

COUNTERPOINTS

Current Controversies in Hematology and Oncology

Can Radiotherapy Be Omitted in Patients With Localized Hodgkin Lymphoma?

Radiation therapy has a dramatic effect on lymphomas, and has played an important role in treating Hodgkin lymphoma during the past 50 years. Over the past decade, however, many oncologists have begun to replace radiation therapy—which may be considered unnecessary, too toxic, or too inconvenient—with additional cycles of systemic therapy.

Do patients with localized Hodgkin lymphoma need radiotherapy? Or do patients continue to benefit from a combination of radiation therapy and the use of systemic agents? The answer is not black and white for our discussants. David J. Straus, MD takes the point of view that radiation therapy is more harmful than clinicians may realize and should be omitted in most of these patients, whereas Eli Glatstein, MD, and John P. Plastaras, MD, PhD, maintain that modern radiation therapy is safe and beneficial for patients at high risk for recurrence.

Radiotherapy Should Be Omitted in Most Patients



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Radiation therapy is more harmful than most clinicians realize. This is well illustrated by a graph from a recent paper.¹ The paper described the historical experience with Hodgkin lymphoma at Stanford, which used radiation therapy—either alone or as part of combination-modality treatment—in all patients between 1960 and 2006. The graph showed that 40-year disease-free survival and freedom from relapse were relatively high: 82% and 70%, respectively. What is astounding is that the overall survival was just 25%. In other words, although the radiation therapy-based approach controlled the Hodgkin lymphoma, it likely contributed to mortality from other causes.

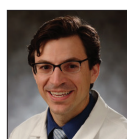
Fortunately, radiotherapy can be omitted in most patients with localized Hodgkin lymphoma. The clinical practice guidelines from the National Comprehensive Cancer Network allow for the use of chemotherapy

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Patients at High Risk For Recurrence Need Radiotherapy



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Not every patient with limited-stage Hodgkin lymphoma requires radiation therapy. Patients who are at high risk for recurrence, however, should receive combined-modality treatment in most cases. The beauty of combined-modality treatment is that you can truncate both the chemotherapy and the radiation. Because most of the morbidities of both modalities are dose-dependent, combined-modality treatment has the potential to improve overall morbidity significantly.

We are currently developing ways to determine which patients are at high risk for relapse, because avoidance of relapse is an important goal. We may not all

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Radiotherapy Should Be Omitted in Most Patients (cont)

alone, and several clinical trials support this option. Such a trial was one we did in the 1990s that compared doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) chemotherapy with ABVD plus radiation therapy for patients with stages IA through IIIA disease. This trial did not meet its accrual target; the data safety monitoring committee recommended closure after 10 years of accrual because the addition of a small number of patients would not change the statistical power of the results. Despite this, we found no difference in complete response rate, freedom from progression, or overall survival between the 2 groups.² We do, of course, need to bear in mind that the trial was not statistically powered for noninferiority, and that small differences in outcome might have been missed.

The H9-F trial, which was presented at the American Society of Hematology meeting but is as yet unpublished, was conducted by the European Organisation for Research and Treatment of Cancer (EORTC).³ This trial included patients with favorable stage I and II disease who were randomly assigned to receive chemotherapy only, chemotherapy plus low-dose involved field radiation therapy (IFRT), or chemotherapy plus standard-dose IFRT. The chemotherapy regimen was epirubicin, vinblastine, bleomycin, and prednisone (EVBP), which has since been shown to be inferior to standard adequate chemotherapy with mechlorethamine, vincristine, procarbazine, and prednisone (MOPP)/ABV chemotherapy.⁴ Although there was no difference in survival, the chemotherapy-only arm was discontinued because of an excess of adverse events. Rather than being a condemnation of chemotherapy alone, however, this trial was actually a condemnation of inferior chemotherapy. It is inferior chemotherapy that requires the addition of radiation therapy in order to get a good result, which is the case with the Stanford V regimen as well: suboptimal chemotherapy with doxorubicin, vincristine, mechlorethamine, vinblastine, bleomycin, etoposide, and prednisone combined with generous IFRT.

