

Clinical Article

The role of Gamma Knife radiosurgery in the treatment of pineal parenchymal tumours

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Summary

Object. The aim of this study was to document the possible role of Gamma Knife radiosurgery, suitable for the treatment of deep and well limited tumors, in the management of pineal parenchymal tumors (PPT).

Population and methods. We reviewed retrospectively a series of 13 patients with PPT treated by Gamma Knife radiosurgery during 16 procedures. Mean age was 31 (range 10 to 74). Eight patients had pineocytomas (61.5%), and 5 had pineoblastomas (38.5%). Radiosurgery was performed alone in 6 cases, after partial microsurgical resection in 3 cases, in association with chemotherapy in 3 cases and following conventional fractionated radiotherapy in 1 case. The marginal dose to these tumors ranged from 11 to 20 Gy (mean 15 Gy).

Results. With a mean follow-up of 34 months (range 6 to 88), all tumors responded to treatment and disappeared or ceased growing. Two patients with pineoblastoma had tumor size progression out of the initial target requiring several radiosurgery procedures. At the end of the follow-up period, 10 out of 12 patients were alive. Two patients with pineoblastoma died because of carcinomatous meningitis or tumor size progression. We observed no mortality or major morbidity related to radiosurgery.

Conclusion. This study confirms that radiosurgery can be an effective and safe primary treatment modality for patients with pineocytomas. It should have a role in multimodality therapy which includes microsurgical resection, fractionated radiotherapy and chemotherapy for the management of malignant pineal tumors.

Keywords: Gamma Knife radiosurgery; pineal region tumors; pineal parenchymal tumors; stereotactic biopsy; pineocytoma; pineoblastoma.

Introduction

Pineal region tumours (PRT) are quite rare tumours, accounting for 0.4 to 1% of intracranial tumours in Europe and the United States, but are 10 times more

common in children than in adults [37]. Individual clinical experience of these tumours is thus limited. Therefore, there is still controversy regarding the management of these tumours which is complicated by the diversity of histological subtypes and their anatomical location close to critical vascular and functional structures. Moreover, this wide variety and rarity of PRT complicates the study of their behaviour, treatment and outcome. Treatment recommendations and prognosis seem to be markedly different depending on the histological diagnosis [5] and the importance of obtaining a tissue diagnosis in patients with pineal tumours has been emphasized [24, 28, 34, 35]. It is well known that PRT pose problems for microsurgery because of their deep location. The earlier combined risk of morbidity and mortality associated with open surgical treatment was reported as 30 to 70% [6, 16, 32, 33] which led to empirical fractionated radiation therapy for many pineal tumours, often resulting in inappropriate or unnecessary irradiation of lesions [19, 27, 32]. Although improvement in microsurgical techniques and anaesthesia have significantly reduced the risk of open procedures, excision remains difficult [4, 40]. The efficiency of radiosurgery in the treatment of pineal parenchymal tumours (PPT) is not well known as few studies have been published in the literature. Therefore, we report the results of Gamma Knife radiosurgery in the treatment of 13 patients with PPT in support of a possible role for radiosurgery in the management of PPT.

Table 1. Summary of patients with PPT treated by Gamma Knife radiosurgery

Patient age/sex	Symptom	Hydrocephalus treatment	CSF markers	Diagnosis	Histology	Other treatment
(1) 32/F	no	yes VPS	no	SB	pineoblastoma	chemotherapy
(2) 14/F	ICH	yes: VC	no	surgery	pineocytoma	surgery
(3) 26/M	ICH	yes: VPS	no	SB	pineocytoma	no
(4) 20/F	ICH	yes: VC	no	SB failed CSF(cytology)	pineoblastoma	chemotherapy
(5) 45/M	oculomotor palsy	no	no	surgery	pineoblastoma	radiotherapy chemotherapy surgery
(6) 32/F	ICH	yes: VPS	no	SB	pineoblastoma	chemotherapy
(7) 30/M	ICH	yes: VC	no	SB	pineocytoma	no
(8) 13/M	ICH	yes: VPS	no	surgery	pineocytoma	surgery
(9) 39/M	trigeminal hypoesthesia	yes: VC	no	SB	pineocytoma	no
(10) 17/F	ICH	yes: VC	no	SB	pineocytoma	no
(11) 10/M	ataxia	no	no	surgery	pineoblastoma	surgery
(12) 52/M	ICH	yes: VC	no	SB	pineocytoma	no
(13) 74/F	cognitive disturbance	yes: VPS	no	SB	pineocytoma	no

