Treatment of pediatric average-risk medulloblastoma using craniospinal irradiation less than 2500 cGy and chemotherapy: single center experience in Korea

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Background: **Although craniospinal irradiation (CSI) of 2340 cGy plus tumor booster with chemotherapy have been established as a standard treatment of childhood average-risk (AvR) medulloblastoma (MBL) in Western counties, there are a few recent reports in outcomes of AvR MBL using this strategy in Korean and other Asian children. We investigated the outcome of the Korean children with AvR MBL who were treated with CSI <2500 cGy and chemotherapy.**

Methods: **Between January 2001 and December 2010, clinical characteristics and outcomes of 42 patients who were diagnosed with AvR MBL postoperatively and treated with radiation including CSI <2500 cGy and chemotherapy in Seoul National University Children's Hospital were analyzed.**

Results: **Their median age was 9 years (range: 3-18.8), and 29 were male. Histological subtypes were classic type in 28 patients, nodular/desmoplastic in 7, and large cell/anaplastic (LCA) in 7. All the patients received adjuvant radiotherapy (CSI with median 2340 cGy and booster) and multiagent chemotherapy as the first-line treatment. With a median follow-up of 54 months, 12 patients experienced relapse or progression of the tumor. The 3- and 5-year disease-free survival (DFS) rates were 78.0%±6.5% and 75.0%±6.9%, respectively, and overall survival (OS) rates were 85.3%±5.6% and 76.8%±6.9%, respectively. The LCA subtype was associated with poorer DFS (*P*=0.023) and OS (*P*=0.008), compared with non-LCA subtypes.**

Conclusion: **The outcomes of children and adolescents with AvR MBL treated with radiation including CSI <2500 cGy and chemotherapy, are compatible to those in Western countries; however, the LCA subtype has a poor outcome with this strategy.**

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Introduction

Medulloblastoma (MBL), an embryonal tumor of the cerebellum, is one of the most common high-grade malignancies of the central nervous system in children, comprising 20% of all childhood brain tumors and 40% of childhood posterior fossa (PF) tumors.[1] Average-risk (AvR) MBL is defined as a totally or near totally resected tumor, with no evidence of intraneural dissemination (Chang's stage M0) in patients who are 3 years or older at diagnosis.[2] AvR MBLs are associated with a relatively good prognosis compared with high-risk (HR) MBLs.

The mainstay in the treatment of MBL is surgical excision, with subsequent radiotherapy (RT) and multiagent chemotherapy.[1,2] Children with AvR MBL have predicted 5-year progression-free survival of 50%-65% following treatment with 3600 cGy of craniospinal irradiation (CSI), supplemented by 1800-2000 cGy of RT to the PF.[3,4] The addition of chemotherapy to RT has enhanced the survival rates of children with AvR MBL.[5,6] However, the higher dose of radiation in CSI is thought to be related with, in part, the increased risk of neurological, cognitive, and endocrinological (including growth retardation) sequelae in children with MBL.[7,8] Therefore, there have been attempts to reduce the dose of CSI for treatment of children with medulloblastoma.

Recent studies of pediatric patients with AvR MBL in Western countries who were treated with a reduced dose of CSI (2340 cGy), followed by booster RT to tumor bed with

various chemotherapies, reported a progression-free survival (PFS) rate of 75%-85%.[1,9-12] At present, this strategy has been established as a standard treatment of childhood AvR MBL. However, there have been few studies on the effect of this dose of CSI with chemotherapy in the treatment of AvR MBL in Korean or other Asian children. We investigated the treatment outcomes and prognostic factors in children with AvR MBLs, who were treated with RT including CSI <2500 cGy and chemotherapy.

Methods

This study included 42 patients who were diagnosed with AvR MBLs postoperatively from January 2001 to December 2010 and treated with RT including CSI less than 2500 cGy and chemotherapy in Seoul National University Children's Hospital. Their magnetic resonance images (MRI) after the operations were analyzed, in addition to their medical records, including demographics, symptoms, disease characteristics, and pathological findings. The pathological findings assessed included pathological subtype and Ki-67 ratio. Their treatments including RT dose and fields or chemotherapeutic regimens, clinical outcomes and survival, and endocrinological medication status during follow-up were also analyzed.

