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BRIEF REPORT

A Scalp Dose Threshold for Preventing Permanent Alopecia in Scalp-Avoidance Whole-Brain Irradiation With Volumetric Modulated Arc Radiation Therapy for Pediatric Patients With Medulloblastomas

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Introduction

With increasing long-term survival, permanent alopecia has received much attention as a crucial late adverse effect caused by dose-intensive chemotherapy and cranial irradiation, particularly for pediatric patients.[1-3] To reduce the scalp dose and prevent permanent alopecia, we started using craniospinal irradiation (CSI) combined with scalp dose-reduced whole-brain radiation therapy (WBRT) and volumetric modulated arc therapy (VMAT): scalp-avoidance whole-brain irradiation with VMAT (SAWB-VMAT).

The present study retrospectively estimated optimal cutoff dose to prevent permanent alopecia and investigated the clinical outcomes for patients with medulloblastoma undergoing treatment using the St. Jude Medulloblastoma-96 protocol.[4]

Methods and Materials

This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the institutional ethical review board of our hospital (approval number: R1048-1).

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Research data are not available at this time.

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Patient population and treatment protocol

Eight pediatric patients (median age, 8.0 years; range, 4.7-12.8 years) with medulloblastoma at our institution who we could photograph after completion of the St. Jude Medulloblastoma-96 protocol treatment from May 2011 to August 2018 were enrolled in this study.[4]

All patients received risk-adapted CSI (23.4-24.0 Gy for average-risk disease and 35.2 Gy for high-risk disease) and boost radiation therapy, followed by 4 cycles of dose-intensive chemotherapy with cyclophosphamide (2000 mg/m^2), cisplatin (75 mg/m^2), and vincristine (1.5 mg/m^2).

The definition of target and treatment planning for SAWB-VMAT

The clinical target volume (CTV) for SAWB-VMAT included regions of the whole brain, cervical spinal cord, cerebrospinal fluid space, and intervertebral foramen. To create the planned target volume, a 3-mm margin was added to the cranial region of the CTV, and 5- to 7-mm margins were added to the cervical region of the CTV.

We defined the skin of the cranial region of the scalp as the organ at risk (OAR).

In addition, the eye, lens, hypopharynx, cochlea, thyroid, oral cavity, and parotid gland were defined as the other OARs. Optimization was performed to achieve coverage of more than 90% of the prescribed dose for most of the planned target volume and more than 95% of the prescribed dose for most of the CTV, while the doses to the OARs were reduced to the maximum possible extent.

Treatment planning for boost irradiation

As indicated in Table 1, the tumor bed, rather than the whole posterior fossa, was the boost irradiation target in most patients. In patients receiving the boost irradiation for the tumor bed, dynamic conformal arc therapy was applied. A representative boost irradiation dose distribution in the tumor bed is shown in Fig. E1.

Evaluation of the dose distribution of scalp and alopecia grading

The structure of the scalp was defined as the inner 5-mm region of the body contour, as suggested by Roberge et al[5] and Mahadevan et al.[6] We further divided the scalp into 4 areas (Fig. 1A, 1B). We calculated equivalent doses in 2-Gy fractions (assuming $\alpha/\beta = 2$) to 50% of the scalp (EQD 50%).[1,7]

Alopecia grading was conducted based on the Severity of Alopecia Tool (SALT) score (Fig. 1C).[8] The grade of SALT score and EQD 50% were evaluated separately for 4 areas in each case. As a result, the grade of SALT score and EQD 50% of 32 areas were evaluated in 8 cases.

We defined permanent alopecia as hair loss persisting for 1 year after radiation therapy completion and 9 months after chemotherapy completion, graded by 2 reviewers for each patient. Alopecia of grades 3 and 4 was defined as "severe".

Statistical analysis

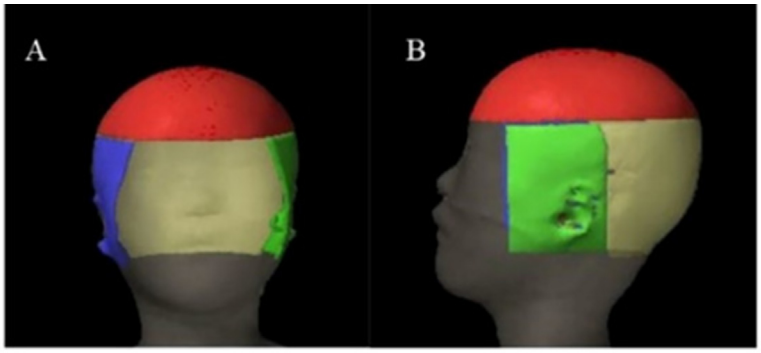
The irradiation doses to the scalp in both techniques were compared using Welch's t tests. To determine the predictive performance of scalp EQD 50% for severe permanent alopecia, we performed receiver operating characteristic analysis. We compared severe alopecia areas using this cutoff value using the Student t and Fisher tests. In these analyses, $P < .05$ was considered statistically significant.

