Over half a century, radiation therapy (RT) for Hodgkin lymphoma has been transformed from a radical, extensive, high-dose therapy (which alone cured most patients) into an essential component of a comprehensive combined-modality program. RT is now used in a “mini” version that encompasses only the clinically involved sites following chemotherapy and is administered in a markedly reduced dose. This change has considerably reduced the long-term complications that were associated with the now-outdated radical RT approach. The use of RT also allows a shorter and safer course of chemotherapy. The combination of reduced chemotherapy followed by mini-RT has produced disease control and even overall results that are significantly superior to those achieved with chemotherapy alone. This review discusses controversial issues regarding RT, the studies that have addressed them, the new indications for integrating RT, and the safety of minimizing the radiation field and dose.

Introduction
Radiation is considered by many oncologists to be the most effective single agent in the curative treatment of Hodgkin lymphoma (HL). The dramatic effect of ionizing radiation on HL tumors was reported as early as 1901, only a short time after Roentgen’s discovery of “x-rays.” Nevertheless, HL remained incurable during the first half of the 20th century, and responses to radiation therapy (RT) were partial or brief because of the limitations of the technology and poor clinical application. As x-ray technology and penetration improved in the 1940s and the concept of irradiating beyond the involved area was adopted, patients with early-stage HL could be cured with RT alone, and this was the only effective curative modality for lymphomas that was available until the late 1960s [1].

During the 1960s and 1970s, before the advent of chemotherapy and the use of a combined-modality approach, RT alone still cured many patients, particularly in early stages. Yet reliance on RT alone required wide extension of the radiation field and a dose that was raised to normal tissue tolerance levels ("radical radiotherapy"). Long follow-up of HL survivors disclosed an unexpected price 20 or 30 years later: morbidity and mortality that was significantly higher than in the normal population. The main complications were secondary tumors, mostly breast and lung cancers [2]. More coronary artery disease than expected was also associated with the use of radical radiotherapy.

The advent of effective and less toxic chemotherapy regimens in the late 1970s merged with attempts to cure more patients, even those with more advanced disease. These efforts resulted in programs that combined full-dose chemotherapy and extended-field RT. Although this strategy indeed cured more patients, it produced a higher rate of short-term and long-term complications. The ensuing reports of survivors’ morbidity caused obvious alarm.

Consequently, in the 1990s, the strategic response to increasing reports of long-term morbidity was to reduce therapy for HL while striving to maintain the cure rate. One approach was to keep the concept of combined-modality therapy but significantly reduce the extent of the irradiated volume, decrease the radiation dose, and simultaneously reduce the number of chemotherapy courses. Others, who considered RT to be the only culprit causing long-term complications, entirely eliminated RT from the treatment regimen and relied on more courses or additional combinations of chemotherapy.

These two conflicting strategies energized passionate debates and editorials, which naturally confused and distressed new and previously treated HL patients. The conflict also was constructive, however, in leading to the design of several prospectively randomized studies that focused on choice between these two approaches [3,4•,5].

Advocates of totally excluding RT and substituting more chemotherapy made several arguments:

- RT is the main and possibly the sole cause of the increased long-term morbidity of HL survivors.
Reducing the extent and/or dose of RT is unlikely to significantly change the risk of complications.

A strategy of chemotherapy alone will provide an excellent outcome that would be similar to (if not better than) the results obtained with the combined modalities. If RT is omitted, the decrease in radiation-related late mortality from causes other than HL would engender better overall survival rates.

Chemotherapy alone, even if escalated or prolonged, is safe and is unlikely to result in more toxicity.

Even if more failures occur without RT, salvage with higher-dose chemotherapy followed by stem-cell transplantation—a procedure that is simple, well tolerated, and safe—will correct them.

