

Clinical Article

Upfront Stereotactic Radiosurgery for Pineal Parenchymal Tumors in Adults

Jong Hoon Park, M.D.,¹ Jeong Hoon Kim, M.D., Ph.D.,¹ Do Hoon Kwon, M.D., Ph.D.,¹ Chang Jin Kim, M.D., Ph.D.,¹
Shin Kwang Khang, M.D., Ph.D.,² Young Hyun Cho, M.D., Ph.D.¹

Departments of Neurosurgery,¹ Pathology,² Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Objective : Pineal parenchymal tumors (PPTs) in adults are rare, and knowledge regarding their optimal management and treatment outcome is limited. Herein, we present the clinical results of our series of PPTs other than pineoblastomas managed by stereotactic radiosurgery (SRS) at upfront setting.

Methods : Between 1997 and 2014, nine consecutive adult patients with the diagnosis of PPTs, either pineocytoma or pineal parenchymal tumor of intermediate differentiation, were treated with SRS. There were 6 men and 3 women. The median age was 39 years (range, 31–53 years). All of the patients presented with symptoms of hydrocephalus. Endoscopic third ventriculostomy and biopsy was done for initial management. After histologic diagnosis, patients were treated with Gamma Knife with the mean dose of 13.3 Gy (n=3) or fractionated Cyberknife with 32 Gy (n=6).

Results : After a mean follow-up of 78.6 months (range, 14–223 months), all patients were alive and all of their tumors were locally controlled except for one instance of cerebrospinal fluid seeding metastasis. On magnetic resonance images, tumor size decreased in all patients, resulting in complete response in 3 patients and partial response in 6. One patient had experienced temporary memory impairment after SRS, which improved spontaneously.

Conclusion : SRS is effective and safe for PPTs in adults and can be considered as a useful alternative to surgical resection at upfront setting.

Key Words : Pineal parenchymal tumor · Pineocytoma · Pineal parenchymal tumors of intermediate differentiation · Stereotactic radiosurgery.

INTRODUCTION

Tumors involving the pineal region are rare and challenging for both diagnosis and management. Among those, pineal parenchymal tumors (PPTs) account for 15% to 30% and other tumors in this region include germ cell tumors of variable subtypes, gliomas, and metastases^{1,9}. To provide an optimal therapy for each specific type of these tumors, correct tissue diagnosis is essential. Simultaneously, strategies for restoration or diversion of cerebrospinal fluid (CSF) dynamics are required, because most of patients present with symptoms of obstructive hydrocephalus caused by the tumors.

Until recently, PPTs had been classified as either benign, indolent pineocytomas (PCs) of World Health Organization (WHO) grade 1 or malignant, aggressive pineoblastomas (PBs) of WHO grade 4. In 2007 WHO classification of tumors of the central nervous system, pineal parenchymal tumors of intermediate differentiation (PPTIDs) of WHO grade 2 or 3 were added to this clas-

sification, which are considered to occur within the spectrum of pathogenesis between PCs and PBs^{21,27}. Of these, PBs comprise 25% to 50% of PPTs and are most commonly seen in pediatric patients. As the biological behavior of PBs is highly malignant, they are managed with aggressive multimodal approaches combining surgery, radiotherapy (RT) and chemotherapy^{10,28}. On the other hand, consensus on the management of PPTs in adults, mostly consisting of PCs and PPTIDs, is limited to date, primarily because of their rarity. Complete surgical resection can provide a chance of cure for PCs^{8,30}. However, it is not always feasible and the risks of morbidity and mortality should be carefully balanced^{3,4,13}. Furthermore, it is still unknown whether or not complete resection could provide a cure for PPTIDs, as PPTIDs of higher histologic grade are potentially more aggressive than PCs. In this background, stereotactic radiosurgery (SRS) can be considered as a safe alternative or adjunct to surgery for local tumor control (LTC) and has been reportedly effective and safe in treating PPTs^{16,20,25,26,30,31}. Since 1997, we elected SRS

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• Address for reprints : Young Hyun Cho, M.D., Ph.D.

