Protons: Moving Therapy for Hodgkin Lymphoma in a Positive Direction

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Dr. Hoppe and colleagues present a strong case supporting the use of proton therapy (PT) for the treatment of patients with Hodgkin lymphoma (HL). They point out a major quandary of modern therapy for HL, which requires that oncologists navigate between the Scylla of relapse due to inadequate therapy and the Charybdis of severe late toxicities that result from over-exuberant treatment. This was highlighted in the recent study by Meyer et al[1] that compared treatment of nonbulky HL with ABVD (Adriamycin [doxorubicin], bleomycin, vinblastine, dacarbazine) alone vs subtotal nodal radiation (alone or in combination with ABVD); the study demonstrated improved freedom from progression in irradiated patients, but this was more than compensated for by an increase in mortality from late toxicity in that same group. The most common cause of death in the irradiated group was secondary malignancies, and the rate was more than double that in the patients treated with chemotherapy only. Additional studies also strongly implicate mediastinal radiation as a significant risk factor for cardiac disease, particularly in younger patients.[2] Unfortunately, similar long-term toxicities might be induced if chemotherapy doses were increased to offset the need for radiation; thus, it is generally accepted that radiation is a critically important aspect of multimodality treatment for many patients with HL.

It is important to realize that, unlike with most other hematologic malignancies, a significant percentage of patients with HL who relapse will still have an excellent chance for long-term cure using salvage therapy. Thus, modern studies should employ freedom from second relapse (FFSR) as a key outcome measure. Indeed, an ongoing debate[3-6] focuses on whether it is better to administer a more aggressive up-front chemotherapy regimen, such as BEACOPP (bleomycin, etoposide, Adriamycin, cyclophosphamide, Oncovin [vincristine], procarbazine, and prednisone), to ensure the highest number of early cures, or to use the reduced-toxicity combination ABVD, which may have higher rates of relapse, but may yield a population with substantially improved salvage rates, thus evening out the overall FFSR rate. In either case, however, we are fortunate that patients with HL have an excellent chance for long-term survival.

Given the relatively young age of many HL patients at presentation, later-stage toxicities are predicted to become increasingly common, with an astoundingly high predicted 40% incidence of grade 3 or higher chronic health problems by 25 years from diagnosis.[7] These will add significantly to the burden of human suffering, as well as to the financial impact on the health care system. As noted by Hoppe et al, multiple independent studies have demonstrated that the PT modality provides lower overall radiation doses to the heart, lungs, breasts, esophagus, and other structures for the vast majority of HL patients. Radiation dose in HL has decreased over time, concomitant with the increased reliance on multi-agent chemotherapy. Although retrospective in nature, data are now becoming available that describe the impact of modern radiotherapy (RT) in trials using doses in the range of 20 Gy (compared with > 40 Gy in RT-alone series). As expected, the reduced RT doses are associated with lower risk of cardiac and valvular dysfunction[8]; however, the effect on secondary malignancy is less clear. O’Brien et al in a recent report from Stanford reviewed their experience with secondary malignancies in patients treated with low-dose RT. Unfortunately, the cumulative incidence of secondary malignancy was still 17% at 20 years.[9] Although it appears that reducing dose to normal tissues will reduce secondary malignancy, the combination with chemotherapy may have a “synergistic” effect with regard to second malignancies, making risk unpredictable based on radiation dose alone.

Reducing irradiated volume will likely contribute the largest gains in reducing the risk of secondary malignancy. As noted by the authors, this has already been shown for the reduction from extended field irradiation (EFRT) to involved field irradiation (IFRT)—and the current move to involved node
irradiation (INRT) will further reduce treatment volume, regardless of radiation modality chosen. PT reduces the irradiated volume by > 50%, even for the same target area, a characteristic ideal for reducing secondary malignancies in HL.

Although dose reduction has not clearly shown an improvement in second malignancies, dose reduction to the heart seems to be more clearly associated with reduced risk of cardiac dysfunction.[8,10] Coronary artery disease is the most common cardiac toxicity to develop after RT for HL. Even with smaller RT fields, the proximal coronary arteries will still be in-field for patients with mediastinal disease, especially if hilar nodes are involved. Doses above 15 Gy[11] are associated with increased cardiac toxicity at 20 years; thus, even modern doses may result in early cardiac disease. As discussed in the Hoppe et al review, PT can preferentially spare normal tissues that are "in-field" with photon RT and thus, it is hoped, translate into a clinical reduction in cardiac morbidity after RT. This is in contrast to valvular disease, which appears less sensitive to RT. A recent report by Cella et al suggests minimal risk of even asymptomatic valvular dysfunction with RT doses below 25 Gy.[12] It is unlikely that modern RT doses with any modality (photon or proton) will result in significant valvular effects.

There has been a recent flurry of interest and controversy in the popular press about the wisdom of proton beam therapy. In part because of general concern about rising health care costs, some have questioned whether the current "rush" to build expensive proton beam facilities at multiple medical centers is warranted. The utility of PT for certain malignancies, such as prostate cancer, is not yet clarified.

We note that the outcomes of treatment for many types of childhood malignancies have significantly improved over the last 40 years, in large part due to the use of systematic controlled clinical trials. Unlike adults, 60% of all children with cancer are enrolled on clinical trial protocols. There is little doubt that increasing the percentage of adult patients who participate in clinical trials from the current 5% would accelerate the rate at which cures can be developed. Similarly, because the final word on PT for certain types of cancers is not yet written, we encourage as many patients as possible who receive PT to do so under the auspices of a clinical trial, so that all can benefit from the knowledge their experience will provide. Although the optimal approach would be to conduct randomized prospective therapeutic trials that directly compare patients receiving IMRT to those being treated with PT, it may be difficult to enroll sufficient numbers of patients, given the significant reduction in irradiated volume and lack of equipoise in both potential patients and providers. On the other hand, appropriately controlled case-control trials should be able to provide definitive data on this question in the future.

As noted by Hoppe et al, studies of PT for the treatment of HL to date clearly confirm the predicted outcome of reduced toxicity with maintenance of effective therapeutic radiation to the tumor. Thus, treatment of HD using PT is highly supported by the data. Projections regarding the economic impact of PT in other solid tumors, such as pediatric medulloblastoma and sites that are less prone to second malignancies and chronic conditions (eg, "young" [< 60 years] patients with breast or prostate cancer), also suggest that PT is cost-effective, given the economic impact of late effects of treatment.[13-15] Because a majority of patients with HL are young and have a substantial number of years of life remaining, due to the high cure rates, it is highly likely that PT will be cost-effective in this population as well. The use of PT for children with solid tumors is arguably one of the more important new developments in the treatment of solid tumors in pediatric and young adult patients and will likely have a significant impact on reduction of late effects in this vulnerable population.

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References:


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