All statistical analyses were performed using EZR software (Saitama Medical Center, Jichi Medical University).[9]

Table 1 Patient characteristics and radiation therapy

Case no.	Age	Sex	Risk	Chang staging	Extent of surgery	CSI dose	Boost dose	Area of boost	WBRT type
1	6 y 7 mo	F	High	M3	STR	35.2 Gy/22 fr.	19.8 Gy/11 fr.	Tumor bed	Conventional
2	7 y 2 mo	M	Standard	M0	GTR	23.4 Gy/18 fr.	32.4 Gy/18 fr.	Tumor bed	Conventional
3	12 y 10 mo	M	High	M2	GTR	35.2 Gy/22 fr.	18 Gy/10 fr.	Tumor bed	Conventional
4	8 y 0 mo	F	Standard	M0	GTR	23.4 Gy/13 fr.	32.4 Gy/18 fr.	Tumor bed	Conventional
5	4 y 8 mo	F	Standard	M0	GTR	24 Gy/15 fr.	30.6 Gy/18 fr.	Tumor bed	Scalp-avoidance
6	11 y 6 mo	M	Standard	M0	GTR	23.4 Gy/13 fr.	32.4 Gy/18 fr.	Tumor bed	Scalp-avoidance
7	10 y 3 mo	M	High	M3	GTR	35.2 Gy/19 fr.	19.8 Gy/11 fr.	Posterior fossa	Scalp-avoidance
8	8 y 0 mo	F	High	M0	STR	35.2 Gy/19 fr.	19.8 Gy/11 fr.	Tumor bed	Scalp-avoidance

Abbreviations: CSI = craniospinal irradiation; F = female; fr. = fractions; GTR = gross total resection; M = male; STR = subtotal resection; WBRT = whole-brain radiation therapy.



C

SALT score	
Grade	Extent of hair loss
0	no hair loss
1	< 25% hair loss
2	25-49% hair loss
3	50-74 % hair loss
4	75-99 % hair loss

Fig. 1. Representative case showing area division of the scalp. (A) Frontal view. (B) Lateral view. (C) Grade of alopecia according to the Severity of Alopecia Tool score.

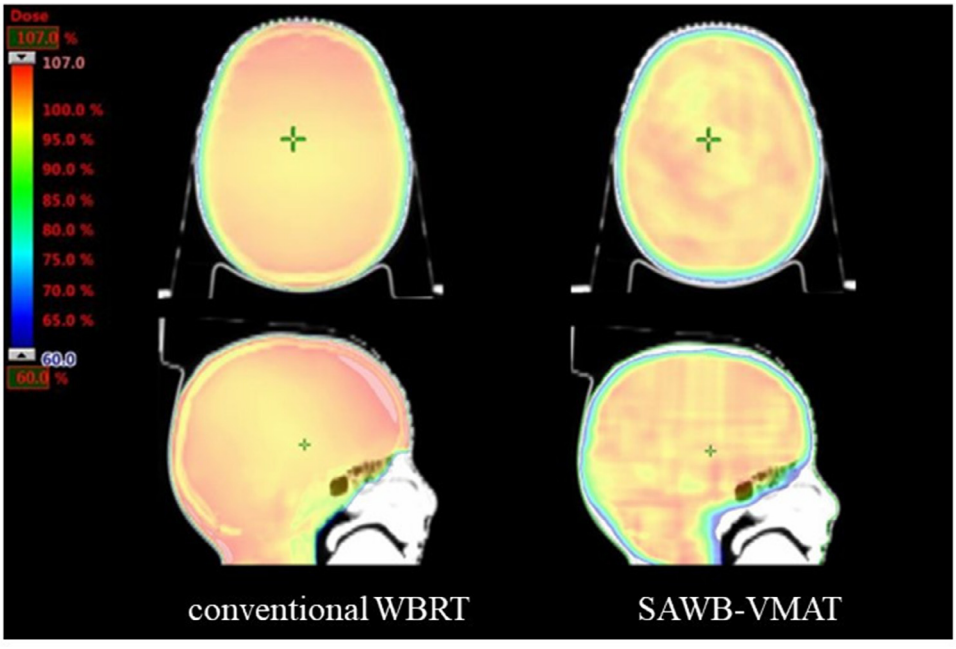


Fig. 2. Comparisons of dose distributions between conventional whole-brain radiation therapy and scalp-avoidance whole-brain irradiation with volumetric-modulated arc therapy. The areas irradiated with >60% of the prescribed dose are shown in the axial and sagittal views.

