Changing Role and Decreasing Size: Current Trends in Radiotherapy for Hodgkin’s Disease

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Introduction
Radiotherapy (RT) was the first cancer treatment modality that offered cure to patients with Hodgkin’s disease (HD) [1]. In 1902, reports on dramatic shrinkage of bulky HD following exposure of the involved lymph nodes to the newly discovered x-rays raised high hopes of curing the disease [2,3]. Unfortunately, the limitations of the crude x-ray tubes available in those early years, and techniques that either administered a single large dose to a small field or delivered weekly low doses to the whole trunk, resulted in early local relapse and eventual systemic disease progression. Disappointingly, HD remained a universally fatal disease, and radiation was reserved only for palliation. More than 50 years would pass before a conceptual change would coincide with improvement in ionizing radiation technology and allow the cure of early-stage HD.

Rene Gilbert, a Swiss radiotherapist (1925), was the first to advocate the use of fractionated higher doses of radiation to larger fields, encompassing not only the palpable nodes but also the surrounding clinically uninvolved areas as well [4,5]. Employing Gilbert’s concepts of larger field and higher fractionated dose, Vera Peters (1950) in Toronto was able to demonstrate an unprecedented 10-year survival rate of 79% following irradiation of patients with limited HD [1,6].

The most credit for dispelling the notion that HD is an incurable disease should be given to Henry Kaplan of Stanford University [7]. His giant contributions touched upon all the aspects of understanding the disease and developing the principles and techniques that have led to modern effective treatment. Kaplan also promoted the early prospective, randomized trials at Stanford that established concepts of RT and combined-modality treatment that are still relevant today [8].

Using new tools for imaging and staging, Kaplan and his team advanced the understanding of the spread of HD and defined the classical fields for its treatment. He advocated the treatment of multiple lymph node chains in continuity with as few fields as possible to avoid gaps or overlaps within the field junctions. The large field, called “mantle field,” was used to treat the lymph nodes in the upper part of the body, and the “inverted Y” field for lymph nodes in the abdomen, pelvis, and groin. The combination of both fields was termed total lymphoid irradiation (TLI), and if the pelvis was excluded, subtotal lymphoid irradiation (STLI). TLI and STLI have become the gold standard fields in treatment of stage I to III HD. The advantage of the large field over the involved field, when radiation alone was used, was documented in prospective randomized studies at Stanford and other institutions. Since the 1970s, RT has been widely recognized as the primary treatment for the early stages of HD [9].

The progress in employing effective RT for HD coincided with unprecedented results obtained at the National Cancer Institute (NCI) in advanced-stage HD using MOPP (mechlorethamine, Oncovin, procarbazine, and prednisone) chemotherapy [10,11]. These achievements extended the option of cure to HD patients at both early and advanced stages and have become a paradigm for successful implementation of modern oncologic principles [12].

Yet, during the 1970s, combining chemotherapy and RT for the treatment of HD was rarely recommended. RT alone dominated the treatment of the early stages (I to IIIA), and MOPP was the primary chemotherapy for management of advanced stages (IIIB to IV) [13]. Because
stage was the most important determinant of modality choice, major efforts were made to stage patients with maximal accuracy. In the absence of adequate imaging, particularly for the abdomen and spleen, surgical staging of the abdomen, including splenectomy, became popular. Furthermore, the single-modality approach stretched the use of each modality to the limits of toxicity. These concepts have gradually changed over the past two decades.

The ‘Classical’ Radiation Fields
Although in recent years, RT alone has rarely been used in most centers for classical HD, it is still an adequate treatment option for patients with favorable early-stage HD. The criteria for favorable disease include age less than 50 years, absence of B symptoms, and no bulky mediastinal involvement. For these patients, staging laparotomy is no longer required, and the standard RT-alone fields include the mantle and the para-aortic-splenic fields, i.e., STLI. The guidelines and limits for the classical extensive fields have been reviewed previously [14]. Another approach for using radiation field alone and still decreasing the total regions exposed was suggested by the Harvard Joint Center group [15]. These investigators advocated use of the mantle field alone (eliminating the para-aortic field) in favorable early-stage patients whose staging laparotomy disclosed no infradiaphragmatic involvement. The “mantle-field alone” option of therapy is probably the only remaining justification for performing a staging laparotomy.

