A retrospective review of the long-term outcomes of postoperative radiation therapyin adolescent and young adult patients with medulloblastoma

การศึกษาย้อนหลังของผลการรักษาระยะยาวจากการฉายรังสีภายหลังการผ่าตัดโรคเมดัลโลบลาสโตมาในผู้ป่วยวัยรุ่นและวัยหนุ่มสาว

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Abstract

Backgrounds: Medulloblastoma (MB) is a rare tumor in adolescent and young adult patients (AYA). Before 2017, there was no standard treatment for AYA with MB due to conflicting data.

Objective: The aim of this study was to evaluate the local control (LC) and overall survival (OS) of MB in AYA at our institute.

Materials and Methods: Patients 15-39 years old with MB who were sent for postoperative radiation therapy (RT) from 2007-2019 at our institute were included. Kaplan–Meier statistics were used to estimate the LC and OS.

Results: Seven patients were included. The median age at RT was 18.3 years (16.7-28.6 years). Males were more common than females, 5 males vs. 2 females. Near total resection or gross total resection was achieved in 71.4% (5 in 7 patients). Only one patient had metastatic disease (M1). The majority (71.4%) of patients were at standard risk. Six patients received RT alone. One patient received combined chemotherapy and RT. The median craniospinal irradiation (CSI) dose and total RT dose were 36 Gy (23.4-46 Gy) and 54 Gy (54-56 Gy), respectively. Local recurrence (LR) was found in one patient 4.3 years after finishing RT. Her initial treatment was subtotal resection (STR) followed by RT alone; CSI 36 Gy and posterior fossa boost to 55.8 Gy. The median clinical follow-up time and the median MRI follow-up time were 5.8 years (1.3-11.4 years) and 5.8 years (0.6-11.3 years), respectively. The median local control was 4.3 years (0.6-11.3 years) and the median overall survival was 7.7 years (1.3-11.7 years).

Conclusions: Treatment outcomes of AYA with MB from a single tertiary hospital in a middle-income country had a good LC and OS with acceptable treatment-related toxicities.

Keywords: Adolescent and young adult, medulloblastoma, radiation therapy, middle-income country

บทคัดย่อ

หลักการและเหตุผล: เมดัลโลบลาสโตมาเป็นโรคที่พบได้น้อยในผู้ป่วยวัยรุ่นและวัยหนุ่มสาว การรักษาเมดัลโลบลาสโตมาในผู้ป่วยวัยรุ่นและวัยหนุ่มสาวก่อนปี พ.ศ. 2560 ยังไม่มีการรักษาที่เป็นมาตรฐาน

วัตถุประสงค์: เพื่อประเมินอัตราการควบคุมโรคเฉพาะที่และอัตราการรอดชีวิตของเมดัลโลบลาสโตมาในผู้ป่วยวัยรุ่นและวัยหนุ่มสาวที่โรงพยาบาลตติยภูมิแห่งหนึ่ง

วัสดุและวิธีการ: ศึกษาในผู้ป่วยอายุ 15-39 ปีที่ได้รับการวินิจฉัยโรคเมดัลโลบลาสโตมา และได้รับการรักษาด้วยการฉายรังสีภายหลังการผ่าตัด ระหว่างปี พ.ศ. 2550 และ 2562 ที่โรงพยาบาลตติยภูมิแห่งหนึ่ง ประเมินอัตราการควบคุมโรคเฉพาะที่และอัตราการรอดชีวิตด้วย Kaplan–Meier

