Favorable Early-Stage Hodgkin Lymphoma

Joachim Yahalom, MD, New York, New York

Abstract
The category of favorable early-stage Hodgkin lymphoma (HL) includes patients with Ann Arbor stages I or II disease with no bulky disease or B symptoms. The precise definition of favorable versus unfavorable early-stage disease may vary among American and European cooperative groups. The overall 10-year survival rate of patients with favorable early-stage HL exceeds 90%. Indeed, effective treatments for this group of patients have been available for more than 4 decades. However, treatment strategies have radically changed over the past 15 years and focus now on maintaining the high cure rate while reducing the risk of treatment-related long-term morbidity. The optimal treatment is still evolving, and more recently, reduction in the total amount of chemotherapy and in radiation field and dose has shown excellent results. Combined modality therapy is the preferred treatment for patients with classical favorable early-stage HL (nodular sclerosis or mixed cellularity histology). Patients with early-stage lymphocyte predominance HL are highly curable using involved-field radiation therapy (IFRT) alone and do not require chemotherapy. Classical favorable HL is also curable with radiotherapy alone or with chemotherapy alone, but larger fields and higher-dose radiation or longer chemotherapy is required compared with combined modality. The freedom from treatment failure rate is significantly better with a combination of short chemotherapy and IFRT than with either chemotherapy or radiotherapy alone. Although combined modality is the standard preferred treatment for favorable disease, radiation therapy alone or chemotherapy alone could be considered under special circumstances or as part of an investigational protocol. (JNCCN 2006;4:233–240)

Key Words
Hodgkin lymphoma, cancer staging, involved-field radiation therapy, chemotherapy, favorable early stage disease

The treatment of favorable early-stage Hodgkin lymphoma (HL) has changed drastically over the past 15 years. The optimal treatment strategy is still evolving and is, at times, spiritedly debated.1–7 The bottom-line question is, how much further can we reduce the treatment to avoid long-term complications without reducing the long established high cure rate? Furthermore, because more than one option of reasonably effective therapy and a salvage option may be available, what should be regarded as the current standard of care and which alternatives should be studied in future trials?

Definition of Favorable and Unfavorable (Intermediate) Early-Stage HL

Although the categories of favorable, unfavorable early-stage, and advanced-stage are widely used in selecting treatment programs and clinical trials, they are not part of the official staging system for HL (Ann Arbor staging with the Cotswolds modification).8 The determinants of favorable early-stage HL vary among study groups and are detailed later. Furthermore, the different clinical trials that we use to guide treatment decisions had heterogeneous eligibility criteria and thus should be applied carefully for individual patient decisions or for establishing treatment guidelines. The fact that most adverse prognostic factors were identified at an era when imaging, staging tools, and treatment philosophy were significantly different than today’s standard is also important.

Most adverse prognostic factors were identified during the era of staging laparotomy followed by radiotherapy alone in early stages (IA or B-IIA or B and even IIIA). The most significant factors were number of involved regions, large tumor mass (primarily mediastinal), B symptoms (mostly fever and weight loss), age (> 50 years), and gender (male). For patients staged clinically (without a staging laparotomy), other factors were also found to be significant, including histology (mixed cellularity);
elevated sedimentation rate; anemia; and low serum albumin. The question of whether E lesions are prognostically significant remains controversial, partly because experts disagree on the definition of an E lesion. Although these factors emerged predominantly from radiation therapy (RT)-alone studies, combined modality trials confirmed their prognostic relevance, even when chemotherapy was added and reduced the risk of failure.9

In the era of combined modality use for early-stage disease, almost all study groups distinguish between favorable and unfavorable disease for trial design or treatment recommendation (Table 1). In principal, more courses or more intensive chemotherapy is recommended for unfavorable disease, as is a slightly higher dose of involved-field radiotherapy. Most studies that experimented with chemotherapy alone were limited to patients with favorable factors.

