

REVIEW ARTICLE

CURRENT CONCEPTS

Early-Stage Hodgkin's Lymphoma

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FOR MORE THAN A CENTURY AFTER THOMAS HODGKIN FIRST DESCRIBED the disease that now bears his name, the illness was considered incurable. The discovery of radiotherapy as a treatment technique in the early 20th century led to long-term survival free of recurrent lymphoma in some patients with what we would today call early-stage disease.¹⁻³ The concept of staging Hodgkin's lymphoma was solidified at the Ann Arbor Conference in 1971.⁴ Whereas staging laparotomy was once used to define the extent of the disease in patients with early-stage (i.e., stage I or stage II) Hodgkin's lymphoma, currently available imaging techniques and effective systemic therapies have relegated staging laparotomy to a historical footnote.

Studies of the use of mechlorethamine in the 1940s showed that the rate of response to systemically administered anticancer agents in patients with Hodgkin's lymphoma could be high. After the discovery of several other active agents, investigators at the National Cancer Institute combined four of these drugs for use in the initial treatment of patients with disseminated Hodgkin's lymphoma. The resulting report, released in 1970, made it clear that a cure was possible with chemotherapy alone.⁵ Studies of chemotherapy administered as adjuvant treatment after radiotherapy in patients with high-risk, early-stage disease showed a reduction in the risk of relapse⁶; subsequent studies investigated the effects of the initial use of chemotherapy followed by the application of adjuvant radiotherapy to smaller treatment fields.^{7,8}

Investigators in Uganda who were studying the treatment of Burkitt's lymphoma in children and young adults in the 1970s^{9,10} also saw patients with early-stage Hodgkin's lymphoma, but radiotherapy was not available to them. These studies showed that chemotherapy alone could yield a high rate of complete and durable remission in patients with early-stage Hodgkin's lymphoma. Increasing recognition of the long-term, toxic effects of treatment and the very high survival rates among patients with early-stage Hodgkin's lymphoma who received the most recent therapy regimens led to a series of studies in which efforts were made to reduce or eliminate the radiotherapy used in these regimens and to minimize the number of chemotherapy cycles. In this issue of the *Journal*, Engert et al. report on a large study in Germany that investigated the efficacy of reduced cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) with or without reductions in the radiation dose.¹¹

Patients with early-stage Hodgkin's lymphoma are not a homogeneous group, and treatment toxicities are changing as chemotherapy regimens and radiotherapy techniques change. However, some of the most serious toxic effects of treatment tend to occur late — after most deaths attributable to the lymphoma have occurred. These issues complicate the process of determining what treatment to recommend for a patient with early-stage Hodgkin's lymphoma.

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 VARIATIONS IN RISK

All cases of early-stage Hodgkin's lymphoma are not the same. The variation in prognosis is wide among patients who have stage I or stage II disease, as defined at the Ann Arbor Conference (with stage I indicating the involvement of one lymph-node-bearing site, with or without extension to an adjacent extranodal site, and stage II the involvement of two or more nodal sites on one side of the diaphragm, with or without extension to an adjacent extranodal site). Many factors can worsen the prognosis for these patients, including the presence of systemic symptoms (i.e., fevers, drenching night sweats, or significant weight loss), a very high erythrocyte sedimentation rate, an increase in the number of nodal sites involved, older age, and a large mediastinal mass. For this reason, in most clinical trials patients with early-stage Hodgkin's lymphoma are stratified on the basis of various combinations of these or other risk factors. Not everyone uses the same definitions; Table 1 shows how the risk of treatment failure is calculated with the use of the International Prognostic Score and how it has been defined in selected clinical trials.

 IMPORTANCE OF TREATMENT-RELATED COMPLICATIONS

For a patient with Hodgkin's lymphoma in any stage, the primary goal of therapy is cure. In recent studies (Table 2), the 5-year survival rate for patients with early-stage Hodgkin's lymphoma has consistently been 90% or higher. Particularly among patients with a good prognosis in studies with a very long period of follow-up, the number who die from treatment-related complications exceeds the number who die from lymphoma. (The risks of recurrent lymphoma, second malignant conditions, and cardiovascular events in relation to the time after therapy are shown in Fig. 1.)

The frequency of late complications is dependent on the particular treatment used. The late treatment-related complications of radiotherapy have been studied extensively. In addition to complications that can affect quality of life but are unlikely to be lethal (e.g., hypothyroidism, dry mouth, and dental caries), there is an increased incidence of several potentially lethal events after radiotherapy. Second malignant conditions occur at an average rate of approximately 1% per year for at least 30 years after treatment.²³ The risk is

particularly high among women younger than 30 years of age who receive thoracic radiotherapy; breast cancer develops in 30 to 40% of these patients in the 25 years after treatment.²⁴ It seems intuitively obvious that reducing the radiation dose and field size would be likely to decrease the rate at which second malignant conditions occur, and case-control studies suggest this might be true.^{25,26} However, the relatively brief follow-up period in most studies and the lack of certainty regarding the relationship between radiation dose and cancer incidence make it impossible to draw definite conclusions. Radiation-related cardiac disease can be manifested as coronary artery disease, myocardial injury, valvular disease, or pericardial fibrosis. The risk of death from myocardial infarction is increased after thoracic radiotherapy, and that increased risk persists for more than 25 years.²⁷ Diastolic dysfunction after radiotherapy seems to be a marker for an increased risk of cardiac events.^{28,29} The incidence of stroke also rises in patients who receive radiotherapy in the neck and mediastinum.³⁰

