The last century has seen a remarkable evolution in the treatment of Hodgkin’s lymphoma, in particular for patients diagnosed with limited-stage disease. The identification of the responsiveness of this disease to radiotherapy at the turn of the twentieth century led to early attempts to cure the disease with high doses delivered to known disease sites in a single fraction [1]; however, it was not until the 1950s that long-term survivals and possible cures were reported using daily, fractionated radiotherapy delivered not only to involved sites but also to adjacent nodal regions [2,3].

Although excellent results were being seen with wide-field radiotherapy techniques, three important observations began to emerge: (1) relapses after radiotherapy were occurring in about 25% of patients, almost always outside the radiation fields, indicating the presence of undetectable, micrometastatic disease at the time of original diagnosis [4]; (2) clinically significant long-term toxicities of radiotherapy emerged, including cardiovascular disease and second malignancies [5]; (3) even as curative strategies of radiotherapy were developed for limited-stage disease, chemotherapeutic agents effective in advanced-stage Hodgkin’s lymphoma were developed. In 1967 DeVita and coworkers [6] reported that a combination of drugs with partially nonoverlapping toxicities, given in 28-day cycles (the MOPP regimen [mechlorethamine, vincristine, procarbazine and prednisone]), could cure about one half of patients who had advanced-stage disease. Over the next three decades, building on the observation of the curative potential of radiation and multiagent chemotherapy, combined modality therapy has emerged as the standard of care for limited-stage Hodgkin’s lymphoma. Because systemic chemotherapy can reduce out-of-field relapses by treating micrometastatic disease, thereby also eliminating the requirement for staging laparotomy, it has made possible an era of clinical
investigation exploring the use of reduced radiation doses and fields in an effort to reduce the long-term toxicities without sacrificing overall disease control. Current and future investigations are now taking these observations a step further by evaluating strategies that treat most patients with limited-stage Hodgkin’s lymphoma with multiagent chemotherapy alone, reserving radiotherapy only for those who would be destined to relapse without it.

**DEFINITION OF LIMITED-STAGE HODGKIN’S LYMPHOMA**

Hodgkin’s lymphoma continues to be staged according to the Cotswolds modifications of the Ann Arbor staging system [7]. For the purpose of treatment algorithms, and in particular for defining patient populations for clinical trials, the classification is simplified to divide patients into limited stage, which was in the past treated with extended-field radiotherapy, or advanced stage, which required multiagent chemotherapy to provide a chance of cure. Staging laparotomy was previously used to better define the population that had disease truly limited to the supradiaphragmatic regions, but this has less usefulness when combined-modality therapy is used for limited-stage disease, presumably because of effective eradication of micrometastatic disease by the chemotherapy [8].

In North America, limited-stage disease is defined as stage I or IIA with no areas of bulk, defined as a mass greater than 10 cm. This definition represents approximately 30% to 40% of newly diagnosed patients [9]. Patients who have B symptoms or bulky disease are believed to have clinical course similar to those who have stage III–IV disease and are treated with full courses of chemotherapy, with radiation therapy considered for sites of initial bulk, particularly mediastinal. European cooperative groups have defined a group of patients who have intermediate risk, described as early-stage unfavorable. This group includes patients who are stage I–II with one or more of: age greater than 50, B symptoms, bulky mediastinal disease, elevated erythrocyte sedimentation rate, or four or more involved sites [10].

**COMBINED MODALITY THERAPY AS STANDARD OF CARE**

Peters and Kaplan [2,3] are credited with demonstrating much of the early success of wide-field radiation for limited-stage Hodgkin’s lymphoma nearly five decades ago. Retrospective studies have addressed the question of adequate dose [11], but the only prospective trial of radiotherapy alone was a German Hodgkin’s Lymphoma Study Group (GHSG) trial that compared 40 Gy of extended-field radiotherapy (EFRT) to 30 Gy of EFRT with additional 10 Gy to involved fields (IFRT) [12]. This multicenter randomized trial included 376 patients who had laparotomy-proven stage I-IIIB disease without risk factors, and showed no difference between the arms, with 5-year freedom from treatment failure and overall survival of 76% and 97%, respectively. Attempts to reduce the radiation field to a supradiaphragmatic mantle field, even when limited to favorable patients with low risk for abdominal disease, have generally been disappointing [1].

