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Proton Therapy for Paediatric Medulloblastoma

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In recent decades, the field of radiation oncology has changed dramatically, driven by mainly by technical advances in treatment planning and delivery. Proton radiation therapy represents a further advancement; however, proton therapy is more expensive, and many argue that its upfront costs are not justified.

Proton therapy is distinct from traditional photon, or X-ray-based therapies. The physical properties of charged particle therapy, such as protons, allow radiation oncologists to control where the radiation dose stops, and thus spare healthy tissues outside the target volume. On first inspection, a visual comparison of photon and to proton therapy treatment plans will always show that low-dose radiation spread is minimized with proton therapy. This is especially true for medulloblastoma, the most common malignant paediatric brain tumor, in which the entire brain and spine must be irradiated to minimize the risk of recurrence. Although such visual comparisons are compelling, even within the radiation oncology community there is a vibrant debate as to the clinical benefits of this low-dose sparing.

Proton therapy has actually been in clinical use for decades; however until recently, only a limited number of centers in the United States and worldwide have had access to proton therapy. This lack of availability is in large part responsible for the paucity of clinical data supporting the routine use of protons for cancer treatment. In this issue of *The Lancet Oncology*, investigators from the Massachusetts General Hospital, one of the institutions that pioneered proton therapy, present outcomes from a prospective study of proton therapy for childhood medulloblastoma.¹ Given the rarity of this disease, the investigators are to be congratulated for their careful assessment of disease control rates and equally as important, its long-term toxic effects.

In addition to having different physical properties, protons and photons also have different biological effectiveness. Some have argued that the biologic uncertainties associated with proton therapy could lead to higher rates of disease recurrence in patients with medulloblastoma.² With 5-year event-free survival rates of 85% for low-risk patients and 70% for high-risk patients, Yock et al.¹ demonstrate disease control rates in line with those seen in large cooperative group studies using photons.^{3,4} Coupling this finding with a detailed analysis of the patterns of failure, the investigators quell concerns regarding disease recurrence.

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Equally as important, in assessing late radiation adverse effects the investigators offer a glimpse into the benefits of the low-dose sparing afforded by proton therapy. Treatment of the spine with standard photon therapy exposes anterior structures such as the heart and bowel to substantial exit doses. With proton therapy, doses to anterior structures such as are reduced to zero. As predicted, in this cohort treated with proton therapy, no cardiac or gastrointestinal sequelae were observed and no secondary malignancies recorded. Conversely, the authors did report a significant decrease in neurocognitive function, with an average decline in full-scale intelligence quotient of 1.5 points per year, driven mainly by outcomes observed for patients treated at ages less than 8 years. Practitioners must remind families that they are out of necessity treating the entire brain and that this exposure can be associated with cognitive impairment.

The rarity of this disease, in combination with the compelling dosimetric data and clinical results presented by York and colleagues, make a randomized trial of photons vs. protons for medulloblastoma unlikely. This situation contrasts with more common malignancies in adults, for which randomized trials comparing the two modalities are underway. However, in the absence of randomized trials, even for pediatric tumors, states such as Oregon have gone so far as to say that no child should be treated with protons, and that all should be treated with photon therapy. If such an approach is widely adopted, survivors of childhood medulloblastoma could unnecessarily suffer a high incidence of cardiovascular disease and other adverse effects.

This study sets a new benchmark for the treatment of pediatric medulloblastoma and highlights the clinical benefits of advanced radiation therapy modalities. Many have voiced concerns that radiation oncology is becoming an antiquated field, focusing only on new technologies rather than actively participating in mapping the genomic landscape of cancer in an effort to eradicate the disease. In some sense this may be true and it is important for our field to embrace change. Medulloblastoma is the poster child disease for the integration of genomics and molecular subtyping.⁵⁻⁷ As treatment paradigms continue to evolve in light of such evidence, it will be increasingly important for radiation oncologist to be involved in the design of new prospective studies, potentially modifying radiation dose and volumes to avoid sequelae such as cognitive decline. It also behooves us to take measures to prevent cognitive decline in this patient population through an understanding of the underlying biologic mechanisms and taking guidance from clinical experiences in adult patients.⁸

By contrast with practitioners in other specialties, I believe that radiation oncologists have always understood that our therapies are associated with the potential for severe adverse effects. I also believe that many in radiation oncology embrace new technology, not simply to have the latest and greatest innovations, but rather to reduce the effect of radiation therapy on patients' quality of life. Nowhere in oncology is this more important than for paediatric cancers.

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