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CLINICAL INVESTIGATION

Challenges in Treating Childhood Infratentorial Ependymoma: A Low- and Middle-Income Country Experience

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Purpose: Patients and physicians in low- and middle-income countries (LMICs) face challenges owing to limited expertise and suboptimal access to appropriate diagnostic and treatment modalities. We report our experience in treating posterior fossa ependymoma (PFE) at MAHAK, a charity organization in Iran whose radiation oncology department is the only one exclusively dedicated to childhood cancer in the whole country.

Methods and Materials: Pediatric patients with PFE referred to MAHAK between November 2008 and January 2016 were identified. Details on investigations and management done before referral were collected. Management at MAHAK and patient outcomes were analyzed.

Results: Of 80 patients diagnosed as having ependymoma, 54 with PFE were identified. Forty-three patients received adjuvant radiation therapy, and 11 were irradiated initially after recurrence. At a median follow-up of 5.1 years (range, 0.3-9.7 years), the latter group had the worst outcome, with a 5-year overall survival (OS) rate of 27% (95% CI, 7%-54%). Patients who started radiation therapy within 77 days after initial surgery had a better outcome compared with those who started later (5-year OS: 74% vs 32%; $P = .05$). Compliance with follow-up recommendations was poor. Only 22% of the patients had at least 2 IQ test assessments, and 50% showed some decline over time. Three cases of growth hormone deficiency were detected, but none of the patients received replacement therapy.

Conclusions: Access to pediatric neurosurgery, anesthesia, and timely radiation therapy are among the most challenging obstacles to be overcome in LMICs. Our series confirmed that chemotherapy is not an appropriate option for delaying radiation therapy, especially in young children. The importance of long-term follow-up should be acknowledged by the parents and medical team.

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Research data are stored in an institutional repository and will be shared upon request.

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Introduction

Ependymoma is the third most common brain tumor in children, with 90% arising intracranially. Two-thirds of ependymomas are located in the posterior fossa, followed by the supratentorial location, whereas spinal ependymomas are rare in the pediatric age group.[1] Ependymoma is primarily a surgical disease, and maximal safe resection followed by radiation therapy (RT) to the tumor bed is the standard of care.[2] The role of chemotherapy is still uncertain, and its use in young children to avoid or delay RT has shown limited success.[3]

The treatment of this condition is challenging in low- and middle-income countries (LMICs). Access to dedicated pediatric neurosurgical care is limited, and there is insufficient basic equipment and training.[4] The same is true for RT facilities; despite being home to 85% of the world's population, only 35% of the world's RT facilities are located in LMICs.[5]

The MAHAK charity organization was established 30 years ago as an independent nongovernmental organization to support children with cancer and their families in Iran. The hospital was inaugurated in March 2007, and the first child was irradiated in July of the same year.[6] The radiation oncology department is the only one exclusively dedicated to childhood cancer in Iran. The unit is equipped with 2 linear accelerators for conformal and intensity modulated RT and 1 computed tomography (CT) simulator. A liaison with the radiology department was established for performing magnetic resonance imaging (MRI) in the treatment position for planning. An anesthesia team was dedicated to the radiation oncology department, and a recovery room was built. Nowadays, 200 to 250 patients are treated annually, including more than 50% with a diagnosis of brain tumor. In this report, we describe our experience in dealing with children with posterior fossa ependymoma (PFE) between November 2008 and January 2016. Although pediatric ependymomas arise both in the supratentorial and infratentorial compartments, PFEs represent a unique entity owing to the technical challenges associated with their resection, their specific molecular characteristics, and their poorer outcome compared with supratentorial ependymoma in most series.[7,8]

Methods and Materials

Patients

Pediatric patients (≤18 years old) with a diagnosis of ependymoma and referred to the MAHAK radiation oncology department between November 2008 and January 2016 were identified. All patients were operated in public or private hospitals outside MAHAK. Details on investigations and management before and after referral and the outcome of patients with PFE were collected. The study was approved by the research ethics committee of MAHAK.