As no nationwide or single-center prospective study of patients with AvR MBL had been conducted prior to Jan 2005, the patients of that time were analyzed retrospectively. In January 2005, a prospective study of patients with AvR MBL began on behalf of the Korean Society of Pediatric Neuro-Oncology (KSPNO) and terminated in 2013.[13] Therefore, the patients during this period were enrolled in this study (KSPNO-M051) and analyzed prospectively.

Statistical analysis

Statistical analysis was performed with SPSS software (version 18.0; SPSS, Chicago, IL, USA). A Chi-square test was used for non-continuous variables, and Student's *t* test and Kruskal-Wallis test were used to compare continuous variables between independent groups. For the analysis of survival status, disease-free survival (DFS) was defined as the duration between diagnosis to occurrence of primary tumor progression or relapse, and overall survival (OS) was defined as the time between diagnosis and death. In estimating event-free survival (EFS), an event was defined as treatment-related mortality (TRM) and disease progression. Kaplan-Meier methods were used to estimate 3- and 5-year DFS, EFS and OS rates. Comparisons of DFS, EFS and OS between subgroups were based on the log-rank test. *P* values less than 0.05 were regarded as a statistically significant difference.

Ethics statement

This study was approved by the Institutional Review Boards at Seoul National University Hospital (IRB number: H-1111-026-384). An informed consent was waived by the IRB.

Results

Patient characteristics

In a 10-year period, a total of 42 patients received RT including CSI less than 2500 cGy and combined chemotherapy. The male:female ratio was 29:13, and the median age was 9.0 years (range: 3.0 to 18.8 years). There was no difference in the median age between male (10 years) and female (8.5 years). At the time of diagnosis, 25 of the patients were younger than 10 years (Table 1).

Pathologic subtypes and Ki-67 percentage

The pathological subtypes of all 42 patients were reviewed. Twenty-eight patients were classified as classic type, with myoblastic differentiation in 1 patient, extensive neuroblastic differentiation in 1 patient, and MBL with a Hormer-Wright rosette in 1 patient. Seven patients were classified as nodular/desmoplastic (ND) and 7 as large cell/anaplastic (LCA). Although the ratio of classic, ND and LCA subtypes (66.7%, 16.7% and 16.7%, respectively) were similar with those found in previous reports,[10,12,14] the pathological subtypes differed according to the sex of the patients, with a higher ratio of the ND subtype in females (5/13, 38.4%) than males (2/29, 6.9%, *P*=0.034) (Table 1).

The percentage of Ki-67 in tumor specimens was available for 33 patients, and the range was 5%-70% (median: 30%) (Table 1).

Treatment

The overview of treatment in 42 patients is summarized in Table 2. All patients underwent resection of the primary tumor as an initial treatment. In all cases,

Table 1. Characteristics of the patients

Variables	*n*
Sex	
Male	29
Female	13
Age (y) (median: 9)	
3-9.99	25
10-18.8	17
Histological subtypes	
Classic*	28
Nodular/desmoplastic	7
Large cell/anaplastic	7
Ki-67 index	
≥40%	7
≥30% but <40%	12
<30%	14
Not assessed	9

*: including 1 myoblastic differentiation, 1 extensive neuroblastic differentiation, 1 medulloblastoma with Hormer-Wright rosette.

there was no residual tumor larger than 1.5 cm^2 on their postoperative MRI. RT was administered to all 42 patients, with the modality of 3-dimension conformal radiation. The dose of CSI was 2340 cGy in 40 patients, 2160 cGy in 1, and 2400 cGy in 1. A focal booster was administered to the tumor site in all 42 patients. In 16 patients, it was administered at the area of the whole PF and in 26 patients, within a 2 cm margin from the primary tumor. Consequently, all the patients received RT, with a total dose of 5400-5580 cGy to the tumor site. Thirty-one patients received RT just after the operation ("upfront RT"), and 11 patients underwent RT with preceding chemotherapy after the operation of the primary tumor ("sandwich RT") because of a planned treatment schedule (*n*=2), mis-stratification of risk group (*n*=1), or poor general status inappropriate for upfront RT (*n*=8). The median time interval between the operation and initiation of RT in the patients was 35 days (range: 24-156 days).

