The Clinical Results of Pediatric Brain Tumors Treated with Linac-Based Stereotactic Radiosurgery and Radiotherapy

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Objective: *Stereotactic radiosurgery (SRS) and fractionated stereotactic radiotherapy (FSRT) for brain tumor is increasingly acceptable worldwide. In Thailand, the first Linac-based stereotactic radiation machine was implemented at the Radiosurgery Center, Ramathibodi Hospital since 1997. This is the first study in Thailand to report the results of pediatric brain tumor patients treated with SRS and FSRT.*
Material and Method: *The clinical outcome of 39 pediatric patients treated with SRS/FSRT between 1998 and 2010 was retrospectively reviewed.*
Results: *The median follow-up time was 26 months (range, 1 to 154 months). The local progression free survival (LPFS) at one and five years after SRS/FSRT for all patients was 87.5% and 54.2%, respectively. The 5-year LPFS by tumor histology was as follow, pituitary adenoma 100%, meningioma 100%, ependymoma, and low-grade astrocytoma 75%, and craniopharyngioma 68.6%. High-grade tumor had the worst LPFS and the median LPFS of this group was only 12 months. On univariate analysis, low-grade tumor (pituitary adenoma and menigioma) and small tumor volume (< 10 ml) were the factors that correlated significantly with good local control. After multivariate analysis, small tumor volume was the only factor associated with good LPFS (HR = 2.35, p = 0.042). No other radiation complication except panhypopituitarism was reported.*
Conclusion: *SRS/FSRT in pediatric brain tumor is technically feasible, with minimal acute side effects. SRS/FSRT plays an important role for the small low-grade tumor.*

Keywords: *Stereotactic radiation, SRS, FSRT, Pediatrics, Brain tumors*

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Brain tumors are the most common solid tumors in children. Approximately 70% can be cured through a variety of treatment approaches including radiation, surgery, and chemotherapy[1]. When radiation is utilized in the treatment of pediatric brain tumors, particularly problematic are the risks of neurocognitive deficits and second malignancy is of great concern[2].

Stereotactic radiosurgery (SRS) and fractionated stereotactic radiotherapy (FSRT) for brain tumors in various settings have emerged over the past 10 years. SRS is a specialized radiation technique, delivering a large single dose of highly collimated radiation to one or more intracranial targets with submillimeter precision. FSRT is an extension of SRS, delivered via fractionated schedule (2 to 30 fractions) by utilizing non-rigid immobilization, thereby providing the precision of stereotaxy while allowing adjacent normal structures to repair sublethal damages. Consequently, SRS/FSRT has the potential to ablate small tumors that are not surgically resectable, while reducing the late effects associated with delivering high radiation dose to the developing brain. To date, there is relatively little information on the outcome for children with primary brain tumors treated with SRS/FSRT. The objective of the present study was to analyze the outcome of pediatric brain tumor patients treated with SRS/FSRT in terms of local progression free survival, overall survival and complications associated with the treatment.

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Material and Method

In 1997, the first Linac-based stereotactic radiation machine in Thailand was implemented at Radiosurgery Center, the Ramathibodi Hospital. The authors retrospectively analyzed the results of pediatric brain tumors treated with SRS/FSRT in each individual tumor. The present study was approved by the Ethics Committee of the faculty.

Patients

Between February 1998 and February 2010, 39 pediatric patients with intracranial tumors underwent SRS and FSRT either as part of initial treatment or for management of recurrent disease. Before treatment, the management for the patient was discussed in the radiosurgery board meeting. Eligibility criteria for treatment included a histological confirmed diagnosis of tumor and a radiographically visible lesion. SRS was used for the lesion not exceeding 4 cm in any dimension and located at least 5 mm from optic apparatus and brain stem. SRS and FSRT were used as part of initial management when imaging studies revealed evidence of residual disease after maximum of surgical resection and conventional radiation therapy (RT). In the recurrent setting, SRS/FSRT was used for gross disease visible on imaging following surgery and/or chemotherapy or conventional radiation. Patients with poor performance status (KPS < 70) or with leptomeningeal spreading were excluded from this treatment.