ผลการศึกษา: ผู้ป่วยทั้งหมด 7 ราย อายุเฉลี่ยขณะรับการฉายรังสี 18.3 ปี (16.7-28.6 ปี) เป็นผู้ป่วยชาย 5 ราย และผู้ป่วยหญิง 2 ราย ผู้ป่วย 5 ราย (ร้อยละ 71.4%) ได้รับการผ่าตัดก้อนมะเร็งออกไปได้เกือบทั้งหมดหรือทั้งหมด มีผู้ป่วยเพียง 1 รายที่มีการแพร่กระจายของโรค (ระยะ M1) ผู้ป่วยส่วนใหญ่ (ร้อยละ 71.4) อยู่ในกลุ่มความเสี่ยงมาตรฐาน โดยผู้ป่วย 6 รายได้รับการฉายรังสีเพียงอย่างเดียวและผู้ป่วย 1รายได้รับการฉายรังสีร่วมกับการให้ยาเคมีบำบัด ค่าเฉลี่ยปริมาณรังสีที่สมองและไขสันหลัง 36 Gy (23.4-46 Gy) และค่าเฉลี่ยปริมาณรังสีโดยรวม 54 Gy (54-56 Gy) ในการศึกษานี้พบผู้ป่วย 1 รายมีการกลับเป็นซ้ำของโรคเฉพาะที่ ผู้ป่วยรายนี้ได้รับการรักษาด้วยการผ่าตัดก้อนมะเร็งออกบางส่วนและฉายรังสีภายหลังการผ่าตัดเพียงอย่างเดียวด้วยปริมาณรังสี 36 Gy ที่สมองและไขสันหลังและเพิ่มปริมาณรังสีที่แอ่งกะโหลกส่วนหลังถึง 55.8 Gy ก่อนจะพบการกลับเป็นซ้ำของโรคเฉพาะที่ที่ 4.3 ปีหลังจากฉายรังสีครบ จากระยะเวลาติดตามอาการเฉลี่ย 5.8 ปี (1.3-11.4 ปี) และระยะเวลาติดตามเอ็มอาร์ไอเฉลี่ย 5.8 ปี (0.6-11.3 ปี) พบว่ามีอัตราการควบคุมโรคเฉพาะที่เฉลี่ย 4.3 ปี (0.6-11.3 ปี) และอัตราการรอดชีวิตเฉลี่ย 7.7 ปี (1.3-11.7 ปี)

ข้อสรุป: ผลการรักษาเมดัลโลบลาสโตมาในผู้ป่วยวัยรุ่นและวัยหนุ่มสาวจากโรงพยาบาลตติยภูมิแห่งหนึ่งในประเทศกลุ่มรายได้ปานกลางมีอัตราการควบคุมโรคเฉพาะที่และอัตราการรอดชีวิตที่ดี

คำสำคัญ: ผู้ป่วยวัยรุ่นและวัยหนุ่มสาว, เมดัลโลบลาสโตมา, รังสีรักษา, ประเทศกลุ่มรายได้ปานกลาง

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Introduction

Medulloblastoma (MB) is a rare tumor in adolescent and young adult patients (AYA). The overall incidence rate of MB is approximately 1.5 per million persons in the USA. The incidence rate of MB in AYA is 10-fold lower than that in children, 0.6 vs. 6.0[1]. The current standard treatment for MB after surgery is craniospinal irradiation (CSI), followed by boost and chemotherapy (CMT). The extent of resection is predictive of outcome, especially in nonmetastatic disease[2, 3]. MB is categorized as standard risk (SR) and high risk (HR). SR was defined as an age of ≥ 3 years, residual disease of < 1.5 cm2, and M0. HR was defined as an age of < 3 years, residual disease of ≥ 1.5 cm2, M1-4, and anaplastic or large-cell histology. In pediatric MB, adjuvant radiation therapy (RT) should be administered within 28-31 days after surgery[4, 5]. The RT dose and treatment volume depend on the risk group. In conjunction with CMT, a reduced dose CSI of 23.4 Gy followed by an involved field boost of 54 Gy in 1.8 Gy per fraction is now the standard of care for SR[4, 6, 7]. CSI 36 Gy followed by

posterior fossa boost to 54-55.8 Gy in 1.8 Gy per fraction is recommended for HR. CSI 39.6 Gy and focal spinal boost to 45-50.4 Gy can be given for diffuse macroscopic spinal disease and focal macroscopic metastasis, respectively[5].

Before 2017, the role of CMT in AYA with MB was controversial because most data were from small retrospective studies with conflicting results[8-11]. More recently, two large studies reported the benefit of adding CMT and supported the role of CMT in AYA with MB. No treatment-related toxicity was reported in either study[12, 13]. At our hospital, a tertiary hospital in a middle-income country, all AYA with MBs received postoperative RT alone until 2017. The purpose of this study was to report the long-term local control (LC), overall survival (OS), and treatment-related toxicities of MB in AYA at our institute.

Materials and methods

Patient selection

A radiation oncology database was used to identify patients aged 15 to 39 years diagnosed with medulloblastoma and treated at the Division of Radiation Oncology, Department of Radiology, Siriraj Hospital, Bangkok, Thailand, between 2007 and 2019. A retrospective medical records analysis was conducted after institutional review board approval (Si 826/2019).

Radiation therapy dose and treatment volume All planning computed tomography (CT) simulations were performed in the supine position with a customized thermoplastic mask on the headrest. CT axial images were obtained from the vertex to the coccyx with a 3 mm contiguous slice thickness. The clinical target volume (CTV) included the entire brain, meninges, and entire spinal canal down to the end of the thecal sac covering the cerebrospinal extension to the spinal ganglia. The CTV boost included the whole posterior fossa or tumor bed boost with 1.5-cm margin. A geometric margin of 5 mm around the CTV and CTV boost was generated for planning the target volume (PTV) and PTV boost, respectively. Prescription doses were based on individual physician practices.