The relapse rates observed using extended-field radiotherapy alone were 20% to 25% even after laparotomy-based staging. The next generation of clinical
investigation combined radiotherapy with chemotherapy in an effort to improve
disease control. Randomized trials established that relapse rates could be reduced
to less than 10% by adding chemotherapy to EFRT, and this finding is supported
by a large meta-analysis [4,13,14]. Toxicity remained an important drawback to
to combined modality treatment (CMT), leading to randomized trials attempting to
reduce toxicity without sacrificing disease control or survival. Strategies included
reduction of radiation fields, reduction of radiation doses, and reduction of num-
ber of cycles of chemotherapy. A detailed discussion of the details of all the clin-
ical trials that addressed this question is beyond the scope of this article. The
major trials are summarized in Table 1 [4,13,15–21]. In general, these trials dem-
onstrated that disease control and survival were not compromised by these strat-
egies. Longer-term follow-up is required to determine if late relapses will become
an issue and to assess the effects on late toxicities, including second malignancies
and cardiovascular disease.

Few direct comparisons of different chemotherapy regimens used as part of
CMT for limited-stage Hodgkin’s lymphoma have yet been published, none
have used the doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD)
regimen, which has been established as the standard of care in both advanced-
stage and early-stage (unfavorable) disease [22,23]. Its favorable toxicity profile
has resulted in its adoption as the standard chemotherapy used as part of CMT
for limited-stage disease. The current GHSG HD13 trial is evaluating whether
toxicity can be further reduced by the elimination of dacarbazine, bleomycin,
or both when two cycles of chemotherapy are given followed by 30 Gy IFRT [24].

CHEMOTHERAPY ALONE FOR LIMITED-STAGE
HODGKIN’S LYMPHOMA
Chemotherapy alone has been the subject of investigation for limited-stage
Hodgkin’s lymphoma in a small number of randomized trials. Several of these
studies used chemotherapy regimens other than ABVD: the Grupo Argentino
de Tratamiento de la Leucemia Aguda (GATLA) and Grupo Latinoamericano
de Tratamiento de Hematopatias Malignas (GLATHEM) studied six cycles of
CVPP followed by IFRT versus observation [25], and the European Organiza-
tion for Research and Treatment of Cancer (EORTC) H9F three-armed trial
randomized patients who achieved complete remission after six cycles of
EBVP to 36 Gy IFRT, 20 Gy IFRT, or observation [21]. Although these stud-
ies produced encouraging results with chemotherapy alone they are of limited
relevance today because they used chemotherapy regimens we now know are
inferior to ABVD, leading to an underestimation of the disease control that can
be achieved with uni-modality treatment.

A Spanish group prospectively treated 95 patients who had stage I or II
Hodgkin’s lymphoma with six cycles of ABVD without radiation and reported
7-year overall survival (OS) and progression-free survival (PFS) of 96% and
84%, respectively [26]. This study included patients who had B symptoms or
bulky mediastinal disease, characteristics that other investigators have usually
reserved to identify more advanced disease. This study was nonrandomized,
<table>
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<tr>
<th>Trial</th>
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<th>PFS</th>
<th>OS</th>
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<td>75</td>
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<td>Sieber et al [4]</td>
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<tr>
<td>SWOG 9133/CALGB 9391</td>
<td>STLI (S) 36–40 Gy</td>
<td>163</td>
<td>96</td>
<td>90</td>
<td>Press et al [13]</td>
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<tr>
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<td>4 ABVD + STNI</td>
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<td>93</td>
<td>96</td>
<td>Bondadonna et al [15]</td>
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<tr>
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<td>70</td>
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<td>Noordijk et al [16]</td>
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<td>Hagenbeek et al [19]</td>
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<td>(A+B)</td>
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<tr>
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<td>(B+D)</td>
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<td></td>
<td>6 EBVP</td>
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</table>

**Abbreviations:** ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; BNLI, British National Lymphoma Investigation; CALGB, Cancer and Leukemia Group B; CMT, combined modality treatment; CT, chemotherapy; EBVP, epirubicin, bleomycin, vinblastine, and prednisone; EFRT, extended field radiotherapy; EORTC, European Organization for Research and Treatment of Cancer; GELA, Groupe d’Etude des Lymphomes de l’Adulte; GHSG, German Hodgkin’s lymphoma Study Group; IFRT, involved field radiotherapy; MOPP, mechlorethamine, vincristine, procarbazine, and prednisone; n/a, not available; OS, overall survival; PFS, progression-free survival; STLI, subtotal lymphoid irradiation; STNI, subtotal nodal irradiation; SWOG, Southwest Oncology Group; VAPEC-B, doxorubicin, cyclophosphamide, vincristine, bleomycin, etoposide, prednisolone, and methotrexate; VBM, vinblastine, bleomycin, and methotrexate.
but the authors argue that the OS and PFS compare favourably to stage I–II patients receiving combined modality therapy on the EORTC H8 trials, in which 5-year OS and PFS were 94% and 86%, respectively [27].