The risk of late complications after chemotherapy appears to be dependent on the type of drugs prescribed. For example, patients prescribed regimens that include mechlorethamine have a significantly increased risk of myelodysplasia, acute myeloid leukemia, and lung cancer. In trials in which patients received chlorambucil rather than mechlorethamine, however, the risk of lung cancer was not elevated.³¹ Regimens that include alkylating agents or etoposide are associated with an elevated risk of myelodysplasia and acute myeloid leukemia, and the incidence of these conditions for patients receiving mechlorethamine, vincristine, procarbazine, and prednisone (the MOPP regimen) is 2 to 5%.³² Doxorubicin, which is included in the commonly used ABVD regimen, is associated with an increased risk of congestive heart failure,³³ and the combination of radiotherapy and treatment with an anthracycline has an additive effect on the frequency of cardiovascular events.³³ Bleomycin, which is also included in the ABVD regimen, is associated with pulmonary fibrosis. The acute pulmonary injury associated with bleomycin can be fatal; frequent monitoring of diffusing capacity is necessary to prevent its occurrence.

The effect of treatment for Hodgkin's lymphoma on quality of life was studied prospectively in an international randomized trial in which pa-

Table 1. Variations in Definitions of Risk among Patients with Early-Stage Hodgkin's Lymphoma.*

Study	Risk
German Hodgkin Study Group ¹¹	High: Mediastinal mass > one third of transthoracic diameter, extranodal disease, ≥ 3 nodal areas, ESR >50 in asymptomatic patients or >30 in symptomatic patients Low: No large mediastinal mass or extra nodal disease, <3 nodal areas, low ESR
National Cancer Institute of Canada and Eastern Cooperative Oncology Group ¹⁶	Very high: Any mass >10 cm, mediastinal mass \geq one third of transthoracic diameter, intraabdominal disease High: Age, ≥ 40 yr; ESR, ≥ 50 mm per hr; mixed-cellularity or lymphocyte-depletion subtype; ≥ 4 sites of disease Low: Age, <40 yr; ESR, <50; no mixed cellularity or lymphocyte depletion; <4 sites of disease Very low: Single node <3 cm in upper neck or epitrochlear region, with lymphocyte-predominant or nodular sclerosis subtype and ESR <50 mm per hr
European Organisation for Research on the Treatment of Cancer ^{12†}	High: ≥ 9 points Low: 1–5 points Very low: 0 points
National Tumor Institute, Milan ⁷	High: Nodal mass >10 cm, mediastinal mass > one third of transthoracic diameter, pulmonary hilus involvement, contiguous extranodal extension, stage 1 with systemic symptoms Low: No large nodal or mediastinal mass, no systemic symptoms
Dana–Farber Cancer Institute ¹³	High: Any mass >10 cm or mediastinal mass > one third of transthoracic diameter Low: No nodal or mediastinal mass
International Prognostic Score ^{14‡}	High: ≥ 3 points Low: ≤ 2 points

* Early-stage Hodgkin's lymphoma is defined according to the standards confirmed at the Ann Arbor Conference in 1971.⁴ ESR denotes erythrocyte sedimentation rate.

† The European Organisation for Research on the Treatment of Cancer defines level of risk on the basis of the cumulative score in the following categories: age (less than 40 years, 0 points; 40–49 years, 1 point, 50 years or more, 9 points); sex (female, 0 points; male, 1 point); number of disease sites (none or one site, 0 points; 2 or 3 sites, 1 point; 4 or 5 sites, 9 points); mediastinal mass (none or one measuring less than one third of transthoracic diameter, 0 points; any larger mass, 9 points); systemic symptoms (none and ESR less than 50 mm per hr, 0 points; none and ESR 50 mm or more per hr, 0 points; present and ESR less than 30 mm per hr, 1 point; present and ESR 30 mm or more per hr, 9 points); histologic subtype (lymphocyte-predominant or nodular sclerosis, 0 points; mixed cellularity or lymphocyte depletion, 1 point).

‡ The International Prognostic Score defines level of risk on the basis of the cumulative score in the following categories, with 1 point assigned for each criterion that is met: male sex; age, 45 years or more; hemoglobin level, less than 10.5 g per deciliter; albumin level, less than 4 g per deciliter; white-cell count, greater than 15,000 per mm^3 ; lymphocyte count, less than 600 per mm^3 or less than 8% of white-cell count.

tients received radiotherapy with or without chemotherapy. Although treatment in general did have a significant adverse effect on quality of life, there was no significant association between quality of life and treatment type.³⁴

TREATMENT STRATEGIES

Several observations can be made concerning the association between treatment type or strategy and the risk of treatment failure on the basis of findings from several trials (Table 2). (These studies used different definitions of low and high risk, which may have affected the results.) First, there was a very high survival rate — 90% or

higher at 5 years — in all the studies except one, in which patients received a chemotherapy regimen that was apparently less effective than the treatments provided in the other trials.¹² Patients who received a single type of treatment (particularly radiotherapy) rather than a combined treatment approach seem to have had a higher rate of relapse. However, the availability of effective salvage therapy led to equivalent survival rates, with one exception: in the study with the longest follow-up period, patients treated with radiotherapy had a lower 25-year survival rate than those treated with MOPP.²¹ In both low-risk and high-risk groups in all the trials, the number of deaths from Hodgkin's lymphoma was lower than the

Table 2. Selected Series of Patients Treated for Early-Stage Hodgkin's Lymphoma According to Level of Risk.

