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CLINICAL INVESTIGATION **Brain**

INTENSITY-MODULATED RADIATION THERAPY FOR PEDIATRIC MEDULLOBLASTOMA: EARLY REPORT ON THE REDUCTION OF OTOTOXICITY

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Purpose: The combination of cisplatin chemotherapy and radiation therapy for the treatment of medulloblastoma has been shown to cause significant ototoxicity, impairing a child's cognitive function and quality of life. Our purpose is to determine whether the new conformal technique of intensity-modulated radiation therapy (IMRT) can achieve lower rates of hearing loss by decreasing the radiation dose delivered to the cochlea and eighth cranial nerve (auditory apparatus).

Patients and Methods: Twenty-six pediatric patients treated for medulloblastoma were retrospectively divided into two groups that received either conventional radiotherapy (Conventional-RT Group) or IMRT (IMRT Group). One hundred thirteen pure-tone audiograms were evaluated retrospectively, and hearing function was graded on a scale of 0 to 4 according to the Pediatric Oncology Group's toxicity criteria. Statistical analysis comparing the rates of ototoxicity was performed using Fisher's exact test with two-tailed analysis.

Results: When compared to conventional radiotherapy, IMRT delivered 68% of the radiation dose to the auditory apparatus (mean dose: 36.7 vs. 54.2 Gy). Audiometric evaluation showed that mean decibel hearing thresholds of the IMRT Group were lower at every frequency compared to those of the Conventional-RT Group, despite having higher cumulative doses of cisplatin. The overall incidence of ototoxicity was lower in the IMRT Group. Thirteen percent of the IMRT Group had Grade 3 or 4 hearing loss, compared to 64% of the Conventional-RT Group ($p < 0.014$).

Conclusion: The conformal technique of IMRT delivered much lower doses of radiation to the auditory apparatus, while still delivering full doses to the desired target volume. Our findings suggest that, despite higher doses of cisplatin, and despite radiotherapy before cisplatin therapy, treatment with IMRT can achieve a lower rate of hearing loss. © 2002 Elsevier Science Inc.

IMRT, Ototoxicity, Medulloblastoma, Cisplatin, Hearing loss.

INTRODUCTION

Surgery, radiotherapy, and chemotherapy are all vital components in the treatment of medulloblastoma. Using a combination of these modalities, cure rates approach 70%. However, these high cure rates are achieved at the cost of delivering higher doses of chemotherapy and radiation, further increasing the incidence of side effects, particularly sensorineural hearing loss (SNHL). Radiation-induced SNHL usually develops within 6 to 12 months after radiation (1). It has been shown to be a dose-related phenomenon (2), affecting the higher hearing frequencies in about 25–50% of patients after curative doses greater than 50–60 Gy (3–5). Although the mechanism remains unproven, it is generally thought to be attributed to radiation-induced changes in the cochlea or vasculature (6, 7).

Platinum agents play an important role in the chemotherapy regimens for medulloblastoma, and cisplatin-induced hearing loss in children is well documented in the literature (8–10). The ototoxicity is bilateral, irreversible, and directly related to the cumulative cisplatin dose. Hearing loss first occurs in the higher frequencies, and continued exposure eventually affects the lower frequencies that are used in speech. The known risk factors

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Table 1. Patient characteristics

Variable	Conventional RT	IMRT
Number	11	15
Male gender—no. (%)	9 (92)	12 (80)
Age		
Median	6	10
Range	3–15	3–14
Risk stratification		
Low — no. (%)	5 (46)	11 (73)
High — no. (%)	6 (54)	4 (27)

for cisplatin ototoxicity are young age, presence of a central nervous system tumor, and prior cranial irradiation (8). Unfortunately, the vast majority of medulloblastoma patients share all of these risk factors.

Ototoxicity has been shown to be even more significant when radiotherapy and cisplatin chemotherapy are used in combination. Cranial irradiation before chemotherapy enhances and potentiates cisplatin ototoxicity (11–14). With cisplatin alone, there is a negligible risk of hearing loss at doses 90–360 mg/m^2; however, this risk increases to 60–80% when combined with prior cranial irradiation (8). This combination of chemotherapy and radiotherapy will cause significant ototoxicity that may impair the child's cognitive function and quality of life.

