Re: Radiation Therapy in the Treatment of Hodgkin's Disease—Do You See What I See?

> Learn what is true in order to do what is right.
>
> Thomas H. Huxley (1825–1895)

In his recent editorial *(1)* regarding our paper *(2)*, Longo suggests that there is no foundation for radiation therapy in combination with chemotherapy for pa-

tients with Hodgkin's lymphoma. We agree that one should always aim at minimal treatment intensity; however, this should not endanger individual patients' cure rates.

Hence, the challenge is to properly select patients requiring radiation therapy. The rationale for radiation therapy is the observation that relapses usually involve initially involved sites and that radiation therapy reduces recurrence rates *(3)*. In a randomized trial carried out by the European Organization for Research and Treatment of Cancer (EORTC) Lymphoma Group, radiation therapy did not improve outcomes in the 57% of advanced Hodgkin's lymphoma patients who were in complete remission after chemotherapy with six to eight cycles of mechlorethamine, vincristine, procarbazine, prednisone–doxorubicin, bleomycin, and vinblastin (MOPP–ABV hybrid) *(4)*. However, the 34% of patients who were in partial remission after chemotherapy and then received field radiation experienced cure rates as high as those experienced by patients in complete remission after chemotherapy. Radiation therapy also appears to be needed for patients with early-stage disease with favorable characteristics who are treated with mild chemotherapy. Indeed, the EORTC Lymphoma Group had to close the arm of an ongoing trial, H9F, in which patients did not receive radiation therapy after achieving a complete remission with epirubicin, bleomycin, vinblastin, and prednisone (EBVP) chemotherapy because of the high number of relapses in that arm (Noordijk EM, Thomas J: personal communication).

Longo's suggestion that 80%–85% of Hodgkin's lymphoma patients can be cured without radiation therapy is not supported by present evidence for patients with early or advanced Hodgkin's disease. For example, Duggan et al. *(5)* reported 5-year failure-free survival rates of only 63% (95% confidence interval [CI] = 59% to 68%) for patients with advanced Hodgkin's disease. Despite successful salvage treatment in a substantial number of patients, the 5-year overall survival was only 82% (95% CI = 79% to 86%). Importantly, salvage treatment has been shown to be related to excess late morbidity and mortality *(6,7)*.

Longo also worries about the interpretation of the risk of breast cancer after a relatively low dose of radiation. Our conclusion, that the risk of breast cancer increases with increasing radiation dose up to at least 40 Gy, has the important implication that the lower radiation doses used presently (20–30 Gy in fractions of 2 Gy) may reduce the increased breast cancer risk compared with the radiation schedules used in the past (equivalent to 40 Gy in fractions of 2 Gy). The relative risk of developing breast cancer was not statistically significantly increased in patients who received doses of 4–23.2 Gy (median 15 Gy) to the area of the breast where the tumor developed as compared with patients who received less than 4 Gy, but we made no suggestions as to "safe" levels of radiation. Indeed, we cautioned readers about the elevated risks of late morbidity after treatment with new modalities *(2)*.

Finally, Longo notes that the ABVD (doxorubicin, bleomycin, vinblastin, dacarbazine) regimen has replaced most alkylating agent–based regimens, and he notes that it has low toxicity. However, doxorubicin-associated cardiovascular damage and bleomycin-induced pulmonary toxicity are important side effects. Moreover, fatal toxicity has been reported in 2%–3% of patients treated with ABVD alone *(5)*.

In conclusion, it is important to restrict the intensity of treatment for young patients with Hodgkin's lymphoma to the greatest extent possible. ABVD is an effective regimen, but unfortunately it cannot, as sole treatment modality, cure 80%–85% of patients. Our primary concern is to cure patients of their Hodgkin's lymphoma. Unfortunately, new trials have to be designed before long-term toxicity results of the previous trials are available. Balancing the risks of primary or secondary treatment failure against the risk of late morbidity is extremely difficult and should be done on the basis of the results of both retrospective and prospective studies.

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RESPONSE

Near the end of "Butch Cassidy and the Sundance Kid," the heroes, surrounded by the Bolivian cavalry, are about to charge out to meet their fate when Butch asks Sundance, "You didn't see Lefors out there, did you?" Joe Lefors was the leader of the highly skilled posse that had tracked the two across much of North America. "Lefors? No," answers Sundance. "Good. For a moment there, I thought we were in trouble." Butch and Sundance did not accurately assess their risks, overestimating a small risk and underestimating a huge one.