Table 2. Treatment status of the patients

Variables	*n*
Operations	42
Craniospinal irradiation dose	
2340 cGy	40
2400 cGy	1
2160 cGy	1
Total radiation dose to tumor site	
5400 cGy	33
5580 cGy	5
5220 cGy	2
5460 cGy	1
5040 cGy	1
Focal boost radiotherapy	
2 cm margin from the primary tumor	26
Whole posterior fossa	16
Chemotherapy	
KSPNO-M051	24
CCG-921 ("8-in-1")	16
CCG-9931 induction and maintenance	2
Order of therapy	
Upfront (radiotherapy→chemotherapy)	31
Sandwich (chemotherapy→radiotherapy→chemotherapy)	11

CCG: Children's Cancer Group; KSPNO: Korean Society for Pediatric Neuro-Oncology.

Table 3. Chemotherapeutic regimens used in the patients

Protocol name	Chemotherapeutics
CCG-9931 induction (every 3 wks)	Regimen A Cisplatin 90 mg/m^2/d (at day 0) Cyclophosphamide 1200 mg/m^2/d (at day 1, 2) Etoposide 75 mg/m^2/d (at day 0, 1, 2) Vincristine 1.5 mg/m^2/d (at day 0, 7, 14) Regimen B Carboplatin 400 mg/m^2/d (at day 0, 1) Etoposide 75 mg/m^2/d (at day 0, 1, 2)
CCG-9931 maintenance (every 7 wks)	Carboplatin 18 mg/kg/d (at day 0) Etoposide 2.5 mg/kg/d (at day 0, 1, 28, 29) Vincristine 0.05 mg/kg/d (at day 0, 7, 14, 21) Cyclophosphamide 65 mg/kg/d (at day 28)
CCG-921 ("8 in 1A", every 4 wks)	Methylprednisolone 300 mg/m^2 (3 times/d) Vincristine 1.5 mg/m^2 Lomustine 75 mg/m^2 Procarbazine 75 mg/m^2 Hydroxyurea 1500 mg/m^2 Cisplatin 60 mg/m^2 Cytarabine 300 mg/m^2 Cyclophosphamide 300 mg/m^2
KSPNO-M051 (every 4 wks)	Cisplatin 90 mg/m^2/d (at day 0)* Cyclophosphamide 1000 mg/m^2/d (at day 1, 2) Vincristine 1.5 mg/m^2/d (at day 0, 7, 14) +tailoring by *cis*-retinoic acid 160 mg/m^2/d†

*: given only in first 8 courses; †: *cis*-retinoic acid given during first 2 weeks in every 4 weeks of a course. CCG: Children's Cancer Group; KSPNO: Korean Society for Pediatric Neuro-Oncology.

Two of the 42 patients received chemotherapy as part of the Children's Cancer Group (CCG)-9931 chemotherapy (course A→B→A→B→A) with 3-week intervals, followed by subsequent radiation and CCG-9931 maintenance chemotherapy at 7-week intervals.[15,16] Sixteen patients were treated with 10 courses of CCG-921 regimen B (8-in-1) chemotherapy,[3] with condensed intervals from 6 to 4 weeks. Later, 24 patients were treated with the KSPNO-M051 treatment regimen (a nationwide study closed), which consists of radiation, 8 courses of cyclophosphamide, cisplatin, and vincristine, and 4 subsequent courses of cyclophosphamide and vincristine, followed by 6 courses of cis-retinoic acid.[13] The schedules and doses of chemotherapeutics agents are summarized in Table 3.

Treatment outcomes and prognostic factors

In a median follow-up of 54 months (range: 10-139 months), 12 patients had events. All the events were relapse or progression of tumor, and there was no TRM. Three of them had local recurrence only, 8 leptomeningeal (LM) seeding, and 1 both local recurrence and LM seeding (metachronous) at event. The median interval between diagnosis and tumor relapse/progression was 21.5 months (range: 9-120 months). Four patients had relapse/progression of tumors during treatment. All 4 relapse in 5 patient of LCA subtype was LM seeding without local relapse.

