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EDITORIAL

Protons, the brainstem, and toxicity: Ingredients for an emerging dialectic

TORUNN I. YOCK[1], LOUIS S. CONSTINE[2] & ANITA MAHAJAN[3]

[1]*Massachusetts General Hospital, Francis H. Burr Proton Therapy Center, Boston, USA,* [2]*University of Rochester Medical Center, Radiation Oncology and Pediatrics, Rochester, USA and* [3]*MD Anderson Cancer Center, Radiation Oncology, Houston, USA*

During the past three decades there has been a growing appreciation of the late side effects that therapeutic interventions inflict on childhood cancer survivors. While brain radiotherapy (RT) remains an essential part of treatment for many pediatric brain tumor patients, it is associated with a spectrum of normal tissue toxicities including impaired neurocognitive, neuroendocrine, auditory and visual functioning, and secondary malignancies [1–3]. These effects can translate into a diminished quality of life (QoL) and even mortality [4–6]. 'Proton therapy' (PT) has been increasingly available and recognized for its potential to attenuate treatment-related side effects. Its physical properties allow a reduction in radiation dose to uninvolved normal tissues while maintaining a therapeutic dose to the tumor. In 2002, only two proton centers were actively treating patients in the US, but now there are 14 in the US and several more elsewhere in the world with many more poised to open. Many children are referred to proton centers due to the promising dose distribution with a real potential to reduce the frequency and severity of late effects [7]. The dose distribution superiority is appealing for dose escalation for tumors with moderate local control.

Risk factors

Over the past several years an increasing number of children have been treated with PT. During this time there has been a growing awareness that toxicities, including brainstem necrosis, can occur with PT just like with photon therapy. Thirty to forty percent of patients with brain tumors between ages 0 and 19 years have tumors that arise within the posterior fossa (PF) that are in close proximity to, or directly infiltrate the brain stem; therefore, these patients are at increased risk for brainstem injury. This complication has developed in a minority of patients treated with PT. Yet, this finding was unanticipated since PT is intended to diminish side effects. However, before the study by Indelicato et al. appearing in this issue was published [8], the rate of brainstem necrosis associated with PT in comparison to photon-treated pediatric cohorts was not known.

Indelicato and his colleagues offer a thorough examination of the patient and treatment factors that may dispose to brainstem injury in pediatric patients [8]. This is the largest pediatric study (n = 313) to analyze factors associated with brainstem toxicity and necrosis and is both a unique and very valuable contribution to a relatively sparse literature which is briefly reviewed below.

Previous pediatric studies have identified some common risk factors for brainstem necrosis and include the following: increasing radiation dose to brainstem or combined brainstem and cerebellum, exposure to chemotherapy, use of high dose chemotherapy, surgical morbidity, multiple surgeries, hydrocephalus and/or shunt placement, PF syndrome, larger tumor size, infratentorial tumor location, young age, and male gender [9–11]. The adult-based literature find many of these same risk factors with the addition of elderly age, diabetes, hypertension, post-radiation chemotherapy and hypofractionation [12–15].

Dose constraints

Dose constraints to the brainstem used by radiation oncologists are not universally agreed upon and are derived from imperfect and heterogeneous adult and

Correspondence: T. I. Yock, MGH, Radiation Oncology, 55 Fruit Street, Proton Center, Boston, 02114 USA. E-mail: tyock@partners.org

