

Radiosurgery

Gamma knife radiosurgery for intracranial mature teratoma—long-term results and review of literature

Cheng-Di Chiu, MD, Wen-Yuh Chung, MD*, David Hung-Chi Pan, MD, Tai-Tong Wong, MD, Yang-Hsin Shih, MD, Liang-Shong Lee, MD

Department of Neurosurgery, Neurological Institute, Veterans General Hospital-Taipei, and National Yang-Ming University, Taipei, Taiwan 11217, Republic of China

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Abstract

Background: The purpose of this report is to present long-term outcomes of gamma knife radiosurgery for intracranial mature teratoma after debulking surgery.

Methods: Three patients with intracranial mature teratoma had initial target volumes of 5.4, 18.7, and 5.1 cm³, respectively, and were treated by gamma knife radiosurgery between 1993 and 2004. Marginal doses of 17, 12.5, and 13.5 Gy, respectively, were delivered to the tumors at isodose levels of 50%, 50%, and 62%, respectively. The first patient received radiosurgery after surgical removal and conventional radiotherapy. The second patient received similar management, including surgery and radiotherapy, with tumor recurrence. Two additional operations and subsequent radiosurgery were performed on this patient. Based on the favorable results of the first 2 patients, we performed radiosurgery instead of conventional radiotherapy after subtotal surgical removal in the last patient. By reviewing literatures concerning the therapeutic modalities and the long-term results of our 3 patients, we discuss the role of radiosurgery in treating intracranial mature teratoma.

Results: A follow-up period of 121, 89, and 31 months, respectively, demonstrated tumor volume reduction rates of 70%, 89%, and 48%, respectively. No evidence of further tumor progression and no radiosurgery-related complication or morbidity was noted. The school performances of the affected children are all above average.

Conclusions: Gamma knife radiosurgery provides a safe and effective alternative as the adjuvant treatment of intracranial mature teratoma after surgical debulking. Previous conventional radiotherapy does not alter final tumor control. Radiosurgery should be considered when residual tumor growth continues with no related symptoms or evaluations of tumor markers during follow-up. © 2006 Elsevier Inc. All rights reserved.

Keywords:

Gamma knife; Germ cell tumor; Mature teratoma; Radiosurgery

1. Introduction

Germ cell tumors are traditionally classified as germinomatous, nongerminomatous germ cell tumors, and their mixed forms. As the geographic variations exist, their incidence is much higher in Asia than in western countries [2,23–25]. Intracranial nongerminomatous germ cell tumors are very rare lesions responsible for less than 0.3% to 0.5% of all central nervous system tumors [2,23]. They can be further classified as choriocarcinoma, endodermal sinus

tumor (yolk sac tumor), embryonal carcinoma, and teratoma according to different cell origins [3,12]. Teratomas account for one tenth of nongerminomatous germ cell tumors and can be further classified as mature, immature, and malignant teratoma depending upon the differentiation of tissues within the tumor [2,21,34,36]. Mature teratomas are identified by the presence of fully differentiated neuroectodermal (such as skin, skin adnexae, and neural tissue), mesodermal (such as cartilage, bone, fat, fibrous tissue, and smooth muscle), and endodermal (such as respiratory and gastrointestinal tract epithelium, liver, pancreas, and salivary gland tissue) elements [34,35]. Mature teratomas are well-differentiated lesions that are usually lobulated and

* Corresponding author. Tel.: +886 2 28757491; fax: +886 2 28757588.
E-mail address: wychung@vghtpe.gov.tw (W.-Y. Chung).



Fig. 1. The pathological picture of specimen from Patient A. In this picture, components of mature teratoma are shown, including some stratified squamous epithelial cells, hair and its follicles, (ectoderm); columnar cell in glandular structure (endoderm); bone islands, muscle, and fatty tissue (mesoderm) can also be seen.

tend to adhere firmly to neighboring tissues [23,26]. Microscopically, they consist of solid and cystic portions of squamous epithelium with keratin debris (Fig. 1) [17]. They possess more benign and radio-resistant behavior, and sometimes, they can be separated from nongerminomatous

germ cell tumors owing to these marked differences [33]. Based on a review of the literature, current widely adopted policy for the treatment of intracranial mature teratoma is complete microsurgical removal, followed by conventional radiotherapy for the remnant tumor or reoperation when local relapse occurs [1,5,6,23]. To our knowledge, only 1 case using stereotactic gamma knife radiosurgery as a salvage therapy for pure mature teratoma (not mixed with other germ cell tumors) after surgery has ever been mentioned [6,13,31]. We present our long-term results of 3 patients examining the role of gamma knife radiosurgery in treating intracranial mature teratoma.