Another relevant trial, the HD-6 trial, was conducted by the National Cancer Institute of Canada (NCIC) Clinical Trials Group and the Eastern Cooperative Oncology Group (ECOG).⁵ In this study, the researchers randomly assigned 405 patients with stage IA or IIA nonbulky Hodgkin lymphoma to either 4 to 6 cycles of ABVD or radiation therapy; those in the radiation group who had an unfavorable risk profile also received 2 cycles of ABVD. This study used subtotal nodal radiation therapy. Although the type of radiation treatment we use now is less extensive, we still see the same types of adverse events with IFRT that we saw with extended

field radiation therapy, as in the German Hodgkin Study Group HD10 trial.⁶

A major attribute of the HD-6 trial was having the primary clinical endpoint be 12-year overall survival, which is far longer and more meaningful than the endpoints that are typical for these studies.⁵ The hypothesis of the study investigators was that overall survival would be worse for radiation therapy with or without chemotherapy because of adverse events due to the radiation, and that is exactly what they found—despite the fact that the relapse rate was 6% higher for ABVD chemotherapy than for combination therapy.

Relapse is not disastrous in these patients because we have highly effective salvage treatment. For patients with limited disease in nodal sites who have not already received radiation therapy, we can administer radiation just to the affected sites. For patients with more extensive relapse, we can give radiation therapy and high-dose che-

Relapse is not disastrous in these patients because we have highly effective salvage treatment.

motherapy with autologous stem cell support. I maintain that it is better to use radiation therapy just in the small number of patients who need it than to subject everyone to the potential toxicity associated with it. I think that medical oncologists in this country have been very influenced by this trial, although radiation oncologists may dispute its findings.

Another relevant study is the RAPID trial from the United Kingdom's National Cancer Research Institute, which was reported at the American Society of Hematology (ASH) meeting in 2012.⁷ This was one of several recent studies using interim positron emission tomography (PET) scans as biomarkers for response to chemotherapy. This study involved patients with stage I and IIA disease who received 3 cycles of ABVD and then had a PET scan. If the PET scan was positive, patients received an additional cycle of ABVD and IFRT. If the PET scan was negative, which was the case 75% of the time, patients were randomly assigned to either no further treatment or IFRT. For patients who were PET-negative, the researchers found no

difference in progression-free survival or overall survival between those who received no further treatment and those who received radiation therapy.

Thanks to the results of the Canadian trial and the RAPID study, more and more patients with localized Hodgkin lymphoma are receiving chemotherapy alone. Patients do not want to receive a therapy that can cause breast and other cancers, heart attacks, heart valve damage, and strokes, as well as nonfatal but uncomfortable side effects such as neck muscle wasting (“neck drop”).

As for people with advanced disease, the definitive study was done by EORTC.⁸ In this study, approximately 400 patients with stage III and IV Hodgkin lymphoma who had a complete response to MOPP/ABV chemotherapy were randomized to either low-dose IFRT or observation. This trial showed no difference in outcomes at follow-up of between 6 and 7 years, although there was a trend with low-dose IFRT toward worse event-free survival, progression-free survival, and overall survival. I suspect that this difference might become statistically significant after 10 years of follow-up, because that is when adverse events due to radiation therapy begin to accelerate.