Evaluation before RT

At first presentation of each referred patient, the pathology report was reviewed by the MAHAK pathology department, and additional immunohistochemistry staining was requested from outside laboratories, depending on immunohistochemistry markers available on the market. No H3K27me3 staining was accessible during this period. After surgery, only postoperative noncontrast CT scans were performed at local institutions. Similarly, no patient underwent a preoperative or early postoperative MRI scan of the spine. Therefore, at the time of admission at MAHAK, all patients underwent full staging that included brain and spinal MRI and cerebrospinal fluid (CSF) analysis. The latter was done at least 2 weeks after the surgery. Subtotal resection was defined as a postoperative residual tumor >5 mm noted on MRI.[2] As per the Children's Oncology Group (COG) ACNS0121 protocol, which included patients registered within 56 days after initial surgery and irradiated within 3 weeks after registration, in this study, up-front RT was defined as the initiation of adjuvant RT within 77 days of surgical resection (56 + 21 days), whereas delayed RT was defined as initiation thereafter.[2] RT for recurrence was excluded in this definition.

Conformal RT

Definitions from the International Commission on Radiation Units and Measurements report 50 were used for target-volume contouring. Brain MRI fused with the simulation CT scan was used for tumor bed contouring. Gross tumor volume (GTV) included the postoperative tumor bed and residual disease in the case of subtotal resection. Clinical target volume (CTV) was a 5-mm, 3-dimensional expansion of the GTV. To spare the brain stem from receiving high doses, a 3-mm anterior margin was chosen instead of 5 mm in case of gross total resection (GTR). The planning target volume (PTV) was a 3- to 5-mm geometric expansion of the CTV. The prescribed dose was 54 Gy before 2013 and 59.4 Gy afterward. The PTV received at least 95% of the 54 Gy. To give a higher dose to the GTV, 2 different plans were used: a boost was given to the GTV as a second treatment step, or a smaller margin around the PTV was chosen as a field margin in such a way that the PTV received at least 95% of the 54 Gy and the GTV 95% of the 59.4 Gy. The CTV received at least 95% of the 54 Gy in case of nearby dose-limiting organs at risk, such as chiasma and the spinal cord, or 95% of the CTV received at least 95% of the 59.4 Gy. The brain stem was spared to receive 58 Gy, or only a small volume was acceptable, as defined by Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC). Craniospinal irradiation (CSI) was used in case of dissemination. The dose delivered to the whole neuraxis was age-adapted (18 Gy for children younger than 3 years of age, 25.2 Gy for children 3-5 years, and 30.6-34.2 Gy for children older than 5 years) in 1.8-Gy daily fractions 5 days per week, from Saturday to

Wednesday. Focal boost up to 54 Gy was delivered to the tumor bed as previously described.

Surveillance

All patients were followed in person until January 2020 before the pandemic. Afterward, most of the surveillance was done by phone and consequently, January 2020 was chosen as the cutoff for the analysis. Imaging follow-up included brain MRI 4 to 8 weeks after the end of the RT, every 3 to 4 months thereafter for the first 3 years, then every 6 months up to 5 years, and then annually. Spinal MRI was done systematically if seeding was detected before RT and in case of recurrence. Pure tone audiometry at frequencies from 0.250 to 16 kHz and otoacoustic emissions tests at frequencies from 1 to 8 kHz for children younger than 5 years were performed before RT and then recommended annually. Chang grading was used for evaluating ototoxicity.[9] Pituitary function (Thyroid stimulating hormone, thyroxine, adrenocorticotropic hormone, Cortisol, insulin-like growth factor 1, and growth hormone [GH]) was assessed before RT and annually thereafter, depending on the dose received by the pituitary gland and clinical examination. Neuropsychological assessment by the Wechsler Intelligence Scale adapted to age was scheduled by the radiation oncology department before RT and annually during follow-up visits thereafter. If parents did not accompany the child for testing after 3 attempts, the assessment was canceled definitively.

Statistical analysis

Overall survival (OS) and event-free survival (EFS) were assessed. Variables included sex, age, tumor grade, surgical extent, chemotherapy, total dose, and timely delivery of RT.

Statistical analysis was performed with IBM SPSS, version 26, and R statistical software, version 4.0.2 (R Foundation, Vienna, Austria). OS was calculated from the date of the surgical resection to the date of death from any cause. EFS was calculated from the date of the surgery to the date of disease progression, relapse, or death from any cause. The probabilities of OS and EFS were calculated using Kaplan-Meier estimates, and a log-rank test was used to compare survival in different groups. Survival data are presented as survival estimates including 95% confidence intervals (CIs). The limited number of cases and events in different groups prevented a multivariable analysis. P values $< .05$ were deemed statistically significant.