Intensity-modulated radiation therapy (IMRT) is a new technology for conformal radiation therapy that uses inverse planning and computer-controlled radiation deposition (15). The chief advantage of IMRT is its ability to precisely deliver radiation to the target tissue while relatively sparing the surrounding tissues, such as the cochlea and eighth cranial nerve (auditory apparatus). This enables escalation of dose to the tumor, providing better disease control, simultaneously minimizing treatment-related morbidity. Our purpose is to determine if the conformal technique of IMRT, by decreasing the radiation dose delivered to the auditory apparatus, can reduce the rate of ototoxicity in children with medulloblastoma.

METHODS AND MATERIALS

Patients and treatment

Forty-nine consecutive patients who received treatment for medulloblastoma at The Methodist Hospital and/or Texas Children's Hospital, Baylor College of Medicine from 1992 through 1999 were identified through departmental records. For the purposes of this paper, only pediatric patients treated with both radiotherapy and chemotherapy were selected. Patients who were omitted included the following: 2 adults, 9 patients who did not receive radiotherapy, and 7 patients who did not receive chemotherapy. Therefore, 31 patients were eligible for this review, but 5 were excluded, because they did not receive any audiometric testing during treatment. The remaining 26 patients formed the basis of this study, and their characteristics are shown in Table 1.

The patients were retrospectively divided into two groups according to the modality of radiotherapy: two-dimensional conventional radiotherapy (Conventional-RT Group) or IMRT (IMRT Group). At the time of diagnosis, the patients had been further divided into subgroups of low risk or high risk. Patients were designated as high risk when one of the following two criteria were met: residual tumor size was greater than 1.5 cm^3 after surgical resection, or there was evidence of metastatic disease within the neuraxis. Depending on their risk stratification, the patients generally received one of the respective radiotherapy regimens shown in Table 2.

The Conventional-RT Group consisted of 11 patients who received a craniospinal radiation dose (low risk: 23.4–24 Gy, high risk: 35.2–36 Gy) followed by a posterior fossa boost (low risk: 30.6–32.4 Gy, high risk: 18–19.8 Gy). The radiation was delivered by conventional parallel-opposed beams for a total dose of 53.2 to 55.8 Gy. Eight patients received chemotherapy consisting of cyclophosphamide, vincristine, etoposide, and cisplatin (mean dose: 220 mg/m^2) delivered over two to four courses. One patient received carboplatin instead of cisplatin, and two patients received MOPP chemotherapy (mechlorethamine, vincristine, procarbazine, and prednisone). Four of the 11 patients received chemotherapy before radiotherapy.

The IMRT Group consisted of 15 patients who first received a craniospinal radiation dose (low risk: 23.4 Gy, high risk: 36 Gy) delivered by conventional technique. This was followed with boosts delivered by IMRT. The low-risk patients first received a posterior fossa boost (12.6 Gy at 1.8 Gy/day). Therefore, the entire posterior fossa in both risk groups received a cumulative radiation dose of at least 36 Gy. Next, both the low-risk and the high-risk patients received a tumor bed boost (19.8 Gy at 1.8 Gy/day) where the clinical target volume was defined as the primary tumor bed, plus a 2-cm margin of adjacent brain tissue in three dimen-

Table 2. Summary of radiation dose according to patient group and risk stratification

	Craniospinal dose (Gy)	Posterior fossa boost (Gy)	Tumor bed boost (Gy)	Total radiation dose (Gy)
Conventional RT				
Low risk	23.4	30.6	–	54
High risk	36	18	–	54
IMRT				
Low risk	23.4	12.6	19.8	55.8
High risk	36	–	19.8	55.8

Table 3. Pediatric Oncology Group's Objective Ototoxicity Code

Grade 0 (Normal)	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Unacceptable)
No change	20–40 dB loss at >4 KHz	>40 dB loss at 4 KHz	>40 dB loss at >2 KHz	40 dB loss at <2 KHz

sions. This combination of conventional craniospinal radiation and IMRT boosts delivered a total dose of 55.8 Gy.