ICH Intracranial hyperpressure; VPS ventriculo-peritoneal shunt; VC ventriculocisternostomy; na non available.

Population and method

Patient characteristics

During an 8-year period, 13 patients with PPT were treated in the university hospital of Marseille with 16 radiosurgical procedures utilizing the Leksell Gamma Knife. Mean age at the time of radiosurgery was 31 years (range 10 to 74 years). There were 7 males and 6 females. Clinical symptoms are summarized in Table 1 and related in almost all cases to intracranial hyperpressure. One patient presented diplopia, 1 patient presented trigeminal hypo-esthesia, 1 patient suffered from ataxia and 1 had cognitive disturbance. Occlusive hydrocephalus was found in 11 cases (85%). To relieve this, ventriculoperitoneal shunts were implanted in 5 cases and ventriculocisternostomy was performed in 6 cases. Shunting was performed prior to stereotactic biopsy and/or radiosurgery.

Method

PPT evaluation

Magnetic resonance images (MRI) were obtained in all cases and consistently demonstrated the morphology of the tumour and its anatomical relationships.

Levels of alpha fetoprotein (AFP), human chorionic gonadotropin (β HCG) and carcino-embryonic antigen in the serum or CSF were measured in all cases but one.

Diagnosis was achieved by partial microsurgical resection in 4 cases and by stereotactic biopsies in 8 cases. In one case, stereotactic biopsy did not allow diagnosis but cytology of CSF led to the diagnosis of pineoblastoma. No patients who were diagnosed with pineoblastomas had evidence of dissemination before radiosurgery. Pathological data are summarized in Table 2.

Treatment modalities

Gamma Knife radiosurgery was the sole treatment in 6 cases of pineocytoma. Radiosurgery followed partial microsurgical resection in 2 cases of pineocytoma and 1 case of pineoblastoma. It was performed

Table 2. Histological diagnosis of patients with PPT

Pathological diagnosis	No. of patients (male/female)	Age range (yr)	Mean age (yr)
Pineocytoma	8 (5/3)	13–74	33
Pineoblastoma	5 (2/3)	10–45	28

before chemotherapy in 1 case of recurrent pineoblastoma initially treated by surgery and radiotherapy. In 2 cases of pineoblastoma radiosurgery was performed as a sandwich protocol between 2 chemotherapy sessions. The radiosurgical goal was local tumour control in all patients.

The Leksell stereotactic frame type G (Elekta Instrument AB, Stockholm, Sweden) was used in all cases. The images for dose planning were obtained with a 1.5 Tesla MRI. Millimetric volumetric images in transverse and frontal orthogonal planes after gadolinium enhancement were used. CT millimetric axial images were performed. The slice interval was 1 mm. Dose planning was performed with the KULA software (Elekta instrument) until 1997 (8 patients) and since then with the Gamma Plan software (Elekta instrument) (5 patients).

The radiosurgical treatments were performed using the Leksell Gamma Knife model B except in 1 case where the upgraded model C (Elekta instrument AB) was utilized. The marginal dose was chosen mainly as a function of the histological type of PPT and the tumour volume, according to the authors experience and taking account of radiation tolerance of surrounding structures, mainly thalami and tectal plates. The isocenter number, the marginal isodose and the central dose to the tumour are summarized in Tables 3 and 4.