Results

Patient demographics

Eighty patients with ependymoma were identified between 2008 and 2016. Seventeen patients with supratentorial ependymomas, 7 patients with spinal ependymoma, 1 patient with PFE who was treated in another center because of linear accelerator breakdown, and 1 patient who received only palliative treatment because of extensive spinal seeding were excluded. The remaining 54 patients with PFE were included for further analysis. The median age was 3.2 years (range, 1-11.4 years) at diagnosis and 3.95 years (range, 1.67-11.5 years) at RT. Twenty-four patients (44.4%) were 3 years old or younger at diagnosis, and the youngest was 1 year. Thirty-six patients (66.7%) were male. Tumor histology was World Health Organization grade 2 in 34 patients (63%) and grade 3 in 20 patients (37%). Patients and treatment characteristics are summarized in Tables 1 and 2.

Treatment characteristics and outcome

Forty-three patients received adjuvant RT as part of their initial treatment (IT), and 11 patients received their first course of radiation only after recurrence (AR). According to the MRI performed immediately before irradiation, 33 (76.7%) of 43 IT patients and 3 (27.3%) of 11 AR patients had a total resection (Table 2). Second-look surgery was offered to only 1 AR patient before irradiation.

The median and mean overall radiation treatment times were 41 and 42 days (range, 33-60 days), respectively. Fifteen patients (28%) received general anesthesia throughout their radiation treatment, and 12 patients received general anesthesia for only 1 to 6 fractions. Eleven patients (7 IT and 4 AR) were considered to have metastatic disease (6 with stage M1, 5 with stage M3) and received CSI. The median CSI dose was 30.6 Gy (range, 18-34.2 Gy).

Three patients received 45 Gy and 4 received 50.4 Gy to the tumor bed because of poor performance status; all except 1 had a subtotal resection. The patient with a completely resected tumor and spinal seeding who received 50.4 Gy discontinued treatment after an episode of neutropenia, and the parents refused to resume RT despite multiple follow-ups by the social worker team. The decision to proceed to RT for 6 patients with poor performance status was made after multiple neurosurgical consultations confirmed the inability of better resection. In these 6 cases, the lack of benefit of RT in this context was explained to parents and the referring physician, who still insisted to proceed with treatment.

The treatment had to be interrupted for 2 patients: 1 had a shunt replacement and the other a complete resection of the remaining tumor. The total prescribed dose was 59.4 Gy for both. Radiation doses to organs at risk are listed in Table 3.

Thirty-six patients (66.7%) received chemotherapy, most (78%) after RT (Table 2). The most common combination was the French Society of Paediatric Oncology protocol[10] (58%), and 81% of patients were treated with a platinum-based regimen.[11] Eight patients, all but 1 younger than 3 years, who received postoperative chemotherapy to delay (4 patients) or avoid (4 patients) RT had lower 5-year OS

Table 1 Patient and treatment characteristics

Characteristic	Patients (N = 54)*
Age at diagnosis, y	
Mean (SD)	3.91 (2.30)
Median (range)	3.25 (1-11.4)
Sex	
Female	18 (33.3)
Male	36 (66.7)
Tumor grade	
II	34 (63)
III	20 (37)
Surgical extent†	
GTR	31 (57.4)
NTR	5 (9.3)
STR	18 (33.3)
M stage	
M0	43 (79.6)
M1	6 (11.1)
M3	5 (9.3)
Total dose, Gy	
54 or less	30 (55.5)
59.4	24 (44.5)
Timing of RT	
Upfront RT	33 (61.1)
Delayed RT	10 (18.5)
RT after relapse	11 (20.4)
Chemotherapy	
No	18 (33.3)
Yes	36 (66.7)

Abbreviations: GTR = gross total resection; NTR = near total resection; RT = radiation therapy; STR = subtotal resection.
* Data are presented as the number (percentage) of patients unless otherwise indicated.
† Forty-eight percent had evidence of a peduncular or hemispheric component.

Table 3 Radiation doses (Gy) to organs at risk for 54 patients

Organ at risk	Minimum	Maximum	Mean (SD)
Brain stem	31.94	55.89	49.23 (4.90)
Chiasma	1.37	54.20	18.12 (15.13)
Pituitary	1.83	54.40	20.12 (15.64)
Right cochlea	4.90	55.70	31.44 (14.01)
Left cochlea	5.97	55.90	30.11 (12.72)