Aleman et al. make two major points. First, radiation therapy may help people

who do not achieve a complete response with chemotherapy alone. I agree. The first study to show this benefit was Southwest Oncology Group (SWOG) Study 7808 *(1)*. Second, ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) cannot cure 85% of patients with Hodgkin's disease. If ABVD alone were as good as MOPP (mechlorethamine, vincristine, procarbazine, prednisone) alone, it would achieve a 92% 10-year survival in early-stage disease *(2)*. The study cited by the authors reports a 5-year survival of 82% in advanced-stage Hodgkin's disease. If chemotherapy cannot cure 80%–85% of all patients with Hodgkin's disease, it comes close.

According to Surveillance, Epidemiology, and End Results (SEER)[1] Program data *(3)*, 5-year survival from Hodgkin's disease for the period 1992 through 1998 was 84%. Despite this high level of successful treatment and the very long period of time that the most successful treatment tools have been available (radiation therapy since the 1960s, MOPP since 1970, ABVD since 1975), a paucity of long-term follow-up data exist to assess the impact of treatment on cured patients.

So far, perhaps because radiation therapists have done a better job of studying the impact of their treatment, the late effects of radiation therapy appear to be alarmingly serious and frequent. Ng et al. *(4)* showed that more of their patients treated for Hodgkin's disease with radiation therapy have died from effects of the treatment (101 deaths) than have died from Hodgkin's disease (60 deaths). They project about 10% of patients dying from second cancers and 3% from heart disease at 20 years after treatment, based on a median follow-up of only 12 years. Other studies have documented a second cancer risk of about 1% per year extending at least 25 years after treatment and possibly beyond.

Comparable data from patients treated with chemotherapy alone are even more sparse. Long-term follow-up of MOPP-treated patients does not suggest any late death or toxicity when chemotherapy alone is used. Patients receiving therapy with MOPP plus radiation have a 3% lifetime risk of acute leukemia, and all the risk occurs in the first decade after treatment *(5)*. In patients who survive beyond 10 years after treatment, the risk of leukemia appears to be no greater than in people who never had Hodgkin's disease. Other life-threatening late toxicities are anecdotal or unsupported by data from large groups of patients.

Data on ABVD-treated patients are virtually nonexistent other than occasional anecdotes. Acute toxicity appears lower with ABVD than with MOPP (the Cancer and Leukemia Group B [CALGB] mortality data quoted by Aleman et al. are several times higher than those reported from other centers). Of course, absence of evidence is not evidence of absence but, given more than 28 years of use, it would be surprising if a life-threatening late toxicity from ABVD affecting as many as 10% of the patients would have been missed.

No one contests the attribution of late toxicity to radiation therapy. However, the magnitude of the risk has not been widely appreciated. I doubt that any research protocol using radiation therapy actually informs the patients that their risk of dying from a radiation therapy–related complication exceeds their risk of dying from Hodgkin's disease. Instead, the approach has been to hope that lowering the dose of radiation therapy and/or limiting the field size will reduce the enormous late risks of second cancer and heart disease. This approach is not currently supported by data. Upton *(6)* demonstrated more than 40 years ago that the risk of cancer in animals receiving radiation follows a bell-shaped dose–response curve. Thus, lowering radiation doses might actually increase the risk of a second cancer. In the absence of data, one cannot assume that lower doses of radiation therapy are safer.

We sorely need additional data on long-term effects of treatment in patients with Hodgkin's disease. In the interim, on the basis of current information, the safest approach to managing these patients is to avoid the routine use of radiation therapy in all patients. Cure as many patients as you can with chemotherapy alone, reserving radiation therapy for two subgroups: those who fail to obtain a complete response to chemotherapy, and those with very large mediastinal masses. Patients who relapse should be rescued with high-dose chemotherapy (without radiation therapy, if possible) and autologous hematopoietic stem cells. This approach needs to be compared in large-scale studies with combined modality treatment approaches for response rate, relapse rate, complications, and survival. To continue with a treatment approach that exposes every patient to the risks of radiation therapy is to repeat the error in judgment of Butch and Sundance: underestimating a huge risk and overestimating a small one.

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[1]*Editor's note:* SEER is a set of geographically defined, population-based, central cancer registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Registry data are submitted electronically without personal identifiers to the NCI on a biannual basis, and the NCI makes the data available to the public for scientific research.

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