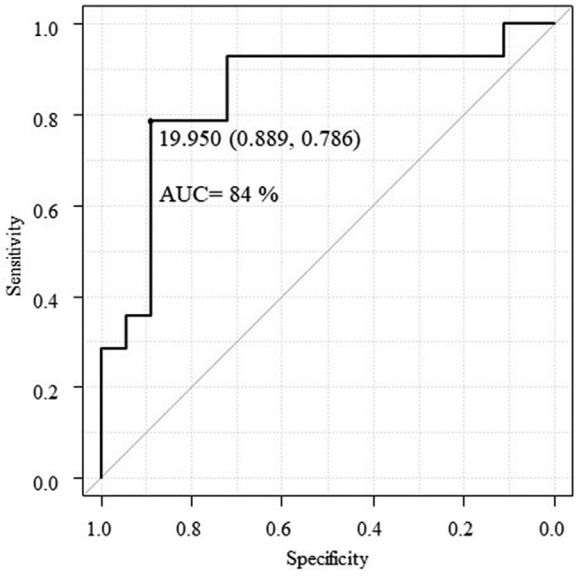


Fig. 3. Receiver operating characteristic curve for the scalp equivalent doses in 2-Gy fractions to 50% of the scalp and severe permanent alopecia.

Results

Patient characteristics and radiation therapy

The details of the patient characteristics and radiation therapy are shown in Table 1. Each group of 4 patients was classified as average risk or high risk based on the Chang staging system.[10] The median follow-up period was 71 months (range, 50.8-109.0) from the day of radiation therapy initiation.

Dosimetry comparisons of the scalp and optimal scalp dose cutoff for severe permanent alopecia

The scalp EQD 50% of SAWB-VMAT was significantly reduced compared with that of conventional WBRT (16.6 ± 3.6 vs 20.2 ± 5.5 Gy; $P = .038$).

Comparison of the dose distributions between conventional WBRT and SAWB-VMAT showed a lower dose to the scalp for SAWB-VMAT compared with conventional WBRT (Fig. 2).

The optimal cutoff EQD 50% in terms of severe permanent alopecia was 19.9 Gy (area under the curve, 84%; sensitivity, 88%; specificity, 78%) (Fig. 3). Comparisons of severe alopecia areas for this cutoff value are shown in Table 2. The areas of severe alopecia differed markedly with a 19.9 Gy cutoff value (15.7 vs 84.6 %; $P = .0001$).

In addition, the EQD 50% and SALT score grading for 4 areas of the scalp in each case are listed in Table 2.

Clinical outcomes

No patients showed disease progression 5 years after radiation therapy initiation with SAWB-VMAT. The representative case with SAWB-VMAT who achieved prevention of permanent alopecia is shown in Fig. 4. At 8 months after completion of SAWB-VMAT, this patient just finished dose-intensive chemotherapy. The hair fully recovered, and permanent alopecia was prevented 14 months after finishing SAWB-VMAT.

Discussion

The results of this study showed that SAWB-VMAT significantly decreased the scalp EQD 50%, and we also proposed

Table 2 Comparisons of severe alopecia areas in scalp EQD 50% and the detail of EQD 50% on the total prescribed dose of whole-brain and boost irradiation and the grade of SALT score for 4 areas of the scalp in each patient

Scalp EQD 50%	Areas with severe alopecia	Areas without severe alopecia	*P* value
≤19.9 Gy	3	16	.0001
>19.9 Gy	11	2	
Case no.	EQD 50% (Gy) (right temporal/left temporal/back/top)	Grade of SALT score (right temporal/left temporal/back/top)	WBRT type
1	21.5/22.9/26.6/27.7	3/3/4/4	C
2	15.2/15.9/19.0/18.1	1/1/2/2	C
3	19.9/20.3/27.7/28.5	4/4/4/4	C
4	10.8/11.1/21.6/16.5	2/2/3/3	C
5	12.8/14.1/12.8/15.3	1/1/1/1	S
6	14.1/14.7/14.2/15.5	1/1/1/1	S
7	22.6/23.2/19.7/15.4	1/1/1/1	S
8	19.9/17.5/11.8/21.4	3/3/3/3	S

Abbreviations: C = conventional; EQD = equivalent doses in 2-Gy fractions (assuming $\alpha/\beta = 2$) to 50% of the scalp; S = scalp-avoidance; SALT = Severity of Alopecia Tool; WBRT = whole-brain radiation therapy.

