Controversies in Early-Stage Hodgkin’s Disease

Review Article [1] | May 01, 2002
By Andrea K. Ng, MD, MPH [2] and Peter M. Mauch, MD [3]

Early-stage Hodgkin’s disease accounts for approximately 60% of all cases of the illness. Because of its excellent cure rate (80% to 90%) and high salvage rate, it is difficult to demonstrate survival advantages for...
The main limitation of currently available radiographic imaging methods is the ability to detect occult abdominal disease, especially occult splenic involvement, with a negative predictive value of only 65% to 75%. Whole-body positron-emission tomography using 18F-fluorodeoxyglucose may offer higher overall diagnostic accuracy. Its role in staging Hodgkin’s disease is currently under investigation, and early results appear promising.[10,11]

Pathologic Staging

Staging laparotomy, a procedure introduced in the 1960s, was developed to detect occult disease below the diaphragm, so that appropriate candidates with pathologically staged early-stage disease could be selected for radiation therapy alone. However, its use has been diminishing with improved radiographic staging, the identification of factors that predict for risk of infradiaphragmatic involvement, and the increasing use of combined-modality therapy in early-stage disease. Furthermore, in the European Organization for Research and Treatment of Cancer (EORTC) H6 trial, which randomized patients with early-stage Hodgkin’s disease and a favorable prognosis to laparotomy and tailored therapy vs no laparotomy (with all patients receiving extended-field radiation therapy), no survival differences were detected between arms.[12]

Although staging laparotomy has been abandoned in most parts of the world, it may still have a role in patients who wish to avoid chemotherapy or large-field irradiation. The results of a laparotomy may help guide the selection of patients for treatment with limited-field radiation therapy alone. Bone marrow biopsy is another invasive procedure performed as part of pathologic staging. However, it is of limited value in most patients with early-stage disease because of its low yield of less than 1%. [13] It is therefore not indicated in early-stage Hodgkin’s disease, unless constitutional symptoms are present at initial diagnosis.

Prognostic Factors

Considerable heterogeneity exists among patients who present with Hodgkin’s disease, even when limited to those with early-stage disease. Identification of prognostic factors is important in these patients, because it not only helps predict individual patient outcome, but also allows the delivery of treatment tailored to the presence or absence of risk factors. Several prognostic indicators have been identified for early-stage Hodgkin’s disease through retrospective studies, which were based largely on patients treated with radiation therapy alone.[14-18] These factors, including the presence of large mediastinal adenopathy and B symptoms, number of involved sites, disease burden, gender, erythrocyte sedimentation rate, and histology, were mostly predictive of freedom from recurrence, but seldom of overall survival. The only factor that has been consistently shown to have a negative prognostic impact on survival is older age at diagnosis.[18-20]

Until recently, the general strategy for the management of early-stage Hodgkin’s disease had been to treat patients with a favorable prognosis with radiation therapy alone, and to add chemotherapy in the presence of unfavorable factors. However, combined-modality therapy is being used increasingly in all early-stage patients because of the safer chemotherapy agents available and concern regarding the toxicity associated with large-field radiation therapy. Many previously identified prognostic factors are no longer significant in the context of combined-modality therapy. However, separating patients into prognostic groups continues to play an important role, especially in the design of clinical trials. Cooperative groups have used various combinations of prognostic factors to stratify patients into favorable and unfavorable prognostic groups to establish eligibility criteria for clinical trials exploring treatment reduction and modification. Some cooperative groups have also separated out a small group of patients with a very favorable prognosis, in whom minimal treatment has been studied [2,21]. Table 1 shows the prognostic classification schemes of two large European cooperative groups, EORTC and the German Hodgkin’s Lymphoma Study Group (GHSG), in their Hodgkin’s disease trials.[4,14]

Summarized below are trials evaluating various treatment options for early-stage Hodgkin’s disease. The more recently completed trials of radiation therapy alone were limited largely to patients with a favorable prognosis, whereas trials of combined-modality therapy generally stratify patients into favorable and unfavorable prognostic groups.

