EDITORIAL

Patterns of Failure After Proton Therapy in Medulloblastoma

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Proton therapy centers and the pediatric oncology community will welcome the article by Sethi et al (1) published in the March 1, 2014, issue of this journal. The technical data regarding over- or underlapping of adjacent treatment fields are useful to prevent further tumor recurrences at these sites. Also, it is reassuring that an excess tumor recurrence risk was not found just beneath the meninges of the widest portion of the head, including after low, highly fractionated doses of 23.4 Gy (relative biological effect [RBE] = 1.1) and below, which provides nearly 70% of the population studied. This finding does need to be confirmed in larger numbers of patients.

The higher-than-expected “spine only” relapse rate found by the authors is a cause for concern. This finding is compatible with the point made previously (2) that tumor control may be reduced by adopting a tumor RBE of 1.1 if a highly radiation-sensitive tumor (with a high \(\alpha/\beta\) ratio) has an RBE in the range of 1.03 to 1.06. Agreement that the RBE for these highly radiation-sensitive tumors is probably less than 1.1 represents an advance, although modeling predictions are prone to many uncertainties including variations in the input parameters as well as interpatient variations. This must be balanced with the realistic possibility that central nervous system (CNS) tissues may have an RBE of greater than 1.1, such as 1.2 (2, 3). The likely RBE values for important late reacting CNS tissue has not been estimated by experiment nor by inference from clinical data sets, and this is an urgent requirement. Only in some late reacting tissues (lung, lens, and skin) have RBEs been determined, using high doses per fraction in the 9- to 12-Gy range (4) but not at the low doses per fraction given in most radical CNS tumor treatments. It is at the low dose per fraction that an elevated RBE is predicted by linear quadratic model theory. This is because with increasing linear energy transfer (LET), the increment in \(\alpha\) exceeds that of \(\beta\), and because \(\alpha\)-related cell killing predominates at low doses, the RBE is inevitably higher at low doses. This is well demonstrated in fast neutron experiments (3), where there is an inverse relationship between the low-LET \(\alpha/\beta\) ratio and the maximum obtainable RBE. There should be no complacency about protons having a low RBE as a consequence of their relatively low LET values (compared with heavier ions), because it has been established that the rise in RBE with LET occurs at much lower LET values in the case of protons but rises to similar maximum values as found with heavier ions (5).

Consequently, for all the above reasons, a comprehensive national and international audit of all children treated with protons for medulloblastoma is indicated, in which outcome analysis is ideally compared with matched controls, using similar methods as in the study of Sethi et al (1) to determine the relevance of any spatial effects. For similar reasons, outcomes for other radiation-sensitive tumors such as rhabdomyosarcoma, neuroblastoma, and others should also be determined and compared to age-matched controls. In view of the significant spare spinal (or CNS) tolerance available, serious consideration should be given to the following proposals: (1) assume that RBE is unity for these types of pediatric tumors, so that physical dose is not

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reduced compared to photons: this would ensure no loss of tumor control in any child due to the RBE issue; and (2) CNS normal tissues could be given a slightly higher RBE of 1.2, which in the case of doses given to attempt elimination of microscopic tumor spread, would continue to respect spinal and brain tissue tolerances, and for intact tumors, those tissues outside the planning target volume.

A definitive answer to these issues will be provided only by a “randomized RBE” study, which would compare these suggested RBE changes with the present policy of an invariant RBE of 1.1. A simulation of such a trial using random sampling techniques is shown in Figure 1, where the central black line shows the expected intact tumor dose-response curve for photons (Fig. 1, red curve for photons), where a conventional RBE of 1.1 has been used, and the curve for protons (Fig. 1, blue curve) was used without any RBE correction, for a tumor with an assumed RBE of 1.05, using equations published elsewhere (3, 6). It is assumed that CNS radiation tolerance is fully respected by all lines for doses below 50 Gy in 25 fractions. The 95% confidence limits for the mean values are shown by the dashed curves (Fig. 1): 100 patients in each treatment arm, in this simulation, was sufficient to provide significant statistical differences in the relevant range (between 70% and 90%).

The alternative to such a trial would be to change the RBE allocation policy, as suggested, for all patients and then assess outcomes compared to historical series.

The potential long-term quality of life advantages provided by proton therapy for medulloblastoma are well known, but it is important not to prejudice a child’s survival prospect by mild or moderate underdosage compared to photons in clinical situations where dose responses are steep. Clinicians need to be aware that underdosage can be due to a combination of protocol dose selection and RBE allocation. Is it wise in “low-risk patients” to follow marked dose reductions that are designed to avoid the long-term side effects of photons anterior to the spinal region when these tissues are not irradiated by proton beams?

The United States has taken the international lead in proton therapy, and there is widespread admiration of these achievements. In order to build on these achievements and allow proton therapy to reach its full potential, it is hoped that rapid, decisive, and cooperative action will now follow in the US.

Fig. 1. Plot shows expected cure with total dose given in 2-Gy fractions, using Poisson statistics. The black solid curve indicates photons, red curves are protons (with relative biological effect [RBE] = 1.1), and blue line is for protons (with RBE = 1). Dashed curves indicate 95% confidence limits of the mean for the proton treatments. Assumptions for radiobiological parameters, given as means ± SD, are as follows: α = (0.5 Gy⁻¹, 0.07); β = (0.03 Gy⁻², 0.005); clonogen doubling time = 10 days, 1.5 with log normal distribution, clonogens (5 × 10⁹, 5 × 10⁸). A color version of this figure is available at www.redjournal.org

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