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pediatric data. The Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) review published in 2010 [14] offers the following dose guidelines: 100% of the brainstem may receive 54 Gy and smaller volumes (1–10 ml) may receive doses of 59 Gy at less than 2.0 Gy per fraction with a limited risk of severe brainstem toxicity. Subsequently (2012), Murphy et al. published an article dedicated to brain necrosis in 236 children with embryonal tumors (195 infratentorial, 28 supratentorial, 3 spinal) treated with surgery, chemotherapy and photon craniospinal irradiation (CSI) (23.4–39.6 Gy) and a primary tumor boost to a dose of 55.8 Gy. The authors reported brain necrosis in eight patients (7 brainstem, 1 cerebellar) representing 3.7% of the whole population and 4.4% of patients with infratentorial tumors. They concluded that dose to the infratentorial brain (brainstem and cerebellum) was more predictive of necrosis than dose to the brainstem alone, perhaps relating to devascularization or other neurologic injury from surgery. The following dosimetric constraints to the combined brainstem and cerebellum were suggested for a necrosis rate of 1% or less: V50 < 73%; V52 < 69%; V 54 < 63% [10]. Notably, these constraints would not be met in the most recently closed standard and high risk medulloblastoma trials since the whole PF required treatment to either 54 or 55.8 Gy. Merchant et al. published results of 153 pediatric patients with ependymoma receiving RT doses of 54 Gy (age < 18 months) and 59.4 Gy (18 months +) with no constraints on brainstem dose. They found three of 122 patients (2.5% at 7 years) with infratentorial tumors developed brainstem necrosis [16]. Notably, while no patient with brainstem necrosis in this study received chemotherapy, all three had peri-operative morbidity which the authors believe was directly related to the radiation necrosis outcomes.

Children's Oncology Group (COG) is the international cooperative group that is very successful in conducting clinical trials and tends to be the US reference standard for treatment strategies for childhood malignancies including brain tumors. Interestingly, the radiation dose guidelines for brainstem constraints have been less stringent than what Emami recommended [17]: 5% risk of necrosis if one third of the brainstem received 60 Gy; or even RTOG, which suggests that maximum dose to the brainstem not exceed 60 Gy. The COG brainstem dose guidelines differ somewhat depending on the study. The closed COG ependymoma study, ACNS 0121, used a target dose of 59.4 Gy for children older than 18 months and did not have brainstem dose constraints. At this time toxicity information is not available for review but a publication is reportedly forthcoming. In contrast, the current COG ependymoma study, ACNS 0831, incorporates the following dose maximum guidelines for the brainstem: D90% < 59 Gy, D50% < 62 Gy and D10% < 64 Gy. The recently closed COG medulloblastoma trials (ACNS 0331 and 0332) do not have specific constraints for the brainstem for boost prescription doses of 54–55.8 Gy, but denote that no more than 5% of the boost volume should receive greater than 110% of the prescription dose. The COG ATRT protocol (ACNS 0333) delineates the following target constraints: goal D50% < 61 Gy and D10% < 63 Gy; and maximum allowed D50% < 62 Gy and D10% < 64 Gy. (COG member web site: https://members.childrensoncologygroup.org/prot/default.asp).

Much of the history of brainstem constraints for pediatric PF tumors may emanate from the experience with diffuse intrinsic pontine glioma (DIPG) patients, in whom the whole brainstem has been treated to 59.4 Gy with conventional fractionation or 70.2–78 Gy with a hyperfractionated regimen. Caution should be used in interpreting this data, however, as the median time to death is 10 months due to tumor progression. The risk of radiotherapy associated brainstem toxicity may be underestimated due to short patient lifespan [18,19] and true brainstem toxicity may be difficult to discern from intratumoral necrosis. It should be noted that the highest rate of necrosis within the tumor (and thus also within the brainstem) was in patients treated to 78 Gy. The authors noted that the higher RT doses may be associated with higher rates of steroid dependency [20].

Previous reports of brainstem toxicity include a mixture of patient populations. Brainstem toxicity was not separated from CNS toxicity, and in some cases only frank necrosis, as defined by imaging characteristics, was reported. Indelicato et al. describes the spectrum of brainstem injury and uses the CTCAE v4 toxicity grading scheme for CNS necrosis and applies it to the brainstem. While the authors report that overall two-year incidence of grade 2 or more brainstem toxicity was 3.8%, it is important to learn from their detailed analysis which patient cohort is at highest risk. The actuarial rate of brainstem toxicity for any age pediatric patient with a PF tumor was 10.7% and somewhat worse in the patients < 5 years, (12.5% vs. 7.2%, 5 + years). Interestingly, chemotherapy was not found to be a contributing factor to the development of brainstem necrosis in this study although heavily implicated in other studies [12,14]. This finding may be in part related to the relatively high proportion of patients with ependymoma (n = 73, 23.3%) where chemotherapy currently is used in only specific circumstances [8,21].