Treatment With Radiation Therapy Alone

Historically, radiation therapy alone has been the mainstay of therapy for patients with early-stage Hodgkin’s disease, with disease control rates of 80% to 85%. Areas of controversy include optimal radiation field size and dose.

Field Size

A number of randomized studies have compared limited vs more-extensive radiation field
In the meta-analysis by Specht et al,[26] which combined data from eight randomized trials in early-stage patients, a significantly lower relapse rate was found in the more- vs less-extensive radiation therapy group, with the risk of recurrence being 31.3% and 43.4%, respectively. This difference in relapse rate, however, did not translate into a difference in survival. In the EORTC H5F trial, selected patients with pathologic stage I/II disease with favorable characteristics were randomized to mantle and para-aortic irradiation vs mantle radiation therapy alone.[17] No significant difference in relapse-free and overall survival was detected at 15 years of follow-up.

We recently reported the results of a prospective study conducted by the Joint Center for Radiation Therapy in 83 patients with early-stage Hodgkin’s disease (but no large mediastinal disease or subcarinal adenopathy) who were treated with mantle radiation therapy alone.[27] At a median follow-up of 61 months, the 5-year rates of freedom from treatment failure and overall survival were 86% and 100%, respectively.

In this study, 77 patients underwent pathologic staging to rule out infradiaphragmatic disease, and 6 selected patients considered to be at low risk of occult abdominal disease (3 with stage IA lymphocyte predominant Hodgkin’s disease and 3 female patients with stage IA nodular sclerosis Hodgkin’s disease) did not undergo surgical staging. These results suggest that in carefully selected patients with early-stage disease (who had been staged pathologically), elimination of the para-aortic field may be possible. However, it is still largely unclear as to which subset of patients require only mantle radiation therapy without a staging laparotomy. This subject has been explored prospectively in EORTC trials H7-VF and H8-VF, in which a selected group of favorable patients (ie, women < 40 years old with clinical stage IA lymphocyte predominant or nodular sclerosis histology and an erythrocyte sedimentation rate < 50 mm/h) were treated with mantle radiation therapy alone without pathologic staging.[21] Results in 40 patients enrolled in the H7-VF trial showed a 6-year event-free, relapse-free, and overall survival of 66%, 73%, and 96%, respectively. The relapse rate was felt to be unacceptably high, and the trial was closed.

Whether a relapse rate of 27% is high enough to justify premature discontinuation of the trial, especially given the minimal initial therapy and the very high survival rate, is debatable. The trial also failed to capture other potential advantages of this treatment approach, including better patient quality of life and reduced late toxicities.

Dose

The original recommended radiation doses of 40 to 44 Gy for curative treatment of Hodgkin’s disease were based on a retrospective analysis of involved-field disease control from data in the 1960s.[28] Vijayakumar et al compiled dose-control data on predominantly megavoltage radiation therapy from the 1960s to 1990s.[29] It was shown that the doses required to achieve a control rate of 98% for subclinical disease, disease ≤ 6 cm, and disease > 6 cm were 32.5 Gy, 36.9 Gy, and 37.4 Gy, respectively.

Mendenhall et al reviewed the effect of radiation dose on involved-field disease control in stage I/II Hodgkin’s disease patients.[30] In patients treated with radiation therapy alone, no significant differences in failure rates were found between doses of ≤ 35 Gy vs > 35 Gy, regardless of whether the initial tumors were ≤ 6 cm or between 6 and 9 cm in size.

The only prospective study of optimal radiation doses was conducted by the GHSG HD4 trial.[31] In this study, 376 patients with pathologic stage IA-IIB favorable-prognosis Hodgkin’s disease were randomized to receive 30 Gy followed by an additional 10 Gy to involved lymph node regions vs 40 Gy of extended-field radiation therapy. The 5-year freedom-from-treatment-failure results favored the 30-Gy extended-field plus 10-Gy arm over the 40-Gy extended-field arm (81% vs 70%, respectively, \( P = .026 \)). The 5-year survival results also favored the 30-Gy extended-field arm (98% vs 93%, respectively, \( P = .067 \)), although the differences did not reach statistical significance. These results suggest that 30 Gy is sufficient to eradicate subclinical Hodgkin’s disease with radiation therapy alone.