There were 20 males and 19 females, with a median age of 13 years (4 to 18 years). Twenty-three patients received SRS/FSRT as part of the initial management (59%). From these 23 patients, 20 patients were treated for residual tumor after surgery (87%), two patients were treated for boost after conventional radiation (9%) and the other (1) patient was treated for inoperable due to medical illness (4%). For recurrent tumor, FSRT was given as the sole modality in seven patients (17%) and eight patients (21%) received salvage surgery followed by external beam radiation before FSRT. The other (1) patient (3%) received salvage surgery before FSRT. Sellar-suprasellar region was the most common location that was treated with SRS/FSRT (51%). The demographic data of the patients are shown in Table 1.

Treatment

The SRS/FSRT technique used the linear accelerator base system (6 MV delicated LINAC, Varian; with X-Knife planning system very 3 & 4, Radionics). A Brown-Robert-Wells steretotactic head frame was used for SRS and the relocatable Gill-Thomas-Cosman frame was used for FSRT patient immobilization and target localization. Individual treatment planning was done based on a contrast-enhanced CT scan, 1.5 mm slice thickness, with or without gadolinium enhanced MRI.

The median target volume was 14.2 ml (range, 1.5 to 84.5 ml). SRS was used in one patient (3%) who had 2.1 ml pituitary adenoma with the average dose of 14 Gy. The other eight patients (20%) were treated with FSRT, hypofraction with the median average dose of 33.2 Gy (range, 25 to 45) in 10 fractions (range, 10 to 15). The remaining 30 patients (77%) were treated with FSRT, conventional fractions. The median average dose given to the tumor was 52.75 Gy (range, 16.4 to 60.7) in the number of 25 fractions (range, 8 to 30). The details of treatment characteristics are shown in Table 2.

When SRS/FSRT was provided as part of initial management, the need for SRS/FSRT was based on the detection of persistent residual tumor following the maximum tumor removal or following shortly after the completion of conventional RT. All patients except one received tumor removal, followed by SRS/FSRT within one to three months. Only one patient who had alveolar soft part sarcoma at right orbit was treated

Table 1. Patient characteristics (n = 39)

Patients' characteristics	
Age:median (range) years	13 (4-18)
Gender	
Female	20 (51%)
Male	19 (49%)
Treatment timing	
Upfront	23 (59%)
Recurrence	16 (41%)
Histology	
Craniopharyngioma	12 (31%)
Meningioma	9 (23%)
Pituitary adenoma	4 (10%)
Anaplastic astrocytoma	4 (10%)
Ependymoma	3 (8%)
Low grade astrocytoma	2 (5%)
PNET	1 (3%)
Other	4 (10%)
Median tumor volume, ml (range)	14.2 (1.5-84.5)
Median follow-up time, months (range)	26 (1-154)

PNET = primitive neuroectodermal tumor

Table 2. Treatment characteristics (n = 39)

	SRS	SRT, hypofraction	SRT, conventional fraction
Number (%)	1 (3)	8 (20)	30 (77)
Min dose	10	22.8 (10-34)	42.2 (8.5-58.1)
Average dose	14	33.2 (25-45)	2.7 (16.4-60.7)
Max dose	16	40 (35-48.6)	561.6 (18.3-73.8)
Number of fraction	1	10 (10-15)	25 (8-30)
Number of collimator	1	5 (1-8)	4 (1-17)
Percent isodose	80%	80% (80-90)	90% (80-95)
Volume (ml)	2.1	12.9 (2-64)	14.9 (1.5-84.5)

Min dose = median minimum dose (Gy) (range)
Average dose = median average dose (Gy) (range)
Max dose = median maximum dose (Gy) (range)

with partial tumor removal followed by chemotherapy and conventional RT with dose of 40 Gy in 20 fractions, then boost with FSRT, conventional fraction for sparing of the right optic nerve. For the recurrence tumor, the salvage treatment was variable. SRS/FSRT was given when gross recurrent tumor was unresectable and salvage conventional RT was either completed or not feasible due to prior radiation. Among 16 patients treated for recurrence, eight patients received prior external beam conventional radiation with the median time to recurrence after prior radiation for two months (range, 1 to 10). Five patients (2 ependymoma, 1 primitive neuroectodermal tumor, and 2 pituitary adenoma) received chemotherapy as the part of salvage treatment. Three patients received SRS/SRT as the sole of salvage treatment.

Follow-up

Patients were followed up from the time of SRS/FSRT until death. The median follow-up time was 26 months (range, 1 to 154 months). Patients were followed with neurologic examination and imaging at regular intervals following treatment.