Three- and 5-year DFS of 42 patients was 78.0%±6.5% and 75.0%±6.9%, respectively (Fig. 1A), and their 3- and 5-year OS was 85.3%±5.6% and 76.8%±6.9%, respectively (Fig. 1B). As there was no TRM during the study, their EFS were same to their DFS. There was no difference on DFS or OS according to sex (male *vs*. female) and age (3-9.99 years *vs*. 10-18.8 years). Considering pathologic subtypes, there was no difference on DFS or OS between classic and ND subtypes. However, the LCA subtype was associated with poorer DFS (3- and 5-year DFS both 42.9%±18.7%) without statistical significance (*P*=0.075), and poorer OS (3-year OS: 57.1%±18.7%; 5-year OS: 42.9%±18.7%) which was significant (*P*=0.028) compared to the other two subtypes (Figs. 2A&B). However, when the patients with these two subtypes were combined in a single group (non-LCA subtype), 7 patients with LCA subtypes had inferior both DFS and OS, which was statistically significant (*P*=0.023 and 0.008, respectively) compared to the DFS (3- and 5-year DFS of 85.3%±6.1% and 81.6%±6.9%, respectively) and OS (3- and 5-year OS of 91.3%±4.8% and 83.9%±6.7%, respectively) of the 35 non-LCA subtypes (Figs. 2C&D).

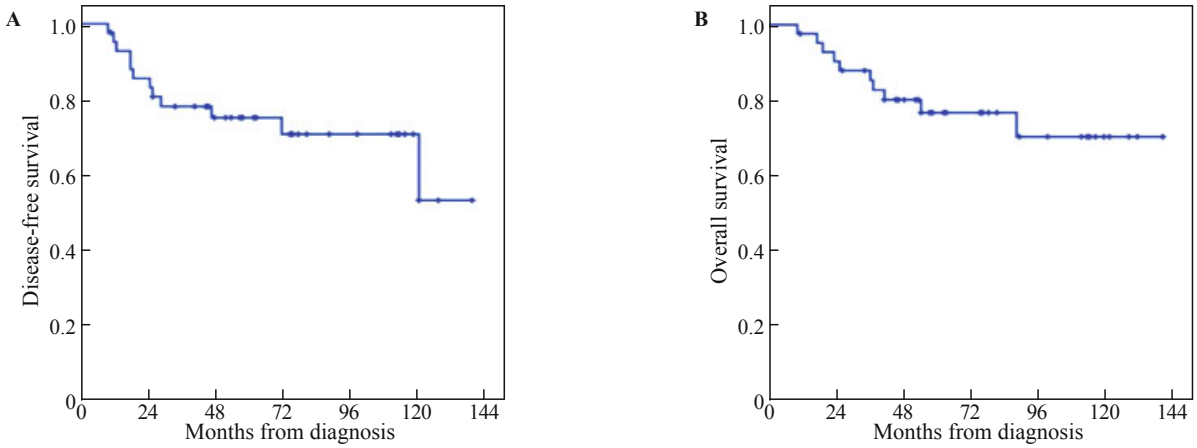

Fig. 1. Disease-free survival (**A**) and overall survival (**B**) of the total 42 patients.