Combined-Modality Therapy

Earlier studies have clearly shown that in patients who have early-stage disease with unfavorable characteristics (such as bulky disease), treatment with radiation therapy alone is inadequate.[32-34] In these patients, combined-modality therapy is warranted. With the development of less toxic and better-tolerated chemotherapy regimens, combined-modality therapy is also increasingly being used in patients with early-stage, favorable-prognosis disease.

The major advantages of this approach are that it obviates the need to perform staging laparotomy,
allows treatment with smaller radiation fields, and is associated with a higher rate of freedom from treatment failure. Studies are under way to identify even safer chemotherapy regimens as well as to determine the optimal number of chemotherapy cycles, radiation field size, and radiation dose in the setting of combined-modality therapy.

**Optimal Chemotherapy Regimen**

The replacement of the MOPP regimen (mechlorethamine [Mustargen], vincristine [Oncovin], procarbazine [Matulane], prednisone) by the less toxic and more effective ABVD regimen (doxorubicin [Adriamycin], bleomycin [Blenoxane], vinblastine, dacarbazine [DTIC-Dome])—initially based largely on data from advanced-stage Hodgkin’s disease[35] and subsequently confirmed in the EORTC H6U trial in early-stage patients[12]—has increased the role of chemotherapy administered in conjunction with radiation therapy in early-stage Hodgkin’s disease. A number of investigators have also studied the efficacy and feasibility of alternative regimens that are associated with a lower toxicity profile. Examples include VBM (vinblastine, bleomycin, methotrexate),[2,36-38] TVB (thiotepa [Thioplex], bleomycin, vinblastine),[39] and NOVP (mitoxantrone [Novantrone], vincristine, vinblastine, prednisone).[40]

The VBM regimen, developed at Stanford, has demonstrated efficacy in early-stage patients based on short-term results, but there is concern about its associated pulmonary toxicity.[2,37] The TBV regimen was compared with the MOPP regimen as part of combined-modality therapy and was found to be equally efficacious with less short-term toxicity. The NOVP regimen was also associated with minimal toxicity, but a higher relapse rate was seen in patients with unfavorable characteristics such as B symptoms and hilar involvement. Recent trials attempting to define the optimal chemotherapy regimen for early-stage Hodgkin’s disease have stratified patients into favorable and unfavorable groups.

**Favorable Prognosis**

The EORTC H7F trial investigated the potentially less toxic EBVP II regimen (epirubicin [Ellence], bleomycin, vinblastine, prednisone) administered monthly at one dose per cycle. In this study, patients with early-stage, favorable-prognosis Hodgkin’s disease were randomized to receive either EBVP II and involved-field radiation therapy or subtotal nodal irradiation. The 6-year relapse-free survival was significantly higher in the combined-modality arm (92% vs 81%, \( P = .004 \)), but overall survival rates were similar between the two arms.[3]

The Stanford V regimen (mechlorethamine, doxorubicin, vincristine, vinblastine, etoposide, bleomycin, prednisone) is a short but intensive regimen administered over a 12-week period.[41,42] It was initially evaluated in patients with unfavorable-prognosis early-stage or advanced-stage Hodgkin’s disease, and early results appear to be promising. A modified version of the Stanford V regimen administered for a shorter period (8 weeks) is currently being tested in a prospective phase II study in patients with favorable-prognosis clinical stage I/II disease. In this trial, patients with initial nodal involvement measuring at least 1.5 cm also receive involved-field radiation therapy after the 8 weeks of chemotherapy.

The VAPEC-B regimen (vincristine, doxorubicin, prednisolone, etoposide, cyclophosphamide [Cytoxan, Neosar], bleomycin) is being evaluated in a randomized study conducted by the British National Lymphoma Investigation. In this phase III study, 4 weeks of chemotherapy followed by involved-field radiation therapy is compared with mantle radiation therapy alone in patients with clinical stage I/II disease without large mediastinal lymphadenopathy.