Study	Treatment	Dose	No. of Patients	Median Follow-up yr	Freedom from Treatment Failure or Progression-free Survival (%)	Overall Survival Rate (%)		Cause of Death
						Hodgkin's Lymphoma	Other	
Low risk								
Canellos et al. ¹³	4-6xABVD	Standard	71	5.0	92 at 5 yr	100 at 5 yr	0	0
Rueda Dominguez et al. ¹⁵	6xABVD	Standard	80	6.5	88 at 7 yr	97 at 7 yr	NA	NA
Meyer et al. ¹⁶	4-6xABVD	Standard	59	4.2	88 at 5 yr	97 at 5 yr	1	1
Fermé et al. ¹⁷	SNRT	35 Gy	64	4.2	87 at 5 yr	100 at 5 yr	0	0
	3xMOPP-ABV + IFRT	Standard + 36 Gy	270	7.6	99 at 5 yr	99 at 5 yr	1	3
	SNRT	36 Gy	270	7.6	78 at 5 yr	94 at 5 yr	7	12
Noordijk et al. ¹²	EFRT	36-40 Gy	165	9.0	78 at 10 yr	92 at 10 yr	5	6
	EBVD + IFRT	36-40 Gy†	163	9.0	88 at 10 yr	92 at 10 yr	3	7
Engert et al. ¹¹	4xABVD + IFRT	Standard + 30 Gy	298	7.5	93 at 5 yr	97 at 5 yr	3	12
	4xABVD + IFRT	Standard + 20 Gy	299	7.5	93 at 5 yr	97 at 5 yr	2	11
	2xABVD + IFRT	Standard + 30 Gy	295	7.5	91 at 5 yr	97 at 5 yr	3	13
	2xABVD + IFRT	Standard + 20 cGy	299	7.5	91 at 5 yr	97 at 5 yr	2	11
High risk								
Meyer et al. ¹⁶	4-6xABVD	Standard	137	4.2	88 at 5 yr	95 at 5 yr	1	4
	2xABVD + SNRT	Standard + 35 Gy	139	4.2	95 at 5 yr	92 at 5 yr	2	7
Pavone et al. ¹⁸	4xVE + IFRT	36 Gy‡	89	5.2	78 at 5 yr	92 at 5 yr	NA	NA
	4xABVD + IFRT	Standard + 36 Gy	92	5.2	95 at 5 yr	95 at 5 yr	NA	NA
Noordijk et al. ¹²	6xMOPP or 6 x ABV + IFRT	Standard + 36-40 Gy	193	9.0	88 at 10 yr	87 at 10 yr	10	14
	6xEBVP + IFRT	36-40 Gy†	193	9.0	68 at 10 yr	79 at 10 yr	23	18
Engert et al. ¹⁹	Alternating cycles of 2xCOPP + 2xABVD + IFRT	Standard for both + 30 Gy + 10 Gy to bulky site	532	4.5	84 at 5 yr	92 at 5 yr	12	22
	Alternating cycles of 2xCOPP + 2xABVD + EFRT	Standard for both + 30 Gy + 10 Gy to bulky site	532	4.5	86 at 5 yr	91 at 5 yr	12	31

Borchmann et al. ²⁰	4×ABVD + IFRT	Standard + 30 Gy	356	7.5	85 at 5 yr	94 at 5 yr	7	19
	4×ABVD + IFRT	Standard + 20 Gy	347	11.0	81 at 5 yr	94 at 5 yr	10	20
	4×BEACOPP + IFRT	Baseline + 30 Gy	341	11.0	87 at 5 yr	95 at 5 yr	10	16
	4×BEACOPP + IFRT	Baseline + 20 Gy	351	11.0	87 at 5 yr	95 at 5 yr	11	12
All risk levels								
Longo et al. ²¹ §	MOPP	Standard	54	25.0	83 at 25 yr	81 at 25 yr	5	5
	XRT	36 Gy	51	25.0	59 at 25 yr	63 at 25 yr	10	8
Straus et al. ²² ¶	6×ABVD	Standard	76	5.6	81 at 5 yr	90 at 5 yr	4	3
	6×ABVD + IFRT or EFRT	Standard + 36 Gy for both	76	5.6	86 at 5 yr	97 at 5 yr	1	1
Bonadonna et al. ⁷	4×ABVD + IFRT	Standard + 36–40 Gy	70	9.7	94 at 12 yr	94 at 12 yr	2	2
	4×ABVD + SNRT	Standard + 36–40 Gy (involved sites) + 30.6 Gy (uninvolved sites)	66	9.7	93 at 12 yr	96 at 12 yr	1	1

* ABV denotes doxorubicin, bleomycin, and vinblastine; ABVD doxorubicin, bleomycin, vinblastine, and dacarbazine; BEACOPP bleomycin, cyclophosphamide, doxorubicin, etoposide, prednisone, procarbazine, and vincristine; COPP cyclophosphamide, prednisone, procarbazine, and vincristine; EFRT extended-field radiotherapy; EBVD epirubicin, bleomycin, vinblastine, and dacarbazine; EVE epirubicin, vinblastine, and etoposide; IFRT involved-field radiotherapy; MOPP mechlorethamine, vincristine, procarbazine, and prednisone; NA not available; SNRT subtotal nodal radiotherapy; and XRT radiotherapy.