**Combined Modality Therapy as Standard Treatment for Favorable Early-Stage Classical HL**

The standard treatment for favorable early-stage classical HL has markedly changed over the past 2 decades. Combined modality therapy consisting of short-course chemotherapy (most often ABVD [adriamycin, bleomycin, vinblastine, dacarbazine]) followed by reduced-dose radiation carefully directed only to the involved lymph node site successfully replaced radiation alone as the treatment of choice. Combined modality is the standard treatment for favorable early-stage disease in Europe, including the European Organisation for Research and Treatment of Cancer (EORTC)/Groupe d’Etude des Lymphomes de l’Adulte (GELA) and German Hodgkin Study Group (GHSG). In the United States, chemotherapy followed by involved-field radiation therapy (IFRT) is the preferred treatment recommended by the NCCN guidelines.10,11

Subtotal lymphoid irradiation (STLI) alone is an effective treatment for favorable early-stage HL, but the guidelines recommend it only for highly selected patients who cannot tolerate chemotherapy.11 Although radiotherapy alone is no longer the primary treatment for classical HL because of its potential long-term risks, consolidating IFRT of smaller volumes, a reduced dose, and with better planning and delivery techniques remains an important component of an effective treatment program after chemotherapy. In lymphocyte-predominant HL, IFRT or regional RT alone (without chemotherapy) is the treatment of choice for patients with favorable early-stage disease.11

<table>
<thead>
<tr>
<th>Table 1 Early Hodgkin Lymphoma Risk Factors and Treatment Groups of the EORTC/GELA, GHSG, and NCCN Guidelines</th>
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<tbody>
<tr>
<td><strong>Risk factors (RF)</strong></td>
</tr>
<tr>
<td>A. Large MM</td>
</tr>
<tr>
<td>B. Age ≥ 50 years</td>
</tr>
<tr>
<td>C. B symptoms* or ESR ≥ 50</td>
</tr>
<tr>
<td>D. ≥ 4 involved sites</td>
</tr>
<tr>
<td><strong>Treatment Groups</strong></td>
</tr>
<tr>
<td>Early stage favorable</td>
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<tr>
<td>Early stage unfavorable</td>
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<tr>
<td></td>
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<tr>
<td>Advanced stage</td>
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</table>

**Abbreviations:** CS, clinical stage; EORTC, European Organization for Research and Treatment of Cancer; ESR, erythrocyte sedimentation rate; GELA, Groupe d’Etude des Lymphomes de l’Adulte; GHSG, German Hodgkin Study Group; MM, mediastinal mass; NCCN, National Comprehensive Cancer Network.

* If based on posteroanterior chest radiograph, the maximal mass width is more than a third of the maximal intrathoracic diameter. If based on a computed tomography scan, a mediastinal mass greater than 35% of the thoracic diameter at T5-6.
† If B symptoms, ESR should be ≥ 30.
Evolution of Treatment for Early-Stage HL and Recent Trials

Because in earlier years (1950–1980) RT was considered the only curative modality for early-stage HL, radiation was designed to maximize field size and dose and was termed radical radiotherapy. Even in later years, radiotherapy remained extensive to reduce the need for the less-effective (compared with ABVD) and relatively toxic chemotherapy combination used then: MOPP (mechlorethamine, vincristine, procarbazine, and prednisone).

Radical radiotherapy alone cured most early-stage patients. For example, long-term follow-up studies involving 392 pathologically-staged patients without large mediastinum adenopathy treated by the Harvard group showed 10- and 20-year freedom from treatment failure rates of 84% and 82%, respectively. The 10- and 20-year overall survival rates were 92% and 82%, respectively. The Harvard group, like many others, documented the late increase in incidence of second solid tumors as the main cause for decreased survival after 10 years.12,13

Although the recognition of late morbidity and mortality that came from pioneering treatments such as radical radiotherapy and MOPP chemotherapy is important, the lesson from the “radiotherapy period” in HL should not be limited to the concerning awareness of long-term risks associated with large-field radiotherapy. We should appreciate that radiotherapy as single modality was effective in curing HL and should adjust its current application after chemotherapy to maximize cure while avoiding toxicity.

The improved efficacy of combining doxorubicin-based chemotherapy with traditional large-field radiotherapy as compared with the same radiotherapy alone was shown in the GHSG HD7 and Southwest Oncology Group (SWOG) 9133 studies of patients with favorable characteristics.14,15 Patients on the combined modality arm had a significantly better freedom from treatment failure. Overall survival remained the same, probably reflecting good salvage or too short a follow-up period.

