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Ototoxicity and cochlear sparing in children with medulloblastoma: Proton vs. photon radiotherapy

Arnold C. Paulino [a,*], Anita Mahajan [a], Rong Ye [b], David R. Grosshans [a], M. Fatih Okcu [c], Jack Su [c], Mary Frances McAleer [a], Susan McGovern [a], Victor A. Mangona [a], Murali Chintagumpala [c]

[a] Department of Radiation Oncology, MD Anderson Cancer Center; [b] Department of Biostatistics, MD Anderson Cancer Center; and [c] Texas Children's Cancer Center and Baylor College of Medicine, Houston, USA

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ABSTRACT

Purpose: To compare ototoxicity rates between medulloblastoma patients treated with protons vs. photons.

Materials and methods: The study included 84 children diagnosed with medulloblastoma treated with either passively scattered protons ($n = 38$) or photons ($n = 46$). Patients underwent maximal safe resection followed by craniospinal irradiation, posterior fossa and/or tumor bed boost and chemotherapy according to one of 3 multi-institutional trials. Median audiogram follow-up was 56 months for protons and 66 months for photons.

Results: Mean cochlear dose (D_{mc}) was lower in patients treated with protons for both standard ($p < 0.0001$) and high-risk disease ($p < 0.001$). Grade 3 and 4 ototoxicity was seen in 7 of 75 (9.3%) and 9 of 91 (9.9%) ears (Brock, $p = 0.91$), 13 of 75 (17.3%) and 19 of 91 (20.9%) ears (POG, $p = 0.56$), and 15 of 75 (20.0%) and 21 of 91 (23.1%) ears (SIOP Boston, $p = 0.63$) with protons and photons respectively.

Conclusions: While cochlear doses were lower in the proton group, patients treated with either protons or photons had similar Grade 3 and 4 ototoxicity rates.

Hearing loss is an important treatment-related toxicity which may result in impairment of scholastic and social development in pediatric brain tumor patients [1]. In medulloblastoma, cisplatin-based chemotherapy is often given as part of the treatment regimen. Moreover, radiation therapy (RT) is routinely used in the treatment of medulloblastoma, and radiation exposure to the cochlea may exacerbate hearing loss.

For decades, photon craniospinal irradiation (CSI) followed by a posterior fossa boost has been the standard radiotherapy (RT) treatment for medulloblastoma. Photon therapy has evolved dramatically. With the advent of intensity-modulated radiation therapy (IMRT) combined with the use of a tumor-bed boost, clinicians are better able to sculpt high dose regions away from critical structures in the posterior fossa, including the cochlea. A cochlear-sparing approach using IMRT in medulloblastoma patients receiving cisplatin has been shown to reduce Grade 3 and 4 ototoxicity [2]. Prior to IMRT, parallel opposed lateral fields to treat the posterior fossa delivered the prescribed dose to the tumor bed and neighboring cochleae with 64% developing Grade 3 and 4 ototoxicity [3]. More recently, proton therapy has been used in medulloblastoma. The obvious benefits of proton therapy when used for CSI include sparing anterior structures such as the heart, lungs and thyroid gland from the exit dose of the spine field [4]. Among proton therapy techniques, passive scattering proton therapy (PSPT) has been used for majority of CSI treatments. While during the CSI component of treatment PSPT does not spare the cochlea, for the tumor bed boost, protons deliver less dose to the cochlea compared to IMRT. A preliminary report from our institution showed a 5% Brock Grade 3 and 4 otoxicity at 1 year post-radiotherapy with the use of protons in 19 patients [5]. With longer follow-up and more patients, an update on our proton experience with regard to ototoxicity was performed and compared to previous patients treated with photons using a cochlear-sparing IMRT approach.