(25%; 95% CI, 7%-83%) than the 28 patients who received chemotherapy after RT (60%; 95% CI, 42%-85%) or the 18 patients who received only irradiation (63%; 95% CI, 42%-96%). At a median follow-up of 5.1 years (range, 0.3-9.7 years), 24 patients (44.4%; 15 IT and 9 AR) died, including 22 from relapse or progression (Appendix E1). The site of relapse was local in 13 patients (6 patients with GTR and 7 with subtotal resection), metastatic in 5, and both local and metastatic in 4. One toxic death occurred during chemotherapy, and 1 patient died after a car accident. Of 25 patients (16 IT and 9 AR) who progressed again after the first course of RT, 10 (8 IT and 2 AR) received a second course of irradiation. Six patients were lost to follow-up, of whom 3 were from Iraq. The 5-year OS and EFS rates were 55% (95% CI, 42%-72%) and 45% (95% CI, 32%-62%), respectively. No significant effect on OS and EFS was observed in the analysis of age at diagnosis, sex, tumor grade, and total dose of RT.

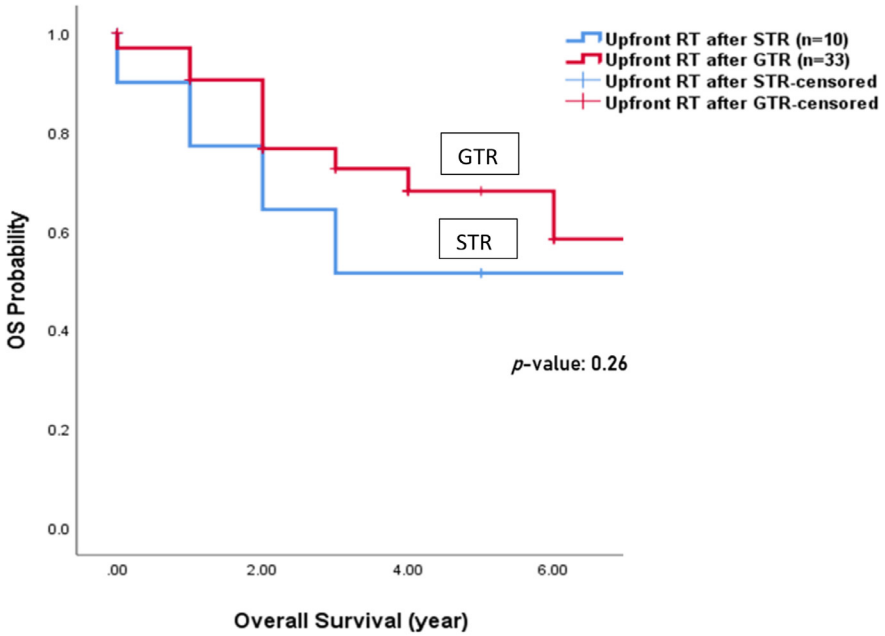
Patients receiving adjuvant RT

Forty-three patients, including 33 who received immediate RT, received RT as part of their initial postoperative management (Table 2, Appendix E1). Thirty-six received focal RT, and 7 (16.3%) who presented with metastatic disease (5 with stage M1, 2 with stage M3) received CSI. Sixteen patients (37%) progressed or relapsed, and 13 (30%) died. Two other patients died of non−tumor-related causes (1 from chemotherapy toxicity and 1 from a car accident). Five-year OS and EFS were 63.5% (95% CI, 45%-77%) and 55% (95% CI, 38%-69%) respectively. Although not statistically significant, patients who had a gross or near-total

Table 2 Treatment details

	Patients who received RT after relapse	Patients who received adjuvant RT	Total
Total	11	43	54
Age at diagnosis ≤ 3 y	7	17	24
Chemotherapy before RT	4	4	8
Chemotherapy after RT	6	22	28
No chemotherapy	1	17	18
Total resection before RT	3*	33	36
Subtotal resection before RT	8*	10	18