The EORTC/GELA H7F and H8F trials significantly reduced the irradiated volume in the combined modality arm to include only the site of the originally involved nodes (involved-field) as opposed to treatment of all lymph node sites (and the spleen) on the radiation alone arm. Still, the combined modality arm yielded a significantly better relapse-free survival rate than radiation alone (Table 2).16,17

The studies summarized in Table 3 show that when combined with chemotherapy, involved-field radiation is as effective as a combination of the same chemotherapy followed by extended-field radiation. These studies clearly indicate that reducing the radiation field has not detracted from the excellent freedom from treatment failure or relapse-free survival rates (84%–95%) or overall survival rates (92%–94%) in patients with favorable or unfavorable early-stage HL.18-20 The detailed analysis of the GHSG HD8 study showed that a smaller radiation field was associated with reduced acute side effects and a trend toward a lower risk of second malignancies (2.8% vs. 4.5%) that may strengthen with longer follow-up.20

Combined modality therapy not only allows for a drastic restriction of irradiated volume but also permits a meaningful reduction (up to 50%) in the effective prescribed radiation dose. The GHSG studies of combined modality therapy in patients with

### Table 2: Studies Comparing RT Alone with Combined Modality Therapy in Patients with Favorable Disease

<table>
<thead>
<tr>
<th>Study Regimens</th>
<th>FFTF or OS (y)</th>
</tr>
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<tbody>
<tr>
<td>GHSG HD774</td>
<td>EFRT 75% 94% (5)</td>
</tr>
<tr>
<td>P value</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>SWOG 913315</td>
<td>STLI 81% 96% (3)</td>
</tr>
<tr>
<td>P value</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>EORTC/GELA H7F</td>
<td>STLI 81% 95% (5)</td>
</tr>
<tr>
<td>P value</td>
<td>.0001</td>
</tr>
<tr>
<td>EORTC/GELA H8F</td>
<td>STLI 80% (4)</td>
</tr>
<tr>
<td>P value</td>
<td>&lt; .0001</td>
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</tbody>
</table>

Abbreviations: EFRT, extended-field radiotherapy; EORTC, European Organization for Research and Treatment of Cancer; FFTF, freedom from treatment failure; GELA, Groupe d’Etude des Lymphomes de l’Adulte; GHSG, German Hodgkin Lymphoma Study Group; IFRT, involved-field radiotherapy; NS, not significant; OS, overall survival; RFS, relapse-free survival; STLI, subtotal lymphoid irradiation; SWOG, Southwest Oncology Group.
unfavorable early-stage disease indicated that disease control with 20 Gy was as effective as with 40 Gy, provided that bulky disease sites were irradiated to 40 Gy.\textsuperscript{21} The recently completed GHSG HD10 study for patients with favorable disease randomized patients to receive either 20 Gy IFRT or 30 Gy IFRT after a short course (2 or 4 cycles) of ABVD. A median follow-up of 4 years showed excellent overall results (freedom from treatment failure, 94%; overall survival, 97%), with no difference among the 4 arms.\textsuperscript{22} Reducing chemotherapy appeared safe, and at this point, no difference was seen among the different RT doses. The HD10 twin study HD11 targeted patients with unfavorable early-stage disease and randomized them to either ABVD times 4 or BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) times 4. Both programs were followed by either 20 Gy or 30 Gy to the involved field. The interim analysis at 3 years has not shown a difference between the arms, with freedom from treatment failure of 87% and overall survival of 96%.\textsuperscript{22,23}

The current GHSG study for patients with favorable disease (HD13) is testing the exclusion of bleomycin (pulmonary toxicity) and/or dacarbazine (questionable efficacy) from the shorter chemotherapy regimen while maintaining IFRT at 30 Gy.

The recent EORTC/GELA trial for patients with favorable H9F evaluated EBVP (epirubicin, bleomycin, vinblastine and prednisone) times 6 to complete remission followed by IFRT of either 36 or 20 Gy. The third arm with complete response after 6 cycles of EBVP and no radiation was closed early because of an excessive relapse rate. The combined modality arms showed similar 4-year event-free survival rates of 88% and 85%, respectively. The EBVP chemotherapy-alone arm showed a significantly inferior event-free survival rate of 69% ($P = \cdot001$).\textsuperscript{24,25}

### Significance of Reducing the Radiation Field and Dose

In the 1960s and 1970s, radiation was the primary and sometimes the only curative modality for HL. It was used alone or with adjuvant MOPP for early and advanced stages. Bulky sites were covered with large radiation field margins, and even the lungs and liver were sometimes intentionally irradiated. Even for patients with favorable characteristics, the standard field was total lymphoid irradiation, with the large size of the field compensating for the lack of good imaging information. The dose was also maximized (the standard dose at Stanford was 44 Gy), and often treatment was given in a technique that delivered even higher doses anteriorly, to the heart and breast.