† See Noordijk et al.²² for chemotherapy dose.

‡ See Pavone et al.¹⁸ for chemotherapy dose.

§ This study included patients with stages IIA, IIIA, and nonperipheral IA Hodgkin's lymphoma.

¶ In this study, 13% of patients had stage IIIA Hodgkin's lymphoma.

SPECIAL CONSIDERATIONS

Several clinical situations can complicate the care of patients with early-stage Hodgkin's lymphoma. These include pregnancy, older age, infection with the human immunodeficiency virus (HIV), and nodular lymphocyte-predominant Hodgkin's lymphoma.

PREGNANCY

Given the relatively high frequency of Hodgkin's lymphoma in young adults, it is not surprising that it is one of the more frequent malignant conditions discovered during pregnancy. Efforts to determine the stage of disease in pregnant patients are somewhat restricted by the need to avoid computed tomography and positron-emission tomography (PET), but abdominal ultrasonography can be used to detect subdiaphragmatic disease. In pregnant patients with asymptomatic, early-stage Hodgkin's lymphoma, treatment can sometimes be delayed until after delivery. Although radiotherapy should be avoided during pregnancy, it is relatively safe to treat patients in the second and third trimesters with ABVD. In selected patients the use of vinblastine alone can help control symptoms until delivery, at which point definitive therapy can be pursued. Patients in the first trimester pose a more difficult problem. If treatment is required and the patient does not want a therapeutic abortion, the successful completion of pregnancy without fetal malformation is possible with ABVD or similar regimens.³⁵

OLDER AGE

Patients with Hodgkin's lymphoma who are 45 to 50 years of age or older have a poorer prognosis than younger patients, and treatment is a particular challenge in patients 60 years of age or older. One reason for the relatively poor treatment outcome in some of these patients is their susceptibility to the toxic effects of intensive therapy. For example, one trial showed that elderly patients

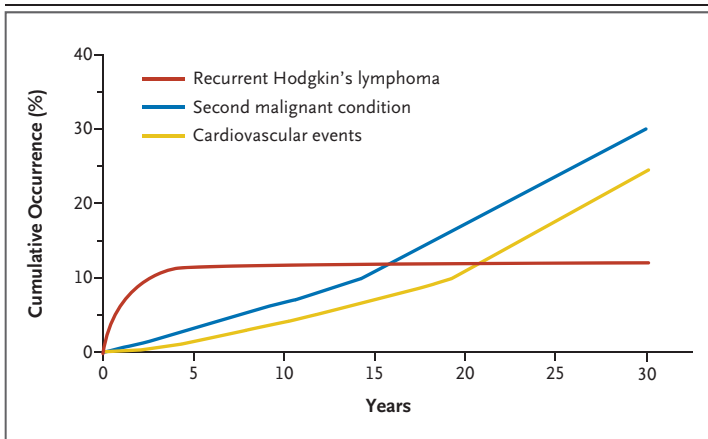


Figure 1. Approximate Cumulative Risk of Recurrent Hodgkin's Lymphoma, Second Malignant Conditions, and Cardiovascular Events among Patients Receiving Both Radiotherapy and Chemotherapy for Early-Stage Hodgkin's Lymphoma.

did significantly less well with extended-field radiotherapy than with involved-field radiotherapy; no such effect was observed in younger patients.³⁶ Acute toxic effects are more likely to develop in elderly patients, and they have a higher relapse rate and a lower overall survival rate.³⁶ Elderly patients are less often included in clinical trials, and many have coexisting conditions that affect their ability to tolerate standard treatments. It has been proposed that Hodgkin's lymphoma in elderly patients is different from the disease in young people.^{37,38} In fact, it has been proposed that in elderly patients Hodgkin's lymphoma should be viewed as a unique, uncommon disease that warrants specific study in clinical trials.³⁹

In general, however, healthy elderly patients can benefit from, and should receive, the treatments that are effective in younger patients. Elderly patients seem to benefit proportionally more than younger patients from the inclusion of doxorubicin in the treatment regimen.⁴⁰

HIV INFECTION

Hodgkin's lymphoma is one of the defining illnesses of the acquired immunodeficiency syndrome (AIDS). Patients with HIV infection in whom Hodgkin's lymphoma develops typically have the mixed-cellularity or lymphocyte-depletion histologic subtype, and they tend to have widespread disease, involvement of extranodal sites, and systemic symptoms. The availability of highly active antiretroviral therapy has dramatically improved

the survival rate among patients with HIV infection who also have Hodgkin's lymphoma.⁴¹ Today, HIV-infected patients with early-stage Hodgkin's lymphoma should receive the same treatment as patients with early-stage disease who are not infected with HIV.