2. Patients and methods

From 1975 to 2004, 138 (14%) intracranial germ cell tumors of 986 pediatric brain tumors were treated in Taipei Veteran General Hospital. Among them, only 8 patients were pathologically diagnosed as pure mature teratoma, and 5 of those patients had total surgical removal. The other 3 patients who experienced subtotal surgical removal received other adjuvant therapies including conventional radiotherapy in 2 patients. All 3 patients were young boys (5, 12, and 16 years old). The tumors were originally located in the pineal region, which is consistent with other

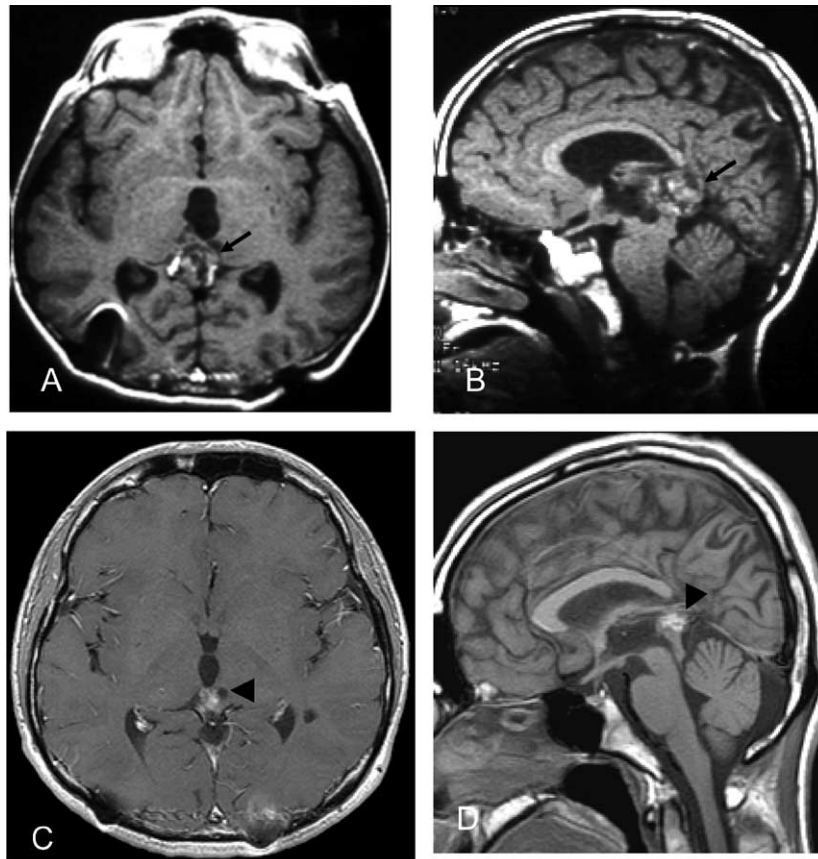


Fig. 2. Patient A received gamma knife radiosurgery after surgical debulking of a mature teratoma and conventional radiotherapy. A and B: The axial and sagittal view of contrast-enhanced brain magnetic resonance imaging on the day of surgery (arrow; tumor volume, 5.4 cm³). C and D: One hundred twenty months after surgery (arrowhead; tumor volume, 1.62 cm³).

reports [14-16,19]. Both tumor markers of α -fetoprotein (α -FP) or β -human chorionic gonadotropin (β -HCG) in serum and cerebrospinal fluid were not elevated. All the pathological specimens obtained from 5 craniotomies in these 3 patients revealed pure mature teratoma without other components (Fig. 1).

The residual or recurrent mature teratoma was treated by gamma knife radiosurgery. Every patient had stereotactic magnetic resonance imaging after application of the Leksell frame. The tumor contours were carefully identified on 3 mm-thick axial, coronal, and sagittal views by both a radiologist and a neurosurgeon. The volume of the tumor was then determined by summation of the volumes measured in the individual image slabs. The subsequent dose planning was based on the Kula or GammaPlan dose-planning system, and irradiation was delivered using the Gamma unit (Elekta Instrument AB, Sweden). The detailed techniques including targeting imaging, volume evaluation, and irradiation doses had been presented elsewhere [35].