Before beginning the IMRT boosts, each patient underwent CT scanning for treatment planning. The patients were immobilized in the supine position using either an aquaplast mask or the Talon system (16). Images from the skull to the upper chest were obtained with a 3-mm-slice thickness. The images were then transferred to a computer system for inverse treatment planning (Peacock Planning System, NOMOS Corp., Sewickley, PA). The radiation oncologist outlined the tumor target, brainstem, optic chiasm, optic nerves, lenses of each eye, orbits of each eye, pituitary gland, hypothalamus, temporal lobes, seventh cranial nerve, eighth cranial nerve, and the cochlea. After a treatment plan was generated, it was reviewed by the radiation oncologist for approval. Each axial image was evaluated for dose coverage of the tumor target as well as dose limitation of the critical structures.

Before beginning radiotherapy, neoadjuvant topotecan was administered to the IMRT Group at doses of 140 ng-hr/mL (high-risk patients only). After this Phase II topotecan window, both high- and low-risk patients underwent peripheral blood stem cell harvest using granulocyte-colony stimulating factor (G-CSF) to mobilize the stem cell compartment. Six weeks after completion of radiotherapy, the IMRT Group received dose-intensified adjuvant chemotherapy consisting of cyclophosphamide, vincristine, and cisplatin (mean dose: 290 mg/m^2) delivered over four cycles. Each cycle of chemotherapy was followed by an infusion of peripheral blood stem cells.

Dosimetry

The computer-generated plans of the IMRT boosts were reviewed. Dose–volume histograms were obtained for each of the organs contoured and for each technique. The maximum, minimum, and mean doses to the auditory apparatus were determined using the dose–volume histogram program in the treatment planning system.

Audiometric evaluation

Hearing thresholds were assessed by pure-tone audiograms conducted at the Texas Children's Hospital. One hundred thirteen audiograms were evaluated for the 26 children. Hearing thresholds were determined for each ear at stimulus frequencies of 250, 500, 1000, 2000, 4000, 6000, and 8000 Hz. Using the audiograms, each patient's hearing function was classified into Grade 0–4 according to the Pediatric Oncology Group's objective criteria for toxicity and complications, shown in Table 3. If the hearing function in a patient's left ear differed from the right ear, the higher grade of ototoxicity was recorded.

Statistical analysis of ototoxicity

The significance of difference between the rates of ototoxicity in the Conventional-RT Group and the IMRT Group was tested using the Fisher's exact test with two-tailed analysis (17).

RESULTS

Radiation dose to the auditory apparatus

The auditory apparatus received 68% of the dose using IMRT compared to conventional radiotherapy ($p < 0.001$). Table 4 summarizes the mean radiation dose delivered to the auditory apparatus according to treatment modality and risk stratification. The mean dose delivered to the auditory apparatus in the Conventional-RT Group ranged from 53.2 to 55.8 Gy (mean: 54.2, median: 53.2, SD ± 0.9 Gy), whereas the dose for the IMRT Group ranged from 23.4 to

Table 4. Summary of the mean dose delivered to the auditory apparatus

	Craniospinal axis (Gy)	Posterior fossa boost (Gy)	Tumor bed boost (Gy)	Total dose to auditory apparatus (Gy)
Conventional RT				
Low risk	28.5 (23.4–36.0)	26.3 (18.0–32.4)	–	54.8 (54.0–55.8)
	Median 24.0	Median 30.6	–	Median 54.6
High risk	35.3 (35.2–36.0)	18.3 (18.0–19.8)	–	53.6 (53.2–55.0)
	Median 35.2	Median 18.0	–	Median 53.2
IMRT				
Low risk	24.0 (23.4–36.0)	4.8 (4.0–6.6)	6.2 (3.9–9.5)	35.0 (23.4–50.8)
	Median 23.4	Median 4.6	Median 6.0	Median 34.3
High risk	35.6 (34.2–36.0)	–	5.9 (5.7–7.5)	41.5 (40.6–42.1)
	Median 36.0	–	Median 6.1	Median 41.7