NODULAR LYMPHOCYTE-PREDOMINANT HODGKIN'S LYMPHOMA

At least 95% of patients who receive a diagnosis of Hodgkin's lymphoma have classic Hodgkin's lymphoma, not nodular lymphocyte-predominant Hodgkin's lymphoma.⁴² The latter is a low-grade, monoclonal B-cell, malignant condition that is usually manifested as early-stage disease. Like other low-grade B-cell cancers, nodular lymphocyte-predominant Hodgkin's lymphoma can undergo transformation to diffuse, large B-cell lymphoma.⁴³ In the early stages, nodular lymphocyte-predominant Hodgkin's lymphoma can be managed with watchful waiting, radiotherapy, a combination of radiotherapy and chemotherapy, chemotherapy alone, or treatment with rituximab. Radiotherapy appears to be a particularly important component of treatment for early-stage disease and can induce a durable remission.⁴⁴

TREATMENT SELECTION

The optimal treatment for a patient with early-stage Hodgkin's lymphoma is not clear. An effective chemotherapy regimen (e.g., ABVD) used alone or various combinations of chemotherapy and radiotherapy are associated with high overall survival rates. The facts that adverse treatment-related events that can be fatal continue to occur (and in some cases steadily increase in frequency) 20 to 30 years after treatment and that most recent studies have a median follow-up of less than a decade do not make the choice easy. A study of how oncologists make treatment recommendations for patients with early-stage Hodgkin's lymphoma is enlightening, but the findings are not surprising.⁴⁵ Radiation oncologists were more likely than medical oncologists to recommend the use of radiotherapy. Oncologists who had been in practice for a long time and had seen late complications of treatment were less likely than radiotherapists to recommend radiotherapy. Physicians identified as "experts" in the treatment of Hodgkin's lymphoma were more likely to select chemotherapy

alone for young women and a combined-approach treatment regimen for older patients. It appears that the actual treatment recommendation is greatly affected by a physician's comfort with a particular treatment and by cumulative clinical experience — not just by data published in the literature.

More than 90% of patients with early-stage Hodgkin's lymphoma survive for more than 5 years after treatment with current therapies (Table 2). The overall survival rate may be slightly lower among those with a poor prognosis — and the relapse rate slightly higher — but the treatment regimens for patients at increased risk for death tend to be more intensive. Patients with a higher risk of death are more likely to receive a combined-approach treatment regimen, but in one study in which ABVD alone was used, the 5-year survival rate was 95%.¹⁶ When chemotherapy is used alone or in combination with radiotherapy, ABVD appears to be the best option. Since the longest median follow-up period in all but one of the studies listed in Table 2 was less than 10 years, and since most late treatment-related deaths would not yet have occurred, it is possible that an advantage of ABVD alone will emerge with longer follow-up. However, even with a short follow-up period, the number of deaths from causes other than Hodgkin's lymphoma is considerably higher than the number of deaths from the lymphoma itself. For the low-risk patients in the studies listed in Table 2, 27 were reported to have died from lymphoma and 76 from other causes.

In the United States, oncologists often refer to the National Comprehensive Cancer Network guidelines when making treatment decisions.⁴⁶ These guidelines suggest that for patients who have asymptomatic, nonbulky, early-stage Hodgkin's lymphoma with an erythrocyte sedimentation rate of less than 50 mm per hour, fewer than four nodal sites, and not more than one site of extranodal extension, physicians should prescribe ABVD alone or a combined approach consisting of either ABVD or the Stanford V chemotherapy regimen (mechlorethamine, doxorubicin, etoposide, vincristine, vinblastine, bleomycin, and prednisone), plus involved-field radiotherapy. The initial treatment for patients at greater risk for treatment failure can also include either ABVD or Stanford V combination chemotherapy, but patients presenting with bulky disease should all

receive involved-field radiotherapy. Patients at increased risk for treatment failure but without bulky disease can be treated with ABVD alone, but they should receive a minimum of six cycles of treatment rather than four, which is the minimum for patients without risk factors. In each subgroup, an early PET scan drives subsequent treatment decisions, with patients who have a complete response after two cycles of ABVD or 12 weeks of the Stanford V regimen receiving the least treatment.

The treatment plans for subgroups of patients with Hodgkin's lymphoma in a number of ongoing international clinical trials are presented in Table 3. A common theme is the attempt to use PET scanning to individualize therapy and minimize the amount of treatment required for cure. It appears that positive PET findings at the end of treatment is a significant adverse risk factor. In one series of 73 patients, 13 had positive PET scans at the completion of ABVD as the first part of a combined radiotherapy–chemotherapy treatment regimen. The 2-year, failure-free survival rate for the patients with positive scans was 69%, as compared with 95% for those with negative scans.⁴⁷ However, among 46 patients who underwent interim PET scanning (after completing two or three cycles of chemotherapy), 20 had positive interim scans, but 13 of these 20 patients had negative scans at the completion of chemotherapy. The 2-year, failure-free survival rate for patients with positive scans during chemotherapy and negative scans after chemotherapy was 92%, as compared with 96% for patients who had negative scans both during and after chemotherapy. In a series of patients treated with ABVD chemotherapy alone, those with a positive PET scan after two or three cycles of a planned six cycles of treatment had a progression-free survival rate of 71%, as compared with 90% for patients who had a negative interim PET scan.⁴⁸ However, if the patients with a positive interim PET scan had a negative PET scan after completing six cycles of treatment with ABVD, the adverse effect of the positive interim PET scan disappeared. Thus, a positive interim PET scan did not necessarily predict a poor treatment outcome, and for patients with a positive interim scan but a negative scan after completion of treatment, a relapse was no more likely than for patients with negative interim and final scans. The question of whether altering therapy on the basis of a positive but

