Early stage Hodgkin’s disease: Can we have our cake and eat it, too?

The optimal management of early stage Hodgkin’s disease continues to evolve. Historically, the use of limited irradiation volumes in unselected, clinically staged [CS] patients resulted in relapse rates in excess of 50%, most often in the unirradiated para-aortic lymph nodes [1, 2]. The staging laparotomy, introduced at Stanford in the 1960s, revealed that approximately 30% of CS I and II patients had involvement of the spleen, para-aortics or liver at laparotomy [3]. This operation became widely adopted as a means to define the extent of Hodgkin’s disease and determine the treatment plan. Superior relapse-free survivals in patients who received extended field irradiation, usually mantle and para-aortic fields, compared to those in patients treated with more limited volumes proved to be highly influential [1]. The standard treatment for many patients therefore became 1) laparotomy staging and, if negative, 2) subtotal lymphoid irradiation. Large institutional experiences demonstrated 80% or greater cure rates with this approach in pathologically staged I and IIA Hodgkin’s disease [4–6]. Patients with large mediastinal masses provided an exception to this experience; combined chemotherapy and radiotherapy were necessary for this group. The successful treatment of early stage Hodgkin’s disease has revealed an array of early and late complications; some of which are more serious than others. These observations have led to interest in reducing the extent of initial staging and treatment with the goals of maintaining high cure rates while reducing early and late morbidities.

In this issue of Annals of Oncology, Abrahamsen and colleagues present very excellent results in selected CS I and IIA patients treated with mantle irradiation only [7]. The disease-free survival in a group of 152 patients at five years was 78%. Patients were selected for this treatment if they had non-bulky disease, defined as mediastinal widening less than 1/3 the maximum chest diameter or less than 6 cm in other sites, 1–3 Ann Arbor nodal sites of disease, and a supradiaphragmatic presentation. The rare lymphocyte depleted histology was an exclusion criterion. A full 60% of patients presenting to a single institution, the Norwegian Radium Hospital, met these entry criteria. The use of mantle radiotherapy alone in clinically staged patients would appear to have many benefits. Patients would maintain splenic function which is characteristically lost after splenectomy or splenic irradiation, they would avoid exposure to chemotherapy and they would be spared the potential side effects of infradiaphragmatic irradiation including bowel toxicity and second malignancy. The key to success of this minimalist approach must relate to the selection of patients at low risk for occult abdominal disease or failure of radiotherapy.

The use of clinically derived prognostic factors to predict the probability of more extensive disease and the likelihood of control by radiation has been carefully studied by investigators in Canada and Europe. Gospodarowicz et al. have described the results of irradiation in CS I and II Hodgkin’s disease at the Princess Margaret Hospital in Toronto [8]. A very favorable or low-risk group of patients was defined as those who were asymptomatic, less than 50 years of age, with lymphocyte-predominant or nodular sclerosing histology, an erythrocyte sedimentation rate [ESR] < 40, no large mediastinal mass and no extranodal lesions. The relapse-free survival rate was 80% at 10 years after mantle irradiation for this group of patients, which represented about 1/3 of those treated with irradiation alone in Toronto. There was no significant advantage in the use of extended field irradiation in this patient cohort, implying that a group with a low risk of occult disease had been selected. The EORTC [European Organization for the Research and Treatment of Cancer] has also used clinical prognostic factors derived from their clinical studies to identify a very favorable group of patients with a low risk of subdiaphragmatic disease and a high probability of cure with mantle irradiation [9]. The characteristics of these patients included CS I, age 40 years or less, no systemic symptoms, female gender, ESR < 50, and no bulky adenopathy. This group represented only 6% of all CS I and II patients, however.

Another approach to the identification of patients at low risk for subdiaphragmatic disease is the retrospective analysis of large laparotomy series. Mauch et al. found that CS IA females and CS IA males with lymphocyte-predominant histology or high neck presentations had less than a 10% incidence of subdiaphragmatic disease [10]. In the Stanford series, patients with a 10% or lower likelihood of subdiaphragmatic disease included CS I women; CS II women with 1–3 disease sites and age less than 27 years; and CS I men with lymphocyte-predominant or interfollicular histology. This low risk group comprised about 20% of the population undergoing laparotomy staging [11].

Mantle irradiation has been used successfully as the sole treatment for Hodgkin’s disease in pathologically staged I–IIA patients with nodular sclerosis or lymphocyte-predominant histology. Mauch et al. published their results of a prospective trial in 37 patients; at four years the actuarial freedom from relapse was 83% [12].
The EORTC H-5 trial reported 69% disease-free survival in favorable (age <40 years, ESR <70, nodular sclerosing or lymphocyte predominant histology) I and IIA patients who received mantle irradiation alone after negative laparotomy staging [13]. These results are superior to those of the earlier EORTC H-1 study in which mantle irradiation alone was found to be inadequate treatment for unselected CS I and II patients [2].

The use of diagnostic staging laparotomy has become restricted on the basis of a number of developments and observations. These include the success of combination chemotherapy for treating minimal or occult Hodgkin's disease and for controlling disease recurring after irradiation. Abbreviated chemotherapy combinations may be effective in the combined modality treatment of early Hodgkin's disease and new combinations with less potential for sterility, leukemogenesis or cardiac or pulmonary toxicity have been introduced and successfully tested [14-17].

The significance of the results reported by Abrahamsen et al. rests in the fact that the majority of CS I and IIA patients (60%) were managed with mantle irradiation alone with only a 20%-25% relapse rate at five years. Older patients, males and cases of mixed cellular histology were included in their study. By way of comparison, combined modality studies using mild chemotherapy and limited irradiation have reported 90%-100% disease-free survival at a similar point in time [14-16]. However, extrapolation of the Norwegian results [that is, 60% of all CS I-IIA patients received mantle RT and >75% were relapse-free] suggests that nearly half of all CS I and IIA patients may be able to avoid three undesirable diagnostic or therapeutic maneuvers: laparotomy, infradiaphragmatic irradiation and combination chemotherapy. The flip side of the coin is that mantle irradiation is associated with a number of early and late complications. A small percentage of patients will experience clinically significant radiation pneumonitis and many will develop hypothyroidism. Excess coronary artery deaths have been associated with a history of tobacco use, is also increased after chest radiation [22]. These and other complications attributed to radiotherapy have led to the investigation of chemotherapy alone or the use of combined modality therapy with lower doses of irradiation, as in the pediatric experience, in early stage Hodgkin's disease [23].

With our expanded knowledge of late effects and the array of choices for effective treatment of early stage Hodgkin's disease, it has become increasingly difficult to select a single treatment of choice. Early stage Hodgkin's disease is more heterogeneous than originally appreciated and we owe a debt of gratitude to those who have contributed to our ability to predict for the success of radiotherapy, for the probability of occult disease and for the likelihood of late effects. Freedom from relapse is no longer the most important endpoint of clinical trial design. Efforts and studies must continue to strive to reduce morbidities of all kinds without compromising the excellent survival rates. Perhaps some day we can have our cake and eat it, too.

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References