2.1. Clinical follow-up

After gamma knife radiosurgery, all patients returned for clinical evaluation and magnetic resonance imaging assessment every 6 months, using the same magnetic resonance scanner with the same image parameters as when the gamma knife radiosurgery was performed. The tumor volume was estimated again, as previously described. The

follow-up period was 121, 89, and 31 months, respectively. The effects of gamma knife radiosurgery were evaluated based mainly on sequential changes of tumor volume on magnetic resonance imaging.

2.2. Case presentations and brief histories

2.2.1. Patient A

A 5-year-old boy initially presented with involuntary shaking of bilateral hands in 1990. A heterogeneous tumor in the pineal region with initial volume of 13.50 cm³ was noted on magnetic resonance imaging. He underwent craniotomy through the interhemisphere approach to remove the tumor subtotally. Conventional whole-brain radiotherapy (5392 cGy in 27 fractions during 6 weeks) for the residual tumor started 2 months after the operation. Locally, the tumor recurred to 5.40 cm³ 3 years later, and gamma knife radiosurgery (17 Gy with 50% coverage) was performed. In the latest follow-up (10 years after gamma knife radiosurgery), tumor volume had been reduced to 1.62 cm³ (Fig. 2). Clinically, the patient developed normally with no hormonal deficiency.

2.2.2. Patient B

A 16-year-old boy presented with headaches and vomiting since 1993. An interhemisphere craniotomy was initially performed. Similarly, subsequent conventional radiotherapy

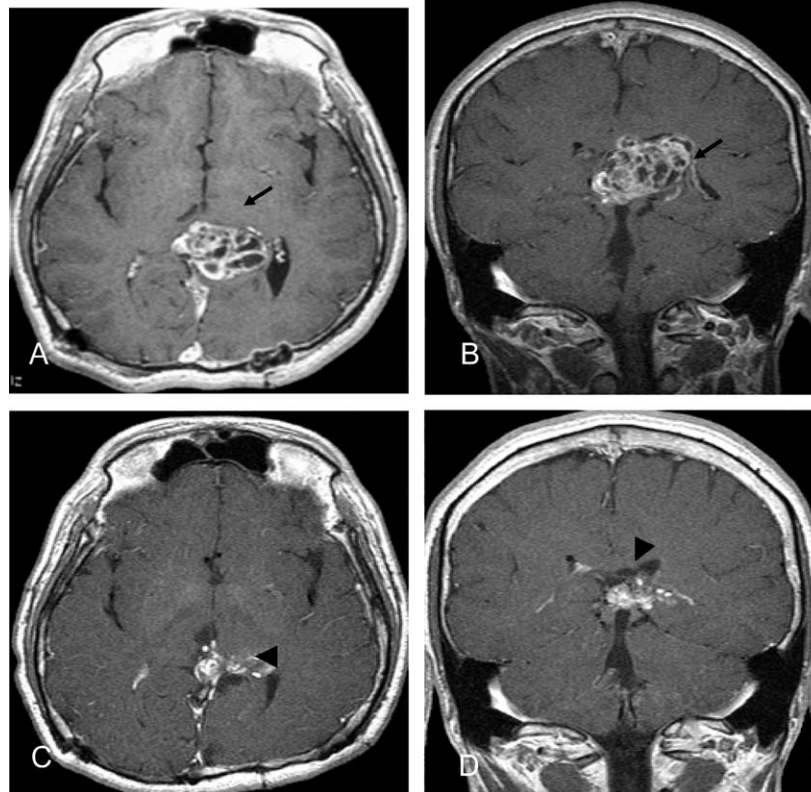


Fig. 3. Patient B received gamma knife radiosurgery after surgical debulking of a mature teratoma and conventional radiotherapy. A and B: The axial and coronal view of contrast-enhanced brain magnetic resonance imaging on the day of surgery (arrow; tumor volume, 18.70 cm³). C and D: Eighty-nine months after surgery (arrowhead; tumor volume, 2.08 cm³).