In the Indelicato study [8], histology was not included in the univariate analyses. Notably, 8 of 11

patients with brainstem toxicity had ependymoma, whereas there was only one each of ATRT, medulloblastoma and low-grade glioma. The crude rate of brainstem toxicity for the ependymoma population for this cohort was 8/73 or 10.9% of patients and that is probably inclusive of some patients with supratentorial ependymomas. As the disease control rates are approximately halved when leaving significant gross disease [16,22], neurosurgeons are more inclined to be more aggressive to achieve a greater chance of cure. PF ependymomas comprise about two thirds of the brain ependymoma cases and typically arise in or around the fourth ventricle. These PF ependymomas commonly invade the foramen of Lushka, become entwined with critical cranial nerves and vessels, and encircle the brainstem. Such insidious intercalation in the nerves and vasculature often makes a complete surgical resection both challenging and morbid – rendering these patients at higher risk of brainstem toxicity with the added insult of radiation [9].

Indelicato et al. identified two useful clinical variables associated with higher risks of brainstem necrosis, namely young age (<5 years) and PF location. They also delineated a variety of dosimetric parameters that correlated with significant brainstem toxicity (see Indelicato table II) and multiple useful dosimetric constraints which can be used to inform proton treatment planning. Two useful guidelines are: 1) that the maximum dose to the brainstem should not exceed 56.6 Gy; and 2) that the mean dose to 50% of the brainstem should be 52.4 Gy or less [8]. These data should be validated in other proton center's data sets, but for now, they provide some real guidance for PT users. Furthermore, these guidelines can be readily incorporated into COG PT guidelines that had previously allowed both these parameters to be exceeded.

RBE of protons versus photons

Although the authors do not state this outright, this study raises the question that brainstem tolerance values for PT may be different than those for photon radiotherapy. This possibility *does not* erase the late effect benefit with proton radiotherapy in the pediatric population. Rather, the radiation oncology community should err on the side of caution with the brainstem. While a lot is known about PT, investigators are still defining tolerance to critical structures and differences between proton and photon radiobiology [23,24]. It is important to note, that we do not possess full knowledge of dose-volume constraints and contributing factors for photon RT as documented by the QUANTEC project. Many QUANTEC papers call for more detailed dosimetric data in order to formulate more definitive conclusions. In fact, a similar study in pediatrics radiotherapy is now ongoing and led by Dr. Louis Constine. It is called Pediatric Normal Tissue Effects in the Clinic (PENTEC), and the site-specific results of which are likely to be published in 2015.

We do know that the physical properties and radiobiology of protons is somewhat different than photon radiation. The relative biological effectiveness (RBE) as compared to photon radiation is on average 1.1 for conventional fractionation [24]. It is known however, that this RBE differs depending on the location within the Bragg peak, by tissue type and by fraction size. At the very distal end of a spread out Bragg peak range, the RBE may be as high as 1.2 or 1.3 [24]. Some of these subtleties and minor differences from photons may be contributing to some of the unanticipated brainstem toxicities. The possibility of a higher RBE at the end of range is incorporated into treatment planning in different ways across institutions. Some centers, depending on the circumstances, will treat the whole structure (i.e. the brainstem) to avoid ranging out within the brainstem [25]. Indelicato's dosimetric data shows that that approach may be detrimental and may increase toxicity because of the volume effects of treating the whole brainstem. Volume effects were also noted by Merchant et al. and Murphy et al. in the pediatric PF brainstem toxicity data as well as in the adult brainstem toxicity literature [9,10,12,14].

Implications

In summary, the study by Indelicato et al. is an excellent work that renders a detailed clinical and dosimetric analysis of brainstem toxicity in the pediatric brain tumor population. Pertinent take home points are: 1) more caution with brainstem dosing should be used than what has being used for current and past COG protocols with proton radiation; and 2) some part of the brainstem should be spared full tolerance dose (i.e. 54 Gy, per QUANTEC) whenever possible. Patients who are young (<5 years) or those with posterior fossa tumors, particularly ependymoma, may be at the highest risk for brainstem toxicity. It is precisely this population in whom we should exercise caution with PT brainstem dose in our treatment plans.

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