**Unfavorable Prognosis**

The safer and less intense chemotherapy regimens have also been tested in patients with early-stage, unfavorable-prognosis Hodgkin’s disease. In the EORTC H7U trial, EBVP II and involved-field radiation therapy was compared with MOPP/ABV and involved-field irradiation.[3] A significantly lower event-free survival (68% vs 90%, \( P = .0001 \)) was reported for the EBVP II arm. A randomized study conducted by the Grupo Argentino de Tratamiento de la Leucemia Aguda (GATLA) compared COPP (cyclophosphamide, vincristine, procarbazine, prednisone) with the less intense AOPE regimen (doxorubicin, vincristine, prednisone, etoposide) as part of combined-modality therapy in patients with unfavorable-prognosis Hodgkin’s disease.[43] A significantly lower event-free survival (66% vs 85%; \( P = .009 \)) was noted in the AOPE arm.

The Southwest Oncology Group (SWOG) tested three cycles of EVA (etoposide, vinblastine, doxorubicin) followed by subtotal lymphoid irradiation in patients with localized Hodgkin’s disease and unfavorable prognostic features.[44] Only 66% of patients achieved a complete remission, with 20% developing disease progression after a complete response. Results of these trials show that reduced treatment may be inadequate in patients with an unfavorable prognosis, and highlight the importance of prognostic factors in selecting patients with early-stage disease for treatment with
modified and less aggressive regimens. Novel regimens for patients with early-stage disease and an unfavorable prognosis have been developed and tested. Mature results of the Stanford V regimen in patients with bulky mediastinal stage I/II or advanced-stage Hodgkin’s disease were recently published.[42] A phase III trial being conducted by the Eastern Cooperative Oncology Group (ECOG) is comparing 12 weeks of the Stanford V regimen with six cycles of ABVD. Another dose-intensified regimen BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone), developed by the GHSG initially for advanced-stage patients,[45] is currently being evaluated in the HD11 trial in patients with stage I-IIB disease and unfavorable risk factors. In this randomized study, four cycles of BEACOPP is being compared with four cycles of ABVD as part of combined chemotherapy and involved-field radiation therapy. This study also addresses the issue of optimal radiation dose in the setting of combined-modality therapy (see below).

In a similar ongoing trial, the EORTC H9U trial is comparing six cycles of ABVD with four cycles of ABVD or four cycles of BEACOPP, followed by involved-field radiation therapy.

Reducing the Number of Chemotherapy Cycles
Another strategy for reducing treatment-related toxicities in early-stage Hodgkin’s disease is to limit the number of cycles of chemotherapy. Ongoing trials addressing the question of the optimal number of cycles of chemotherapy as part of combined-modality therapy are summarized in Table 2.

Favorable Prognosis
In the GHSG HD7 trial, patients with early-stage, favorable-prognosis disease are randomized to receive two cycles of ABVD followed by extended-field irradiation vs extended-field radiation therapy alone. The randomized trial conducted by SWOG comparing three cycles of doxorubicin and vinblastine plus subtotal nodal and splenic irradiation vs subtotal nodal and splenic irradiation alone in patients with clinical stage IA-IIA Hodgkin’s disease showed a significantly higher freedom from treatment failure in the combined-modality therapy arm (94% vs 81%).[46] However, similar to the GHSG HD7 study, this trial does not address the key question of the minimum number of cycles of chemotherapy needed to control occult infradiaphragmatic disease so that abdominal irradiation can be safely eliminated.

Two randomized studies, the GHSG HD10 and the EORTC H8F trial, will hopefully address this question. In the ongoing GHSG HD10 trial, patients without unfavorable risk factors are being randomized to one of four arms: two cycles of ABVD followed by 30-Gy involved-field irradiation; two cycles of ABVD followed by 20-Gy involved-field irradiation; four cycles of ABVD followed by 30-Gy involved-field irradiation; or four cycles of ABVD followed by 20-Gy involved-field irradiation. In the EORTC H8F trial, three cycles of MOPP/ABV hybrid and involved-field irradiation were compared with mantle and para-aortic-splenic irradiation in patients with a favorable prognosis and clinical stage IA-IIA disease. The trial is closed to accrual, but the results are not yet available.