Treatment planning

Before 2018, all patients were treated with 3-dimensional conformal radiation therapy (3DCRT). In 2018, the patient was treated with volumetric arc radiation therapy (VMAT). For 3DCRT planning, lateral opposed fields with the half beam block technique were used for the brain, and a direct posterior field was used to treat the spine. The isocenter was located at the level of C2-C4 based on the anatomy of the patients for the brain field and at the level of T10-T12 with a fixed distance of 20 cm from the brain isocenter for the spine fields. The second spine isocenter was placed at the level of S2-S3. The isocenter placements were set as a reference for the entire treatment course, and a longitudinal shift was designed for the isocenter shift. The collimator was rotated for the brain field to match the divergence of the spine field. The moving gap junction technique between

2 spine fields using an asymmetric field was proposed. All plans used 6 MV photons. Beam weighting was adjusted to ensure that the dose of the PTV covered the 95% isodose curve. PTV boost treated with two lateral opposing fields. For VMAT, the plan was optimized and calculated by Eclipse version 13.6. The dose calculation was performed with the Anisotropic Analytical Algorithm (AAA). Two coplanar full rotations (360 degrees) for the brain and one complete arc for the spine were used. PTV dose coverage was the first priority in the optimization process. More than 95% of the volume of the PTV was covered by 95% of the prescribed dose, and the maximum dose did not exceed 107%. The PTV boost used two coplanar full rotations (360 degrees). VMAT used 6 MV photons at a dose rate of 600 MU/min.

Chemotherapy

The national protocol for the treatment of childhood cancer 2018 has been adopted to treat MB in AYA since 2018. The chemotherapy regimens for SR and HR were the same. During RT, vincristine 1.5 mg/m2 was given weekly for 6 weeks. Adjuvant chemotherapy started within 28 days after completing RT as follows: cyclophosphamide (800 mg/m2/day on Days 1-3) and vincristine (1.5 mg/m2/day on Days 1, 8, 15) alternating with carboplatin (200 mg/m2/day on Days 1-3) and etoposide (150 mg/m2/day on Days 1-3) every 21-28 days for 10 cycles.[14]

Variables and assessment

Sex, age at the start of RT, the interval between surgery and radiation, the extent of surgery, histology subtype, M stage, CMT administration, and RT dose were extracted from electronic medical records. The extent of surgery was categorized as subtotal resection (STR), near total resection (NTR), and gross total resection (GTR) in which defined by individual neurosurgeon. Treatment-related toxicities were graded according to CTCAE version 5.0 and subdivided into acute and late complications.[15] Radiation side effects occurring during RT or within 6 months after completing RT were defined as acute complications. Radiation side effects occurring at least 6 months after completing RT were defined as late complications.

The primary endpoints of this study were the LC and OS. All follow-up MRIs of the brain and spine were reviewed to assess the local recurrence.

Statistical analysis

All analyses were performed using SPSS (version 21, SPSS Inc., Chicago, IL., USA). Data were described using frequency, percentage, median and range. Kaplan–Meier statistics were used to estimate the LC and OS. LC reflected the interval between the last date of RT and clinical and/or radiological progression. OS was the interval between the last date of RT and death. Complications were described in number and percentage.

Results

Patient demographics

Seven patients were included and analyzed. Patient demographics are shown in **Table 1**. There were 5 males (71.4%) vs. 2 females (28.6%). The median age at the start of RT was 18.3 years (16.7-28.6 years). The median time between surgery and the start of radiation was 41 days (28-63 days). Near-total resection (NTR) or gross total resection (GTR) was achieved in 71.4% (5 of 7 patients). Five patients (71.4%) were at standard risk. Histology subtype was reported in 5 patients. The remaining 2 patients had no histology subtype. Four (80%) were classic medulloblastomas, and one (20%) was melanocytic differentiation. No anaplastic/large cells were observed in this cohort. No molecular study was performed at the time of analysis. Only one patient (14.3%) had metastatic disease (M1). The remaining patients (85.7%) were M0.

Radiation therapy and chemotherapy

Six patients (85.7%) were treated with three-dimensional conformal radiation therapy. One patient (patient no. 7) was treated with volumetric modulated arc therapy. Radiation dose and treatment volume were based on individual physician practices. The median CSI dose was 36 Gy (23.4-46 Gy). Patient no. 3 received an escalated CSI dose (46 Gy) due to M1 disease. Patient no. 7 received a reduced CSI dose (23.4 Gy) concurrent with chemotherapy followed by adjuvant chemotherapy. The posterior fossa was treated for a boost in all patients. The median total RT dose at the primary site was 54 Gy (54-56 Gy).