Follow-up

After radiosurgery, clinical and neuroradiological examinations were conducted with a 1-week interval for pineoblastomas and a 6-months interval for the other types of PPT. Later, a current clinical follow-up was performed by means of patient interviews and interviews of the referring physician each year. A radiological follow-up, with MRI, was also regularly performed, to compare the evolution of the PPT size before and after radiosurgery and to screen uneventful parenchymal

Table 3. *Radiosurgical protocol and outcome of patients with pineocytomas*

Patient	Number of shots and collimator size	Peripheral isodose (%)	Central dose (Gy)	Radiosurgical protocol	Follow-up (month)	Tumor size	Outcome
2	1: 18	50	40	comp (after surgery)	lost	?	?
3	1: 18	50	36	Initial	36	PR (90%)	alive
7	2: 14/8	50	32	Initial	48	PR (50%)	alive
8	2: 14/8	50	24	comp (after surgery)	12	PR	alive
9	4: 3 × 14/18	50	28	Initial	36	no change	alive
10	11: 4 × 14/5 × 8/2 × 4	45	26.5	Initial	72	CR	alive
12	6: 14/2 × 8/3 × 4	50	24	Initial	12	PR (70%)	alive
13	7: 14/6 × 4	45	31	Initial	6	no change	alive

CR Complete regression; PR partial regression.

Table 4. *Radiosurgical protocol and outcome of patients with pineoblastomas*

Patient	Number of shots and collimator size	Peripheral isodose (%)	Central dose (Gy)	Radiosurgical protocol	Follow-up (month)	Tumor size	Outcome
1a	2: 14W/8	40	50	comp (after chemotherapy)	88	CR	alive
1b	6: 2 × 8/3 × 4/14	50	28	sandwich (chemotherapy)		CR	
1c	7: 8/5 × 4/18	50	36	alone		PR (90%)	
4	1: 18	50	32	sandwich (chemotherapy)	10	PR (90%)	died
5	3: 14/2 × 8	50	28	comp (after chemotherapy)	38	progression	died
6a	4: 14/2 × 8/4	50	32	Initial	44	CR	alive
6b	10: 14/4 × 8/5 × 4	50	28				
11	12: 18/14/7 × 8/3 × 4	40	35	comp (after surgery)	23	CR brain metastasis	alive

comp Complementary; CR complete regression; PR partial regression.

modifications related to radiosurgery. These data were prospectively collected in a computerized data base. The mean follow-up was 34 months (range from 6 to 88). One foreign patient was lost to follow-up. Follow-up results are summarized in Tables 3 and 4.

Results

Diagnosis

The pathological diagnosis was pineocytoma in 8 cases and pineoblastoma in 5 cases (Table 2).

Markers titration results in serum and CSF were negative in all cases.

Treatment related morbidity and mortality

No patient died or suffered significant neurological morbidity as a result of stereotactic biopsy. One patient presented left hypo-esthesia after stereotactic biopsy by a right orthogonal approach through right thalamus. Indeed, when we ourselves performed stereotactic biopsy of PRT we usually used a frontal double obliquity through a precoronal entry point.

All patients were discharged from the hospital on the day after radiosurgery. There was no treatment-related mortality. Treatment-related morbidity was low, while

only 1 patient (3.8%) presented a new permanent neurological deficit in the form of diplopia after radiosurgery. Three patients presented, after radiosurgery, with a transient diplopia which rapidly resolved under steroid medication.

Treatment results

Survival rate

At the end of the follow-up period, 10 out of 12 patients were alive. Two patients with pineoblastomas died.

Tumour control rate

Local tumour size control was obtained in 11 cases out 12.

Pineocytomas

Six patients with pineocytoma were treated by radiosurgery alone (Table 3). Two patients had a radiosurgical procedure complementary to partial surgical removal. The mean follow-up was 32 months (range from 6 to 72). One foreign patient was lost to follow-up. All patients were alive at the end of the follow-up period.

Concerning tumour size control, 1 patient had a complete regression of tumour size, 4 patients had more than 50% decrease in tumour size, and 2 patients had a stable lesion.