Table 3. New Trials of Treatments for Early-Stage Hodgkin's Lymphoma.*

Study and Risk Group	Treatment
Cancer and Leukemia Group B	
Low risk, nonbulky disease	2×ABVD, then PET — if results negative, 2×ABVD; if positive, 2× escalated BEACOPP + 30 Gy IFRT
High risk, bulky disease	2×ABVD, then PET — if results negative, 4×ABVD; if positive, 4× escalated BEACOPP + 30 Gy IFRT
German Hodgkin Study Group	
Low risk	
Group 1	2×ABVD, then PET, followed by 20 Gy IFRT regardless of PET results
Group 2	2×ABVD, then PET — if results negative, no further therapy; if positive, 20 Gy IFRT
High risk	
Group 1	2× escalated BEACOPP, followed by 2×ABVD, then PET, followed by 30 Gy IFRT regardless of PET results
Group 2	2× escalated BEACOPP, followed by 2×ABVD, then PET — if negative, no further therapy; if positive, 30 Gy IFRT
European Organisation for Research on the Treatment of Cancer and Group for the Study of Adult Lymphoma	
Low risk	
Group 1	2×ABVD, then PET, followed by 1×ABVD + 30 Gy IFRT, regardless of PET results
Group 2	2×ABVD, then PET — if negative, 2×ABVD; if positive, 2× escalated BEACOPP + 30 Gy IFRT
High risk	
Group 1	2×ABVD, then PET, followed by 4×ABVD + 30 Gy IFRT, regardless of PET results
Group 2	2×ABVD, then PET — if negative, 4×ABVD; if positive, 2× escalated BEACOPP + 30 Gy IFRT
United Kingdom NCRI Lymphoma Study Group	3×ABVD, then PET — if negative, patients undergo randomization to 30 Gy IFRT or no further therapy; if positive, 3×ABVD + 30 Gy IFRT

* ClinicalTrials.gov numbers for these studies are as follows: Cancer and Leukemia Group B, low risk, nonbulky disease — NCT01132807, and high risk, bulky disease — NCT01118026; German Hodgkin Study Group, low risk — NCT00736320, and high risk — not yet available; EORTC and GELA, low risk and high risk — NCT00433433; and the United Kingdom NCRI Lymphoma Study Group — NCT00943423. ABV denotes doxorubicin, bleomycin, and vinblastine; ABVD doxorubicin, bleomycin, vinblastine, and dacarbazine; BEACOPP bleomycin, cyclophosphamide, doxorubicin, etoposide, prednisone, procarbazine, and vincristine; CT computed tomography; IFRT involved-field radiotherapy; NCRI National Cancer Research Institute; and PET positron-emission tomography.

improved interim PET scan will ultimately benefit patients who do not go on to have a complete remission is being addressed in a number of clinical trials; such an approach should not be used as standard therapy at this time.

CONCLUSIONS

The treatment of patients with early-stage Hodgkin's lymphoma is one of the success stories of modern oncology. Today, more than 90% of such

patients will survive for at least 5 years after diagnosis, regardless of their presenting characteristics, and treatment results have been so good that clinical trials are now focusing on minimizing the intensity of treatment to avoid late, potentially fatal toxic effects. It appears that the use of a standard chemotherapy regimen alone and use of fewer cycles of chemotherapy plus involved-field radiotherapy yield equivalent rates of survival among patients with low-risk, early-stage Hodgkin's lymphoma, and this may also be the

case for patients with high-risk, early-stage disease. Given the trend toward less intensive treatment, it will be important to watch for a point at which treatment becomes inadequate and the number of deaths from Hodgkin's lymphoma will begin to increase. For example, in the German Hodgkin Study Group trial,²⁰ treatment with ABVD and 20 Gy of involved-field radiotherapy in patients with high-risk disease was less effective than treatment with either the same amount of ABVD and 30 Gy of involved-field radiotherapy or a more intensive chemotherapy regimen (i.e., bleomycin, cyclophosphamide, doxorubicin, etoposide, prednisone, procarbazine, and vincristine [BEACOPP]) and 20 Gy of radiotherapy. However, the higher rate of long-term complications with regimens that include radiotherapy as compared

with chemotherapy alone may ultimately result in a lower rate of long-term survival, particularly among low-risk patients.²⁶ These issues are being addressed in several ongoing clinical trials comparing the efficacy of a brief course of ABVD alone with a regimen consisting of both ABVD and radiotherapy (Table 3).