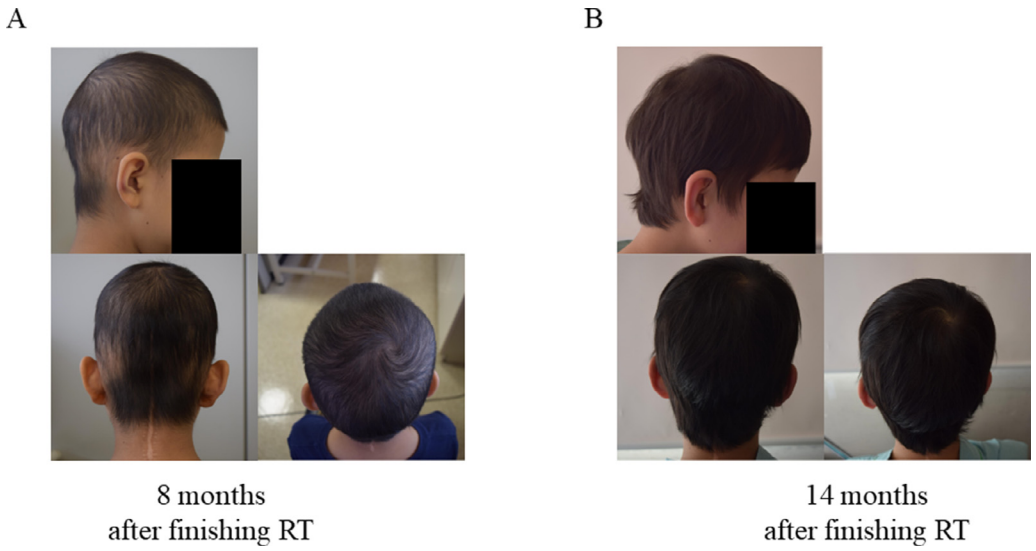


Fig. 4. The representative case in scalp-avoidance whole-brain irradiation with volumetric modulated arc therapy (SAWB-VMAT) who achieved prevention of permanent alopecia. The prescribed dose of SAWB-VMAT was 35.2 Gy. (A) Photograph of the scalp 8 months after finishing SAWB-VMAT. (B) Photograph of the scalp 14 months after finishing SAWB-VMAT.

an estimated cutoff EQD 50% of the scalp for severe permanent alopecia of 19.9 Gy. Severe permanent alopecia was significantly reduced at this cutoff value. None of the patients who received SAWB-VMAT showed disease progression 5 years after starting radiation therapy.

The α/β ratio of the hair follicle cell for temporary alopecia is considered high, as it is an acute reaction. However, permanent alopecia is regarded as a late effect rather than an acute response. In fact, the α/β ratio of 2 was used for hair follicles to evaluate permanent alopecia in the articles reported by Lawenda et al[1] and Lambrecht et al.[7] Therefore, we adopted the α/β ratio of 2 for the scalp in the present study.

Permanent alopecia prevention in pediatric patients with medulloblastoma treated with proton therapy was reported, but hair regrowth was not uniform.[11] Because VMAT allows for a more flexible dose distribution and shorter treatment time than proton therapy, SAWB-VMAT may be an effective treatment technique for pediatric patients treated with high-dose chemotherapy and cranial irradiation to prevent permanent alopecia.[11,12]

This study had some limitations. The study design was retrospective, and the sample size was small. In addition, creating SAWB-VMAT plans places a heavier burden on radiation oncologists, radiotherapists, medical physicists, and other personnel involved in the treatment compared with conventional WBRT.

Conclusion

CSI with SAWB-VMAT significantly reduced the scalp EQD 50% compared with CSI with conventional WBRT. The estimated EQD 50% cutoff was 19.9 Gy for severe permanent alopecia. SAWB-VMAT may improve the quality of life of children by promoting uniform hair regrowth.

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