Pineoblastomas

Five patients with pineoblastoma were treated. In all cases but one, radiosurgery was associated with chemotherapy (Table 4). Three were alive 23 (patient 11), 44 (patient 6) and 88 months (patient 1) after the first radiosurgical treatment. Three had complete response, but one of them presented brain metastasis (patient 11). Two of them had delayed tumour size progression out of the initial target requiring respectively two (patient 6) and three radiosurgical protocols (patient 1). Two patients died: one 20 months after radiosurgical treatment because of carcinomatous meningitis, the other 36 months after radiosurgical treatment because of tumour size progression (patient 5). In this case, radiosurgery had been performed for tumour regrowth at the primary site after surgery and local irradiation. Radiosurgery allowed tumour size regression during 36 months (patient 5). In 1 patient with pineoblastoma, shunt infection necessitated removal of the shunt system 7 days after Gamma Knife radiosurgery. For this patient, further alternative treatment of hydrocephalus was not necessary because of tumour size regression.

Discussion

Radiosurgery

Few studies, concerning radiosurgery of PPT, have been reported in the literature over the last ten years [7, 8, 12, 22, 26, 34, 35]. Both the data collected in the literature and that of this series shows that radiosurgery constitutes a safe and effective treatment for PPT. Obviously, the efficiency of radiosurgery and of surgery in PPT is related to the type of tissue. It is generally agreed that PRT types have a wide histological variance with some of the tumours being mixed in nature, containing benign elements as well as malignant ones. Therefore, several authors stressed that histological diagnosis is mandatory for all patients with pineal region tumours to optimally guide clinical management [1, 4, 7, 8, 30, 34, 35]. Histological diagnosis and markers titration in serum and CSF are a main condition prior to radiosurgery. Therefore stereotactic biopsies are advocated as a procedure preliminary to radiosurgery.

However the diagnosis and therapeutic relevance of the stereotactic approach for the management of lesions of the pineal region is debated. In opposition to this approach, it was argued that there is a high risk of haemorrhage [31], that stereotactic biopsies cannot adequately differentiate the heterogeneous composition of pineal tumours, which may lead to misdiagnosis and undertreatment [3] and that the potential advantage of cytoreductive surgical intervention is ignored. Therefore, some authors do not usually use stereotactic procedures to obtain biopsy specimens of PRT and prefer an open procedure for diagnosis and resection [3]. The advantage of reduced tumour burden has been advocated for patients with pineoblastoma. However, given the functional risks, the incidence of radical surgical intervention is extremely low for all infiltrative benign or malignant lesions of this region [4, 15]. Thus it is impossible to estimate the therapeutic benefit of cytoreductive surgical treatment for these infiltrative malignant lesions [25]. Nevertheless radiosurgery is indicated only for 3 cm maximum diameter size tumours. Conversely, several authors documented the risk profile, accuracy of diagnosis, and the therapeutic relevance of the stereotactic approach in many patients presenting PRT [23, 34, 35]. These studies clearly demonstrated that the mortality, morbidity and diagnosis rates for stereotactic biopsies in the pineal region are not different to those reported for other locations of the brain [2, 29, 30, 34]. But in case of failure of the stereotactic approach, histological diagnosis should be obtained by a surgical approach and radiosurgery could be performed in case of postoperative residual tumour. In any case, these considerations illustrate that PRT diagnosis requires a multidisciplinary approach with clinical, radiological, biological and histological features. Stereotactic biopsies and open surgical intervention are often only a starting point for additional multimodality treatment [11, 13, 14, 17, 23, 34].

For Dempsey *et al.* [7, 8], radiosurgery was indicated mainly in cases of pineocytoma and only in cases of residual tumour after microsurgery or fractionated radiation therapy for the other types of PRT. But, recent data [12] such as ours infer that pineoblastomas can initially be treated by radiosurgery in association with chemotherapy or as a boost to initial fractionated radiotherapy. Moreover, radiosurgery is a very safe therapeutic modality for PPT, without mortality and with very low morbidity. In the case of elderly patients, radiosurgery constitutes a safe alternative treatment even for tumours usually treated surgically, such as pineocytomas.