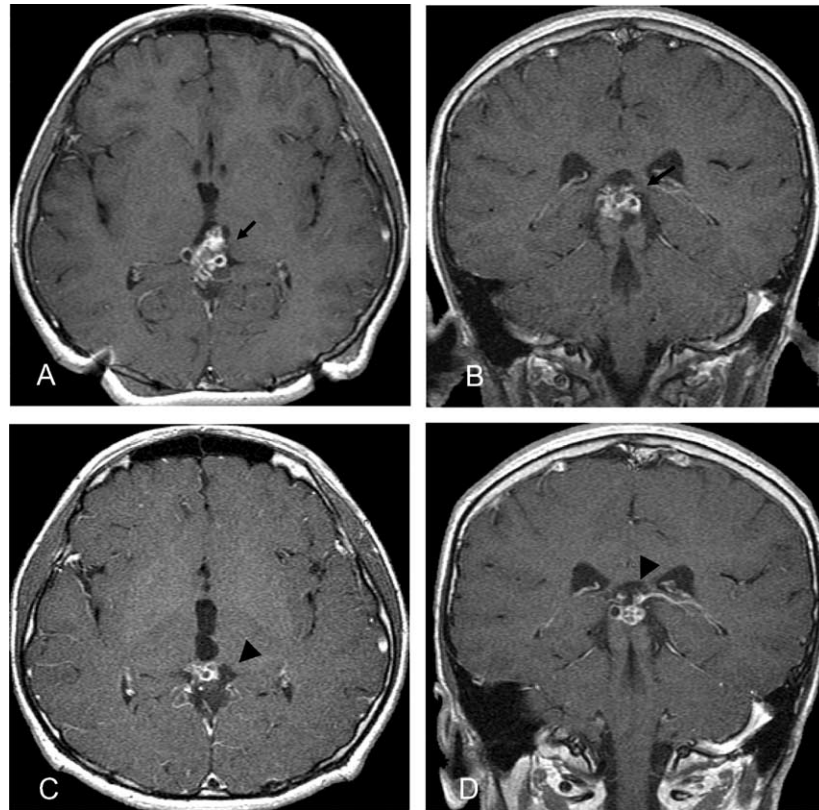


Fig. 4. Patient C received gamma knife radiosurgery after surgical debulking of a mature teratoma. A and B: The axial and coronal view of contrast-enhanced brain magnetic resonance imaging on the day of surgery (arrow; tumor, volume 5.10 cm³). C and D: Thirty-one months after surgery (arrowhead; tumor, volume 2.67 cm³).

was performed 2 months after the operation. It was stopped because of marked radiation side effects at the accumulated dosage of 3060 cGy in 24 fractions during the first 3 weeks.

Image studies revealed further tumor progression instead of reduction. A second craniotomy (infratentorium and supra-cerebellum approach) was performed. One year after the

Table 1

Summary of data in all patients who have ever received gamma knife radiosurgery for pineal mature teratoma including patients in this study (patients A, B, and C) and patients from other studies (patients D and E)

	Age (y)/sex	Clinical presentation	Tumor markers α -FP / β -HCG	Prior operation	Pathology	Conventional radiotherapy dose/fraction	C/T	GKRS dose/coverage	Tumor volume reduction Rate (cm ³)	F/U (m)
A	5/M	Involuntary hands shaking	—/—	Once, subtotal	Mature teratoma	Whole brain 5329 cGy/27 fractions	NP	17 Gy/50%	5.4 1.62/5.4 (70%)	121
B	16/M	HA, N/V	—/—	3 times ^a , subtotal	Mature teratoma	Whole brain 3060 cGy/24 fractions	NP	12.5Gy/50%	18.7-2.08/18.7 (89%)	89
C	12/M	HA, double vision	—/—	Once, subtotal	Mature teratoma	NP	NP	13.5Gy/62%	5.1-2.67/5.1 (48%)	31
D ^b	18/M	HA, diplopia	+/+	Once, partial resection	Mixed germ cell tumor (germinoma and teratoma)	36 Gy (entire ventricle) 14.4 Gy (local boost)	Etoposide cisplatin ifosfamide	12 Gy/ 50%	23.4 (0%, with some necrotic change)	4
E ^c	ND	ND	ND	Once, subtotal	Mature teratoma	ND	ND	ND	ND	60

M, male; F, female; HA, headache; N/V, nausea and vomiting; +, elevated; —, not elevated; NP, not performed; ND, not defined; GKRS, gamma knife radiosurgery; C/T, chemotherapy; F/U, follow-up period.

^a Surgical intervention first, then adjuvanted with conventional radiotherapy, which failed. Two additional surgeries were performed before gamma knife radiosurgery.

^b Reference [13].

^c Reference [16].