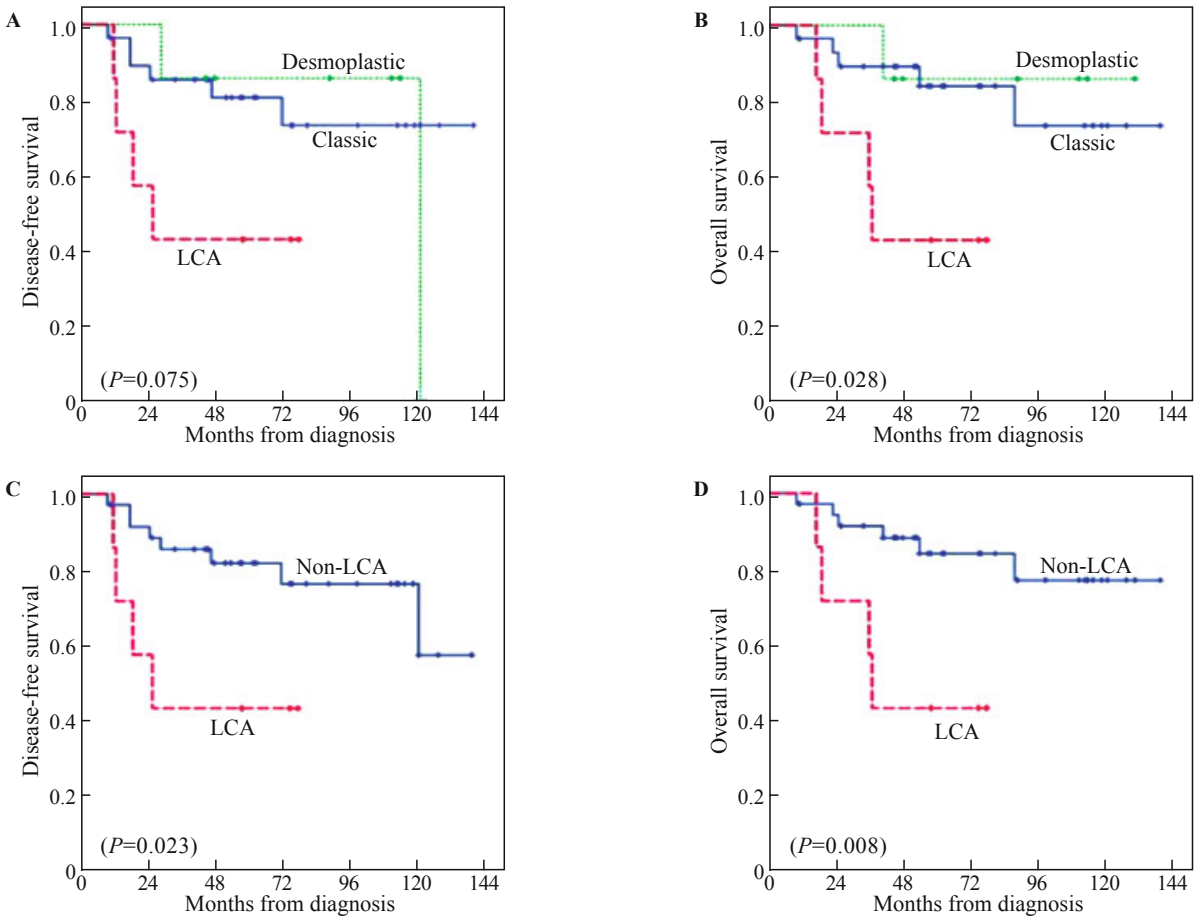

Fig. 2. Both DFS (**A**) and OS (**B**) of LCA subtype were inferior to DFS and OS of the classic or nodular/desmoplastic subtype, without and with statistical significance, respectively. When the patients with classic and nodular/desmoplastic subtypes were combined in a single "non-LCA subtype" group, both the DFS (**C**) and OS (**D**) of the LCA subtype were inferior, with statistical significance. DFS: disease-free survival; OS: overall survival; LCA: large cell/anaplastic.

There was no difference in the interval from the operation to RT between the patients with or without event (median: 34 *vs*. 39 days, respectively). At cut-off intervals of 4, 5, and 6 weeks, there was no difference on DFS (P=0.209, 0.168 and 0.818, respectively). The area where the focal booster was administered (2 cm of tumor margin *vs*. PF) did not influence on DFS (P=0.455) or local relapse rate (2/26 *vs*. 2/16, P=0.606). When we compared Ki-67 index of the patients' tumor tissues according to event outcomes, there was no difference between two groups with (n=8) and without (n=25) tumor progression/relapse (P=0.665). In addition, there was no significant difference

in DFS between the two groups when we compared outcomes between groups according to a Ki-67 index of 30% or 40% (P=0.745 and 0.627, respectively).