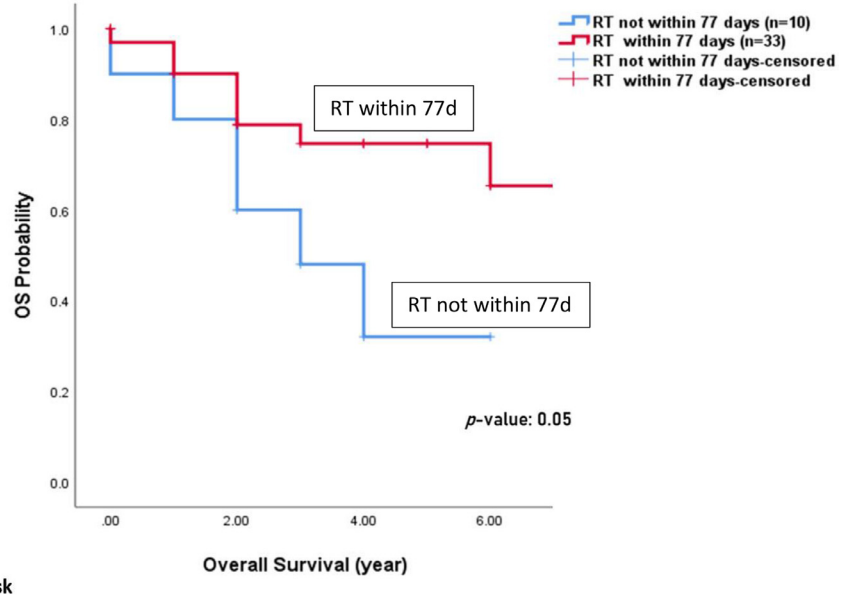
Abbreviation: RT = radiation therapy.
* Resection at the time of recurrence.



Patients at risk				
STR	10	5	4	2
GTR	33	25	15	6

Fig. 1. Overall survival: gross total resection (GTR) versus subtotal resection (STR). *Abbreviation:* RT = radiation therapy.

resection had greater 5-year OS and EFS than those who had subtotal resection (OS: 66.8% [95% CI, 42%-78%] and 51% [95% CI, 26%-78%], respectively; P = .26; EFS: 60.6% [95% CI, 43.2%-78%] and 38.1% [95% CI, 4.3%-71.8%], respectively; P = .18) (Fig. 1). Owing to delayed referral, only 33 patients (76.7%) initiated RT within 77 days after surgery (including 6 with subtotal resection) and had a significantly better outcome compared with those who were treated later (5-year OS: 74% [95% CI, 53%-87%] and 32% [95% CI, 6%-63%], respectively; P = .05; EFS: 64.6% [95% CI, 46.7%-82.4%] and 26.7% [95% CI, 0%-56.1%], respectively; P = .08) (Fig. 2). Chemotherapy used after RT did not show a survival advantage (the P value was not significant).



Patients at risk				
RT not within 77d	10	7	2	1
RT within 77d	33	23	16	7

Fig. 2. Overall survival: the effect of timely radiation therapy (RT).

Patients receiving first RT after relapse

Eleven patients, all with tumors that were reported completely resected by the referral physician, did not receive RT as part of their initial treatment. Seven (64%) did not receive any adjuvant treatment before relapse, and 4 received chemotherapy as decided by the treating physician (Table 2). All but 1 were younger than 5 years at the time of the initial diagnosis. They all experienced recurrence at a median time of 9 months (range, 3-80 months). Only 3 were completely resected at the time of the recurrence, including 1 who had had 2 surgeries.

At the time of relapse, 4 were considered to have metastatic disease (1 with stage M1, 3 with stage M3), including 1 with subtotal resection, and received CSI. The other 7 patients were treated with local RT. At the last follow-up, 9 patients (82%) had died, and the 5-year OS and EFS for this group were 27% (95% CI, 7%-54%) and 9.1% (95% CI, 0%-26.5%), respectively (Appendix E1).

Late effects

The median follow-up for surviving patients was 4.5 years (range, 0.3-9.7 years). Only 21 patients underwent neuropsychological assessments, including 17 who were living outside the capital, suggesting that distance was not the main factor for poor adherence to follow-up recommendations. All other families declined to participate. Only 12 patients were assessed at least twice, and 6 showed some decline over time (Fig. 3, Table 4).

Pre-RT audiometric data were available in 85% of patients. Of 29 who had follow-up evaluations, 3 had new Chang grade 1a (cochlear dose: 25, 40, and 45.5 Gy) and 2 had unilateral new Chang grade 2b (cochlear dose: 31 and 54 Gy) hearing loss (Tables 3 and 4). All 5 patients also received cisplatin. No one needed hearing aids.

Of all patients, 40% had completed the requested hormonal investigations at least once, which were not available at the hospital. There were 3 cases of growth hormone deficiency (pituitary dose: 47, 41, and 7 Gy) (Tables 3 and 4) and 2 cases of primary hypothyroidism. One case of renal failure owing to cisplatin was reported. The same patient had cataract surgery for lens replacement as well. No brain stem necrosis or second cancer was detected (Tables 3 and 4).