The IFRT that is used now in combined modality programs is considerably smaller; radiation is limited to the involved site and is often tailored to include only the reduced post-chemotherapy volume.\textsuperscript{26} Researchers estimate that, compared with total lymphoid irradiation, the average involved field will reduce the irradiated volume by more than 80%. This is particularly relevant with irradiation of the breast, heart, and lungs. With the old indiscriminate “mantle” field radiotherapy, most of the breast tissue was irradiated. Most breast exposure resulted from routine irradiation of the axillae and most second breast cancers developed in the outer part of the breast.

### Table 3: Studies Comparing Involved Field Radiation with Extended Radiation in Combined Modality Programs for Favorable and Unfavorable Early-Stage HL

<table>
<thead>
<tr>
<th>Study (No. of patients)</th>
<th>Treatment Regimens (No. of courses)</th>
<th>FFTF or RFS</th>
<th>OS (y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milan (133) ABVD (4) + STLI</td>
<td>97%</td>
<td>93% (5)</td>
<td></td>
</tr>
<tr>
<td>GHSG HD8 (1064) COPP/ABVD (4) + IFRT</td>
<td>86%</td>
<td>91% (5)</td>
<td></td>
</tr>
<tr>
<td>EORTC/GELA H8U (995) MOPPI/ABV (4) + STLI</td>
<td>96%</td>
<td>93%</td>
<td></td>
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</tbody>
</table>

Abbreviations: EFRT, extended-field radiotherapy; EORTC, European Organization for Research and Treatment of Cancer; FFTF, freedom from treatment failure; GELA, Groupe d’Etude des Lymphomes de l’Adulte; GHSG, German Hodgkin Study Group; IFRT, involved-field radiotherapy; NS, not significant; OS, overall survival; RFS, relapse-free survival; STLI, subtotal lymphoid irradiation.
However, approximately two thirds of women with early-stage HD do not require radiation of the axillae, and additional protection to the upper and medial aspects of the breast can now be provided by further reducing field size using careful computed tomography–based planning that usually allows for smaller mediastinal volumes, particularly after chemotherapy. We can now avoid irradiating the breast in most women and substantially reduce exposure of the heart and lungs. The large fields of the past limited the radiation technique to simple opposed anterior and posterior fields. The conversion to smaller and better-defined radiation volumes allows use of more conformal RT based on better imaging, computed planning programs, and when indicated, advanced tools such as intensity modulated radiotherapy. Modern breakthroughs in radiotherapy technology that have been implemented recently in HL have already shown better sparing of the heart and coronary arteries. They provide increased accuracy, avoid irradiating normal organs, and thus improve the therapeutic ratio.

Earlier studies clearly indicate that the risk of secondary solid tumor induction is radiation dose–related; these studies were carefully analyzed for secondary breast and lung cancers and for other tumors. Although displaying the full magnitude of risk tapering by current reduction of radiation field and dose will take more years of careful follow-up, recent data suggest that this is likely. In a recent Duke University study, 2 groups of patients with early-stage HL were treated with different radiation approaches over the same period. One group received radiotherapy alone, given to extended fields with a median dose of 38 Gy. The second group received chemotherapy followed by low-dose IFRT (median of 25 Gy). Although 12 patients in the first group developed second tumors, with 8 fatalities, no second tumors were detected in the second group. The median follow-up times were 11.7 and 8.1 years, respectively. Similar observations with an even longer follow-up time were made by the Yale group. In a randomized study from Milan, ABVD times 4 followed by subtotal lymphoid irradiation was compared with ABVD times 4 followed by IFRT only. Three patients developed second cancers after subtotal lymphoid irradiation, but no second cancers were detected after IFRT. Median follow-up was 10 years.