Endocrinologic follow-up

Among 30 patients who survived without relapse or progression of tumors, 23 patients visited the pediatric endocrinology clinic at least once and underwent endocrinological evaluations during their follow-up periods. Thirteen patients received growth hormone (GH) therapy during the follow-up periods. Among the 10 patients who did not have GH therapy, 2 refused the treatment, and 1 showed borderline growth retardation not requiring treatment. Fifteen patients received other endocrinological medications, such as calcium with vitamin D, synthyroid (7 patients, including 1 with congenital hypothyroidism), estrogen, and atorvastatin. Among the 9 patients who did not receive endocrinological medication, thyroid function tests showed a subclinical abnormality in 1 patient.

Discussion

RT is a very important modality in the treatment of pediatric brain tumors. CSI is one of the most important strategies in the treatment of childhood MBL. Postoperative CSI (3000-3600 cGy) with PF boost irradiation (5400-5600 cGy) was the standard treatment strategy for children older than 3 years during two to three decades before 2000.[5] With this approach, the 5-year OS was about 46%-65% in AvR MBL patients and 50% in the HR MBL. However, its late effects, including endocrinolgical, auditory and neurocognitive sequelae, limited its use. Therefore, many efforts have been made to reduce the CSI dose while maintaining good treatment outcomes. The introduction of combination chemotherapy, including cisplatin, methotrexate, vincristine, carboplatin, and cyclophosphamide, enabled reduced doses of CSI to be used in the treatment of MBL.[17] Combination chemotherapy with reduced CSI resulted in non-inferior outcomes of MBL.[2,5] In a phase 3 trial of the Children's Oncology Group, a reduced dose of CSI (2340 cGy) with two kinds of adjuvant multidrug chemotherapy (lomustine, cisplatin and vincristine *vs*. cisplatin, vincristine and cyclophosphamide) were given to the children with AvR MBL.[1] In this study, the 5-year DFS and OS of the 379 enrolled patients was 81%±2.1% and 86%±9.0%, respectively, which is better than that reported with the previous strategy of higher-dose CSI. Recently, a European group reported a similar outcome (5-year EFS of 82%±2%) using reduced CSI (conventional or hyperfractionated) of 2340 cGy with a PF boost to 5400 cGy and subsequent adjuvant chemotherapy of cisplatin, lomustine and vincristine.[12] These results indicate that intensive adjuvant chemotherapy can improve treatment outcomes in AvR MBL, despite reduced CSI doses.

Some studies have investigated outcomes of AvR MBL in Korea, Japan or other Asian countries,[18-23] but most have dealt with both AvR and HR MBL, and none have analyzed the effect of CSI <2500 cGy on AvR MBL or prognostic factors in Asian children or adolescents. This is the most recent report of treatment outcomes and endocrine complications in children and adolescents with AvR MBL treated with a reduced dose of CSI <2500 cGy, combined with multiagent chemotherapy, in Korea. In this study, the 3- and 5-year DFS of the 42 patients was 78.0%±6.5% and 75.0%±6.9%, respectively. Furthermore, after excluding seven LCA subtypes, the 3- and 5-year DFS of the 35 patients was 85.3%±6.1% and 81.6%±6.9%, respectively, which are comparable to previous reports of patients in Western countries who were treated with reduced CSI and chemotherapy.[1,4,9-12,24] However, the outcome in our study may be somewhat inferior to those of the Western countries. The differences in outcomes may also partly result from racial/biologic difference between the study populations. A recent study from Thailand reported 5-year PFS of 64.2%±13% and OS of 65.5%±12.6% using a reduced CSI of 2400 cGy with chemotherapy,[23] which are worse than our results. In that study, outcomes in AvR MBL treated with a higher dose of CSI (3600 cGy) with chemotherapy were similar (60.6%±15.8% for 5-year DFS and 77.9%±14.1% for 5-year OS).[23] These results may suggest that outcomes in Asian children with AvR MBL may be worse than in children from Western countries because of biologic differences. Despite similar outcomes, it is also important that intensities of the chemotherapeutic regimens used in our patients (CCG-9931 every 3 weeks, CCG-921 with interval compression to 4 weeks, and KSPNO-M051 every 4 weeks) are similar with previous regimens for HR MBL in Western countries, pointing to biologic differences in chemo-radio-sensitivities of the MBLs.[3,13,16,25] In addition, in the present study, most of the relapse/progressions were LM seedings, indicating the need for more intensive chemotherapies.

