Ependymoma is the third most common pediatric brain tumor [1]. Thirty percent of all pediatric ependymomas occur in children below 3 years of age [2]. The 7-year local control and event-free survival rates in pediatric ependymoma patients undergoing current treatment regimens (maximal safe resection, followed by focal adjuvant radiotherapy [RT]) were reported to be 83.7% and 69.1%, respectively [3]. In particular, both progression-free survival (PFS) and overall survival (OS) were significantly worse in patients with anaplastic ependymoma (grade III) than in patients with grade II ependymoma [4].

Although RT is indispensable for the prevention of local recurrence of anaplastic ependymoma, the exposure of normal tissue to radiation may lead to acute or late toxicity. There are many reports of long-term sequelae of central nervous system (CNS) tumors,
such as neurocognitive dysfunctions, growth disorders, psychological and behavioral disorders, ototoxicity, and increased risk of secondary malignancy [5–7]. On the basis of this evidence, many physicians try and avoid RT in children below 3 years of age who are particularly vulnerable to the damaging effects of radiation.

Despite concerns regarding RT-related toxicity, there is an emerging need for adjuvant RT in patients below 3 years of age with CNS tumors. The prospective German brain tumor trials HIT-SKK 87 and 92 [8] evaluated the role of RT in anaplastic ependymoma in children below 3 years of age and showed that delaying RT increased the risk of local recurrence even after intensive chemotherapy. In addition, according to the Children’s Oncology Group trial (ACNS0121) [9], the effectiveness of chemotherapy is not yet clear and thus extensive delays in or avoidance of adjuvant RT should be avoided.

Recent developments in RT technology, such as intensity-modulated radiotherapy (IMRT), have led to more accurate and precise treatments than the three-dimensional conformal radiotherapy (3D-CRT) plans (Fig. 1), thereby reducing unnecessary radiation exposure of surrounding normal tissues. As shown on the dose

![Comparison of three-dimensional conformal radiotherapy (A) versus intensity-modulated radiotherapy (B) in the treatment of brain tumors. The difference between preservation of optic chiasm, brainstem, and both cochlear among treatment plans can be compared visually to some extent.](https://doi.org/10.3857/roj.2020.00073)
volume histogram, there was a sharp reduction in the planning target volume (PTV) in the IMRT plan, representing the superior PTV dose homogeneity (Fig. 2). Moreover, dose-volume histograms showed a lower dose to the optic chiasm, brainstem, and both co-chleae on IMRT, demonstrating that RT-related neurologic toxicity can be significantly reduced.

The aim of this study was to evaluate the safety and feasibility of IMRT in children under 3 years of age who received IMRT for anaplastic ependymoma.

Materials and Methods

1. Patient selection
Patients below 3 years of age with anaplastic ependymoma who underwent postoperative IMRT at our institution between October 2011 and December 2017 were included in this study. All patients were diagnosed on the basis of histological confirmation and underwent magnetic resonance imaging (MRI) for disease evaluation and follow-up. Pathology was confirmed by surgical resection. A total of 9 patients were included in our study. This study was approved by the Institutional Review Board of the Yonsei University Health System (No. 4-2019-0939). The informed consent was waived by Institutional Review Board.

2. Follow-up and assessment of neurologic morbidity
During the RT period, patients were followed up clinically once a week. After RT, patients were followed up clinically within 1 month, then every 3 months for the first 2 years, every 6 months for 1 year, and once a year thereafter. MRI examination was also performed 1 month after RT, followed by every 3 months for the first year, every 6 months for next 2 years, and once a year thereafter. Recurrence was determined by comprehensive evaluation of MRI images and clinical findings.

Three categories related to neurologic morbidity (neurocognitive...
dysfunction, motor dysfunction, and hearing impairment) were retrospectively evaluated through medical records maintained by physiatrists, pediatric neurosurgeons, pediatric medical oncologists, and pediatric radiation oncologists as well as using the Denver Developmental Screening Test II (DDST-II) and the Bayley Scales of Infant and Toddler Development. The DDST-II is a revised version of the Denver Developmental Screening Test designed to identify developmental problems in children aged 0–6 years; it is divided into four areas: personal-social, fine motor-adaptive, language, and gross motor [10]. The Bayley Scales of Infant and Toddler Development (Bayley-III is the current version) are a standard series of measurements primarily used to assess the development of infants and toddlers aged 1–42 months [11]. Neurocognitive dysfunction was defined as the occurrence of declining intellectual function or of problems with attention, processing speed, or working memory [12]. Because treatment and clinical features were different for each patient, each patient’s record was reviewed in detail by radiation oncologists (JL, HIY, and COS) and a neurosurgeon (DSK) to analyze the exact causes of neurologic morbidity.