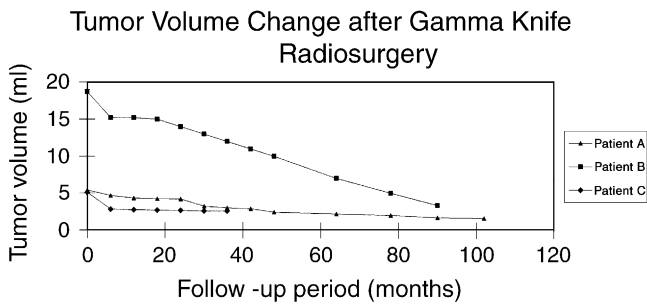


Fig. 5. The sequential tumor volume changes after gamma knife radiosurgery based on the data collected every 6 months during the follow-up period.

second operation, the tumor volume had again increased. A third craniotomy was performed, this time via a bifrontal interhemisphere approach. Two years after the second surgery, the tumor was still progressing with a volume of 18.70 cm³. Gamma knife radiosurgery (12.5 Gy with 50% coverage) was subsequently performed and finally stopped these exhausting therapeutic sufferings. In the latest follow-up (8 years after gamma knife radiosurgery), tumor volume had been reduced to 2.08 cm³ (Fig. 3).

2.2.3. Patient C

A 12-year-old boy presented to our hospital with headache and double vision in 2000. Brain magnetic resonance imaging revealed a 17.50 cm³, lobulated, well-enhanced tumor with a cystic and calcification component located in the pineal and third ventricular region. An interhemisphere craniotomy was performed to remove the tumor. One year after surgery, the tumor volume increased to 5.1 cm³. Gamma knife radiosurgery was performed (13.5 Gy with 62% coverage) directly based on the promising results from the previous 2 patients. In the latest follow-up (3 years after gamma knife radiosurgery), tumor volume had been reduced to 2.67 cm³ (Fig. 4) (Table 1).

3. Results

All 3 patients underwent microsurgical resection at least once (1 patient underwent microsurgical resection 3 times). Two patients received postoperative conventional radiotherapy, but the tumor recurred or progressed. They were all finally treated with stereotactic gamma knife radiosurgery. The initial tumor volumes before gamma knife radiosurgery were 5.4, 18.7, and 5.1 cm³, respectively, with a mean volume of 9.73 cm³. The marginal doses were 17 Gy at 50%, 12.5 Gy at 50%, and 13.5 Gy at 62%, respectively. A tumor reduction rate of 70%, 89%, and 48%, respectively, was achieved in an average follow-up period of 80.3 months (Fig. 5).

4. Discussion

4.1. Therapeutic considerations

Mature teratomas are benign tumors, which are usually radioresistant [23]. Radical excision is advocated despite the benign nature because the long-term outcome is excellent after such treatment. The long-term prognosis based on the study of 153 intracranial germ cell tumors at different sites showed that 10-year survival rates for mature and immature teratoma are 93% and 86%, respectively [27,29]. Although most mature teratomas can be cured by microsurgery alone, sometimes, the deep location and critical surrounding structures makes total removal difficult and results in residual tumors. The recurrent tumor frequently results from the mixed germ cell components or, less frequently, from the possible metachronous tumor. Thus, a multimodality strategy had been suggested for adjuvant therapies such as conventional radiotherapy and even chemotherapy (Table 2). In reviewing the literature, stereotactic gamma knife radiotherapy for intracranial teratoma has only been reported in 2 patients. One was pure mature teratoma and

Table 2
Therapeutic modalities for pineal mature teratomas reviewed in the literature

Authors (reference)	Case no.	Age/sex (case no.)	Location (case no.)	α -FP/ β -HCG	Surgical excision (case no.)	R/T dosage (case no.)	C/T	F/U	Outcome
Matsutani et al [23]	19	11.6 ± 8.5/M (18), F (1)	Pineal (17) Other site (2)	—/—	Total or subtotal (17) biopsy or partial removal (2)	WB (2) / 50 Gy ^a	NP	10 y	Survival rate 92.9%
Aoyama et al [1]	5 ^b (4+1)	ND	ND	ND	Totally removed (4), partial removal (1)	WB (3) LF (2)	After R/T ^c	10 y	5-y relapse-free rate 100%
Choi et al [6]	5	ND	Pineal (5)	—/(4) —/(1)	Totally removed (4), subtotally removed (1) with subsequent GKRS	NP	NP	5 y	5-y survival rate 80% ^d , no recurrence
Cho et al [5]	4	0-4 (1) 5-9 (3) All male	Pineal (4)	ND	Totally removed (3), subtotally removed (1)	NP	NP	50 m	No evidence of disease (3) stable disease (1)

VA, visual acuity; VF, visual field; GKRS, gamma knife radiosurgery; R/T, conventional radiotherapy; WB, whole brain; LF, local field.