Four randomized trials using ABVD or an equivalent chemotherapy regimen have evaluated chemotherapy alone versus chemotherapy followed by radiotherapy [22–25]. In a Children's Cancer Group trial (CCG 5942), 501 patients who achieved complete remission with risk-adapted chemotherapy were randomized to observation or IFRT [28]. The chemotherapy was four cycles of cyclophosphamide, vincristine, procarbazine, prednisone, doxorubicin, bleomycin, and vinblastine (COPP-ABV) for Stage I–IIA patients who did not have adverse risk factors, six cycles of COPP-ABV for stage I–III patients who had adverse risk factors or B symptoms, and an intensification of COPP-ABV with high-dose cytarabine and etoposide for stage IV patients. For all treated patients, 3-year event-free survival (EFS) favored those who received radiotherapy, but there was no difference in overall survival (3-year EFS 92% and 3-year OS 98% for chemotherapy plus radiation; 87% and 99% for chemotherapy alone, respectively). For the 42% of patients who had limited-stage lymphoma, 3-year EFS was 97% after IFRT and 91% without radiation ($P$ for subgroup not reported), but 3-year OS was 100% for both groups.

A trial conducted in India considered a similar question in 179 adult patients who had various stages of Hodgkin’s lymphoma who achieved complete remission after six cycles of ABVD, then were randomized to IFRT or no further treatment [29]. This trial also showed improved 8-year EFS with the use of radiotherapy (88% for ABVD plus IFRT; 76% for ABVD alone; $P = .01$) but interestingly also showed an overall survival advantage (8-year OS 100% for ABVD plus IFRT, 89% for ABVD alone, $P = .002$). Interpretation of these results is complicated by the inclusion in this trial of both adult and pediatric patients, patients of all stages, patients who had bulky disease, and patients who had B symptoms. Subset analysis of 99 patients who had stage I–II disease showed no difference in 8-year EFS or OS with the addition of IFRT (97% versus 94%, $P = .29$, and 100% versus 98%, $P = .26$, respectively).

A trial conducted at Memorial Sloan-Kettering limited enrolled 152 adult patients who had stage I–IIIA non-bulky disease who were randomized to six cycles of ABVD versus the same chemotherapy plus IFRT [30]. Unlike the other trials, this one showed no significant difference in freedom from progression (FFP), but a trend toward a survival benefit with combined modality therapy. The trial only had sufficient power to detect differences greater than 20%, and the inclusion of stage IB, IIB, and IIIA makes application of the results less relevant to patients who have limited-stage disease.

For the various reasons described, the above trials did not answer the specific question of whether chemotherapy alone with ABVD is sufficient therapy for adult patients who have limited-stage Hodgkin’s lymphoma. In 1994 the National Cancer Institute of Canada–Clinical Trials Group (NCIC-CTG), with the participation of the Eastern Cooperative Oncology Group, initiated a multicenter randomized controlled trial comparing a risk-adapted approach,
including extended-field radiation therapy with or without ABVD, to an experimental arm using ABVD chemotherapy alone, for previously untreated limited-stage Hodgkin’s lymphoma. The primary outcome was 12-year overall survival based on the hypothesis that an approach that avoided radiation would provide adequate disease control and improve long-term overall survival by decreasing the number of deaths attributable to cardiovascular disease and secondary neoplasms in the arm without radiation. Over the life of this trial standard radiation for the management of limited-stage Hodgkin’s lymphoma changed from extended-field to involved-field radiation eventually making the “standard arm” of the trial no longer relevant. Because of this the trial was closed in 2005 and an initial analysis has been reported [31]. At a median follow-up of 4.2 years, there was no difference in estimated 5-year overall survival or event-free survival but the estimated 5-year freedom from disease progression modestly favored the radiation arm (93% versus 87%, P = .006). Interestingly, second cancers and cardiovascular events were already observed, with a trend to increased events in patients randomized to receive radiation therapy. These results suggest that with further follow-up, the original hypothesis of NCIC-CTG HD6 may be confirmed showing that overall survival will be reduced in the radiation-included arm because of excessive mortality from second cancers and cardiovascular disease.

The change in standard practice that brought about the early closure of the NCIC-CTG HD6 trial illustrates an important consideration for clinical trials in such a highly curable condition. The number of patients required to show significant improvements in survival, which is already expected to be greater than 90%, and the length of follow-up required to assess for fatal late toxicity of the treatments, create the risk that the standard arm will become obsolete during the lifetime of the trial. Despite this, the NCIC-CTG HD6 trial maintains its relevance as having the largest published cohort of adult limited-stage patients randomized to receive ABVD alone.