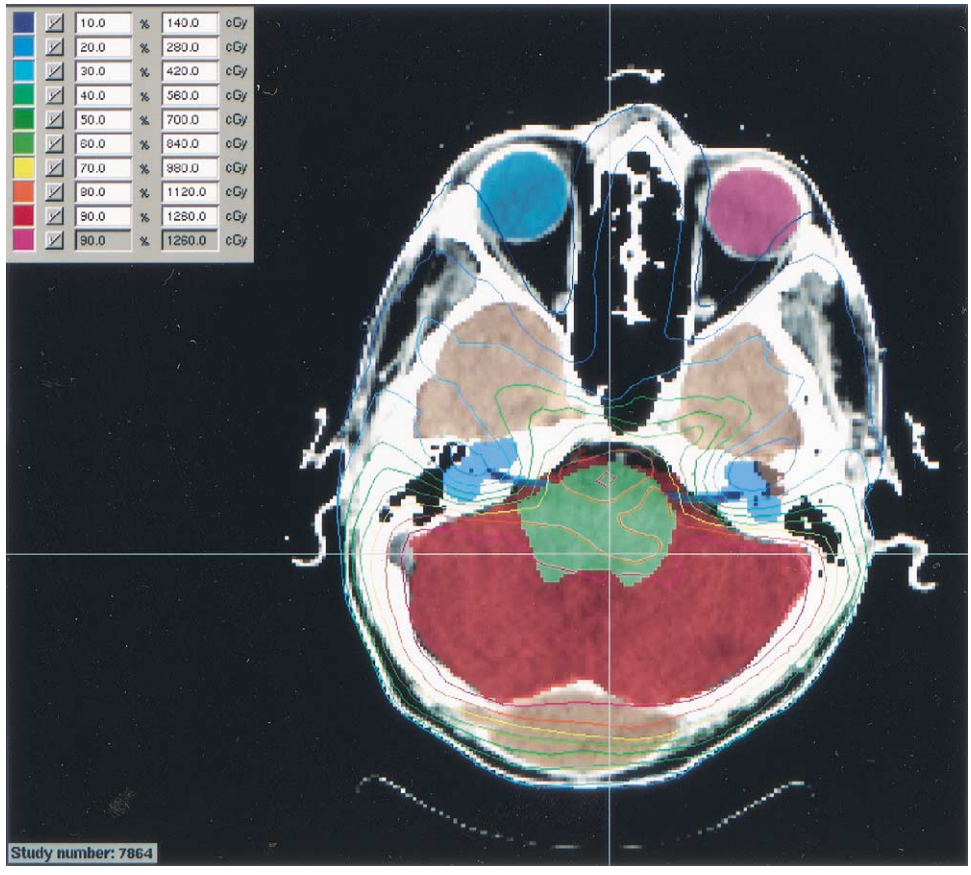

Fig. 1. Isodose distributions from a representative IMRT plan of the posterior fossa boost. The 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, and 90% lines are shown.

50.8 Gy (mean: 36.7, median: 35.2, SD ± 0.6). Figures 1 and 2 illustrate the conformal avoidance of the cochlea and eighth nerve during the IMRT boost to the posterior fossa and the primary tumor bed, respectively.

Audiometric evaluation

The median follow-up period for audiometric evaluation of the Conventional-RT Group was 51 months (9–107 months). The median follow-up period for the IMRT Group was 18 months (8–37 months). Fifty percent of the patients had baseline audiograms, and 70% had audiograms after radiotherapy but before beginning chemotherapy.

Table 5 summarizes the audiometric results according to the number of patients at each grade of ototoxicity. When hearing function was assessed after completing radiotherapy and before starting cisplatin therapy, none of the 15 patients from the IMRT Group had a detectable loss of hearing function. At the most recent hearing evaluation, 47% of the IMRT Group did not show any degree of hearing loss, and 27% developed mild Grade 1 toxicity that would not affect normal speech. Thirteen percent had Grade 3 or 4 hearing losses. The Conventional-RT Group had an 82% rate of ototoxicity, with 64% having Grade 3–4 hearing loss.

The IMRT Group showed a significantly lower rate ($p < 0.014$) of Grade 3–4 ototoxicity compared to the patients treated with conventional RT. The development of Grade 3–4 ototoxicity occurred within a median follow-up time of 10 months after starting cisplatin chemotherapy. Figure 3 shows that the mean decibel hearing thresholds at every frequency were lower in the IMRT Group, even though the patients in that group had received higher doses of cisplatin than those in the Conventional-RT Group.