Department of Neurosurgery, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05535, Korea
Tel : +82-2-3010-3550, Fax : +82-2-476-6738, E-mail : yhyunc@amc.seoul.kr

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as a primary therapy following CSF diversion and biopsy for PPTs other than PBs in adults, and nine consecutive patients have been treated accordingly.

MATERIALS AND METHODS

This retrospective study was approved by our institutional review board. Between 1997 and 2014, nine consecutive adult patients with PPTs other than PBs were treated with SRS at upfront setting. There were 3 patients with histologic diagnosis of PCs, 5 with PPTIDs, and one with only clinical diagnosis (described elsewhere in this section). All the medical records and neuroimages of the patients were analyzed.

Demographic data and clinical features

There were 6 men and 3 women. The median age of the patients was 39 years (range, 31–53 years). All patients presented with symptoms of obstructive hydrocephalus caused by the tumor, including headache in 6 patients, diplopia in 2, and gait disturbance and dizziness in each one patient. Papilledema was seen in 4 of 5 patients with available fundoscopic examination data. Table 1 summarizes the clinical data of the patients.

Neuroimages

On magnetic resonance imaging (MRI), tumors represented low signal intensity on T1-weighted images and high signal intensity on T2-weighted images, and enhanced well heterogeneously (5 of 9) or homogeneously (4 of 9) with gadolinium. Five tumors were irregular in shape and had a fuzzy margin, suggesting suspicious infiltration into surrounding structures (3 PPTIDs, 1 PC, and 1 unspecified). The median tumor volume was 7.7 cc (range, 3.6–13.4 cc). Obstructive hydrocephalus was observed in all patients. No evidence of CSF seeding was seen on initial MRI. On computed tomography (CT), tumors were isodense or slightly hyperdense. Intratumoral calcification was noted in one patient.

Surgery

For initial management, 8 of the 9 patients underwent the endoscopic third ventriculostomy (ETV) and biopsy of the tumor. One patient (Case No. 2) had been referred from another hospital after a craniotomy and biopsy with placement of a ventriculoperitoneal shunt. With the initial endoscopic surgery, patient symptoms were relieved immediately and tumor tissue was obtained successfully in all but one patient (Case No. 9; biopsy failed owing to massive intraoperative bleeding). This patient refused a second operation and was treated empirically with platinum-based chemotherapy, because the incidence of germinoma is highest in this location of tumor in Far Eastern Asian population. However, the tumor did not respond at all to the chemotherapy, and treatment was switched to SRS, as PPTs were considered as a second possible diagnosis.

Table 1. Clinical summary of nine cases with pineal parenchymal tumors

Case No.	Gender	Age	Clinical presentation	MR findings		Hydrocephalus	Initial management	Diagnosis	Tumor volume (cc)	SRS (No. of fractions)	Marginal dose (Gy)	Isodose line (%)	FU period (mo)	Local tumor response	Progression or recurrence	Alive or dead	Radiation toxicity	
				T1 (SI)	T2 (SI)													Enhancement
1	M	31	Diplopia	Low	High	Homogenous	(+)	ETV & biopsy	PPTID	7.8	GK (1)	16	50	213	CR	Yes (CSF seeding)	Alive	(-)
2	M	44	Headache	Low	High	Heterogeneous	(+)	Open biopsy & VP shunt	Pineocytoma	7.7	GK (1)	12	50	223	PR	No	Alive	(-)
3	M	39	Headache	Low	High	Heterogeneous	(+)	ETV & biopsy	PPTID	7.3	GK (1)	12	50	103	PR	No	Alive	(-)
4	M	53	Dizziness	Low	High	Homogenous	(+)	ETV & biopsy	Pineocytoma	3.6	CK (5)	36	80	32	CR	No	Alive	(-)
5	F	50	Gait disturbance	High	High	Heterogeneous	(+)	ETV & biopsy	Pineocytoma	13.4	CK (5)	36	77	44	PR	No	Alive	Temporary memory impairment
6	M	50	Headache	Low	High	Homogenous	(+)	ETV & biopsy	PPTID	5.1	CK (5)	30	82	14	PR	No	Alive	(-)
7	F	34	Headache	Low	High	Heterogeneous	(+)	ETV & biopsy	PPTID	11.9	CK (5)	30	80	41	CR	No	Alive	(-)
8	M	33	Headache, diplopia	Low	High	Heterogeneous	(+)	ETV & biopsy	PPTID	3.8	CK (5)	30	80	17	PR	No	Alive	(-)
9	F	36	Headache	Low	High	Homogenous	(+)	ETV & biopsy (failed)	Unspecified	9.1	CK (5)	30	81	20	PR	No	Alive	(-)