Those who maintained reservations about omitting RT strongly disagreed with these arguments. They expected the disease control rate without RT to decrease and the risk of complications. They also argued that the modern reduction in both extent and dose of radiation, which was designed for use in combined-modality treatment, would markedly reduce or eliminate the radiation-related long-term toxicity caused by the RT regimens of the past. At the same time, the associated reduction in chemotherapy would further enhance the safety profile of combined therapy. They also argued that this approach would markedly reduce the need for salvage therapy using high-dose chemotherapy and autologous stem-cell transplantation (ASCT), which causes physical and psychological trauma to young patients and their families and increases the risk of serious short-term and long-term complications, especially sterility and secondary leukemia.

Studies Comparing Combined-Modality Therapy With Chemotherapy Alone

Several groups have tested the hypothesis that chemotherapy alone can provide disease control equal to that achieved with combined-modality therapy. The studies from Europe [6], Asia [7], and North America [8–10] targeted mostly patients with early-stage HL (both favorable and unfavorable), including adults, children and adolescents, or both. In some studies, the randomization was upfront, but in others it was limited to patients who achieved a clear complete response (CR) with chemotherapy. The trials are detailed below and are summarized in Table 1.

Children’s Cancer Group

The Children’s Cancer Group tested the role of radiation therapy in young patients who attained a CR with risk-adapted chemotherapy (mostly four to six cycles of COPP/ABV) [10]. This study (CCG 5942) enrolled 829 patients (68% early-stage), of which 501 achieved a CR and were then randomized to receive either low-dose (21 Gy) involved-field radiotherapy (IFRT) or no further treatment. The accrual stopped earlier than planned because of a significantly higher number of relapses on the no-RT arm.

In an intent-to-treat analysis, the 3-year event-free survival (EFS) was 92% for patients randomized to receive RT and 87% for those randomized to no further treatment ($P = 0.057$). Because 30 patients switched their treatment after randomization, an analysis “as treated” was also performed and showed a 3-year EFS of 93% for those who received RT and 85% for those who were only observed ($P = 0.0024$). At this early analysis, no survival difference was detected.

Tata Memorial Hospital

In a large, prospectively randomized study from the main cancer center in Mumbai, India, 251 patients with HL (55% early-stage) received six cycles of ABVD chemotherapy [7]. Of those, 179 patients (71%) who achieved a CR were randomized to IFRT of 30 Gy (plus a 10-Gy boost to bulky sites) or no further therapy.

At a median follow-up of 63 months, the 8-year EFS and overall survival (OS) were significantly better for the patients who received consolidation with IFRT than for those who received ABVD alone (EFS, 88% vs 76%, $P = 0.01$; OS, 100% vs 89%, $P = 0.002$). Most relapses in the ABVD-alone arm were early and systemic, whereas in the ABVD + RT arm, the relapses were late and localized.

National Cancer Institute of Canada/Eastern Cooperative Oncology Group

This intergroup study included 399 patients with stage I or II nonbulky HL and no B symptoms [9]. The less favorable subgroup (elevated erythrocyte sedimentation rate, three or more sites, age 40 years or greater, mixed cellularity on histology) totaled 276 patients. For this subgroup, the experimental arm consisted of six cycles of ABVD and no RT (or four cycles of ABVD alone if CR was attained after two cycles). The “standard” arm for them consisted of two cycles of ABVD followed by subtotal lymphoid irradiation (STLI)—a combined-modality approach.

At a median follow-up of 4.2 years, the estimated 5-year progression-free survival (PFS) rate in those treated with ABVD alone (87%) was significantly inferior to the rate (93%) for those treated with “standard therapy” (HR, 2.6; $P = 0.006$). At this early point, no survival difference has been detected. Although RT alone is no longer considered the standard of care for patients with favorable HL, the inferior performance of ABVD alone compared with the “standard therapy” in patients with nonbulky, early-stage disease cannot be ignored. At a median follow-up of 4 years, no difference in OS was detected. Originally, the study was statistically designed for a 12-year analysis of survival. It should also be mentioned that combined-modality treatment with STLI rather than IFRT is no longer used.

EORTC/GELA

This large trial (H9) in favorable early-stage patients with classic HL was sponsored by the European Organization