^a Only 2 nonextensive resection patients received postoperative conventional radiotherapy.

^b Four patients are pure mature teratomas and 1 patient was mixed with germinoma.

^c One of 2 primary relapses 8 years after total resection and radiotherapy out of the irradiated field. Pathology revealed germinoma along the third ventricular wall. Patient was alive at 5 years after irradiation for the relapse.

^d One patient died because of postoperative complications. One of the patients had never received trial treatment of GKRS and achieved stable disease.

the other was mixed with germinoma and teratoma [6,13,22,31]. In a study by Choi, et al [6], a patient with pure mature teratoma received gamma knife radiosurgery after subtotal tumor removal. But they did not clearly describe the outcome of the gamma knife radiosurgery. An 18-year-old male patient with mixed germinoma and mature teratoma in a study by Hasegawa, et al [13] received fractionated radiotherapy to the entire ventricle system (36 Gy) with a boost to the pineal region (14.4 Gy) for the residual tumor recurring after partial surgical removal. One year later, radiosurgery was performed because of tumor recurrence. The initial tumor volume was 23.4 cm³. The maximum and marginal doses were 24 and 12 Gy, respectively. Image follow-up 4 months after radiosurgery revealed the tumor was unchanged in size, except for some degree of necrotic change [13] (Table 1). In our study, salvage gamma knife radiosurgery achieved a tumor control rate of 100%, although only 3 cases have been documented in the past 10 years. They gained an average 69% tumor volume reduction rate during as long as 80 months follow-up. We thought that a 4-month follow-up in previous reports might have been too short to evaluate the benefits of gamma knife radiosurgery. In our study, Patient C achieved 48% tumor volume reduction and was the only patient defined as having a minor response because of the brief follow-up period [7]. According to the reduction curve shown in Fig. 3, we believe that the tumor volume of Patient C may continue to reduce or at least remain stable if a longer follow-up period can be achieved. On the other hand, Patient B underwent more surgeries and seemed to progress easier or be more refractory as compared with Patients A and C. It is possible that the tumor in Patient B mixed with some other malignant components. This issue may remain unknown because of the lack of other pathological proof beyond mature teratoma and their tumor markers not elevated during the 89-month follow-up period.

4.2. Diagnostic considerations

The diagnosis of germ cell tumors relies on the detection of elevated tumor markers in serum or cerebrospinal fluid—specifically, α -FP and β -HCG. When the tumor markers are negative, mature teratoma or germinoma are always suspected. Most teratomas are midline, located in the pineal region, followed by the suprasella or hypothalamic region, and rarely, they have been described in the fourth ventricle [15,20,28]. Based on neuroimaging techniques, the magnetic resonance imaging of mature teratomas demonstrates a nonhomogenous signal pattern and a clearer picture of the different tissue that constitutes the teratoma. When contrasted, the enhancement is heterogeneous; it is not confined to the lesion's periphery, and the intratumoral contents enhance as well. Solid teratomas usually contain a significant proportion of immature or malignant tissue as opposed to cystic teratomas, which are mainly mature, clinically benign elements [8]. These images characteristics help us to recognize the components of mature teratomas

and differentiate them from other tumors, but sometimes, it is still hard to tell whether other mixed germ cell tumors combined exist. Thus, tissue proof obtained from either stereotactic biopsy or craniotomy is essential for further differential diagnosis. However, according to a study by Bruce and Stein [4], 15% of these patients had mixed histologic character. Therefore, a specimen obtained from a simple biopsy may be nonrepresentative of the complex histologic character and may be of limited value. Owing to these difficulties in the diagnosis of pure nongerminomatous germ cell tumors, result in careful images and tumor markers follow-up is mandatory even for patients with mature teratoma. Stereotactic biopsy may be reserved for patients with disseminated or invasive tumors or patients whose medical conditions mean that a lengthy operation is contraindicated. So, the benefits of surgery extend beyond that of establishing a histologic diagnosis, particularly for most pineal tumors that are benign and treatable with surgery alone [31]. Even malignant tumors may benefit from aggressive surgery because complete resection or at least radical debulking will improve the response to adjuvant radiation or chemotherapy [5].