Statistical analyses

Primary endpoint, the local-progression- free survival (LPFS), was defined as the time from the date of starting SRS/FSRT until local tumor progression (detected from clinical examination or imaging study) or the date of last follow-up. Secondary endpoint, the overall survival (OS), was defined as the time from the date of start SRS/FSRT until the patient's death or the date of last follow-up. Adverse events were graded according to the Common Terminology Criteria for adverse events version 3.0.

The survival probability was calculated by using Kaplan-Meier methods, and the survival curves were compared by using the log-rank test. In the univariate analysis of histology and LPFS, high-grade tumor such as anaplastic astrocytoma, PNET, and alveolar soft part sarcoma was collapsed together due to the small sample size. Multivariate analysis was done by using Cox proportional hazard model. Significant was set at p-value < 0.05. All statistical analyses were performed using SPSS software version 16.0

Results

At the last follow-up, local failure in overall was observed in eight patients (20.5%). The LPFS at 1-, 5-, and 10-year LPFS for all patients was 87.5%, 71.3%, and 54.2%, respectively (Fig. 1). Four patients died at the last follow-up, the OS at one and five years was 93.3% and 84.2%, respectively (Fig. 2).

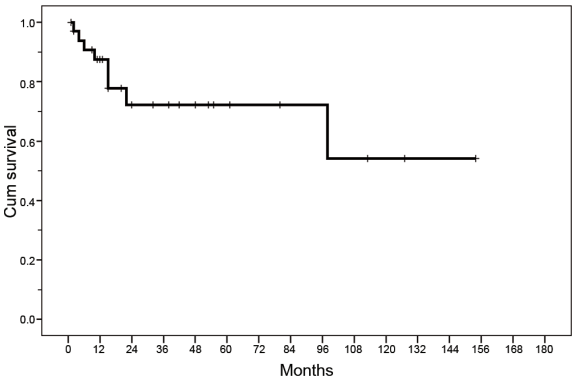

Fig. 1 Local progression-free survival (LPFS) following SRS/FSRT

In eight patients that had local tumor progression (3 craniopharyngioma, 2 ependymoma, 2 anaplastic astrocytoma, and 1 low grade astrocytoma), seven of them failed at primary site, which was treated by salvage surgery, and another one anaplastic ependymoma patient had relapse disease of whole spine, and received palliative care. These results indicated that local control remained the major problem for patients with craniopharyngioma, ependymoma, and astrocytoma compared to the other histology such as pituitary adenoma and menigioma, which had the better local control after SRS/FSRT. The 5-year LPFS by tumor histology was as follow, pituitary adenoma = 100%, meningioma = 100%, ependymoma + low grade astrocytoma = 75%, and craniopharyngioma = 68.6%. High-grade tumor that included anaplastic astrocytoma, anaplastic ependymoma, primitive neuroectodermal tumor (PNET) and alveolar soft part sarcoma had the worst LPFS. The median LPFS of this group was only 12 months (Fig. 3). Patients who had small tumor volume (< 10 ml) had better LPFS than those who had larger volume (> 10 ml) (Fig. 4).

Univariate test of factors associated with the LPFS revealed that histology (p = 0.002) and tumor volume (p = 0.011) were the significant predictors of local control. Patients who had pituitary adenoma, meningioma and other histology (juvenile angiofibroma, giant cell tumor) and smaller volume < 10 ml had better LPFS. Multivariate analysis showed that tumor volume was the only significant factor. Patients who had volume < 10 ml had better LPFS with the hazard ratio of 2.35, p = 0.042.

Patients were found to tolerate treatment very well. There was no need of any premedication before and during treatment. Five patients (13%) developed newly detected panhypopituitarism that needs further hormonal replacement. No other severe radiation complication was found in the present study.

Discussion

Radiation therapy plays an important role in the management of many childhood brain tumors. Stereotactic radiotherapy technique is the one of advanced conformal radiation technique for treating a pediatric brain tumor with favorable local control and minimal side effect.