The one situation in which combined modality treatment remains the standard is bulky disease, particularly bulky mediastinal disease. Even in this case, however, there are certain patients who may not need radiation therapy. We do not have robust data on this, but one relevant study was presented at the 2007 annual meeting of ASH.⁹

In this retrospective review, the investigators looked at patients who had stage IIB, III, and IV disease who were treated with 6 cycles of ABVD, and then received a computed tomography scan. Those with a residual mass of at least 2.5 cm received a PET scan, and only those who were PET-positive received radiation therapy. The progression-free survival for patients with initially bulky disease who were PET-negative at the end of treatment was no different than that for patients without initially bulky disease, suggesting that there is a subgroup of patients with initially bulky disease who do not need radiation therapy if their PET scans are negative at the end of treatment with ABVD. The results of the HD15 trial from the German Hodgkin Study Group also found that patients with a residual mass of 2.5 cm that was PET-negative following bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone (BEACOPP) had a low relapse

rate, further supporting the concept that some patients with residual masses at the end of chemotherapy with bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) do not need additional radiation therapy.¹⁰

In summary, I think that chemotherapy alone is a good option for untreated, favorable-prognosis, early-stage Hodgkin lymphoma. The relapse rate may be slightly higher than for combined-modality treatment, but relapses can be treated effectively. I also believe that chemotherapy-only treatment should be the standard of care for advanced-stage disease as long as adequate chemotherapy is used. Combined-modality treatment remains the standard for bulky disease, although some data suggest that patients with initially bulky disease who are PET-negative after ABVD do not need radiation therapy.

References

1. Canellos GP, Rosenberg SA, Friedberg JW, Lister TA, Devita VT. Treatment of Hodgkin lymphoma: a 50-year perspective. *J Clin Oncol*. 2014;32(3):163-168.
2. 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(12):3483-3489.
3. Eghbali H, Brice P, Creemers GY, et al. Comparison of three radiation dose levels after EBVP regimen in favorable supradiaphragmatic clinical stages (CS) I-II Hodgkin's lymphoma (HL): preliminary results of the EORTC-GELA H9-F trial [ASH abstract 814]. *Blood*. 2005;106(11)(suppl).
4. Fermé C, Eghbali H, Meerwaldt JH, et al; EORTC-GELA H8 Trial. Chemotherapy plus involved-field radiation in early-stage Hodgkin's disease. *N Engl J Med*. 2007;357(19):1916-1927.
5. Meyer RM, Gospodarowicz MK, Connors JM, et al. ABVD alone versus radiation-based therapy in limited-stage Hodgkin's lymphoma. *N Engl J Med*. 2012;366(5):399-408.
6. 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(7):640-652.
7. Radford J, Barrington S, Counsell N, et al. Involved field radiotherapy versus no further treatment in patients with clinical stages IA and IIA Hodgkin lymphoma and a 'negative' PET scan after 3 cycles ABVD: results of the UK NCRI RAPID trial [ASH abstract 547]. *Blood*. 2012;120(21)(suppl).
8. Aleman BM, Raemaekers JM, Tirelli U, et al. Involved-field radiotherapy for advanced Hodgkin's lymphoma. *N Engl J Med*. 2003;348(24):2396-2406.
9. Savage KJ, Connors JM, Wilson D, et al. FDG-PET guided consolidative radiotherapy in patients with advanced stage Hodgkin lymphoma with residual abnormalities on post chemotherapy CT scan [ASH abstract 213]. *Blood*. 2007;110(11)(suppl).
10. Engert A, Haverkamp H, Kobe C, et al. Reduced-intensity chemotherapy and PET-guided radiotherapy in patients with advanced stage Hodgkin's lymphoma (HD15 trial): a randomised, open-label, phase 3 non-inferiority trial. *Lancet*. 2012;379(9828):1791-1799.

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Patients at High Risk For Recurrence Need Radiotherapy (cont)

agree on what constitutes “high risk,” but clearly certain patients fall into this category. For example, we believe that patients who have had chemotherapy that has been adulterated in any way, such as with reduced or delayed doses, should be considered high risk. The best option for patients who relapse is high-dose second-line chemotherapy and an autologous stem cell transplant. Transplants are not always feasible, however, and they are expensive. Transplants are very tough on patients, who generally develop thrombocytopenia and do not tolerate further treatment very well. The cure rate with transplants for relapse hovers at around 50%.^{1,2}

As far as safety is concerned, radiation can be administered safely using modern techniques—understanding, of course, that nothing in medical practice is 100% safe. It is the responsibility of the radiation oncologist to keep these treatments as safe as possible for the patient without missing the target. Some of these cases take a lot of time to map out, but this is time well spent. Furthermore, advanced techniques like proton therapy may decrease the risk of long-term problems like cardiac disease and radiation-induced breast cancer.