SI : signal intensity, SRS : stereotactic radiosurgery, FU : follow-up, M : male, F : female, ETV : endoscopic third ventriculostomy, PPRID : pineal parenchymal tumor of intermediate differentiation, GK : Gamma Knife, CR : complete response, CSF : cerebrospinal fluid, VP : ventriculoperitoneal, PR : partial response, CK : Cyberknife

Histopathological examinations

PCs are primarily composed of well-differentiated cells with resemblance to mature pineocytes. Pineocytomatous rosettes are frequently observed in PCs. On the contrary, PPTIDs show moderate nuclear atypia and higher mitotic counts than PCs. Pineocytomatous rosettes are inconspicuous in PPTIDs, consistent with partial loss of differentiation¹¹⁾. In reviewing 8 cases with histologic diagnosis of PPTs, PCs represented sparsely cellular tumors composed of monotonous small round cells, even smaller than normal parenchymal cells of the pineal gland. Pineocytomatous rosettes composed of acellular areas of neuropils surrounded by small round tumor cells were observed. No mitoses were seen. PPTIDs were of moderate or high cellularity with some tumors showing tightly compacted tumor cells while

others being less cellular and lobulated. Tumor cells exhibited more or less nuclear pleomorphism. Considerable numbers of bizarre giant tumor cells were mixed, but mitoses were rare and the proliferative activity measured by MIB-1 index was low (<5%). Necrosis was not observed. Tumor cells were diffusely immunoreactive for synaptophysin.

Stereotactic radiosurgery

Gamma knife (GK) (Elekta AB, Stockholm, Sweden) was performed on patients during the early period (Case No. 1 to 3). Since 2011, Cyberknife (CK) (Accuray Inc., Sunnyvale, CA, USA) has been used to treat patients with the intention of fractionation delivery of SRS to minimize radiation toxicity to adjacent critical structures. For GK treatment, the mean marginal dose