Relapsed patients after RT

Ten of 25 patients who relapsed after RT received a second course of radiation[12-14] (Appendix E1): 6 underwent local treatment (45-59.4 Gy) and 2 underwent CSI (30 and 45 Gy, 2 fractions per day). Two other patients were retreated with Gamma Knife. Two completely resected and locally reirradiated patients (54 and 59.4 Gy) were still alive at the time of the last follow-up.

Discussion

This study highlights the many challenges that patients and physicians face in LMICs to access treatment modalities and expertise. The extent of surgical resection is the first important treatment-related prognostic factor that affects survival in intracranial ependymoma. One-third of our patients, including 10 who received adjuvant RT and 8 who were first irradiated after relapse, had a subtotal resection before RT. Patients were young, with 66% and 89% under the age of 3 and 5 years, respectively. Posterior fossa surgery in infants and young children is challenging owing to the risk of excessive blood loss, posterior fossa mutism, cranial nerve damage, and brain stem injury.[15,16] This situation is more complicated in the context of limited resources and expertise in LMICs.[4,17] There is still a maldistribution and lack of

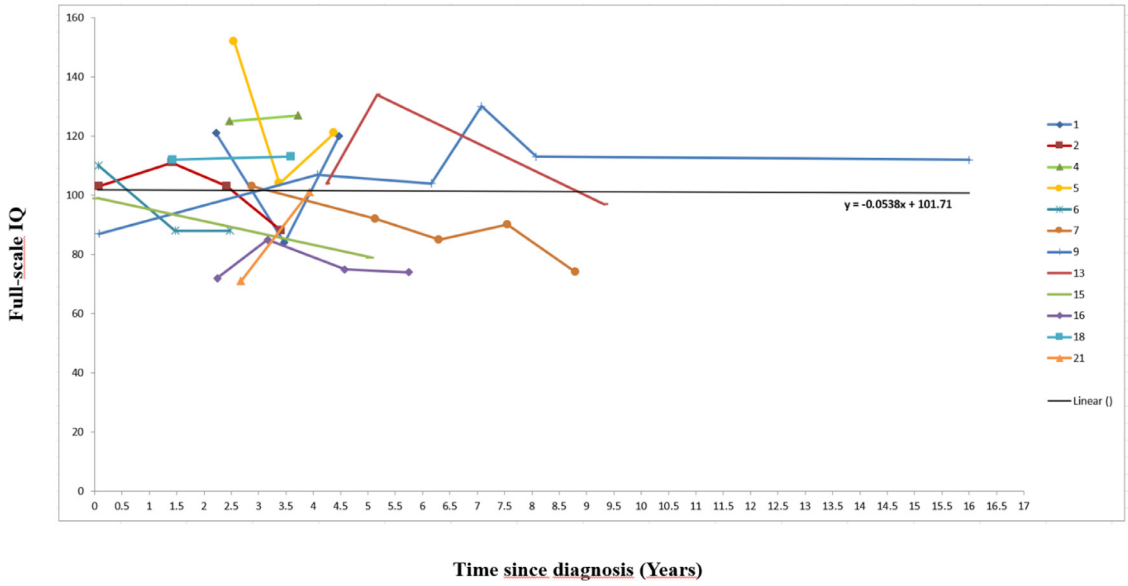


Fig. 3. Evolution of neurocognitive outcomes for 12 patients.

Table 4 Late effects

	Patients tested before RT, no. (%)	Results	Patients tested after RT, no. (%)	Results	Total	Long-term results
Cognitive dysfunction (WIS)	8 (15)	87-110 (range)	17 (31)	71-152 (range)	47 tests from 21 patients	12 patients assessed twice; 6 showed a decline
Hearing loss (OAE, PTA)	46 (85)	6 Chang 4 (unilateral; owing to surgery or tumor) 1 Chang 2a (cisplatin) 1 Chang 2b (cisplatin) 1 Chang 1a (cisplatin)	29 (54)	3 Chang 1a (cisplatin) 2 Chang 2b (cisplatin)	96 tests from 46 patients	No hearing aids needed
Pituitary dysfunction	9 (17)	Normal	15 (28)	3 GH deficiency 2 primary hypothyroidism	45 tests from 22 patients	2 thyroid hormone replacements
Renal failure	-	-	-	-	-	1 patient
Cataract	-	-	-	-	-	1 patient

Abbreviations: GH = growth hormone; OAE = otoacoustic emissions; PTA = pure tone audiometry; WIS = Wechsler Intelligence Scale.