Treatment outcomes

All patients had follow-up MRI brain and sagittal whole spine screening. The median clinical follow-up time and the median MRI follow-up time were 5.8 years (1.3-11.4 years) and 5.8 years (0.6-11.3 years), respectively. Local recurrence (LR) was found in one patient 4.3 years after the completion of RT (**Figure 1**). Her initial treatment was subtotal resection (STR) followed by CSI 36 Gy and posterior fossa boost to 55.8. No chemotherapy was administered. She received salvage stereotactic radiotherapy 30 Gy in 5 fractions followed by chemotherapy as follows: cisplatin (100mg/m2/d on Day 1), etoposide (80mg/m2/day on Days 1-2), and cyclophosphamide (1g/m2/d on Day 3) every 28 days for 4 cycles. The 2-year and 5-year LC rates were 100% and 66.7%, respectively. Both the 2-year OS and 5-year OS were 100%. The median LC was 4.3 years (0.6-11.3 years) and the median OS was 7.7 years (1.3-11.7 years).

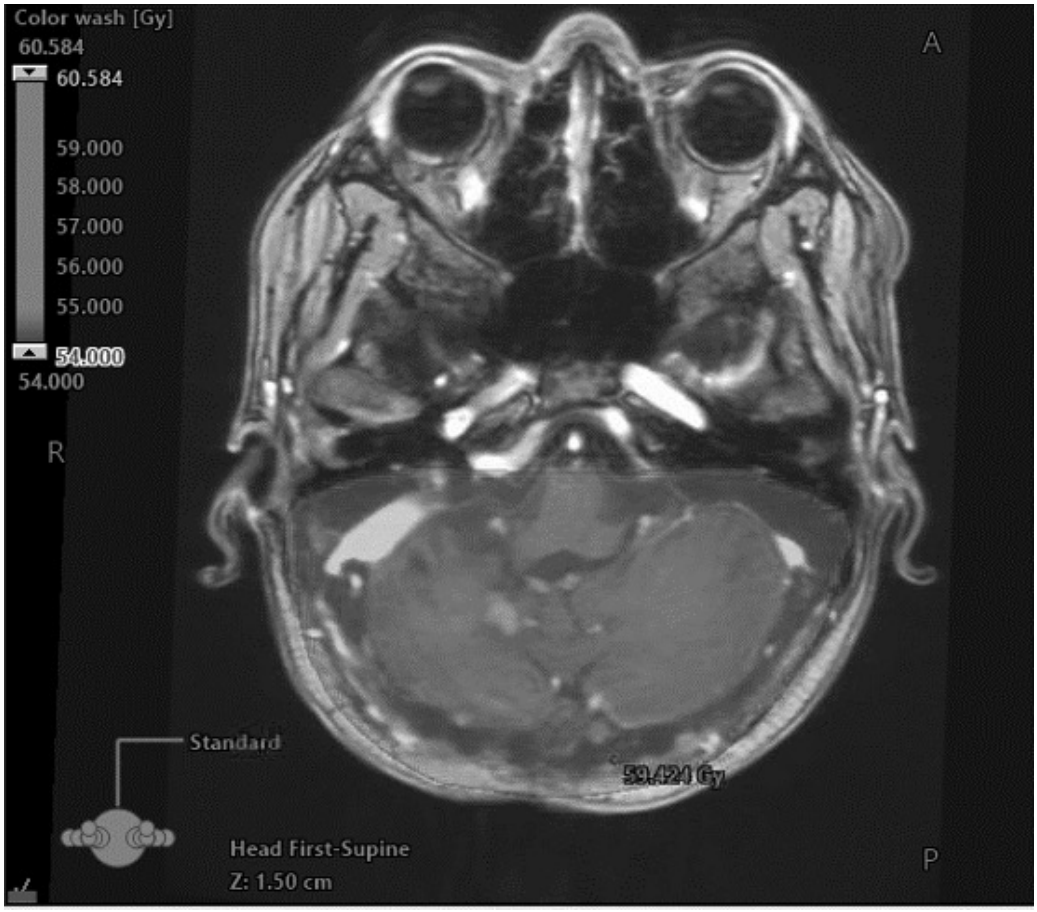

Figure 1. Fused follow-up MRI with planning CT shows local recurrence (arrow) within posterior fossa boost volume. Patient No. 6 underwent subtotal resection followed by radiation therapy alone. The local recurrence was detected 4.3 years after completion of radiation therapy.

