests that patients with night sweats without other B-symptoms treated with RT alone had a prognosis similar to patients with PS IIA–IIIA disease. However, the presence of fevers, weight loss, LMA, or age 40 or older independently predicted for an increased risk of relapse, and survival was impaired in patients who had the presence of both fevers and weight loss [10].

In summary, LMA, fevers, and weight loss are adverse features for FFR. Patients with these features should be treated with CMT without staging laparotomy and splenectomy.

**Prognostic factors in CS I–II patients**

A number of studies have evaluated adjusted prognostic factors in clinically staged patients [19, 25, 42, 55, 56, 57]. Adverse factors for relapse include male sex, large number of sites involved, age, high ESR, MC/LD histology, involved field RT, and LMA. 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 in part explain why these factors are identified for CS patients but usually not for PS patients [31, 38]. Prognostic factors for survival include age in all nearly all studies. Identification of adverse prognostic factors is essential for determining treatment of CS I–II patients in centers that do not routinely utilize staging laparotomy and splenectomy. For example, in the EORTC H7 and H8 trials poor prognostic factors for CS I–II patients include ESR >30 and B-symptoms, ESR >50 and no B-symptoms, LMA, age ≥50 and number of sites ≥4. Patients with poor prognosis CS I–II disease in these trials are randomized to different regimens of combined CT and RT. The remainder of this review will focus on favorable prognosis CS and PS I–II patients.

**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 with CS I–II supradiaphragmatic HD. Twenty to 35% of CS I–II patients with HD will have occult splenic or upper abdominal nodal involvement not detected by bipedal lymphangiography, computed axial tomography, magnetic resonance imaging, or gallium imaging [31, 38]. A number of studies have evaluated the ability of selected prognostic factors to predict for occult abdominal involvement in CS I–II patients [2, 6, 31, 38, 48]. Approximately 20% 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 at lowest risk for occult abdominal involvement (6%–9%). The remaining 80% of CS I–II patients remain at substantial risk for HD in the spleen or abdominal nodes (24%–36%) [31, 38].

Surgical staging allows for selection of early stage patients to receive radiation therapy alone and reduces the overall need for chemotherapy [38]. 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. Large, single institutional studies demonstrate greater than an 80% actuarial 10–15 year freedom from relapse and less than a 10% mortality from HD following STLI for PS IIA–IIIA patients [14, 27, 37]. In patients with early HD a negative laparotomy may allow treatment with mantle field radiation alone (see subsequent discussion). This approach requires only 4–5 weeks of treatment and is quite successful in selected PS IIA–IIIA patients, but is too risky for most patients who do not undergo surgical staging [17, 39, 53, 57].

Patients are candidates for diagnostic staging laparotomy and splenectomy only if the outcome influences treatment. This approach continues to be utilized by some centers in the United States, and is based on the philosophy that more extensive staging reduces the treatment needed. An alternative approach favored in many of the recent clinical trials utilizes 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 which predict for likelihood of occult disease in the abdomen, and for the effectiveness of treatment to prevent relapse (see previous discussion). Based on the presence of adverse factors, patients are placed into favorable or unfavorable prognostic groups. The most favorable patients are treated with mantle or extended field-splenic irradiation alone [19, 53, 57]. For example, recent data from the Princess Margaret Hospital, notes that 55% of all CS I–II patients have favorable prognostic features. These patients have greater than an 80% 5-year actuarial FFR following mantle and para-aortic-splenic irradiation.

**Reduction of staging or treatment: Ongoing and completed studies**

The treatment of early stage HD has become so successful that 15–20 years after HD the cumulative mortality from other causes may approach that seen from HD itself [9, 20, 24, 40]. A Stanford University Medical School study provides some of the most detailed data. The report evaluates PS IIA–IIIB patients treated on clinical trials either with radiation therapy alone or
with CMT. A total of 107 out of 326 patients had died at the time of the study. Causes of death included 41% from HD, 26% from second cancers, and 16% from cardiovascular events [20]. These and other studies have prompted some investigators to reexamine the aggressive approach developed for the staging and treatment of early stage HD in the 1960's and 1970's.

A number of trials have been developed in attempt to reduce the long-term effects of treatment without increasing the 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, 4) utilization 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 (i.e., greater than 30%-40%) or significant acute toxicity are used as measures of adverse outcome.

**Standard chemotherapy alone versus MPA (PS I–II)**

Two randomized studies have evaluated treatment with radiation therapy alone versus MOPP chemotherapy alone, both with median follow-up times of 7.5–8 years. However, the NCI study evaluated patients with PS IIA, IIB, and IIA HD, as well as patients with LMA, and excluded patients with PS IA HD and thus does not address the role of CT alone in early HD [33]. In contrast, the Italian Prospective Randomized Study restricted patients to PS IA–IIB disease for randomization to either 6 months of MOPP or STLI [3]. There are no differences in freedom from progression. However, survival was significantly higher in patients treated with STLI (93%) compared to 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. This study also demonstrated greater acute toxicities in patients receiving MOPP chemotherapy compared to STLI.

**Mantle irradiation alone (PS IA–IIA)**

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, small bowel obstruction), and the potential for salvage with combination chemotherapy is not compromised. Results with mantle alone in unselected CS I–II patients are disappointing with the FFR at 10–15-year ranging from 38%–54% [53, 57] and a survival of only 58% at 15-year [57]. Improved results with 10–15-year FFR of 58%–81% are seen in selected patients with CS IA disease [17, 53]. The EORTC H-7 trial is studying treatment with mantle irradiation alone in CS IA female patients with NS or LP histology, age less than 40 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 (NS or LP histology, an ESR <70, and age ≤40) was studied in the randomized EORTC H-5 trial. Disease free and overall survivals were identical for patients treated with mantle irradiation or STLI [8, 57]. These excellent results with mantle irradiation alone have been corroborated in other retrospective studies [17, 34] and in a single arm prospective study [39]. Because of the increased risk of abdominal relapse following 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 this approach. Subgroups of patients suitable for mantle irradiation alone are still being defined [39].

**Six cycles of modified chemotherapy and regional radiation therapy versus subtotal nodal and splenic irradiation for favorable CS I–II patients**

Five recently completed or ongoing trials for CS patients with early stage (favorable) HD are listed in Table 1. All trials exclude patients with B-symptoms. Most trials exclude patients with LMA and the EORTC trials exclude patients with >4 sites of involvement or ≥50 years of age. All trials compare STLI and splenic irradiation versus CMT with a modified number of cycles of chemotherapy, a modified regimen, and/or modified extent of RT. All these trials employ more extensive treatment than would be given for PS patients treated with mantle irradiation alone.

**Conclusion**

The treatment of early stage 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 patients 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 modified 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


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