3. Radiotherapy

All Patients underwent simulation computed tomography (CT) for RT planning. During simulation CT, the patient’s head and neck were immobilized with a thermoplastic mask in the supine position. Simulation CT images were imported into MIM software (MIM Software Inc., Cleveland, OH, USA) for target delineation. Gross tumor volume 1 (GTV1) consisted of any residual or recurrent lesions. GTV2 was defined as GTV1 plus the surgical cavity. Clinical target volume (CTV) was defined as GTV2 plus 0.5–1.0 cm margins. PTv was defined as the CTV plus 0.3 cm margins. The Tomotherapy (Accuray, Sunnyvale, CA, USA) or RayStation (RaySearch Laboratories, Stockholm, Sweden) software was used for IMRT plans. In an IMRT plan, higher doses were prescribed in the order of GTV1, GTV2, and CTV using a simultaneous-integrated boost technique. The median total dose of GTV1, GTV2, and CTV was equivalent to a dose of 2 Gy fractions (EQD2) 57.0 Gy (range, 56.0 to 60.0 Gy, α/β = 3), 52.0 Gy (range, 48.0 to 60.0 Gy, α/β = 3), and 40.0 Gy (range, 38.0 to 52.0 Gy, α/β = 3), respectively (Table 1). If the patient was unable to fall asleep during RT, we attempted conscious sedation by administering 25–100 mg/kg chloral hydrate orally. In cases wherein chloral hydrate failed, we administered 0.05–0.1 mg/kg midazolam intravenously. If the second option also failed, we attempted general anesthesia by administrating propofol. Of our 9 patients, 2 went to sleep before RT, 3 were under conscious sedation with chloral hydrate, 1 was sedated with midazolam because of failure of chloral hydrate, and the other 3 were treated under general anesthesia with propofol.

4. Statistical analysis

OS is calculated from the date of RT to the date of death, regardless of the cause of death. Local recurrence is defined as recurrence within the RT field. Freedom from local recurrence (FFLR) is defined as the time from the date of RT to local recurrence. PFS is defined as the time from the date of RT to any recurrence or death. Survival outcomes were analyzed using the Kaplan-Meier method and log-rank test. Statistical analyses were performed using IBM SPSS version 23.0 software (IBM Corp., Armonk, NY, USA).

Results

1. Patient and treatment characteristics

The baseline and treatment characteristics of all 9 patients are listed in Table 1. The median patient age was 20.9 months (range, 12.1 to 31.2 months). Five patients were male and 4 were female. The median tumor size was 5.1 cm (range, 2.4 to 7.0 cm). The most common tumor location was the 4th ventricle (6 patients, 66.7%), and the remaining tumors were located in the cerebellopontine angle cistern, temporo-parieto-occipital lobe, or frontal lobe. When...
the location of the tumor was divided by the tentorium cerebelli, the tumors were in the infratentorial area in 7 patients.

All patients underwent surgery. Five patients underwent gross total resection (no residual tumor), 2 underwent near total resection (>90% of tumor removed), and 2 underwent subtotal resection (50%–90% of tumor removed) [13]. The time interval from surgery to RT was 20–140 days (median: 28 days). No patient received chemotherapy or peripheral blood stem cell transplantation. All patients except one received IMRT postoperatively at initial diagnosis. The remaining patient received salvage RT because of recurrence after the initial surgery.

2. Survival outcomes
The median follow-up duration was 28.0 months (range, 19.3 to 76.0 months). The 5-year OS, FFLR, and PFS rates for all patients were 40.6%, 53.3%, and 26.7%, respectively (Fig. 3A–3C).

Recurrence occurred in 5 patients: 3 had local recurrence, 1 had both local recurrence and cerebrospinal fluid (CSF) seeding, and 1 had CSF seeding alone. Four patients without recurrence had undergone gross total resection and received EQD2 52–60 Gy to the tumor bed. None of these 4 patients underwent additional surgery or chemotherapy after RT.

Of the 3 patients who underwent local recurrence, 1 received surgery and adjuvant chemotherapy as salvage treatment; however, residual tumor progression was observed. The second patient underwent gamma knife surgery as salvage treatment but developed CSF seeding thereafter. Despite subsequently undergoing palliative re-irradiation targeting the whole ventricle, the patient died because of disease progression. The third patient underwent surgery and gamma knife surgery for residual lesions, followed by adjuvant chemotherapy as salvage treatment. However, 1 year after the end of chemotherapy, a recurrent tumor was observed. Gamma knife surgery was repeated, but the patient died because of disease progression.

One patient with local recurrence and CSF seeding underwent surgery as salvage treatment and was expected to receive adjuvant chemotherapy; however, the treatment was delayed because of the patient’s poor physical condition, and the patient died because of progression of leptomeningeal seeding.