Overall and disease-free survival with regard to histological diagnosis

Pineocytomas

Several authors report lasting tumour control in the case of pineocytomas undergoing focal treatment such as surgery, interstitial radiotherapy, limited field radiotherapy and in one case with simple observation [23]. PPT account for 15 to 30% of PRT [20, 39] and are therefore quite uncommon. Due to the small number of reported cases, their histological, biological and clinical features are still being defined. Although most series separated these tumours into pineocytomas and pineoblastomas, Schild *et al.* described a continuum for the histopathological characteristics of pineocytoma and pineoblastoma [38, 39], classifying PPT into 4 groups: pineocytomas, PPT with intermediate differentiation, mixed pineocytomas-pineoblastomas and pineoblastomas. The 1993 World Health Organization (WHO) recognized pineocytomas, pineoblastomas, and mixed pineocytomas-pineoblastomas exhibiting features of both components. Other authors graded PPT according to morphological and immunohistochemical features into 4 grades of increasing malignancy [21]. Therefore, the pathological variability of these tumours makes it difficult to draw general conclusions about their behaviour [5]. In our series, radiosurgery allowed local tumour size control in all patients with pineocytomas, a size decrease in 70% of these patients and even a complete regression in one case. No patient with grade 1 tumour suffered recurrence in other authors experience, whether or not radiotherapy was initially given [10]. Therefore, in these cases radiotherapy, previously advocated by some authors [39], should be considered with caution. This constitutes an argument for focal treatment as the primary surgical approach or radiosurgery of pineocytomas.

Pineoblastomas and mixed tumours

Pineoblastomas are closely aligned pathologically with cerebellar medulloblastomas and have been described as “medulloblastoma pineales” [36]: Both are classified as PNETs and are highly cellular and mitotically active. They infiltrate and extend into adjacent supratentorial and infratentorial structures by direct contiguity or seeding along the third ventricle. Like other PNETs they tend to metastasize widely throughout the CSF pathways. Spinal deposits are common with pineoblastoma [9, 18, 39], while in paediatric series, 16 to 45% of patients presented with spinal spread (CSF cytology or spinal imaging) at the time of diagnosis [9, 38].

This incidence is 45% in adults [5]. Medulloblastoma patients with negatively staged minimal residual disease are often treated with craniospinal irradiation; adjuvant systemic chemotherapy is reserved for patients with poor-risk factors such as bulky residual or disseminated disease. The therapeutic choices for patients with pineoblastomas are less clear. As their incidence is extremely low (0.1% according to the Japanese Brain Tumour Registry) there is no complete report describing the generally accepted therapeutic approach and the outcome of the disease. Several fundamental issues regarding their therapeutic management in adult patients remain to be investigated such as the prognostic effect of the extent of resection, the radiation dosage to the pineal region and the spine and the role of chemotherapy [25]. As the clinical behaviour of pineoblastomas resembles medulloblastoma in its propensity to spread throughout the neuraxis, and as a gross total resection is often difficult, authors [5] have treated pineoblastomas as poor risk and assessed patients for their ability to undergo craniospinal irradiation followed by adjuvant systemic chemotherapy. For others, given the young age of most of the patients and the risk of delayed radio-induced neuropsychological sequelae, potentially craniospinal radiotherapy was avoided [10]. Nevertheless, it appears that histopathological diagnosis and neuraxis staging remain the major indicators of prognosis [5, 25]. Several authors stressed the prognostic importance of complete staging of the neuraxis for adults with pineoblastoma [6, 11, 24, 25]. A complete staging of the entire neuraxis is obviously mandatory before a focal treatment such as radiosurgery. The site of relapse is closely related to the tumour grade. The risk of local recurrence occurs in grade 2 patients, whereas Grade 3 patients have a significant risk of metastatic spread [10]. It is still unclear in grade 2 patients whether radiotherapy at diagnosis can delay the time of relapse and whether it is beneficial for patients having undergone complete resection [10, 25]. Indeed a recent study highlights the prognostic impact of residual disease for the patient with malignant PPT. On the basis of multivariate analysis, residual disease independently produced overall survival. This variable might help to detect poor-risk patients shortly after the end of therapy [25]. Therefore, radiosurgery should be beneficial for this group of patients, mainly in case of residual disease. In this connection, this report argues the efficiency of the combination of radiosurgery and chemotherapy in the management of pineoblastomas with negatively staged disease. Indeed, radiosurgery allowed local tumour