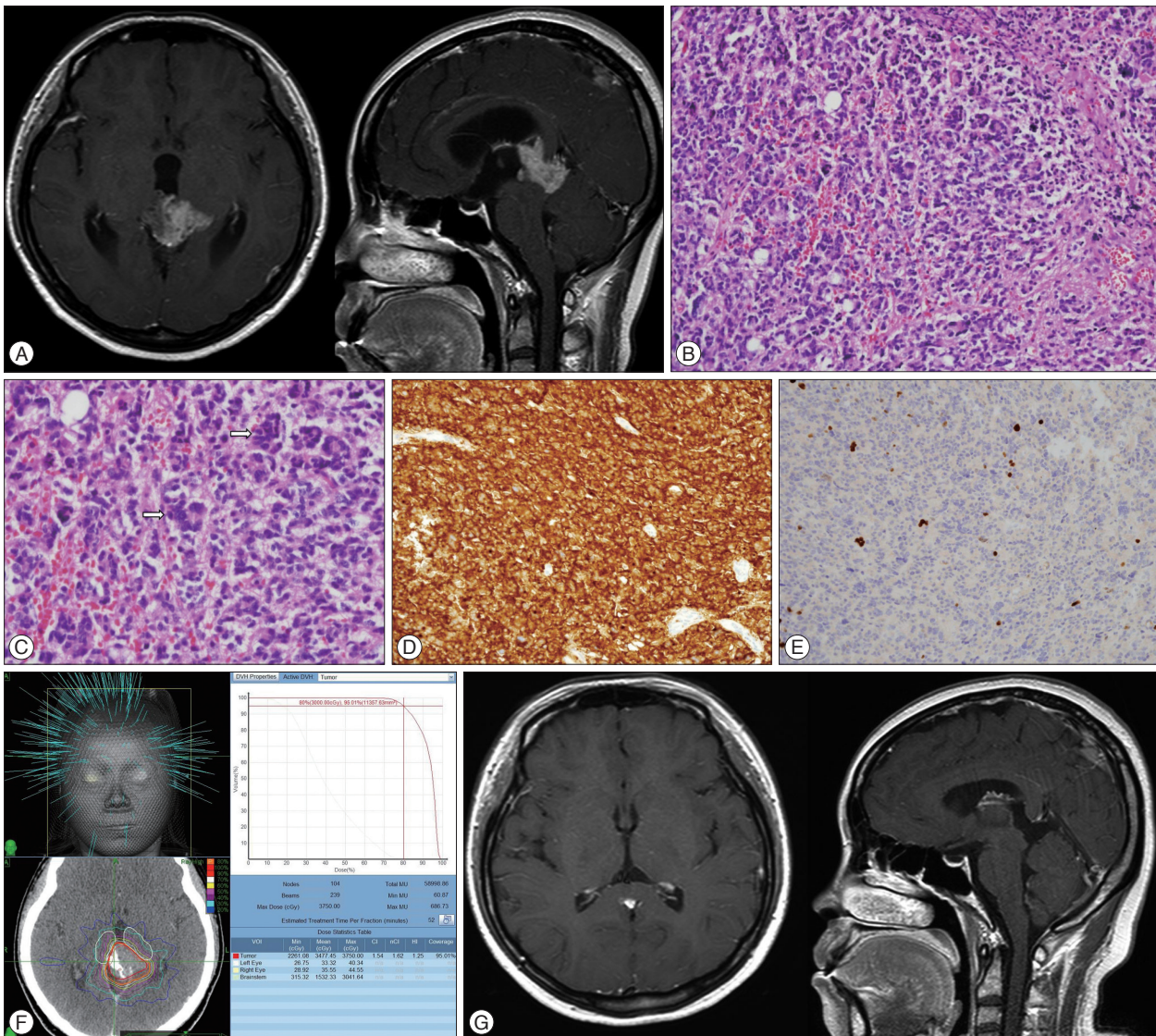


Fig. 1. A 34-year-old woman with pineal parenchymal tumor of intermediate differentiation (Case No. 7). A : Gadolinium-enhanced magnetic resonance images showing a 3.2×2.4×2.0 cm sized tumor in the pineal region with obstructive hydrocephalus. B : Tumor shows diffusely high cellularity and tumor cell nuclei are pleomorphic. C : Multinucleated giant tumor cells are frequently seen (arrows). D : Tumor cells are diffusely immunoreactive for synaptophysin. E : Proliferation activity assessed by MIB-1 is low. F : She received 5-fraction Cyberknife (CK) treatment with marginal dose of 30 Gy. G : Tumor disappeared completely in 9 months after CK, and no evidence of disease was seen at the last follow-up of 3 years.

of 13.3 Gy (range, 12–16 Gy) was prescribed to 50% isodose lines, and for fractionated CK, the mean marginal dose of 32 Gy (range, 30–36 Gy) was prescribed to the mean 80% isodose line (range, 77–82%) and delivered in 5 daily fractions.