4.3. Alternative pathway of treatment

When the diagnosis of pure mature teratoma is confirmed from the specimen of debulking surgery, the following conditions should be taken into consideration (Fig. 6). The first condition is when the tumor is progressively enlarging and causing associated symptoms without the presence of elevated tumor markers. The only option for immediate resolution of symptoms is reoperation for tumor removal. However, a second operation has inherent risks, such as poorer identified anatomy and tissue adhesion. Gamma knife radiosurgery should be considered in those less emergent and higher-surgical-risk patients. The second condition is when the tumor is progressively enlarging and there is no resulting associated symptoms or elevation of tumor markers. We can then choose either close observation or performing gamma knife radiosurgery immediately. Similar to the indication in the patients in our study who achieved successful results through gamma knife radiosurgery, a more aggressive application in this particular patient is quite reasonable because of its safety and effectiveness. Conventional radiotherapy is not recommended in treating these patients not only because it is often ineffective, but also to prevent the untoward side effects [30]. The third condition is when the tumor size remains stable without associated symptoms or elevated tumor markers. Observation and regular follow-up are recommended in this situation before any further treatment is initiated. When tumor markers are elevated, it means that there is some tumor marker secreting cells occurring or recurring. Possible reasons include mature teratoma with malignant transformation, residual mixed germ cell component that was missed in pathological diagnosis, or even a metachronous tumor [11]. Usually, these tumor marker-secreting

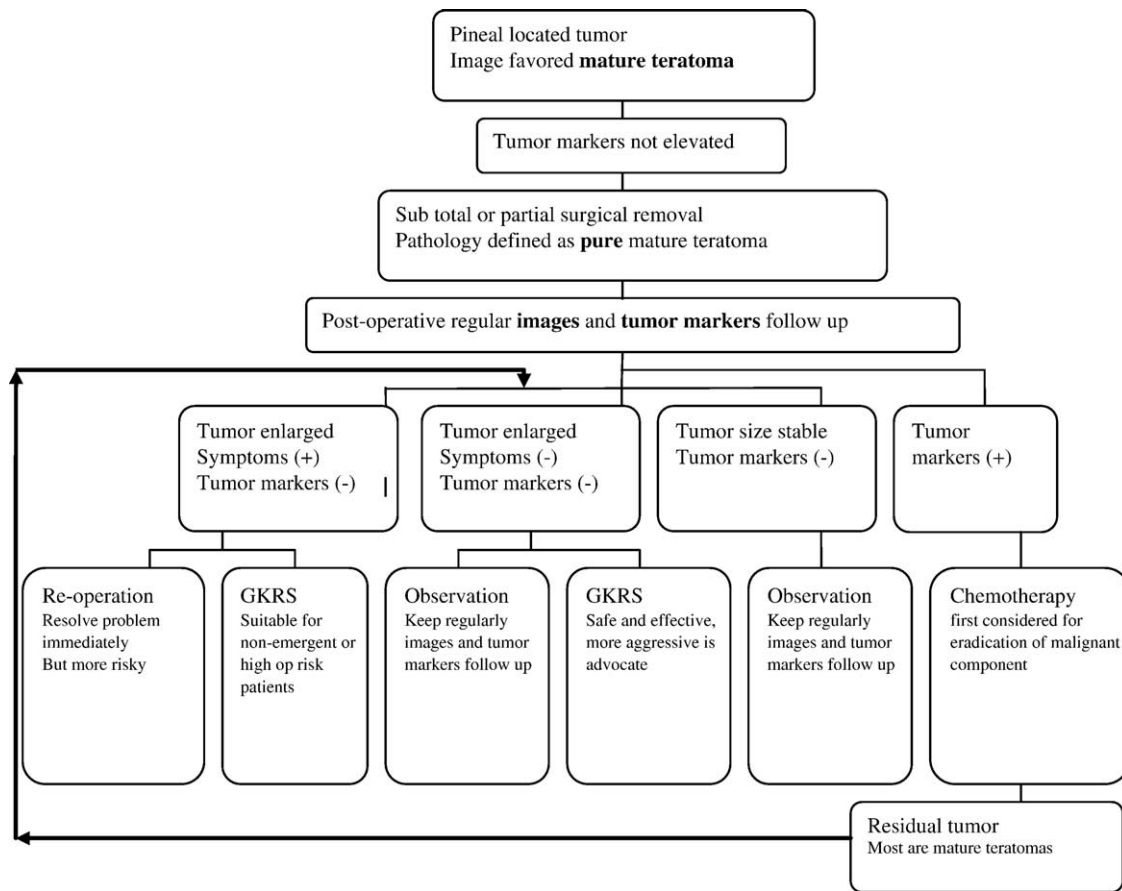


Fig. 6. Flow chart showing our suggestions on how to handle the pineal tumor with suspicion and diagnosis of mature teratoma.