Unfavorable Prognosis
For patients with unfavorable-prognosis, early-stage disease, four vs six cycles of chemotherapy plus involved-field radiation therapy are being evaluated in the ongoing EORTC H8U and H9U trials. The EORTC H8U trial addresses the issue of optimal radiation field size as well as optimal number of chemotherapy cycles. It is a three-arm study comparing six cycles of MOPP/ABV followed by involved-field irradiation to four cycles of MOPP/ABV followed by extended-field irradiation. At a median follow-up of 39 months, preliminary results in 995 patients revealed no significant differences in failure-free or overall survival among the three arms.[47] The EORTC H9U trial (also a three-arm study), in addition to investigating the efficacy of the alternative regimen BEACOPP, is examining the question of optimal number of cycles of chemotherapy. In this study, six cycles of ABVD plus involved-field radiation therapy is being compared with four cycles of ABVD or BEACOPP plus involved-field radiation therapy.

Optimal Radiation Field Size
The optimal radiation field size in the setting of combined-modality therapy in early-stage Hodgkin’s disease is being studied predominantly in patients with an unfavorable prognosis. In an earlier randomized trial conducted by the French Cooperative Group,[48] patients with unfavorable-prognosis clinical stage I/II Hodgkin’s disease were randomized to six cycles of MOPP and involved-field irradiation vs six cycles of MOPP and extended-field irradiation, with radiation administered after three cycles of chemotherapy. At 6 years, no significant differences in disease-free survival were noted between the limited-field and extended-field arms (87% vs 93%, $P = .15$).
Preliminary results of the previously described EORTC H8U trial showed no significant differences in failure-free survival between patients who received either involved-field or extended-field radiation therapy after completing four cycles of MOPP/ABV. Therefore, the results thus far seem to indicate that involved-field irradiation may be adequate when administered with four to six cycles of chemotherapy.

The ongoing GHSG HD8 trial will clarify the issue of radiation field size after only two cycles of chemotherapy. In this study, patients with an unfavorable prognosis and early-stage Hodgkin’s disease are randomized to receive two cycles of COPP/ABVD, followed by involved-field or extended-field radiation therapy (see Table 3).

**Optimal Radiation Dose**

In addition to reducing the number of chemotherapy cycles and the radiation field size in combined-modality therapy, lower radiation doses are being studied as part of an effort to reduce treatment intensity for early-stage Hodgkin’s disease (Table 4).

**Favorable Prognosis**

The ongoing GHSG HD10 study is a four-arm trial looking at two vs four cycles of ABVD followed by 20 vs 30 Gy of involved-field radiation therapy in stage I/II, favorable-prognosis Hodgkin’s disease patients. In addition to addressing the question of the optimal number of chemotherapy cycles, it will help determine the optimal radiation dose after chemotherapy in these patients. In the EORTC H9F trial, two of the three arms are comparing 36 Gy with 20 Gy to involved sites in a similar group of patients who have achieved a complete remission after six cycles of EBVP II.

**Unfavorable Prognosis**

Combining results from two trials (HD1 and HD5), the GHSG showed that, after 4 months of chemotherapy in patients with poor-prognosis, early-stage Hodgkin’s disease, there were no significant differences in freedom from failure or survival between patients receiving 20, 30, or 40 Gy to prophylactic sites. In patients with early-stage disease and poor prognostic features, radiation doses of 20 vs 30 Gy to an involved field after four cycles of either ABVD or BEACOPP are being studied prospectively in the GHSG HD11 trial.