Follow-up

Clinical examinations and MRI scans were performed at 6-month intervals during the first year, annually for two years, and biennially thereafter. Treatment responses were divided into four categories according to the criteria of Macdonald et al.²⁴: complete response, partial response (>50% reduction in size), progressive disease (>25% increase in size), and stable disease. LTC was defined as complete or partial response and stable disease.

RESULTS

After a mean follow-up of 78.6 months (range, 14–223 months), all patients were alive and all of their tumors were locally controlled except for one instance of CSF seeding metastasis (Case No. 1). On MRI, tumor size decreased in all patients, resulting in complete response in 3 patients and partial response in 6. Treatment-related adverse event was observed in one patient who had experienced temporary memory impairment one year after SRS, which improved spontaneously (Case No. 5).

Illustrative cases

Case 1 (Case No. 7; Fig. 1)

A 34-year-old woman presented with a one-month history of

headache. Papilledema was observed on fundoscopic examination. MRI revealed a 3.2×2.4×2.0 cm sized tumor in the pineal region with obstructive hydrocephalus (Fig. 1A). The tumor was irregular in shape and appeared to infiltrate into surrounding structures. After ETV and biopsy, her headache was relieved and histologic diagnosis proved to be PPTID (Fig. 1B–E). She received fractionated CK treatment with marginal dose of 30 Gy one month after surgery (Fig. 1F). A marked decrease in tumor size was observed in 3 months after CK and tumor disappeared completely in 9 months. No evidence of disease was seen at the last follow-up of 3 years (Fig. 1G).

Case 2 (Case No. 2; Fig. 2)

A 44-year-old man was referred for pineal region tumor. He previously underwent a craniotomy and biopsy of the tumor with ventriculoperitoneal shunt placement at another hospital. On MRI, a 2.8×1.8×2.2 cm sized tumor was observed in the pineal region (Fig. 2A), and histologic examination confirmed the diagnosis of PC (Fig. 2B). After GK treatment with marginal dose of 12 Gy, he achieved durable tumor response with more than 18 years of follow-up (Fig. 2C).

Case 3 (Case No. 1; Fig. 3)

A 31-year-old man presented with a 4-month history of diplopia. MRI revealed a 1.4×1.8×3 cm sized tumor in the pineal and tectal region with obstructive hydrocephalus (Fig. 3A). After ETV and biopsy, PPTID was diagnosed. He received GK treatment with marginal dose of 16 Gy. Complete tumor response was achieved and the primary site remained free of dis-