Ramathibodi Hospital is the first radiosurgery center in Thailand and the lack of information in the outcome of children with primary brain tumor treated with SRS/FSRT. The authors reported the first study

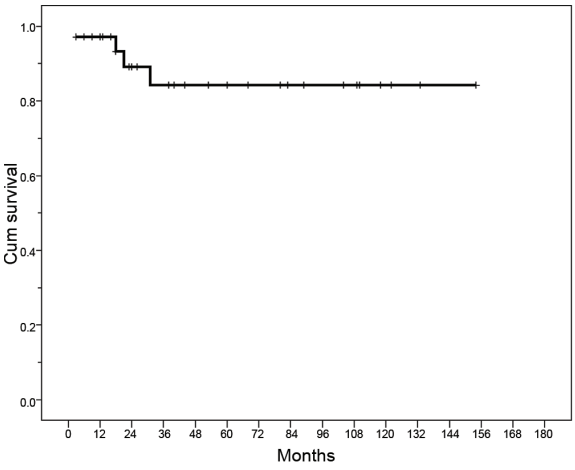

Fig. 2 Overall survival (OS) following SRS/FSRT

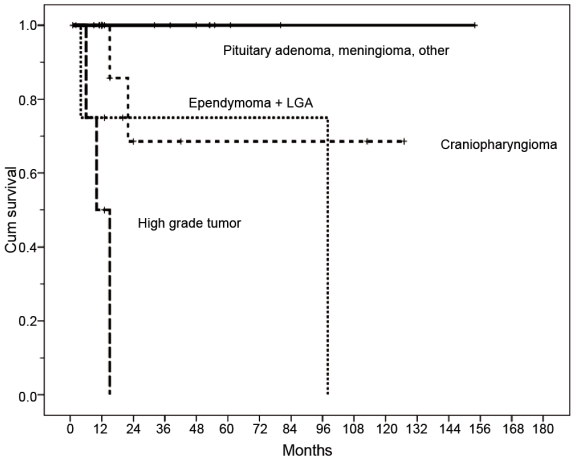

Fig. 3 Local progression-free survival (LPFS) according to the histology (p = 0.002)

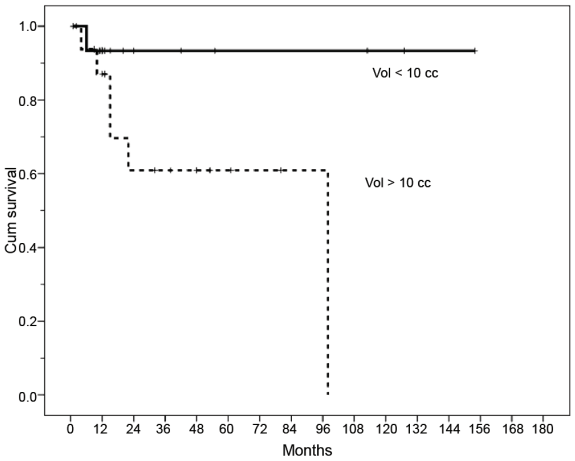

Fig. 4 Local progression-free survival (LPFS) according to tumor volume (p = 0.011)

of the pediatric brain tumor patients treated with SRS and FSRT.

Previous studies including, the present report, have confirmed that SRS/FSRT could be used safely with good local tumors control with the LPFS at 1- and 5- year LPFS was 87.5% and 71.3%, respectively[3-9].

With regard to factor associated with the outcome, the present results revealed that favorable histology, such as meningioma and pituitary adenoma, had better local control (LPFS = 100%) when compared to the other histology such as craniopharyngioma (LPFS = 68.8%) and other high grade tumor. For SRS/FSRT in craniopharyngiomas, the reported tumor control was 69% to 90%[10-14]. The cystic portion of craniopharyngiomas is the main problem for local progression. In the present study, all patients, who had local failure had enlargement of cystic portion of the tumor and underwent further surgery or cyst aspiration. A possible explanation for this failure might be that the active cyst can continue to grow throughout the course of radiation, thus it is very important to include the entire cyst in the treatment volume. If possible, weekly to bi-weekly CT scan should be obtained and re-planing is necessary if the cyst or tumor is threatening to exceed the margins of the prescription dose. In the authors' routine practice, the authors did not do re-scanning or re-planing for SRS/FSRT treatment due to a limitation of the resource. Therefore, adding a larger margin around the tumor to allow for growth during the course of their radiation is recommended.

Histological features can also influence the outcome. For low-grade tumor, marginal failures have not been observed frequently and the use of limited margins to minimize late sequelae using stereotactic radiation is supported[15]. In contrast, infiltrative or high-grade lesions often extended beyond the visible lesion. Therefore, adding more margin from the gross visible tumor is recommended. The large treatment radiation volume should be the cause of the worst outcome of the treatment. The present study also confirmed the limited role of SRS/FSRT in treatment of a high grade tumor, which is consistent with the report of Weprin et al[7].