Many factors, such as sex, age, neuraxis metastasis, pathologic subtype, apoptosis index of the tumor, and hyperdiploidy of the tumor, are known to be prognostic in childhood MBL.[17,26,27] In this study, the sex and age of the patients were not associated with the outcomes. In the analysis of pathological subtype, only the LCA subtype was associated with poor prognosis compared to non-LCA subtypes, with statistical significance. Our results suggest that our treatment regimens consisting of a reduced dose of CSI, together with chemotherapy, is not a sufficient treatment for AvR MBL with the LCA subtype. Although this result is consistent with some previous reports,[28-30] it is in contrast to that of a large study by Packer et al[1] and Lannering et al.[12] The differences in the results may be due to the small number of patients in our study. However,

it is possible that they may also be the result of biologic differences, such as the frequency of c-myc amplification, between races.[14] Recently, many reports indicate that MBL with the LCA subtype consistent with the criteria of AvR MBL clinically is a HR MBL and requires more intensive treatment,[31,32] such as a higher dose of CSI or high-dose chemotherapy with autologous stem cell rescue. Our data also indicate that MBL with LCA subtype in Korean children should be treated with more intensive strategy regardless of clinical risk group. Although some studies reported that a higher MIB-1 index (Ki-67) is associated with poorer outcomes in MBL,[33,34] Ki-67 had no prognostic significance in this study. This finding may be related to the small number of our patients. However, based on the findings of previous studies, which included both AvR MBL and HR MBL, the prognostic importance of Ki-67 index appears to be lower in AvR MBL.

In this study, the LCA subtype was the only statistically significant prognostic factor of poor outcomes. The KSPNO-M051 study protocol has been amended to exclude the LCA subtype from AvR MBL, regardless of metastasis status or area of surgical excision. Recently, molecular prognostic factors are of interest in childhood MBL, including conventional molecular factors such as TrkC, ErbB2/ErbB4 expression, loss of heterozygote of 17p isochromosome in tumor cells, and expression of platelet-derived growth factor receptor and newer factors such as expression of c-myc or n-myc, activation of the Wnt or Sonic Heghog pathway, and such factors also have important roles in the prognosis of MBL, irrespective of age, surgical resection, metastasis, or histological subtype.[27,35-38]

Despite the reduced CSI dose to less than 2500 cGy, our results showed that many patients with long-term survival experience endocrinological and/or growth problems after completion of the treatment. Among the 23 long-term survivors who underwent endocrinological evaluation, 13 received GH therapy, and two refused, despite growth problems. Fifteen survivors also received endocrinological medications, such as vitamin D, synthyroid, or estrogen. Of course, not all the recorded endocrinological problems may be related to radiation including CSI. However, Yun et al[7] reported that CSI is one of a number of important factors determining the final height of Korean childhood brain tumor survivors. The prevalence of growth or endocrinological problems points to the need for a new treatment strategy with much lower CSI doses.

There are some limitations in our study. First, this is a retrospective study with a small patient population and a relatively short duration of analysis (10 years). Second, the CSI dose and area of focal booster irradiation were not the same in all patients. Third, the patients received various chemotherapeutic drugs, and some had upfront chemotherapy before RT, making it difficult to interpret the exact outcomes. Fourth, there was no information on the Ki-67 positivity rate of about 20% of the patients, interfering with the analysis. Fifth, not all the patients underwent endocrinological evaluations, and we analyzed only the medication status of the patient rather than the patient's growth pattern or endocrinological function. Last, there was no information on the neurocognitive or auditory functions of the enrolled patients.

In conclusion, our results showed that the outcome of childhood AvR MBL treated with reduced CSI and chemotherapy was good and not inferior compared to that reported in Western countries, although it is still unsatisfactory. The LCA subtype resulted in poor outcomes with the reduced CSI and chemotherapy strategy. Despite the reduced CSI doses, many patients had endocrinological problems. A safe and effective radiation and chemotherapy strategy is needed to improve the survival and long-term outcome of children with AvR MBL, as well as investigations of biological aspects of this disease.

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