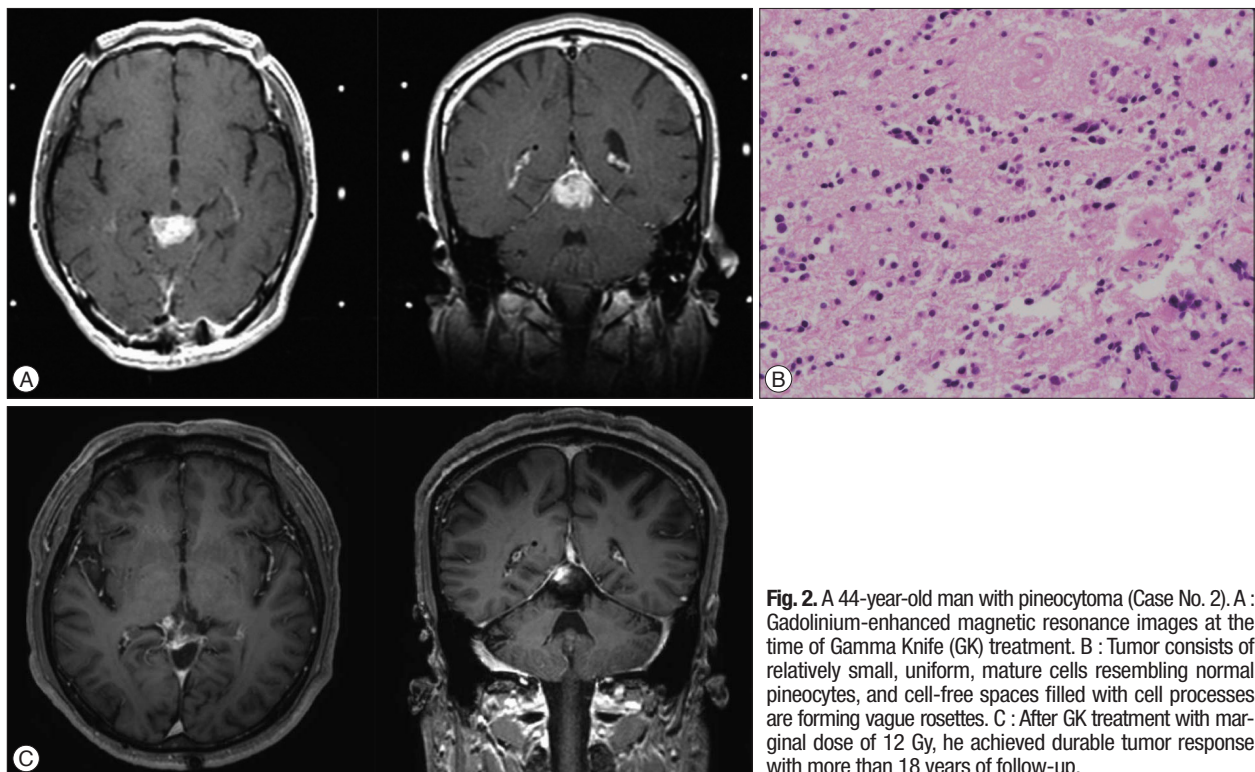


Fig. 2. A 44-year-old man with pineocytoma (Case No. 2). A : Gadolinium-enhanced magnetic resonance images at the time of Gamma Knife (GK) treatment. B : Tumor consists of relatively small, uniform, mature cells resembling normal pineocytes, and cell-free spaces filled with cell processes are forming vague rosettes. C : After GK treatment with marginal dose of 12 Gy, he achieved durable tumor response with more than 18 years of follow-up.