One patient who experienced CSF seeding at the age of 6 years 2 months was treated with tumor removal for recurrent lesions at the L2-L5 vertebrae of the spinal cord, followed by 36 Gy craniospinal irradiation and boost RT of 18 Gy to the tumor bed. Approximately 10 months after the end of RT, the patient showed no evidence of disease.

Of the 4 patients without recurrence, 2 received EQD2 52 Gy to the tumor bed after gross total resection of the 4th ventricle tumor and 40 Gy to the tumor bed plus margins. They showed no evidence of disease for approximately 2 years after RT completion. Another patient received EQD2 56 Gy to the tumor bed after gross total resection of the left temporal-parietal-occipital lobe tumor and 52 Gy to the tumor bed plus margins. This patient showed no evidence of disease for 6 years after RT completion. The last patient received EQD2 60 Gy to the tumor bed after gross total resection of the right frontal lobe tumor and 52 Gy to the tumor bed plus margins. The patient showed no evidence of disease for 2 years and 6 months after the RT completion.

Fig. 3. Kaplan–Meier curves of overall survival (A), freedom from local recurrence (B) and progression-free survival (C) in patients with anaplastic ependymoma.
3. Neurologic morbidity
Neurologic morbidity after treatment was evaluated in all patients, 3 (33.3%) of whom showed neurologic morbidity; all had motor dysfunction alone (Table 2). The first patient had a 5.0-cm-sized tumor located in the 4th ventricle, causing hydrocephalus. Before diagnosis, the patient was able to stand with support, but at the time of disease diagnosis and after surgery, the patient’s motor function had declined, and the patient was only able to sit with support for 1 minute. There was no difference in motor dysfunction before and after RT. The Denver Developmental Screening Test at 18 months of age showed that the development levels were those of an 11-month-old, characterized by difficulty standing alone because of a decline in overall muscle strength.

The second patient had a 5.0-cm-sized tumor located in the 4th ventricle, causing hydrocephalus. Hydrocephalus improved after surgery but was still observed. The patient showed delayed gross muscle development after surgery, and the Denver Developmental Screening Test at 18 months of age showed gross motor development levels equivalent to those of a 14-month-old. The motor dysfunction seen before RT was maintained after RT, and the patient subsequently underwent rehabilitation therapy.

The third patient had a 5.9-cm-sized tumor located in the left cerebellopontine cistern, causing hydrocephalus. There was no deterioration in motor function after the first surgery. However, left-hand weakness and overall postural tone deterioration developed with progression of the residual lesion. RT was performed on these residual lesions. Motor dysfunction present before RT persisted after RT. The patient underwent rehabilitation therapy, but persistent motor function deterioration was observed.

| Patient no. | Sex | Age at RT (mo) | Tumor size (cm) | Tumor site | Surgery extent | Hydrocephalus at diagnosis | Neurologic morbidity classification | Sx related to neurologic morbidity | Denver developmental screening test | Interval between onset of neurologic Sx and RT |
|-------------|-----|----------------|-----------------|------------|----------------|---------------------------|-------------------------------------|-------------------------------------|----------------------------------------|--------------------------------------------|
| 1           | F   | 12.1           | 5               | 4th ventricle | STR           | Yes                       | MD                                 | Sitting with arm support for only 1 minute | Gross motor: 11-month-old level (at 18 months of age) | 1 month before RT                           |
| 2           | M   | 18.4           | 5               | 4th ventricle | NTR           | Yes                       | MD                                 | Delayed gross muscle development | Gross motor: 14-month-old level (at 18 months of age) | 1 month before RT                           |
| 3           | M   | 31.2           | 5.9             | Left CPA cistern | STR           | Yes                       | MD                                 | Left hand weakness, overall postural tone deterioration | Gross motor: 9-month-old level (at 43 months of age) | 1 month before RT                           |

RT, radiotherapy; Sx, symptoms; F, female; M, male; CPA, cerebellopontine angle; STR, subtotal resection; NTR, near total resection; MD, motor dysfunction.

Discussion and Conclusion
In pediatric patients, the immature CNS is vulnerable to RT; therefore, the adverse effects of RT can be more severe than those in adults, which in turn may lead to problems such as delayed development [5,14]. Some studies have suggested that RT therapy should be delayed or excluded as a treatment option in pediatric patients, instead utilizing intensive chemotherapy until the age of 3 years, when CNS cell division is nearly complete [15,16]. However, delays in RT can compromise oncologic outcomes [8,17]. With advances in RT techniques, IMRT enables a more targeted delivery, sparing the normal tissue and markedly reducing toxicity compared to that with 3D-CRT. In our hospital, IMRT has been performed in patients below 3 years of age, resulting in an improvement in neurologic morbidity and treatment outcome.