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Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

REFERENCES

- Easson EC, Russell MH. Cure of Hodgkin's disease. *Br Med J* 1963;1:1704-7.
- Peters MV, Middlemiss KC. A study of Hodgkin's disease treated by irradiation. *Am J Roentgenol Radium Ther Nucl Med* 1958;79:114-21.
- Kaplan HS. The radical radiotherapy of regionally localized Hodgkin's disease. *Radiology* 1962;78:553-61.
- Carbone PP, Kaplan HS, Musshoff K, Smithers DW, Tubiana M. Report of the Committee on Hodgkin's Disease Staging Classification. *Cancer Res* 1971;31:1860-1.
- Devita VT Jr, Serpik AA, Carbone PP. Combination chemotherapy in the treatment of advanced Hodgkin's disease. *Ann Intern Med* 1970;73:881-95.
- Rosenberg SA. Development of the concept of Hodgkin's disease as a curable illness: the American experience. In: Mauch PM, Armitage JO, Diehl V, Hoppe RT, Weiss LM, eds. *Hodgkin's disease*. Philadelphia: Lippincott Williams & Wilkins, 1999:47-57.
- Bonadonna G, Bonfante V, Viviani S, Di Russo A, Villani F, Valagussa P. ABVD plus subtotal nodal versus involved-field radiotherapy in early-stage Hodgkin's disease: long-term results. *J Clin Oncol* 2004;22:2835-41.
- Bartlett NL, Rosenberg SA, Hoppe RT, Hancock SL, Horning SJ. Brief chemotherapy, Stanford V, and adjuvant radiotherapy for bulky or advanced-stage Hodgkin's disease: a preliminary report. *J Clin Oncol* 1995;13:1080-8.
- Ziegler JL, Fass L, Bluming AZ, Magrath IT, Templeton AC. Chemotherapy of childhood Hodgkin's disease in Uganda. *Lancet* 1972;2:679-82.
- Olweny CL, Katongole-Mbidde E, Kire C, Lwanga SK, Magrath I, Ziegler JL. Childhood Hodgkin's disease in Uganda: a ten year experience. *Cancer* 1978;42:787-92.
- Engert A, Plütschow A, Eich HT, et al. Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. *N Engl J Med* 2010;363:32-44.
- Noordijk EM, Carde P, Dupouy N, et al. Combined-modality therapy for clinical stage I or II Hodgkin's lymphoma: long-term results of the European Organisation for Research and Treatment of Cancer H7 randomized controlled trials. *J Clin Oncol* 2006;24:3128-35.
- Canellos GP, Abramson JS, Fisher DC, LaCasce AS. Treatment of favorable, limited-stage Hodgkin's lymphoma with chemotherapy without consolidation by radiation therapy. *J Clin Oncol* 2010;28:1611-5.
- Hasenclever D, Diehl V. A prognostic score for advanced Hodgkin's disease. *N Engl J Med* 1998;339:1506-14.
- Rueda Domínguez A, Márquez A, Gumá J, et al. Treatment of stage I and II Hodgkin's lymphoma with ABVD chemotherapy: results after 7 years of a prospective study. *Ann Oncol* 2004;15:1798-804.
- Meyer RM, Gospodarowicz MK, Connors JM, et al. Randomized comparison of ABVD chemotherapy with a strategy that includes radiation therapy in patients with limited-stage Hodgkin's lymphoma. *J Clin Oncol* 2005;23:4634-42.
- Fermé C, Eghbali H, Meerwaldt JH, et al. Chemotherapy plus involved-field radiation in early-stage Hodgkin's disease. *N Engl J Med* 2007;357:1916-27.
- Pavone V, Ricardi U, Luminari S, et al. ABVD plus radiotherapy versus EVE plus radiotherapy in unfavorable stage IA and IIA Hodgkin's lymphoma: results from an Intergruppo Italiano Linfomi randomized study. *Ann Oncol* 2008;19:763-8.
- Engert A, Schiller P, Josting A, et al. Involved-field radiotherapy is equally effective and less toxic compared with extended-field radiotherapy after four cycles of chemotherapy in patients with early-stage unfavorable Hodgkin's lymphoma: results of the HD8 trial of the German Hodgkin's Lymphoma Study Group. *J Clin Oncol* 2003;21:3601-8.
- Borchmann P, Diehl V, Goergen H, et al. Combined modality treatment with intensified chemotherapy and dose-reduced involved field radiotherapy in patients with early unfavourable Hodgkin lymphoma (HL): final analysis of the German Hodgkin Study Group (GHSG) HD11 Trial. *Blood* 2009;114:299. abstract.
- Longo DL, Glatstein E, Duffey PL. A prospective trial of radiation alone vs combination chemotherapy alone for early-stage Hodgkin's disease: implications of 25-year follow-up to current combined modality therapy. *Blood* 2006;108:33a. abstract.
- Straus DJ, Portlock CS, Qin J, et al. Results of a prospective randomized clinical trial of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) followed by radiation therapy (RT) versus ABVD alone for stages I, II, and IIIA nonbulky Hodgkin disease. *Blood* 2004;104:3483-9.
- Franklin J, Plütschow A, Paus M, et al. Second malignancy risk associated with treatment of Hodgkin's lymphoma: meta-analysis of the randomised trials. *Ann Oncol* 2006;17:1749-60.
- Travis LB, Hill D, Dores GM, et al. Cumulative absolute breast cancer risk for young women treated for Hodgkin lymphoma. *J Natl Cancer Inst* 2005;97:1428-37.
- Travis LB, Gospodarowicz M, Curtis RE, et al. Lung cancer following chemotherapy and radiotherapy for Hodgkin's