equal access to pediatric neurosurgical and anesthetic care in Iran, and reluctance to second-look surgery in case of subtotal resection was obvious, because only 1 patient underwent further resection. That case concerned a patient who experienced a life-threatening complication during radiation and required emergent resection. In a recent study from Toronto,[18] the rate of GTR increased over 3 decades, with a better outcome achieved in the cohort treated between 2004 and 2015, and extent of surgical resection was one of the strongest predictors of outcome (subtotal resection: hazard ratio [HR], 3.8; 95% CI, 1.65-8.78). In 4 other cohorts treated from 1990 to 2014,[19] the rate of GTR ranged between 53.3% and 82.1%, and in each cohort, incomplete resection carried a worse outcome (HR, 2.13; 95% CI, 1.60-2.82; $P < .001$). In the COG trial ACNS0121,[2] 5-year EFS after subtotal resection of all ependymoma subgroups was only 37.2%, compared with 69.5% for patients with GTR. Similarly, subtotal resection carried a worse EFS in comparison to GTR in our small cohort (38.1% vs 60.6% for patients who received up-front adjuvant RT) (Table 2, Fig. 1). The GTR rate of CNS tumors including ependymoma in other studies from LMICs ranged from 25% to 62.9% and was associated in all series with better outcomes.[20-24]

Another challenge in LMICs is the availability of RT facilities, especially facilities dedicated to pediatric patients. As highlighted in a recent report, 4 times more linear accelerators are needed in Iran.[25] Considering the growing number of cancer cases diagnosed in the country,[26,27] scaling up health care capacities, including human resources, is becoming a must. The situation is even more complicated when treating childhood cancer,[28,29] which demands an experienced anesthesia team[30] and special training beyond what is necessary for the treatment of adult cancer.[31] MAHAK is the only radiation oncology department in Iran exclusively dedicated to children and is based in the capital city.[6] Two-thirds of our patients were living outside Tehran, and although treatment costs are covered by the charity, it is often challenging for families to immediately move to our center for a 6- to 7-week RT period. Loss of parental income, disruption of family life, and costs of travel are the main issues. Consequently, many parents decided to postpone the radiation treatment or requested for their child to be treated locally with postoperative chemotherapy.[3,11] The lack of national guidelines and the paucity of multidisciplinary discussions between neurosurgeons, pediatric oncologists, and radiation oncologists aggravate this circumstance.[32] Our experience also highlights the importance of early postoperative RT: children who were irradiated beyond 77 days after surgery had a significantly worse outcome (5-year OS: 32% vs 74% for those who received timely RT) (Table 2, Fig. 2). This suggests that, as in medulloblastoma, the interval between resection and initiation of RT may affect survival of patients with ependymoma. This observation is in keeping with the St. Jude experience, where children who received chemotherapy before conformal RT had lower survival.[2] It also highlights the fact that delayed access to radiation, a frequent issue in LMICs, affects survival. Eleven patients did not receive RT as part of their initial treatment. They all experienced relapse. The study from Toronto[18] demonstrated the poor outcome if RT was omitted (HR, 28.33; 95% CI, 8.43-95.24). In our study, all nonirradiated patients relapsed, and only 3 patients had a GTR at

that time (Table 2). Nine of 11 patients who received RT after the first relapse died of progression (5-year OS, 27% vs 63.5) (Appendix E1). Two of these 9 patients were reirradiated after a second relapse without any survival advantage, confirming the importance of the role of up-front radiation.

Of 33 patients who underwent timely RT, 57% received chemotherapy, including 74% platinum-based protocols[11] (Table 2). We did not find any evidence of survival advantage from adjuvant chemotherapy in our series. We hope the recently closed COG trial ACNS0831 and the ongoing SIOP Ependymoma II trial will contribute to answering this important question.[33]

For recurrent ependymoma, surgery followed by reirradiation is the recommended approach.[12-14] This treatment benefits mainly patients who relapse locally after a long disease-free interval and receive CSI at relapse after GTR.[34,35] Of our reirradiated patients, only 2 who relapsed locally after 2 and 5 years were still alive after undergoing GTR and local reirradiation (Appendix E1).