Radiotherapy in a Combined-modality Program for Early-stage Hodgkin’s Disease
The early randomized studies from Stanford documented the advantage of the extended field over the involved field when RT is used alone. However, they also demonstrated that the extended field could be successfully substituted with a smaller (“involved”) field RT (IF-RT) if chemotherapy was added to the program [16]. The main reason that chemotherapy was not routinely used with IF-RT at that time was the acute and late toxicity (sterility and leukemia) associated with the prime chemotherapy combination of the time, MOPP. Chemotherapy was reserved for salvage of RT failures. Still, in early-stage HD with unfavorable features (mostly bulky mediastinum), RT alone resulted in treatment failure in more than half of the patients. Adding chemotherapy improved freedom from treatment failure significantly, but overall survival (OS) remained similar (due to better salvage of RT-only failures). Although in patients with no adverse factors the addition of chemotherapy to TLI or STLI has not improved disease control, the appeal of the combined-modality approach resulted from the prospect of reducing the radiation field size and dose and simultaneously using shorter or less toxic chemotherapy with favorable results. When the less toxic combinations of chemotherapy such as ABVD (Adriamycin, bleomycin, vinblastine, and dacarbazine) proved to be even more effective than the original MOPP, combining chemotherapy and RT became the standard approach in treatment of favorable and unfavorable early-stage HD.

Although the results obtained with chemotherapy and IF-RT were equivalent or surpassed the results achieved with TLI or STLI in favorable early-stage HD, a comparison of chemotherapy plus STLI with the same chemotherapy plus IF-RT was still required. Several randomized studies were designed to answer this question. The French Cooperative study showed no difference in 6-year disease-free survival (DFS) between MOPP X6 and IF-RT versus MOPP X6 and extended-field [17]. The more modern Instituto Nazionale Tumori Milan trial provided the clearest data regarding the adequacy of radiation volume reduction. From 1990 to 1996, 140 consecutive patients with clinically staged early HD (I bulky and/or B; IIA; IIA bulky; and IIEA) entered a randomized trial. The trial compared four cycles of ABVD followed by STLI with the same regimen followed by IF-RT. The dose of RT ranged from 30 to 36 Gy to uninvolved and involved sites, respectively. The main characteristics were fairly well balanced between the two arms. After a median follow-up of 87 months, treatment outcome was as follows: complete remission (CR), 100% after ABVD plus STLI vs 97% after ABVD plus IF-RT; freedom from progression (FFP), 97% versus 94%, and total survival, 93% versus 94%, respectively. The long-term results of this trial indicate that four cycles of ABVD followed by IF-RT can achieve results comparable with those for the same regimen followed by extensive RT [18]. The European Organization for Research and Treatment of Cancer (EORTC) H8U trial compared in unfavorable patients four cycles of MOPP–ABVD and IF-RT (36–40 Gy) with the same chemotherapy followed by STLI (36–40 Gy). No difference in the 4-year failure-free survival (FFS) rate (92% in each arm) between IF-RT and STLI was detected [19]. The German Hodgkin Study Group (GHSG) HD8 study randomized unfavorable early-stage patients to receive two cycles of COPP (CCNU, Oncovin, procarbazine, and prednisone)/ABVD followed by either extended-field or involved-field RT. At a median follow up of 56 months, freedom from treatment failure was 86% (in each arm), and no difference in relapse rate or survival was observed. Acute side effects were more frequent in patients who received extended-field RT [20].

Although these randomized studies clearly indicate that reduction of field size has not compromised the efficacy of treatment, it may take another decade to demonstrate whether the decrease in irradiated volume will translate into a significant reduction in long-term side effects, the most concerning of which are second malignancies. Collection and analysis of long-term data from the previously mentioned randomized studies is critical. Thus far, results from retrospective studies that analyzed the effect of field size on risk of second tumors suggest that the risk is lower in patients treated with IF-RT compared with extended-field RT [21–23].