**Chemotherapy Alone**

Because of concern about solid tumor risk after irradiation, especially in young patients, chemotherapy alone has been regarded by some as an attractive option for patients with early-stage disease. Two earlier randomized trials compared mantle and para-aortic radiation therapy with MOPP chemotherapy in pathologically staged patients with predominantly early-stage disease. In the study by Biti et al, a significantly higher 8-year overall survival was reported for the radiation therapy arm, which was attributed to the poor salvage results in patients who relapsed after MOPP chemotherapy.

In the National Cancer Institute (NCI) study, when limiting the analysis to patients with pathologic stage IA (central sites), IB, IIA, and IIB disease without large mediastinal involvement, no significant differences in disease-free or overall survival were detected at 10 years. The applicability of the results of both trials to current practice, however, is questionable because of the outdated chemotherapy regimen used.

The NCI in Canada is conducting a trial in which patients with clinical stage I/II disease and unfavorable features—mixed cellularity/lymphocyte depleted histology, age $\geq$ 40, erythrocyte sedimentation rate $\geq$ 50 mm/h, or $\geq$ 4 sites of disease; patients with bulky disease are excluded—are randomized to either subtotal nodal irradiation or four to six cycles of ABVD. Perhaps a more pertinent question is whether radiation therapy can be omitted from combined-modality therapy in patients with early-stage Hodgkin’s disease. One trial, conducted by GATLA, attempted to address this issue.

In the GATLA study, 277 patients with clinical stage I/II Hodgkin’s disease were randomized to CVPP (cyclophosphamide, vinblastine, procarbazine, prednisone) alone for six cycles or to CVPP plus involved-field irradiation. In patients with favorable-prognosis disease, no significant differences in disease-free or overall survival were noted between the two arms. However, in patients with unfavorable prognostic features (age $> 45$, more than two involved sites, or bulky disease), treatment with CVPP and involved-field radiation therapy produced a longer disease-free survival (75% vs 34%, $P = .001$) and overall survival (84% vs 66%) than did treatment with CVPP alone. That said, a high proportion of pediatric patients were included in this study, thus limiting the applicability of the results to the adult population.

Two other trials are evaluating the feasibility of chemotherapy alone in early-stage patients. The
EORTC H9F trial is seeking to define the optimal radiation dose (20 vs 30 Gy) after EBVP II; patients in the third arm of the study are receiving six cycles of EBVP II alone. In a trial at Memorial Sloan-Kettering Cancer Center, patients with clinical stage I-IIIA disease—the presence of B symptoms was not an exclusion criterion—who achieved a complete remission after six cycles of ABVD were randomized to either mantle irradiation or no further treatment. This study is now closed due to slow accrual. Preliminary results suggested that the maximum difference for complete remission duration, freedom from progression, and overall survival was at most 18%.[51]

Table 5 lists the trials exploring the feasibility of chemotherapy alone in patients with early-stage Hodgkin’s disease.

**Conclusions**

Because of the excellent cure rate in early-stage Hodgkin’s disease and the long follow-up required to fully appreciate the late effects of various treatments, no management option has shown a clear overall superiority, especially among patients with favorable-prognosis disease. Therefore, it is important to carefully present the pros and cons of each management option, take patient preferences into account, and include patients in the decision-making process.[52]

A number of clinical trials have been (and are being) developed in an attempt to search for ideal management strategies for various subsets of patients with early-stage Hodgkin’s disease. Patients with newly diagnosed disease should be encouraged to participate in these trials. On one end, ongoing efforts are being made to fine-tune therapeutic strategies by minimizing complications without compromising the high cure rate of early-stage Hodgkin’s disease. On the other end, long-term follow-up of patients who have achieved cure should be continued to confirm the long-term safety of newer regimens as well as to identify patients at high risk for delayed, life-threatening complications, so that they can be targeted for more rigorous follow-up programs.

**References:**


Source URL: http://www.cancernetwork.com/printpdf/controversies-early-stage-hodgkin%E2%80%99s-disease-1/page/0/1

Links:
[1] http://www.cancernetwork.com/review-article
[2] http://www.cancernetwork.com/authors/andrea-k-ng-md-mph
[3] http://www.cancernetwork.com/authors/peter-m-mauch-md