Radiation Therapy in Hodgkin Disease: Why Risk a Pyrrhic Victory?

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Pyrhus became King of Epirus in Northern Greece in 306 BC. He was a brilliant warrior and strategist; for example, he employed elephants in his attack force 60 years before Hannibal’s famous use of these animals in the Second Punic War. In 280 BC, he invaded Italy and won a great battle at Heraclea but suffered enormous losses of men in his army. A few months later, in 279 BC, he won a second major battle at Asculum, again enduring severe and irreplaceable casualties. After being complimented on his success by one of his men, he is said to have responded, “Another such victory and we are undone.” Thus, through the centuries the term “Pyrrhic victory” has been used to mean a conquest won at too great a cost for the victor.

In this issue of the Journal, Travis et al. (1) have studied the largest number of cases of secondary breast cancer after treatment for Hodgkin disease (106 patients) published to date. Most epidemiologic studies provide relative risks but never translate the results into an absolute risk that can be shared in a way the patient understands. However, Travis et al. have done a case–control study and computed absolute risks for developing breast cancer as a function of dose of radiation therapy and use of alkylating agent–based chemotherapy. The results are shocking. For a 25-year-old woman who received typical mantle-field radiation therapy for her Hodgkin disease, the risk of developing breast cancer by age 55 years is 29% (95% confidence interval [CI] = 20.2% to 40.1%). For a 25-year-old woman receiving a lower dose of radiation (20–40 Gy), the risk of developing breast cancer by age 55 years is 24.6% (95% CI = 16.6% to 24.8%). In addition, no evidence suggests that the risk declines after 30 years. According to Surveillance, Epidemiology, and End Results (SEER) data, a 25-year-old woman in the general population has about a 3% risk of developing breast cancer by age 55 years.

Absolute risks are much easier to put in proper perspective than relative risks. Recall that millions of women stopped taking hormone replacement therapy that was controlling their menopausal symptoms and preserving their bone mineral density because of an increased relative risk of breast cancer that translates into quite a modest cumulative absolute risk (2). A 50-year-old woman has one chance in 16 of developing breast cancer over the next 30 years (6.25%). A 50-year-old woman who takes hormone replacement therapy for 10 years has one chance in 13 of developing breast cancer over the next 30 years (7.7%). The absolute risk is increased 1.5% in 30 years; yet women and physicians have largely abandoned hormone replacement therapy. Unlike Hodgkin disease, menopausal symptoms are not life-threatening; however, the point is that some medical practices change dramatically as a consequence of only small changes in absolute risk.

We have been slow to recognize the many costs to the patient of using radiation therapy to treat Hodgkin disease; or, if not slow to recognize the costs, then slow to change our choice of therapy because of the costs. Most of the 7350 people diagnosed with Hodgkin disease in 2005 will be treated with combined modality therapy. The rationale for this physician behavior appears to be the hope (for there is precious little evidence) that lowering the dose of radiation therapy to 24 Gy or so will dramatically lower the risk of the major side effects, including second cancers and accelerated coronary artery disease.

Most evidence suggests that lower doses of exposure to radiation produce a lower risk of developing second cancers, but the risk never reaches zero. In the dose range for therapeutic radiation in Hodgkin disease, the dose–risk curve is not deeply sloped. The article by Travis et al. does not suggest that the risk falls very much in the range of 20–40 Gy (see their table 2). Most therapeutic radiation for Hodgkin disease used as a supplement to chemotherapy is given in the dose range of 20–24 Gy. Breast cancer incidence increases as a consequence of therapeutic radiation administered at low doses for benign diseases and even from repeated diagnostic radiography [for review, see the work of Boice (3)]. Factors affecting risk are complicated and include age, age at exposure, dose, energy of the radiation, duration of exposure, condition being treated, and overall risk of breast cancer in the individual and in the population exposed (4). In women who receive breast irradiation as part of their treatment for primary breast cancer, the nonirradiated breast receives an average radiation dose of 2.82 Gy (5). Such women younger than 45 years at time of treatment experience a 60% increase in second cancers in the incidentally irradiated contralateral breast. Even the internal radiation that makes it to the breast during radiation therapy for cervical cancer can increase the risk of breast cancer. In one series (6), the relative risk of breast cancer was 3.1 (95% CI = 0.5 to 20.0) for exposures of 0.5 Gy or greater in women without ovaries with cervical cancer (the absence of which would be expected to reduce the risk). No increased risk was noted in the group whose breasts received 0.24 Gy or less. As pointed out in the June 2005 report of the 7th Biological Effects of Ionizing Radiation (BEIR) Committee, done under the auspices of the National Academy of Sciences, there is no safe dose of radiation. Resistance to this notion must play a role in the continued use of radiation therapy in Hodgkin disease treatment, especially its use in the face of an effective alternative, combination chemotherapy alone.