Patients and methods

From 1997 to 2013, 107 children with medulloblastoma were diagnosed at Texas Children's Hospital and treated with craniospinal RT (photons 63, protons 44) and cisplatin-based chemotherapy. For the 63 photon patients, 8 had audiogram follow-up <1 year from RT, 8 died in <1 year from RT, and 1 was

* Corresponding author at: Department of Radiation Oncology, MD Anderson Cancer Center, 1515 Holcombe Blvd, Box 97, Houston, TX 77030, USA.
E-mail address: apaulino@mdanderson.org (A.C. Paulino).

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treated with non-cochlear sparing RT, leaving 46 photon patients for analysis. For the 44 proton patients, 4 had audiogram follow-up <1 year from RT, 1 died in <1 year from RT and another had congenital hearing loss, leaving 38 proton patients for analysis. Therefore, the 84 patients (photons 46, protons 38) comprise the total number of patients analyzed in this study.

Before 2007, all patients were treated with 3-dimensional (3-D) photons to the craniospinal axis followed by IMRT to the boost field ($n = 46$). Thereafter, patients were treated with passively scattered protons to the craniospinal axis and the tumor bed at the MD Anderson Proton Center ($n = 38$). There were 60 (71.4%) male and 24 (28.6%) female patients. Median age at diagnosis was 8.9 years (range, 35 months to 18 years). Twenty-six (31.0%) had high-risk disease. Patients underwent maximal safe resection followed by craniospinal irradiation (CSI), posterior fossa (PF) and/or tumor bed (TB) boost and cisplatin-based chemotherapy according to one of 3 multi-institutional trials. Standard-risk patients received 18–23.4 Gy/CGE while high-risk patients received 36–39.6 Gy/CGE to the craniospinal axis. Dose to the tumor bed and any residual was 54–55.8 Gy/CGE. For photon therapy, the boost treatment was delivered using IMRT to the entire PF in 6, PF to 36 Gy followed by TB in 29, and TB alone in 11. For proton therapy, the boost was given to the tumor bed alone.

Chemotherapy was delivered 4 weeks after RT. None of the children received concurrent chemotherapy during radiotherapy. All patients treated with protons had amifostine with the cisplatin chemotherapy, whereas only 19 (41.3%) of the patients treated with IMRT had amifostine.

Contoured cochlear volumes were reviewed to make sure they were standardized. Cochlear volume delineation examples have been reported previously by our group [2,5]. Hearing thresholds were assessed by pure tone audiograms. Hearing thresholds were determined for each ear at stimulus frequencies of 0.25, 0.5, 1, 2, 4, 6 and 8 kHz. In all, 501 audiograms were reviewed, analyzed and graded according to the International Society of Pediatric Oncology (SIOP) Boston (Grade 0: ≤20 dB loss at all frequencies, Grade 1: >20 dB loss at >4 kHz, Grade 2: >20 dB loss at ≥4 kHz, Grade 3: >20 dB loss at ≥2 kHz, Grade 4: >40 dB loss at ≥2 kHz), Brock (Grade 0: <40 dB at all frequencies, Grade 1: ≥40 dB loss at 8 kHz, Grade 2: ≥40 dB loss at 4 kHz, Grade 3: ≥40 dB loss at ≥2 kHz, Grade 4: ≥40 dB loss at ≥1KHz) and Pediatric Oncology Group (POG) objective scale (Grade 0: normal, Grade 1: 20–40 dB loss at >4 KHz, Grade 2: >40 dB loss at 4 kHz, Grade 3: >40 dB loss at >2 kHz, Grade 4: 40 dB loss at < 2 kHz) [6,7]. Each patient's hearing was also classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (Grade 1: threshold shift or loss of 15–25 dB relative to baseline, averaged at 2 or more contiguous test frequencies in at least 1 ear or subjective change in the absence of a Grade 1 threshold shift, Grade 2: threshold shift or loss of >25–90 dB, averaged at 2 contiguous test frequencies in at least 1 ear, Grade 3: hearing loss sufficient to indicate therapeutic intervention including hearing aids e.g., ≥20 dB bilateral hearing loss in the speech frequencies; ≥30 dB unilateral hearing loss; and requiring additional speech-language related services, Grade 4: audiologic indication for cochlear implant and requiring additional speech-language related services). Audiograms were scheduled before and 6 weeks after RT; after each cycle of chemotherapy; and 6 months, 1 year and thereafter. In a few cases, auditory brainstem response (ABR) was performed prior to radiotherapy because of young age or posterior fossa syndrome. Audiogram follow-up was calculated from the end of RT to the last audiogram. Median audiogram follow-up was 66 months (range, 13–163 months) for photons and 56 months (13–101 months) for protons.