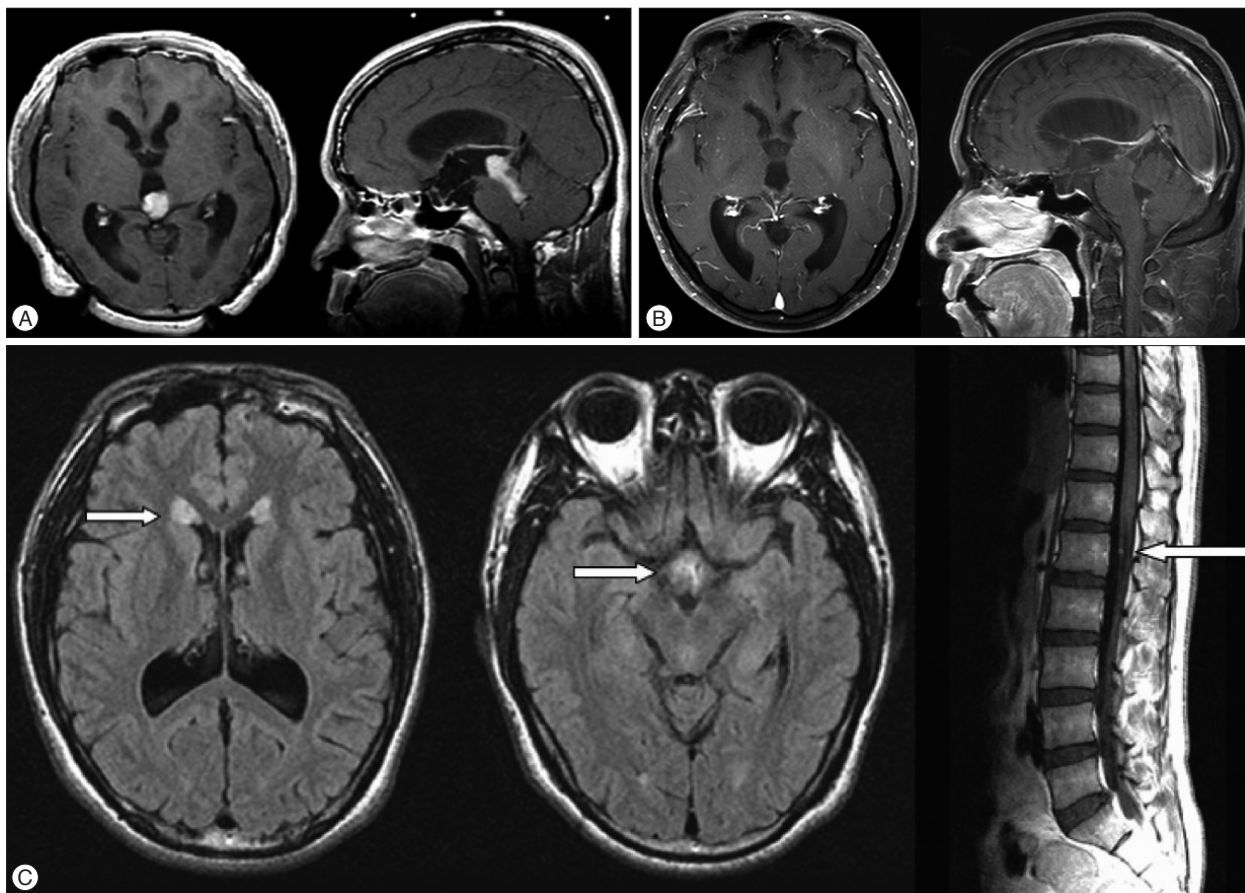


Fig. 3. A 31-year-old man with pineal parenchymal tumor of intermediate differentiation (Case No. 1). Gadolinium-enhanced magnetic resonance images before (A) and 84 months after Gamma Knife treatment (B). Although the primary site remained free of disease at this time, cerebrospinal fluid seeding metastases were observed in the ventricles and the cauda equina (C, arrows). He received additional craniospinal irradiation and his disease was stable at 17 years.

ease, until remote CSF seeding metastases were found in the ventricles and the cauda equina 7 years after GK (Fig. 3B, C). He received additional craniospinal irradiation and his disease was stable at 17 years.

DISCUSSION

Pineal region tumors, although rare, consist of variable histologic entities including germ cell tumors most frequently followed by PPTs, gliomas, and metastases. To make a differential diagnosis among these entities, multiple factors, such as patient age, presenting symptoms, imaging features, and serum/CSF biochemical markers, are considered and may help in predicting tumor type. Those factors, however, are not characteristic to a certain specific histologic entity. As different treatment strategies are required according to the histologic diagnosis, correct tissue diagnosis is essential to provide an optimal therapy. Together with this, as a majority of patients with tumors in this region present with symptoms of hydrocephalus, simultaneous ETV and tumor biopsy frequently offers an initial management of choice, obviating the risks of unnecessary craniotomy and permanent shunt placement. All of our patients were managed in

this way except for one referred from another hospital.

