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Is the side effect profile of protons really safer than photons for intracranial disease?

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Over the past year, multiple studies have been published reporting on the side effect profile of proton radiation therapy (RT) for both adult and pediatric intracranial disease. Kralik et al. reported a seven percent rate of radiation-induced large vessel cerebral vasculopathy in children treated with proton RT, 80% of whom manifested with acute stroke with demonstrated MRI evidence of acute infarcts in clinically expected vascular distributions; all strokes occurred in vessels proximal to targeted tumors and occurred at a median time of 1.5 years following proton RT [1]. A prospective randomized study involving 47 patients with subtotally resected benign meningiomas treated with an 80% to 20% proton/photon ratio revealed a greater than 20% stroke rate [2], far higher than that expected from either natural history [3,4], following photon RT [5], or following photon stereotactic radiosurgery [6]; stroke developed at a median time of 5.6 years after RT completion [2–6]. These findings beg the question of whether the differences in radiation delivery between proton and photon RT are in some way responsible for the vasculopathy seen following proton RT in the aforementioned studies.

Most recently, Underwood et al. compared breast cancer patients treated with photon versus proton RT and found that follow-up CT scans revealed evidence of lung fibrosis consistent with a relative biological effectiveness (RBE) exceeding the 1.1 for proton RT generally presumed for clinical practice and recommended by the International Commission on Radiation Units and Measurements; this elevated dose was not prevalent in patients who received photon-based RT [7]. Given that the region they examined was located within their radiation field, the conclusion they draw that the proton RBE (unlike the photon RBE) exceeds 1.1 has substantial implications for treatment of intracranial disease. As Kralik et al. stated following their analysis: “At this time there is no reason to anticipate a difference in toxicity, including radiation-induced large vessel cerebral vasculopathy, to normal tissues within a radiation treatment volume receiving a given dose, whether that dose is delivered by photon or proton beam therapy” [1]. However, the finding by Underwood et al. may in fact provide the explanation that despite the superiorly steep fall-off between target and normal tissue provided by protons, normal tissue adjacent to the target may be more likely to receive an abnormally high dose. Furthermore, the variable linear energy transfer (LET) over the length of the beam (particularly at the beam edge) will cause the RBE to vary within the field [7–9]. Not surprisingly, this has increased implications in the brain, where extremely important normal anatomy lies much closer to pathology (and is much more likely to fall within the radiation field) than elsewhere in the body. Further prospective study is needed to determine whether this logical explanation of the increased stroke rate seen following proton intracranial RT in adults and children is in fact substantiated in a hypothesis-driven manner. This aspect of proton therapy should certainly be taken into account for intracranial disease, particularly when a major selling point of proton over photon RT (particularly for pediatric patients) is the decreased radiation dosage to surrounding normal tissues.

Conflict of interests

No authors have any conflicts of interest.

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