Wilcoxon rank sum test, Fisher's exact test or Chi-square was used to evaluate the difference in the continuous variables and the categorical variables between the photon and proton treatment groups. A two-side Wilcoxon rank sum test was performed to compare the mean cisplatin doses between the 2 groups. Likewise, the Wilcoxon rank sum test was used to compare the mean cochlear doses between grades 0–2 and 3–4 according to the SIOP Boston, POG, Brock ototoxicity scales and the CTCAE scale.

The cumulative incidence rates of Grade 3 and 4 ototoxicity were estimated using Kaplan–Meier method. The log-rank test was adapted to evaluate the difference in time to event (Grade 3 or higher toxicity) between photon and proton therapy.

Results

Patient, tumor and treatment characteristics

The patient, tumor, treatment and follow-up characteristics according to type of radiation delivered are presented in Table 1. There was no difference between the photon and proton patients with regard to gender, age, risk-category, posterior fossa syndrome and number of audiograms. Thirty-seven patients (44.0%) had a shunt; there was no difference in distribution of proton vs. photon patient with regard to shunt placement. Patients treated with photons were more likely to have the entire posterior fossa treated as part of the boost portion of RT ($p < 0.0001$). All patients treated

Table 1
Patient, tumor, treatment and follow-up characteristics in patients receiving photons and protons.

	Photons $n = 46$	Protons $n = 38$	*P*-value
Gender			0.678
Male	32 (69.6%)	28 (73.7%)	
Female	14 (30.4%)	10 (26.3%)	
Age, years			0.262
Mean ± standard deviation	9.0 ± 4.0	7.9 ± 3.4	
Median (range)	9.0 (3.0–18.0)	7.6 (2.9–14.5)	
Risk category			0.289
Standard-risk	34 (73.9%)	24 (63.2%)	
High-risk	12 (26.1%)	14 (36.8%)	
Shunt placement			0.099
Yes	24 (52.2%)	13 (34.2%)	
No	22 (47.8%)	25 (65.8%)	
Posterior fossa syndrome			0.788
Yes	7 (15.2%)	5 (13.2%)	
No	39 (84.8%)	33 (86.8%)	
Radiotherapy boost			<0.0001
Posterior fossa boost	6 (13.0%)	0 (0)	
Posterior fossa followed by tumor bed boost	29 (63.0%)	0 (0)	
Tumor bed boost	11 (23.9%)	38 (100%)	
Cochlear dose, cGy			<0.0001
Mean ± standard deviation	3725.5 ± 543.3	3149.3 ± 785.5	
Median (range)	3590.0 (2520.0–5490.0)	2931.7 (1598.0–5245.4)	
Cisplatin dose, mg/m2			0.004
Mean ± standard deviation	350.5 ± 140.1	281.3 ± 59.5	
Median (range)	318.0 (55.0–860.0)	300.0 (135.0–473.0)	
Number of audiograms			0.388
Mean ± std dev	6.0 ± 3.6	6.2 ± 1.5	
Median (range)	5.5 (2–15)	6 (4–9)	
Audiogram follow-up, months			0.105
Mean	68.6	52.5	
Median (range)	65.5 (13–163)	55.5 (17–101)	
Amifostine use			<0.0001
Yes	19 (41.3%)	38 (100%)	
No	27 (58.7%)	0 (0)	

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