**RESPONSE-ADAPTED THERAPY OF LIMITED-STAGE Hodgkin’s Lymphoma**

In the NCIC-CTG HD.6 trial, patients randomized to chemotherapy alone underwent response assessment with CT scan after two cycles of ABVD. Thirty-five per cent of patients achieved complete remission (CR) or complete remission-unconfirmed (CRu). Those in complete remission received two additional cycles and those who did not achieve CR received four additional cycles. A subgroup analysis showed a significant difference in FFP between these groups (5-year estimates 95% versus 81%, respectively; P = .007). For the 69 patients randomized to chemotherapy alone who achieved a CR or CRu, the progression-free survival was similar to that for all patients randomized to treatment that included radiotherapy. Early complete response to chemotherapy, as assessed after two cycles of ABVD, may therefore be an important predictor for progression-free survival. The response as assessed by CT scanning does not do this well, however. In the NCIC CTG HD.6
trial 80% of patients who had less than a CR or CRu after two cycles of ABVD remained free of progression even though managed without radiation. Clearly, a better assessment tool is needed to identify patients who have a sufficiently high risk for relapse to justify a change in treatment to radiation.

As seen in HD.6, two thirds of patients who have limited-stage Hodgkin’s lymphoma treated with chemotherapy alone have small but detectable residual masses on CT after two cycles of ABVD. CT scanning cannot distinguish fibrosis from persistent viable tumor; therefore a CT-based response-adapted strategy would result in overuse of radiotherapy. Positron emission tomography using glucose tagged with radioactive fluorine (FDG-PET), when used for posttherapy evaluation, is superior to CT for making this distinction, with excellent negative predictive value [32,33]. Recently, a small study has suggested that FDG-PET may even have excellent negative predictive value after just one cycle of ABVD [34]. Seventeen of 23 patients had a negative FDG-PET after one cycle of chemotherapy. All 17 also had a negative FDG-PET at the completion of therapy and remain in continued remission at the end of follow-up (range 17–38 months). This study included patients who had advanced disease. Of the 6 patients who had positive PET after one cycle, 4 had entered the study with advanced-stage disease. Based on this small study it is reasonable to estimate that only 10% to 20% of patients who have limited-stage Hodgkin’s lymphoma will have a positive FDG-PET early in treatment with ABVD, and therefore a PET-based response-adapted strategy might avoid radiotherapy in 80% of patients who have limited-stage HL without sacrificing disease control.

Such a strategy of PET-based, response-adapted therapy has not yet been proven in a clinical trial. The current EORTC–Groupe d’Etude des Lymphomes de l’Adulte (GELA) H10 trial is evaluating this question in a large randomized trial. The standard arm involves three cycles of ABVD (favorable cohort) or four cycles (unfavorable cohort) followed by involved nodal radiotherapy (INRT). The experimental arm involves two cycles of ABVD followed by FDG-PET. PET-negative patients receive additional ABVD chemotherapy alone: two more cycles for favorable and four more for unfavorable. PET-positive patients receive two cycles of escalated BEACOPP followed by INRT. This trial recently started and has a target accrual of 1600 patients.

SUMMARY
Limited-stage Hodgkin’s lymphoma is a highly curable disease with expected long-term disease-free and overall survival rates close to 90% and 95%, respectively. This success has come at a cost of long-term treatment-related toxicity, such that the newly diagnosed patient who lives beyond 10 to 15 years is more likely to die from late complications of treatment than from the disease itself. Efforts to improve survival must therefore endeavor to reduce toxicity without sacrificing long-term disease-specific survival. Combining chemotherapy and radiation allows a reduction of radiation field size and number of cycles of chemotherapy facilitating achievement of the goal of reducing late toxicity.
Because a strategy of two cycles of ABVD followed by involved-field radiation reduces the risks of secondary cancers and infertility while maintaining excellent disease control this approach has been widely adopted. To further reduce the risks of radiotherapy, chemotherapy with ABVD alone has been investigated and is emerging as a reasonable option for patients, recognizing that there may be some reduction in local disease control but that relapses in these patients can often be treated effectively. The next step in this ongoing evolution will be the use of highly predictive tools for response assessment, such as FDG-PET, to better define which small fraction of patients are destined to relapse after chemotherapy alone and thus are good candidates for the preemptive use of radiotherapy.

References