control in all cases of our series. This tumour control is consistent with results of radiosurgery in patients with pineoblastomas reported by Hasegawa *et al.* [12]. These authors stressed that it is not known whether radiosurgery improved the clinical outcome for patients with this tumour type having regard to patients with leptomeningeal dissemination despite of local tumour control. Therefore aggressive chemotherapy and/or craniospinal irradiation are required to reduce the risk of distant failure, radiosurgery combined with adjuvant therapy to assist in local tumour control.

Conclusion

To distinguish the histological types of pineal parenchymal tumours remains the main aim for rational treatment planning. We feel that stereotactic biopsy is the safest and most efficient way of achieving this [7, 8, 23, 34, 35]. The risk of stereotactic biopsy in the pineal area lies in the upper range of the rate of complications generally reported in larger series after stereotactic biopsy in any location of the brain.

As concerns the results of our series and those of other ones [7, 8, 12], it seems that Gamma Knife radiosurgery may represent a useful therapeutic modality in selected cases of pineal parenchymal tumours as part of a multidisciplinary approach. Our experience with that of others has shown that stereotactic radiosurgery can also serve as the sole means of treating benign tumours that occur in the pineal region as pineocytomas thereby avoiding the risks associated with craniotomy and resection. It can be combined with chemotherapy, and even with fractionated irradiation, to treat more malignant tumours such as pineoblastomas. In these cases, it constitutes a safe and effective adjuvant treatment in association with chemotherapy to avoid delayed deterioration associated with fractionated radiation therapy in the paediatric age group. Nevertheless, extended series with long term follow-up are needed which will determine the role of radiosurgery in the treatment of PPT.

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Comments

Reines *et al.* here present their experience with 13 patients from 2 centres during an 8 year period with pineal parenchymal tumours treated with radiosurgery. They conclude that radiosurgery can be effective and a safe primary treatment for patients with pineocytomas. In the case of pineoblastomas the role is not so clearly defined. Whereas the pineocytoma is a tumour of the 3rd decade, rather circumscribed and non infiltrative the pineoblastoma is a tumour of the 1st decade, ill defined, infiltrative with usually dismal prognosis. In their series the pineoblastomas are not exclusively child age tumours, i.e. there might be some intermediate tumour in between. The authors correctly emphasize that a histological diagnosis as a primary step is mandatory. The experience correlates well with our experience with interstitial implants in pineocytomas [1]. Adults with malignant pineal parenchymal tumours have a far less favourable prognosis. Radiation therapy alone can yield cure in a substantial number of patients, late relapses are common whatever procedure is used.

This is a valuable contribution from an experienced group.

Reference

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The authors present their results with radiosurgery for a well-defined subset of pineal region tumours, pineocytomas and pineoblastomas. They demonstrate excellent tumour control for the benign variety but losing some of the malignant cases to dissemination.

In this article the authors present a convincing case to avoid open surgery if histology is obtained by stereotactic biopsy. Although heterogeneity may result in failures, this was not borne out from their results. I would agree with their recommended line of management. We have been following the same and obtained very similar results: pineocytomas, as a rule, are controlled by radiosurgery.

It was interesting to read that they have also treated patients where the diagnosis was made indirectly, through CSF examination. This is obviously controversial. The problem arises when this test is negative.

We also agree on the need for systemic treatment for pinealoblastomas.

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