DISCUSSION

Radiation tolerance of the auditory apparatus

Radiation-induced SNHL has been shown to be a dose-related phenomenon with the threshold of injury occurring at doses of 50 to 60 Gy (2, 3, 7, 18). Thibadoux *et al.* did not find any hearing loss in children receiving 24 Gy of cranial radiation for acute leukemia (19). In a series of nasopharyngeal carcinoma, Grau *et al.* reported a 7% rate of SNHL with doses less than 50 Gy, but this increased to 44% when the dose was increased above 59 Gy (2).

Because the cochlea and eighth nerve were within the radiation field during the craniospinal dose and the two-dimensional posterior fossa boost, the auditory apparatus of the Conventional-RT patients received the full dose of radiation. By delivering the boosts with IMRT, the auditory apparatus of the IMRT patients received only 68% (36.7 vs.

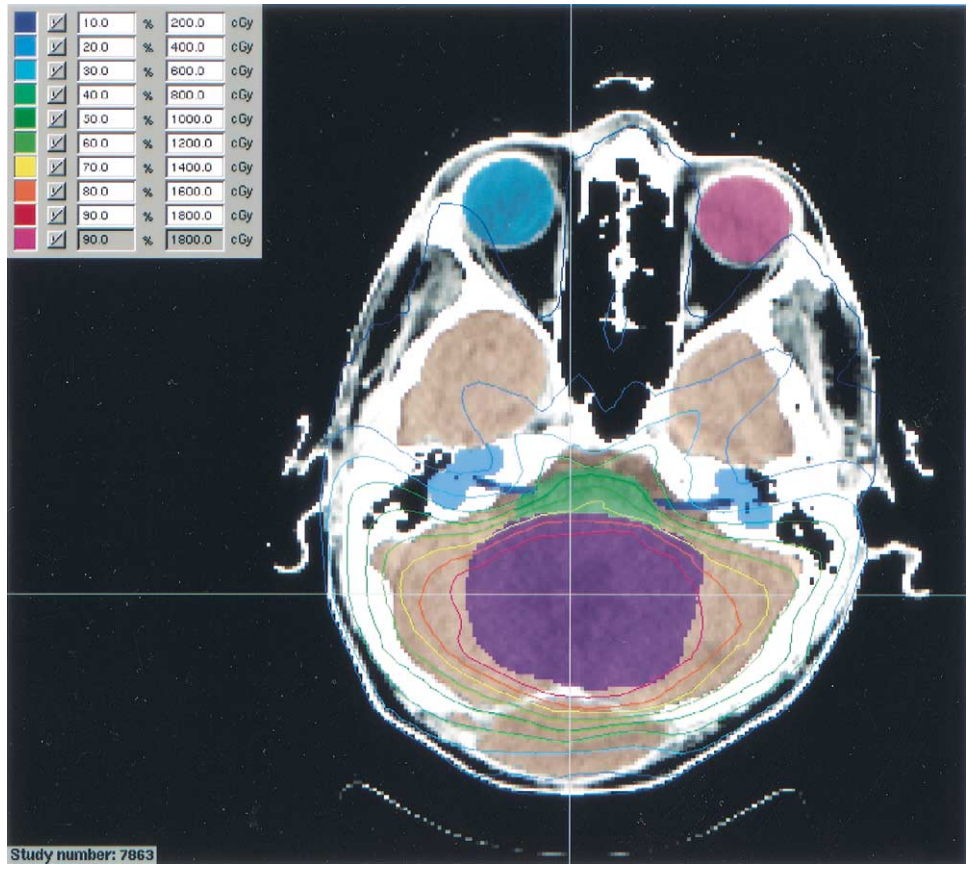

Fig. 2. Isodose distributions from a representative IMRT plan of the primary tumor bed boost. The 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, and 90% lines are shown.

54.2 Gy) of the total prescribed dose. IMRT not only reduced the dose to the auditory apparatus below its tolerance limit, but it simultaneously delivered a higher dose to the tumor target (55.8 vs. 54.2 Gy).