Treatment-related toxicities

Treatment-related toxicities are shown in **Table 2**. Overall, acute complications developed in 57.1% (4/7). Of 6 patients treated with RT alone, one (16.7%) patient developed grade 3 vomiting and required a treatment break. Others were grade of <3 nonhematologic toxicities, including grade 1 oral mucositis, grade 2 radiation dermatitis, and grade 2 vomiting. One patient who received CMT had grade 4 neutropenia twice during RT and once during adjuvant CMT. Late complications developed in 28.6% (2/7). All late complications were grade of <3, including grade 1 vertigo and grade 1 alopecia. No radiation necrosis was detected.

Table 1 Clinical and treatment-related information

Patient no.	Gender	Age at the start RT (years)	M stage	Extent of surgery	Histology	Risk group	CSI dose (Gy)	Boost volume	Total dose (Gy)	Any CMT	Disease progress after RT	Follow-up time (years)	Status
1	M	17.2	M0	NTR	Classic	SR	36	PF	54	No	No	9.8	NED
2	M	28.6	M0	GTR	Melanocytic differentiation	SR	36	PF	56	No	No	11.4	NED
3	M	27	M1	STR	NR	HR	46	PF	54	No	No	1.0	NED
4	F	20.5	M0	GTR	Classic	SR	36	PF	55.8	No	No	3.5	NED
5	M	18.3	M0	NTR	NR	SR	36	PF	54	No	No	7.3	NED
6	F	17.8	M0	STR	Classic	HR	36	PF	55.8	No	LR	5.8	AWD
7	M	16.7	M0	GTR	Classic	SR	23.4	IFRT	54	Yes	No	1.3	NED

NOTE: Patient no.6 was designated high risk due to subtotal resected disease. None had focal spinal boost. Patient no.3 was loss follow-up.

Abbreviations: M=male, F=female, RT=radiation therapy, NTR=near total resection, GTR=gross total resection, STR=subtotal resection, NR=no report, SR=standard risk, HR=high risk, CSI= craniospinal irradiation, PF= posterior fossa boost, IFRT = involved-field boost, CMT=chemotherapy, LR = local recurrence, NED = no evidence of disease, AWD = alive with disease

Table 2 Treatment-related toxicities

Patient no.	Acute complication	Grade	Late complication	Grade
1	NR	-	NR	-
2	NR	-	NR	-
3	NR	-	NR	-
4	Vomiting	3	Vertigo	1
5	Vomiting	2	NR	-
6	Alopecia	1	Alopecia	1
	Oral mucositis	1		
	Radiation dermatitis	2		
7	Decreased neutrophil count	4	Not evaluable	-

NOTE: Patient no. 7 has a follow-up time <6 months at time of analysis.

NR = no report

Discussion

We reported the long-term outcomes of postoperative RT in AYA with MBs from a single tertiary hospital in a middle-income country. Before 2018, all AYA with MBs who were treated at our institute received postoperative radiation therapy alone due to conflicting data supporting the role of CMT and concerns about CMT intolerability in AYA. After 2018, all AYA with MBs received postoperative RT and CMT due to a change in practice at our institution.

The Rare Cancer Network reported a large series of MB in adults, including 206 patients with a median follow-up of 31 months (0.2-179 months). Ninety-eight (48%) patients received CMT (32% before RT, 31% concurrent with RT, and 37% after RT). Patients who received CMT had better outcomes. The 5-year LC was 50% in RT and 74% in CMT and RT (chemo-RT). The 5-year OS rates were 55% in RT and 73% in chemo-RT [13]. Kann et al. used National Cancer Data to identify patients ≥18 years old with MB. Of 751 patients, 520 (69.2%) received CMT (47.9% concurrent with RT, 52.1% before or after RT). The median follow-up time was 5 years. Patients who received CMT had better 5-year OS (71.6% in RT vs. 86.1% in chemo-RT)[12]. Neither study reported treatment-related toxicities[12, 13]. Compared to these two large studies, this cohort showed good LC and OS with acceptable treatment-related toxicities. The predominantly standard-risk patients in this cohort may have led to the favorable outcomes. The treatment-related toxicities in this study may underestimate due to retrospective review of medical records. The limitation of our study was that it was a retrospective study with a small number of patients and no molecular study. Only one patient in this study received CMT and had the shortest follow-up time.

Conclusion

Treatment outcomes of AYA with MB from a single tertiary hospital in a middle-income country had good LC and OS with acceptable treatment-related toxicities. The median local control was 4.3 years (0.6-11.3 years) and the median overall survival was 7.7 years (1.3-11.7 years).

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Not applicable

Conflicts of interest

None

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