Apart from PBs which are common in pediatric patients and are managed by aggressive multimodal approaches, optimal management of non-malignant PPTs in adults remains an issue of debate. For benign PCs, attempting an aggressive total resection of tumor is justifiable with an enhanced chance for cure compared with incomplete resection with or without adjuvant RT, which is supported by a recent systematic review of the literature⁷. Although radical surgery via the supracerebellar infratentorial or the occipital transtentorial routes has been advocated based on this grounds, complete tumor resection was achieved only in a half of patients^{4-6,18}, and perioperative mortality and permanent morbidity have been reported in 0–11% and 19–28%, respectively^{15,18,19,22,29}. Thus, decision-making on aggressive surgery should be carefully balanced against the potentially life-threatening risks. In case of incomplete resection or biopsy, adjuvant fractionated RT is usually employed, but it appears to provide no benefit in overall survival as well as LTC for this radioresistant, indolent subtype of PPTs⁸. Alternatively, SRS is used increasingly to treat PPTs. Recent studies reported excellent long-term LTC and survival in patients with PPTs, especially with PCs after SRS, mostly at adjuvant or salvage settings and

Table 2. Recent studies on stereotactic radiosurgery for pineal parenchymal tumors in adults

Author (year)	No. of cases	Tumor volumes (cc), median	Marginal doses (Gy), mean	Follow-up (months), mean	Outcomes
Yianni et al. ³¹⁾ (2012)	11	3.8	20	52.9 (median)	81% & 54% PFS at 1 & 5 yr
Wilson et al. ³⁰⁾ (2012)	5	2.6	14.6	53 (median)	100% LTC for PCs
Mori et al. ²⁵⁾ (2009)	9	3.7	16.7	33.5 (median)	85% LTC for PCs
Kano et al. ¹⁶⁾ (2009)	20	3.1	15 (median)	54.1	100% LTC for PCs
Lekovic et al. ²⁰⁾ (2007)	10	6.2	14 (median)	17.3	100% LTC for PCs
Reyns et al. ²⁶⁾ (2006)	13	NA	15	34	91.7% LTC & 83.3% OS
The present study	9	7.7	13.3 (GK), 32 (CK)	78.6	100% LTC & 100% OS

PFS : progression-free survival, LTC : local tumor control, PCs : pineocytomas, NA : not applicable, OS : overall survival, GK : Gamma Knife, CK : Cyberknife

occasionally at upfront setting (Table 2)^{12,16,20,25,26,30,31)}, suggesting SRS may be a useful alternative or adjunct to surgical resection. In extension from these observations, we elected SRS as a primary therapeutic modality after histologic confirmation of PPTs other than PBs and achieved LTC and survival in all patients except for one instance of CSF seeding metastasis. All those previous studies including our own demonstrated a great safety of SRS without any treatment-related permanent morbidity or mortality.

One unique characteristic of our series is incorporation of many cases diagnosed with PPTIDs. The biological behavior of PPTIDs of higher WHO grade is generally considered less predictable than that of PCs, and sometimes exhibits an aggressive nature²⁷⁾. The 5-year survival rates have been estimated at 74% for WHO grade 2 PPTIDs and 39% for grade 3 PPTIDs⁹⁾. Recurrence rates are reportedly also higher in grade 3 PPTIDs. Along with these, local invasion of PPTIDs was frequently observed on MRI¹⁷⁾, which was similar in our series. Despite all those relatively dismal features of PPTIDs compared to PCs, these tumors responded well to SRS as PCs, yielding 100% rates of LTC and overall survival in our study. Yet, remote CSF metastases occurred in one patient 7 years after SRS. Currently, questions regarding the optimal management of PPTIDs are largely unanswered including which treatment option would be most beneficial among surgical resection, RT, SRS, and chemotherapy and whether a combination of therapy would be better or not, although these tumors have been reported to be radiosensitive as seen in our cases^{2,14,23)}. Further studies are needed to elucidate the pathogenesis, biological behavior, and an optimal therapy for this particular kind of new entity.

CONCLUSION

Simultaneous tissue diagnosis and CSF diversion can be achieved safely using ETV and biopsy as an initial management for pineal region tumors causing obstructive hydrocephalus. For PCs and PPTIDs, the frequent subtypes of PPTs in adults, SRS appears to be effective and safe and can be considered as a useful alternative or adjuvant option to surgical resection.

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