cells are malignant and easily metastatic, so adjuvant chemotherapy should be considered first. Traditionally, the treatment of malignant intracranial germ cell tumors in the pineal region has been surgical extirpation, followed by postoperative radiotherapy with or without adjuvant chemotherapy [9,28]. Recently, neoadjuvant chemotherapy has been shown to be efficacious as initial therapy in patients with malignant intracranial germ cell tumors. However, the persistence or recurrences of tumors after neoadjuvant therapy does occur. According to a report by Friedman, et al [10], the eradication of malignant tumors may spare benign tumor components. And these residual tumors are mature teratoma. They advised a “second-look” operation for pathology and advocated surgical resection for residual tumor results in long-term remission with minimal associated morbidity. However, the indication and the timing for surgery are still controversial. Serial follow-up of tumor markers and images are essential for finding residual malignant components for early detection of tumor recurrence or metastasis and for monitoring tumor progression. Gamma knife radiosurgery provides a beneficial alternative for these patients. It can not only irradiate residual local malignant components by detailed image, preventing a suffering second-look craniotomy, but also reduce mature teratoma volume, as evidenced by the case reports in our

study. We believe that in the future, gamma knife radiosurgery can be used as an alternative choice or even routine procedure in addition to conventional radiotherapy in the management of malignant pineal germ cell tumors with residual mature teratoma.

4.4. Gamma knife radiosurgery and conventional radiotherapy

In our study, Patient A had tumor recurrence 3 years after conventional radiotherapy. The residual tumor was well controlled by radiosurgery throughout the 10-year follow-up period. Patient B had poor response to conventional radiotherapy and achieved good tumor control through radiosurgery. We applied radiosurgery instead of conventional radiotherapy to Patient C after surgical debulking and gained a 48% tumor reduction rate during the 31-month follow-up period. Compared with conventional radiotherapy, radiosurgery seems to play a more important adjuvant role in treating mature teratoma by our limited case experience. The advantage to reducing the radiation dose to the surrounding normal brain while augmenting the radiation effect on the identifiable tumor volume is prevention of pituitary dysfunction, hypothalamic damage, or intellectual decline in prepubescent patients, especially those with large mature teratomas [18].

4.5. Limitation of gamma knife radiosurgery

Mature teratoma was traditionally considered to have a good prognosis and a low recurrence rate after total surgical resection. Second germ cell tumors, although rare, do occur at a different site and with different histologic types long after total removal of mature pineal teratomas. These reported metachronous tumors were believed to be de novo neoplasms rather than a recurrence owing to only 1 reported case having ever received adjuvant radiotherapy after surgery [32]. It was supposed that if all patients had received adjuvant therapy, primordial germ cells straying into multiple regions where second tumors commonly occur would have disappeared, and the second tumors would not have occurred [32]. But their incidence is extremely rare, and it is, of course, not worthy to put all patients with mature teratoma at risk with whole brain radiotherapy or systemic chemotherapy. Gamma knife radiosurgery has no role in preventing metachronous tumors according to this hypothesis. Regular follow-up of tumor markers and images, especially during the adolescent stage, is believed to be the cornerstone for early detection and prevention of side effects.

5. Conclusions

Based on the results from this study, stereotactic gamma knife radiosurgery is an important alternative in treating residual or recurrent mature teratoma because of its responsiveness, good long-term tumor control, reduced risk of complication, and less suffering. It is also the first therapeutic choice of patient whose tumor size increases without associated symptoms or elevated tumor markers in the follow-up period. Especially for prepubescent patients, it works not only in reduction of the radiation dose to the surrounding normal brain, but also in augmenting the radiation effect on the identifiable tumor. For these patients, we suggest gamma knife radiosurgery rather than conventional radiotherapy. However, the routine use of gamma knife radiosurgery in the intracranial mature teratoma after incomplete tumor resection may need further supports from larger database of patients and longer follow-up period.

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