The patients in the IMRT Group were treated in a protocol setting. Presently, a posterior fossa boost is the standard of care for medulloblastoma patients. The use of a tumor bed boost in a protocol setting was based on the patterns of failure data from various studies (20–25). When given adjuvant chemotherapy, craniospinal irradiation of 36 Gy is probably sufficient for subclinical disease sites in the craniospinal axis (20, 22). Parenchymal failures within the posterior fossa but outside the primary tumor bed are rare (21), and posterior fossa dose has not been shown to correlate with overall survival (20, 23–25). The tumor bed boost is currently under investigation as a method to minimize ototoxicity and other morbidity associated with full posterior fossa irradiation without compromising tumor control. Long-term follow-up and larger cohorts of patients are needed to confirm the efficacy of this new approach. However, the early results presented here that show a reduction of ototoxicity are encouraging and promising.

It has been suggested that the reduction in dose to the auditory apparatus in the IMRT Group may be a result of the smaller target volume selected—a tumor bed boost rather than a posterior fossa boost. We believe, however, that the IMRT technology, which allows the targeting of the tumor bed rather than the mere reduction of target volume, is more important in reducing the radiation dose to the auditory apparatus. This conclusion is supported by a study

Table 5. Summary of ototoxicity results

	Mean radiation dose to auditory apparatus (Gy)	Mean cisplatin dose (mg/m^2)	Ototoxicity (no. of patients)				
			Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Conventional RT	54.2 (53.2–55.8) Median 53.2	220 (180–270) Median 200	2	2	0	6	1
IMRT	36.7 (23.4–50.8) Median 35.2	290 (180–340) Median 300	6	4	3	1	1

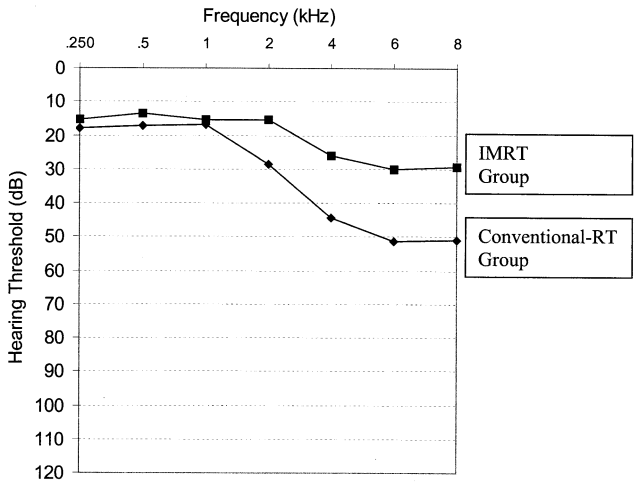

Fig. 3. Mean hearing thresholds for each patient group. Mean dose of cisplatin for the Conventional-RT Group was 220 mg/m^2. Mean dose of cisplatin for the IMRT Group was 290 mg/m^2.

from Paulino *et al.* (26) that compared posterior fossa boosts with tumor bed boosts using two-dimensional radiotherapy techniques. They found that the cochlea was in the treatment field of every patient, regardless of which target volume was selected. This suggests that the conformal technique of IMRT, rather than the size of the target volume, was largely responsible for the observed dose reduction.

This reduction of dose to the auditory apparatus using IMRT is comparable to the three-dimensional conformal radiotherapy techniques developed by other investigators to boost the posterior fossa in medulloblastoma patients. Fukunaga-Johnson *et al.* used a pair of posterior oblique fields to treat the posterior fossa, reducing the cochlear radiation dose to 65% of the prescribed dose (27). Paulino *et al.* reported similar cochlear dose reductions using a pair of posterior oblique fields plus an additional vertex field (28). It would be interesting to assess whether or not these three-dimensional conformal radiotherapy techniques would also result in less ototoxicity. The chief advantage of IMRT is that its technology and inverse treatment planning facilitate the application of conformal technique.