Chemotherapy Alone for Favorable Early-Stage HL

The recent NCCN guidelines for favorable early-stage HL lists chemotherapy alone as an option for highly selected patients for whom RT is contraindicated. Because some editorials have advocated the option of chemotherapy alone and some practices have already adopted this approach, it is worthwhile to examine the results of recent trials that address this controversial issue.

Several groups tested the hypothesis that chemotherapy alone could provide equivalent disease control to that achieved with combined modality therapy. The studies from Europe, Asia, and North America targeted mostly patients with early-stage favorable and unfavorable disease and were conducted in adults, children and adolescents, or both. The randomization was upfront in some and limited to patients who experienced a clear complete response with chemotherapy in others. The results are summarized in Table 4.

All studies (with the exception of a small study from Memorial Sloan-Kettering Cancer Center) showed a significantly superior event-free survival or freedom from progression when radiation was added to chemotherapy. Only in the study with the longest follow-up time (8 years) did superior initial disease control translate into a significantly better overall survival. In HL, most randomized studies have not been able to document a significant survival advantage for the superior disease control arm, even when one treatment was clearly more effective (e.g., MOPP vs. ABVD vs. MOPP/ABVD or the stem cell salvage trials) and thus accepted as the standard treatment. Many reasons for this phenomenon exist: good salvage for treatment failure; long survival with disease; and possibly more toxic events in the more effective arm. Longer and more complete follow-up than most study groups currently provide is needed to make conclusions based on survival in HL. Without adequate follow-up, dismissing significantly superior disease control because no significant survival advantage is seen may be misleading. Furthermore, although salvage with high-dose therapy is often effective, it is associated with a very high risk of acute and late toxicity and is physically and psychologically difficult for the patient.
Lymphocyte-Predominant Hodgkin Lymphoma

The treatment of lymphocyte-predominant HL (LPHL) is different than the treatment of classical HL. Modern immunostaining should allow an explicit diagnosis of this less common but distinct subtype. Most (> 75%) patients present with a favorable early-stage disease, commonly limited to one peripheral site (neck, axilla, or groin). Involvement of the mediastinum is extremely rare. The treatment recommendations for LPHL differ markedly from those for classic HL. The NCCN guidelines, the GHSG, and the EORTC currently recommend IFRT alone as the treatment of choice for early-stage LPHL. Physicians should note that that even if regional radiation fields are selected, the uninvolved mediastinum should not be irradiated. This allows physicians to avoid the site most prone to radiation-related short- and long-term side effects. Although no study to date has compared extended-field RT (commonly used in the past) with IFRT, retrospective data suggest that IFRT is adequate. Chemotherapy is rarely indicated in early-stage LPHL. Anti-CD20 treatment with rituximab may have a role in advanced or relapsed disease, but it is not indicated in early-stage LPHL. Recently, investigators suggested that patients who underwent a full excisional biopsy of the involved lymph node could undergo observation with no further therapy. This interesting approach requires more follow-up to determine its safety, because more local relapses have been seen after excisional biopsy alone than when biopsy was followed with radiation or chemotherapy.

Summary and Future Directions

Treatment results of favorable early-stage HL with combined modality therapy that includes short course ABVD and reduced-dose IFRT (freedom from treatment failure > 90%) set a high standard to challenge. At the same time, the trials that attempted to omit radiotherapy in favorable disease after complete response was achieved with chemotherapy thus far have shown inferior outcomes. Thus, chemotherapy alone should be given only in the context of a clinical trial or to highly selected individuals with contraindications to combined modality therapy. Functional imaging may allow the identification of patients who experience complete response for whom treatment could possibly be further reduced. However, this approach should be assessed carefully because a recent study from Vanderbilt University showed that 24% of patients (HL and non-Hodgkin’s lymphoma) who obtained a positron emission tomography–negative complete
response after chemotherapy alone experienced relapse at the original sites. The drive for further treatment reduction should not lead to compromised disease control, even when improved salvage options are available. The consequences of relapse remain serious and further enhance the risk of long-term toxicity.

The current approach that reduces both chemotherapy and RT is likely to curtail toxicity substantially. However, 10- and 20-year follow-up data from recent and current studies will need to be collected and analyzed to confirm the results. At the same time, the approach of intensifying or prolonging chemotherapy to eliminate RT in early-stage HL may backfire by exposing patients to chemotherapy-related side effects. Thus, this approach should be considered with much caution.

References