The most important issue in the treatment of ependymoma is that it often occurs in children below 3 years of age who are more vulnerable to the damaging effects of RT [18]. Some studies have shown a poor outcome if RT was deferred for more than 1 year after surgery and therefore recommended immediate RT, even in children below 3 years of age [19]. In the analysis of the HIT-SKK 87 and 92 trials that exclusively enrolled patients below 3 years of age with anaplastic ependymoma, the 3-year OS was 66.7% when RT was administered immediately after chemotherapy, compared to 38.5% when RT was delayed [8]. As availability of IMRT has increased, recent studies analyzing pediatric ependymoma patients have shown that despite a reduction in treatment volumes treatment with IMRT results in favorable local control rates that do not increase the risk of marginal failure or neurologic toxicity compared to those published historically [20,21]. Together with the results presented here, these findings reveal that the use of IMRT...
can reduce toxicity while maximizing therapeutic outcomes for ependymoma patients below 3 years of age.

Until the 2000s, it was not possible to determine the optimal radiation dose for ependymoma because of small cohort sizes or heterogeneity between studies. Although some retrospective studies have recommended RT of 45 Gy or higher at the tumor site [22,23], the European Association of Neuro-Oncology (EANO) guidelines recently recommended a postoperative RT dose of 59.4 Gy for patients older than 18 months with World Health Organization (WHO) grade II or III ependymoma, whereas a dose of 54 Gy was recommended for patients younger than 18 months because of neurological vulnerability [24]. Given that the studies that were the basis for the EANO guidelines mainly used 3D-CRT, in the modern era, IMRT can be safely used to administer this radiation dose with lower toxicity. In the current study, the median total doses for residual lesions were EQD2 57.0 Gy (range, 56.0 to 60.0 Gy) and those for the tumor cavity were EQD2 52.0 Gy (range, 48.0 to 60.0 Gy). Although the statistical comparison was difficult because of the small number of patients, the median total dose of tumor cavity in patients with in-field recurrence was EQD2 48.0 Gy (range, 48.0 to 52.0 Gy), whereas in patients without in-field recurrence, the median total dose was EQD2 54.0 Gy (range, 52.0 to 60.0 Gy). Thus, a sufficient radiation dose may be critical to achieve local control, and IMRT can be used for the administration of high radiation doses.

Regarding RT field, the German HIT-SKK 87 and 92 trials included neuraxis in the RT field [8], but more recent studies defined the RT field as the tumor bed plus margins [3,4]. The recently revised the EANO guideline also recommended setting the CTV to tumor bed plus margins [24]. In line with previous reports, our institution’s practice also defined RT field as tumor bed plus margins.

Radiation to critical tissues is known to be associated with the development of neurologic morbidity [5,14]. Previous studies that applied IMRT or proton therapy to brain tumors concluded that the use of advanced RT technique for brain tumors allows for improved target conformity and better critical tissue sparing, resulting in lower neurologic toxicity [25-27]. Therefore, on the basis of multiple studies, the application of a modern RT technique is important in pediatric patients.

In our study on very young children treated with IMRT, neurologic morbidity was observed in 3 patients (Table 2), all of whom had tumors located around the 4th ventricle. At the time of initial diagnosis, these 3 patients suffered from hydrocephalus due to the location of the tumor. Following RT, hydrocephalus worsened in only 1 patient. Considering the relationship between time of onset and RT, we can conclude that RT was not a direct cause of the hydrocephalus. This patient also exhibited motor dysfunction before RT, which did not worsen after RT. Issues arising from pediatric hydrocephalus, including surgical complications, academic achievement, and neurologic sequelae, have been the focus of numerous studies. Motor handicap in pediatric patients with hydrocephalus was reported in 30%–60% of cases [28-30], and low IQ was reported in 12.5%–54.7% of cases [31,32]. Our findings suggest that most toxicities are caused by mass effects from the tumor itself combined with sequelae from surgery.

One of the limitations of this study was the small sample size, making statistical analysis difficult. In addition, because we did not conduct longitudinal studies that prospectively measured neuromotor sequelae, our study was difficult to analyze the changing patterns of neurologic deficiencies. Thus, although neurologic morbidity was thought to be caused by a combination of mass effects from the tumor and sequelae from surgery, it was difficult to determine how RT affected neurologic morbidity exactly. Despite these limitations, our results are still meaningful. Few previous studies have collected data from many anaplastic ependymoma patients below 3 years of age who received IMRT from one institution. As well, we tried to analyze each case in detail and compared related factors to the greatest extent possible.

In conclusion, pediatric anaplastic ependymoma patients below the age of 3 years who received IMRT showed an encouraging local control rate and tolerable toxicity. These outcomes were comparable to those of other studies. Although neurologic morbidities were observed in 3 patients, these appear to be caused by the tumor itself and/or sequelae from surgery. On the basis of these results, when performing RT for anaplastic ependymoma in very young patients, a high-precision modern RT approach such as IMRT should be actively considered.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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