Tumor volume was a significant factor associated with the LPFS and was the only factor significantly related to LPFS in multivariate analysis. Generally, stereotactic radiosurgery was originated as a mean to give single high dose radiation to a small volume, usually not more than 3 cm in diameter. Later development has enabled fractionated treatment to be more suitable for malignancy or larger lesions abutting critical structure. With FSRT, there is no restriction to the size since the treatment is delivered within the radiation tolerance limits or normal tissue. However, the results still support the use of SRS and FSRT for selected small lesions.

Acute side effects of SRS/FSRT were tolerable and could be managed on an outpatient basis. The patients did not need any premedication before radiation. Because the majority of the locations of tumors in the present study were in the sellar/suprasellar area, panhypopituitarism was the most common complication. No severe radiation complication was reported in the present study.

Conclusion

Stereotactic radiation in pediatric brain tumors is technically feasible, with minimal acute side effects. SRS/FSRT plays an important role in selected small low-grade tumors.

Potential conflicts of interest

None.

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ผลทางคลินิกของโรคเนื้องอกสมองในเด็กโดยการฉายรังสีศัลยกรรมและรังสีร่วมพิกัด

พุฒิพรรณ พัวทวีพงศ์, มัณฑนา ธนะไชย, สมใจ แดงประเสริฐ, ลดาวัลย์ นาควงษ์, ชมพร สีตะธนี, ทวีศักดิ์ จันทร์วิทยานุชิต

วัตถุประสงค์: *การฉายรังสีศัลยกรรม และรังสีร่วมพิกัดในโรคเนื้องอกสมองได้รับการยอมรับอย่างเพิ่มขึ้นทั่วโลก โดยในประเทศไทยเครื่องฉายรังสีร่วมพิกัดชนิดเร่งอนุภาคเครื่องแรกได้ติดตั้งและเปิดใช้ที่ศูนย์รังสีศัลยกรรม โรงพยาบาลรามาธิบดี ตั้งแต่ปี พศ. 2540 รายงานนี้จัดทำขึ้นเพื่อรายงานผลการรักษาโรคเนื้องอกสมองในเด็กโดยเทคนิคดังกล่าว*

วัสดุและวิธีการ: *ผลการรักษาผู้ป่วยเด็ก 39 ราย ที่ได้รับการฉายรังสีศัลยกรรม และรังสีร่วมพิกัด ระหว่างปี พ.ศ. 2541-2553 ได้ถูกทบทวนจากข้อมูลย้อนหลัง*

ผลการศึกษา: *เมื่อติดตามผลการรักษาที่ค่าเฉลี่ยของเวลาเท่ากับ 26 เดือน พบว่าผู้ป่วยมีอัตราการควบคุมโรคเฉพาะที่เมื่อ 1 ปี, 5 ปี และ 10 ปี เท่ากับ 87.5%, 71.3% และ 54.2% โดยอัตราการควบคุมโรคเฉพาะที่เมื่อ 5 ปี แยกตามชนิดของเนื้องอก ได้แก่ Pituitary adenoma 100%, meningioma 100%, ependymoma และ low grade astrocytoma 75%, craniopharyngioma 68.6% โดยพบว่ากลุ่มเนื้องอกชนิด high grade มีการควบคุมโรคที่สั้นที่สุด โดยมีค่าเฉลี่ยการควบคุมโรคเท่ากับ 12 เดือน และจากการวิเคราะห์แบบ univariate พบว่า เนื้องอกชนิด low grade และเนื้องอกที่มีขนาดเล็กมีการพยากรณ์โรคที่ดีกว่าปัจจัยอื่น ๆ อย่างมีนัยสำคัญทางสถิติ แต่หลังจากการวิเคราะห์แบบ multivariate พบว่า เนื้องอกที่มีขนาดเล็กเพียงปัจจัยเดียวที่มีผลต่อการควบคุมโรคที่ดี (HR = 2.35, p = 0.042) และจากการศึกษานี้มีผลข้างเคียงที่พบได้คือ ภาวะพร่องฮอร์โมนของต่อมใต้สมอง*

สรุป: *การฉายรังสีศัลยกรรมและรังสีร่วมพิกัดในโรคเนื้องอกสมองในเด็กเป็นเทคนิคที่เข้าถึงได้ และผลข้างเคียงน้อย โดยการฉายรังสีเทคนิคนี้จะมีบทบาทสำคัญในผู้ป่วยเนื้องอก low grade ที่มีขนาดเล็ก*