Trials that appropriately compare combined-modality therapy with chemotherapy alone generally show that the addition of radiation decreases the rate of relapse.^{3,4,5}

One study that has wrongly been used to support the omission of radiation therapy is the HD-6 trial by the NCIC Clinical Trials Group and ECOG.⁶ The first limitation of this study is that it used subtotal nodal radiation therapy, which is simply not used today and has been largely out of use for 25 years. The second problem with the study is the way it has been interpreted; some clinicians have used data from this study to say that radiation is unnecessary because patients in the chemotherapy-only arm did better than those in many of the historical arms.⁷ We believe this argument is flawed because a single arm from 1 study should never be used to rationalize treatment policies.

Another argument in favor of omitting radiation is the idea that advanced imaging tools will allow us to determine which patients will do well with chemotherapy alone. This approach has been the subject of at least 2 randomized trials, neither of which has been published in manuscript form yet. The first one that came out was the RAPID trial from the United Kingdom, which was presented at the ASH meeting in 2012.⁴ The hypothesis was that if patients had a PET-based response to chemotherapy, they could potentially skip radiation therapy. In the trial, patients who were PET-negative after 3 cycles of ABVD chemotherapy were randomized to 30 Gy of radiation or

no further therapy. The trial was intentionally designed to allow up to 7% more failures in the chemotherapy-only arm than in the combined-modality arm.

The intent-to-treat analysis indicated that progression-free survival at 3 years was 94.5% among the patients who received radiation and 90.8% among those who did not, a difference that was not statistically significant (hazard ratio, 1.51; $P=.23$). When analyzed per protocol treatment, however, the difference in progression-free survival was 6.3%, which is very close to that 7% mark. The real question is whether that trial design was appropriate. Medical oncologists will often say they can allow additional relapses because they can give high-dose chemotherapy and autologous stem cell transplants. But the cure rate with stem cell transplant is only about 50% of those who have the procedure,^{1,2} and not everyone is able to receive a stem cell transplant. Whether we are talking about a 3% or 7% excess in risk, we believe that allowing people to die who might have been cured initially is the

Everything that goes wrong tends to get blamed on the radiation—even when the chemotherapy is at fault.

wrong direction for our field to be heading. Although it was true that the patients who were PET-negative were less likely to experience relapse, there still were some relapses.

Another important study is the EORTC/Lymphoma Study Association (LYSA)/Fondazione Italiana Linfomi (FIL) intergroup H10 trial, which was recently published.⁵ This was a properly randomized trial that was looking at a strategy to omit radiation through the use of PET scans. In both the favorable-risk and unfavorable-risk groups, the PET-adapted arms had to be stopped early owing to excessive failures. There is good reason to be skeptical that PET scanning will provide the advantages we were hoping it would.

One of the biggest arguments against radiation is that only about 10% of patients benefit from it. But there has been a major sea change in the world of radiation oncology for lymphoma, which is the introduction

of involved-site radiation therapy. The International Lymphoma Radiation Oncology Group (ILROG) published guidelines supporting the idea that patients who respond well to chemotherapy should have a smaller volume treated with radiation therapy.⁸ Although not everyone agrees with that, we think we will see more and more practitioners adopting more modern volume-based radiotherapy techniques. I think everyone can agree that truncated doses of radiation to small volumes are very well tolerated. Something else that is important to mention is that one size does not fit all when it comes to treatment. Patient factors include patient preferences; some patients take the approach that they want everything possible done to prevent a recurrence, whereas other patients may be terrified of radiation. We are in favor of customizing treatment for the patient, and the patient's views can be just as important as the clinical presentation.