Another important issue in this study concerns the histopathologic diagnosis. A study from St. Jude showed a 25% major disagreement resulting in treatment modifications in collaboration with International Outreach Program LMIC partner sites.[36] Central nervous system tumors were the most challenging, with a 32.8% major disagreement rate. Although all present cases were reviewed at MAHAK, there is still limited expertise in pediatric neuropathology in the country. The lack of appropriate tools for molecular assessment is another obstacle to be overcome.[37,38] Recent work has highlighted the heterogeneity and complexity of posterior fossa ependymomas, particularly PFA ependymomas, which arise in young children. However, although some PFA subtypes are associated with better outcomes, there is no consensus regarding the possibility to postpone RT in specific subtypes.[39] In our series, 1 long-term survivor was initially diagnosed at the age of 15 months and was managed with a radiation-sparing approach. She experienced a local recurrence more than 5 years later and received RT after relapse (AR group). Identification of subtypes of PFE that can be spared postoperative RT is one challenge that could benefit patients in LMICs. The other illustration concerning neuropathology services is the high rate of M1 metastatic disease in our cohort (6 of 54 patients [11%]), a figure that should be considered with caution.[40] Differentiating normal exfoliated ependymal cells or atypical macrophages after surgery in the CSF can be difficult.[41] To avoid this confusion, it is advised to have the CSF examination at least 2 weeks after surgery. In our case, this interval was not an issue, because all CSF examinations were done at least 2 weeks after surgery. We now repeat the CSF analysis after 1 or 2 weeks, in case of a positive result, to avoid unnecessary CSI in a young child. Similarly, the high number of M3 patients in our series is raising questions. All staging procedures in this series were performed postoperatively. Misinterpretation of the nonspecific subdural enhancement on the spinal MRI, which is done for the first time before RT planning but after surgery, could be another reason for false-positive results.[42]

The last, but not least, challenge is the management of late effects.[43-45] The concept of long-term follow-up is still poorly understood in many LMICs. Of 6 patients who were lost to follow-up, 3 were from Iraq and could not afford long-term, in-person contact with the medical team; they never returned after the first few years. The same was true for families who were living in remote areas of the country. Nowadays, a call system is put in place by the social workers and the new dedicated RT nurse to encourage and schedule appointments according to the availability of the parents. Another issue is the attitude toward handling adverse treatment effects. In this experience, many families were reluctant to have their child evaluated with IQ tests and felt that it could be stigmatizing.[46,47] Only 22% of our patients had at least 2 IQ test results, and 50% showed some decline over time. Hearing loss aggravates neurocognitive function and social integration of survivors, particularly infants.[48] The risk of hearing loss is increased when RT is combined with platinum-based chemotherapy.[49] Fifty-four percent of our patients belonged to this group, but only 52% of them had an audiometry evaluation during their follow-up. This is concerning, considering the decline in cognitive function seen over time in these patients and the paucity of rehabilitation programs and social supportive care in LMICs.[50] We tried to keep the cochlear dose as low as possible (mean, 30-31 Gy) (Table 3). No patient had severe hearing loss in both ears, and no patient required hearing aids.

Three cases of growth hormone deficiency were detected, 2 with pituitary doses of 47 and 41 Gy, higher than the average pituitary dose (20 Gy) (Table 3). No patients received GH replacement because of the concern of pediatric oncologists and neurosurgeons at that time about its role in tumor regrowth. We hope that, as more studies are being published about GH safety in Western series, there will be less reluctance in the LMIC medical community in the future.[51-53]

Conclusion

Although radiation is using the same paradigms as recommended in international protocols, our results lag behind those reported by North American and European institutions. Several factors may play a role, such as the availability of pediatric neurosurgery, anesthesia, and RT expertise and the lack of timely referrals. Our experience confirms that chemotherapy is not an option for delaying RT after GTR and should not be offered to patients as an alternative to RT. Ideally, and in particular in LMICs, pediatric patients with brain tumors should be offered all necessary involved disciplines in a dedicated and centralized neuro-oncology program under 1 roof.[54] Additionally, implementing national guidelines, multidisciplinary team working, and national tumor boards facilitates interdisciplinary communication and patient referral

and improves the prognosis. On the other hand, setting up an international twinning program could overcome in part the lack of pediatric neuro-oncology expertise in the country.[55] The other point is the global awareness of childhood cancer and treatment that could affect the future life of the child. Parents' education about cancer and the treatment journey through parent groups and organizations plays an important role in raising general understanding and sensibility and adjusting parents' expectations. Identifying late effects through rigorous surveillance protocols and managing them have paramount importance and should be acknowledged by the parents and the medical team. Because reports on pediatric ependymomas are scarce in LMICs, this experience illustrates current gaps in the management of these patients in this setting and the magnitude of the work needed to improve their outcomes. The Global Initiative for Childhood Cancer, initiated in 2018, is aiming for highly specialized care in LMICs, and our data could be used to address issues and challenges in the management of this condition.

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