Ototoxicity

This is the first report demonstrating the potential benefits of IMRT in the treatment of medulloblastoma. Although our sample size was small, this initial experience shows that IMRT before cisplatin therapy resulted in a 13% rate of Grade 3–4 ototoxicity, significantly less than the 64% observed using the conventional technique. Two factors may have contributed to this decrease in ototoxicity. The most apparent is that delivering the boosts by IMRT resulted in a 32% decrease in cumulative radiation exposure to the inner ear. A second explanation is that IMRT allowed a lower dose per fraction to be delivered to the auditory apparatus, with a probable decrease in biologic effect to the organ.

The rates of ototoxicity that we report here compare favorably with larger prospective studies in the literature that have combined conventional radiotherapy with cisplatin chemotherapy. In a study involving 63 pediatric medulloblastoma patients who received standard radiotherapy of 54 to 55.8 Gy followed by adjuvant cisplatin chemotherapy, Packer *et al.* reported a 48% incidence of patients with Grade 3–4 ototoxicity (29). In another study involving 65 medulloblastoma patients receiving radiotherapy with adjuvant chemotherapy, Kortmann *et al.* reported that ototoxicity occurred in 34% of patients, reaching Grade 3–4 toxicity in 9% (12). Several other series with smaller sample sizes combining cranial radiation with cisplatin have reported even higher rates of ototoxicity, ranging from 83% to 100% (10, 13, 30). By analyzing a large sample of children, Schell *et al.* predicted that the probability of developing substantial hearing loss with cranial radiation was 40–60% at cisplatin doses of 270 mg/m^2. With doses of 450 mg/m^2, the risk increased to 80–100% (8).

One of the limiting factors in this initial review is the length of follow-up in the IMRT Group. This was primarily because of the relatively recent development of IMRT technology, allowing a median follow-up period of 18 months for audiometric evaluation. Based on the data presented here, we found that the first audiometric test documenting Grade 3–4 ototoxicity occurred within a median time period of 10 months after starting cisplatin therapy. This time to development of ototoxicity is similar to that reported in other reports. In a study conducted by Kretschmar *et al.*, 8 out of 22 patients who received neoadjuvant chemotherapy for medulloblastoma developed substantial hearing loss. Six of these 8 patients reached their maximum grade of ototoxicity just after the third course of cisplatin, approximately 6–9 weeks after initiating chemotherapy and before starting radiation. Only two patients showed further progression that was detected at 12 and 35 months (31). Other reports have consistently found that radiation-induced hearing loss occurs within 6 to 12 months (1, 4). Although it is possible that the hearing function of our IMRT patients could further deteriorate with time, these data suggest that the follow-up times for the IMRT Group have encompassed the most vulnerable period for developing ototoxicity. This concern highlights the importance of extended follow-up periods in future studies.

The second limiting factor is the small sample size. However, we believe that our results remain convincing for two reasons. First, the patients from the IMRT Group received radiotherapy *prior* to cisplatin therapy. This distinction is made because *prior* or *concurrent* radiation has been shown to potentiate the frequency and severity of ototoxicity to a much greater extent than postchemotherapy radiation (11, 12). Despite having received radiation before cisplatin, the IMRT Group demonstrated less Grade 3–4 and overall ototoxicity. This strongly suggests that the reduction of dose to the auditory apparatus by IMRT mitigates the "radiation-enhanced cisplatin toxicity" that has been found after conventional radiotherapy. Second, the severity of cisplatin ototoxicity is directly related to the cumulative dose of cisplatin (8). Despite having received higher doses of cisplatin (290 vs. 220 mg/m^2), the IMRT Group had significantly less Grade 3–4 ototoxicity than the Conventional-RT Group.

CONCLUSION

This is the first report on the potential benefits of IMRT in decreasing the rate of treatment-related ototoxicity in children with medulloblastoma. Our current practice is to limit the mean radiation dose to the auditory apparatus to 37 Gy. Further studies in the future should examine larger cohorts, seek longer follow-up times, and integrate cisplatin/radioprotectant agents such as amifostine (32, 33). It is important to note that IMRT is still a new technology. Long-term results to determine patterns of failure in children treated with this approach are still awaited. Another concern is that the physics of IMRT generally result in a large volume of brain receiving a low dose of radiation, and this low-dose region may have an increased risk of developing secondary malignancies. Though beyond the scope of this review, these issues must be investigated by long-term studies.

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