Decisions about radiation are also highly institution-dependent. In many institutions, the medical oncologist will direct treatment of Hodgkin lymphoma with no input from a radiation oncologist. There may even be an adversarial relationship between the medical oncologists and the radiation oncologists. Other institutions take a true multidisciplinary approach, and the relationship between medical oncologists and radiation oncologists is a collaborative one. This collaborative approach is valuable because it takes into account that not every patient is the same. For example, we recently saw a patient with limited-stage Hodgkin lymphoma who had experienced a myocardial infarction in his 40s. He was responding well to chemotherapy, so we decided to omit radiation to avoid the potential insult to his heart.

Another barrier to radiation therapy is the fact that not all patients live near radiation centers. If a patient lives in a rural area and will need to travel a distance for radiation therapy, the path of least resistance is often a chemotherapy-only approach. That is why the use of radiation tends to be lower than one might expect in an

ideal world, even for conditions such as breast cancer and limited-stage follicular lymphoma, where the data for radiation therapy are generally well-accepted.

Finally, we would like to emphasize that radiation therapy is not nearly as toxic as some would make it out to be. After we have administered radiation to a patient, everything that goes wrong tends to get blamed on the radiation—even when the chemotherapy is at fault. Ultimately, it is the responsibility of the radiation oncologist to strive diligently to limit radiation dose to uninvolved regions and keep the toxicity as low as possible.

References

1. Linch DC, Winfield D, Goldstone AH, et al. Dose intensification with autologous bone-marrow transplantation in relapsed and resistant Hodgkin's disease: results of a BNLI randomised trial. *Lancet*. 1993;341(8852):1051-1054.
2. Schmitz N, Pfistner B, Sextro M, et al. Aggressive conventional chemotherapy compared with high-dose chemotherapy with autologous haemopoietic stem-cell transplantation for relapsed chemosensitive Hodgkin's disease: a randomised trial. *Lancet*. 2002;359(9323):2065-2071.
3. Eghbali H, Brice P, Creemers GY, et al. Comparison of three radiation dose levels after EBVP regimen in favorable supradiaphragmatic clinical stages (CS) I-II Hodgkin's lymphoma (HL): preliminary results of the EORTC-GELA H9-F trial [ASH abstract 814]. *Blood*. 2005;106(11)(suppl).
4. Radford J, Barrington S, Counsell N, et al. Involved field radiotherapy versus no further treatment in patients with clinical stages IA and IIA Hodgkin lymphoma and a 'negative' PET scan after 3 cycles ABVD: results of the UK NCRI RAPID trial [ASH abstract 547]. *Blood*. 2012;120(21)(suppl).
5. Raemaekers JM, André MP, Federico M, et al. Omitting radiotherapy in early positron emission tomography-negative stage I/II Hodgkin lymphoma is associated with an increased risk of early relapse: clinical results of the preplanned interim analysis of the randomized EORTC/LYSA/FIL H10 trial [published online March 17, 2014]. *J Clin Oncol*. doi:10.1200/JCO.2013.51.9298.
6. Meyer RM, Gospodarowicz MK, Connors JM, et al. ABVD alone versus radiation-based therapy in limited-stage Hodgkin's lymphoma. *N Engl J Med*. 2012;366(5):399-408.
7. Connors JM. The case for chemotherapy alone for limited-stage Hodgkin's lymphoma. *Oncologist*. 2012;17(8):1011-1013.
8. Specht L, Yahalom J, Illidge T, et al; ILROG. Modern radiation therapy for Hodgkin lymphoma: field and dose guidelines from the International Lymphoma Radiation Oncology Group (ILROG) [published online June 18, 2013]. *Int J Radiat Oncol Biol Phys*. doi: 10.1016/j.ijrobp.2013.05.005.

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