- disease. *J Natl Cancer Inst* 2002;94:182-92.
26. van Leeuwen FE, Klokman WJ, Stovall M, et al. Roles of radiation dose, chemotherapy, and hormonal factors in breast cancer following Hodgkin's disease. *J Natl Cancer Inst* 2003;95:971-80.
27. Swerdlow AJ, Higgins CD, Smith P, et al. Myocardial infarction mortality risk after treatment for Hodgkin disease: a collaborative British cohort study. *J Natl Cancer Inst* 2007;99:206-14.
28. Adams MJ, Lipsitz SR, Colan SD, et al. Cardiovascular status in long-term survivors of Hodgkin's disease treated with chest radiotherapy. *J Clin Oncol* 2004;22:3139-48.
29. Heidenreich PA, Hancock SL, Vagelos RH, Lee BK, Schnittger I. Diastolic dysfunction after mediastinal irradiation. *Am Heart J* 2005;150:977-82.
30. De Bruin ML, Dorresteijn LD, van't Veer MB, et al. Increased risk of stroke and transient ischemic attack in 5-year survivors of Hodgkin lymphoma. *J Natl Cancer Inst* 2009;101:928-37.
31. Swerdlow AJ, Schoemaker MJ, Allerton R, et al. Lung cancer after Hodgkin's disease: a nested case-control study of the relation to treatment. *J Clin Oncol* 2001;19:1610-8.
32. Blayney DW, Longo DL, Young RC, et al. Decreasing risk of leukemia with prolonged follow-up after chemotherapy and radiotherapy for Hodgkin's disease. *N Engl J Med* 1987;316:710-4.
33. Aleman BM, van den Belt-Dusebout AW, De Bruin ML, et al. Late cardiotoxicity after treatment for Hodgkin lymphoma. *Blood* 2007;109:1878-86.
34. Heutte N, Flechtner HH, Mounier N, et al. Quality of life after successful treatment of early-stage Hodgkin's lymphoma: 10-year follow-up of the EORTC-GELA H8 randomised controlled trial. *Lancet Oncol* 2009;10:1160-70.
35. Rizack T, Mega A, Legare R, Castillo J. Management of hematological malignancies during pregnancy. *Am J Hematol* 2009;84:830-41.
36. MacMahon B. Epidemiology of Hodgkin's disease. *Cancer Res* 1966;26:1189-201.
37. *Idem*. Epidemiological considerations in staging of Hodgkin's disease. *Cancer Res* 1971;31:1854-7.
38. Klimm B, Eich HT, Haverkamp H, et al. Poorer outcome of elderly patients treated with extended-field radiotherapy compared with involved-field radiotherapy after chemotherapy for Hodgkin's lymphoma: an analysis from the German Hodgkin Study Group. *Ann Oncol* 2007;18:357-63.
39. Weekes CD, Vose JM, Lynch JC, et al. Hodgkin's disease in the elderly: improved treatment outcome with a doxorubicin-containing regimen. *J Clin Oncol* 2002;20:1087-93.
40. Evens AM, Sweetenham JW, Horning SJ. Hodgkin lymphoma in older patients: an uncommon disease in need of study. *Oncology (Williston Park)* 2008;22:1369-79.
41. Hentrich M, Maretta L, Chow KU, et al. Highly active antiretroviral therapy (HAART) improves survival in HIV-associated Hodgkin's disease: results of a multicenter study. *Ann Oncol* 2006;17:914-9.
42. Swerdlow SH, Campo E, Harris NL, et al., eds. WHO classification of tumours of haematopoietic and lymphoid tissues. 4th ed. Lyon, France: International Agency for Research on Cancer, 2008.
43. Al-Mansour M, Connors JM, Gascoyne RD, Skinnider B, Savage KJ. Transformation to aggressive lymphoma in nodular lymphocyte-predominant Hodgkin's lymphoma. *J Clin Oncol* 2010;28:793-9.
44. Chen RC, Chin MS, Ng AK, et al. Early-stage, lymphocyte-predominant Hodgkin's lymphoma: patient outcomes from a large, single-institution series with long follow-up. *J Clin Oncol* 2010;28:136-41.
45. Ng AK, Li S, Neuberg D, Silver B, Weeks J, Mauch P. Factors influencing treatment recommendations in early-stage Hodgkin's disease: a survey of physicians. *Ann Oncol* 2004;15:261-9.
46. National Comprehensive Cancer Network. NCCN guidelines & clinical resources. (Accessed July 16, 2010, at http://www.nccn.org/professionals/physician_gls/f_guidelines.asp.)
47. Sher DJ, Mauch PM, Van Den Abbeele A, LaCasce AS, Czerninski J, Ng AK. Prognostic significance of mid- and post-ABVD PET imaging in Hodgkin's lymphoma: the importance of involved-field radiotherapy. *Ann Oncol* 2009;20:1848-53.
48. Barnes JA, LaCasce AS, Toomey CE, et al. Early interim FDG-PET scan predicts outcome in non-bulky limited stage Hodgkin lymphoma, but may not guide use of consolidative radiotherapy. *Blood* 2008;112:518. abstract.

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