Travis et al. suggest that their projections do not apply in patients treated with “modern approaches” involving limited-field...
radiation therapy. That suggestion seems weak at best. The last person treated in their cohort had been disease free for 1 year on December 31, 1994, 11 years ago. Has someone invented a method of delivering mantle-field radiation therapy that is novel in the last decade? Does any new method permit radiating axillary nodes without irradiating the breast? Can one deliver radiation to the mediastinum without it passing through the overlying skin and skin appendages? Has any new method been proven effective in curing the disease or in improving the efficacy of chemotherapy? Has this novel, effective modification of the mantle field been used in patients monitored for 20 years or more and been shown to reduce the risk of second cancers and premature coronary artery disease? Would these not normally be the minimal requirements for routinely using an intervention that had been shown to produce breast cancer in up to 30% of the women in whom it was used?

What is most perplexing about the persistent practice of using radiation therapy in the treatment of Hodgkin disease is the availability of alternative approaches (combination chemotherapy alone) that are just as successful in curing the disease and are not associated with such a magnitude of late fatal complications. The literature is quite clear that combined radiation therapy and chemotherapy does not produce a superior overall survival to chemotherapy alone in any stage of disease (7–9). Why accept any increased risk of breast cancer from a treatment that is not required?

Travis et al. provided us with an important, quantitative way to speak to our patients with Hodgkin disease about the risk of developing breast cancer after radiation therapy. We need similar information about all the other kinds of radiation-induced cancers and about the radiation-accelerated coronary artery disease that affects patients cured of Hodgkin disease with therapy that includes radiation. Indeed, we need similar information about long-term risks for all interventions for all the diseases we treat. Given the facts about the enormous risk of breast cancer after mantle-field radiation therapy, we now need to act on them.

For the patients who have already been exposed to radiation therapy and remain at risk, we need to counsel them and provide heightened surveillance. We should look at the risk of male breast cancer in men who were treated with mantle-field radiation therapy for Hodgkin disease. We know very little about how radiation-induced breast cancer relates to sporadic breast cancer biologically. What percentage of patients has estrogen and progesterone receptor–positive disease? Does the pattern of gene expression resemble sporadic localized breast cancer or metastatic breast cancer? Although there is much that remains unknown, we have some tools to combat this problem. From the lower incidence of secondary radiation-induced breast cancers in women without ovaries, women whose ovaries have been irradiated, and women with alkylating agent–induced menopause, we can infer that many (perhaps half) of these radiation-induced breast cancers might be prevented by 5 years of tamoxifen therapy. In addition, women who received mantle-field radiation therapy should be included with other women at increased risk in clinical trials evaluating newer chemoprevention strategies (e.g., aromatase inhibitors). Given that the level of risk in some subsets of women (e.g., women treated with 20–40 Gy at age 25 or 30 years have a 25%–34% risk of developing breast cancer in 30 years) are as high as some women with hereditary breast cancer, consideration needs to be given to prophylactic mastectomy for those at greatest risk. Finally, we need to stop exposing women to the risk of subsequent breast cancer (and other malignancies and heart disease) by needlessly using radiation therapy as a component of their Hodgkin disease treatment. A Pyrrhic victory in the absence of reasonable alternative ways to accomplish the goal can be tragic but necessary; a Pyrrhic victory that could be avoided while still accomplishing the goal is just foolish.

References