Pineal Tumors

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29.1 Introduction

Pineal region tumors are rare, accounting for 2.6–3.2% of primary brain tumors in children and adolescents, or 0.4–1.2% overall and in young adults [1]. These tumors represent a heterogeneous group of diverse histological entities, which originate from different cell types that form the pineal gland. Pinealocytes, arranged in lobules to form the pineal parenchyma, contribute about 95% of cells of the pineal gland, with the remainders mainly consisting of interstitial cells such as astrocytes and microglia which are embedded in a network of blood vessels and nerve fibers [2].

The pineal gland contains nerve endings from sympathetic nervous innervation to the pinealocytes [3]. The ependymal cells of the third ventricle adjoin the gland along its anterior border [4]. Tumors in the pineal region arise from these histological origins. Meanwhile, germ cell tumors (GCTs) are the most common type of pineal region tumors, which arise from pluripotent germ cells usually not inhabiting the pineal gland.

Theoretically, these germ cells mistakenly migrate to the pineal gland during embryogenesis and fail to undergo apoptosis [5]. GCTs account for more than 50% of tumors in this region [6, 7]. Pineal parenchymal tumors (PPTs) are the next most common entity, which are classified into pineocytomas, that are pineal parenchymal tumors of intermediate differentiation (PPTIDs) and pineoblastomas based on their cell maturity and aggressiveness in behavior. A newer entity named papillary tumors of the pineal region (PTPRs), which presumably originate from specialized ependymocytes of the sub-commissural organ located in the lining of the posterior commissure, has been included in the World Health Organization (WHO) classification of tumors of the central nervous system (CNS) in 2007 [8, 9]. Based on the review of the French Register of primary CNS tumors with 25,756 cases [10], pineal region tumors consist of 27% GCTs, 27% PPTs, 17% gliomas, 8% PTPRs, 7% pineal cysts, and 1% primitive neuroectodermal tumors. PPTs are represented by 13% pineocytomas, 66% PPTIDs, and 21% pineoblastomas.

Practically, tumors arising in the pineal gland region can be classified into five main categories: GCTs, PPTs, PTPRs, glial tumors, and other miscellaneous tumors such as meningioma, choroid plexus papilloma, and lymphoma [4].

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A. Conti et al. (eds.), *CyberKnife NeuroRadiosurgery*,
https://doi.org/10.1007/978-3-030-50668-1_29

Given their heterogeneity, appropriate management for pineal region tumors can be complex. The procedure of obtaining tumor tissue for diagnosis is crucial because of varied biological behaviors according to different histological entities, as well as the lack of diagnostic specificity of imaging alone [4, 7].

Biopsy in any form of stereotactic, endoscopic, or craniotomy should be an initial step for optimal management of tumors in this region. Following histological verification, specific therapy including surgical resection, radiation therapy (RT), and chemotherapy is administered.

In the recent era, stereotactic radiosurgery (SRS) has emerged as a useful or added alternative to surgery or fractionated RT in a variety of intracranial tumors. Here, we have critically reviewed current knowledge on the use of SRS in the treatment of pineal region tumors.

Table 29.1 The 2016 WHO classification of tumors of the pineal region and germ cell tumors [35]

Tumor class	Grade	ICD-O code
Tumors of the pineal region		
Pineocytoma	I	9361/1
Pineal parenchymal tumor of intermediate differentiation	II or III	9362/3
Papillary tumor of the pineal region	II or III	9395/3
Pineoblastoma	IV	9362/3
Germ cell tumors		
Germinoma		9064/3
Embryonal carcinoma		9070/3
Yolk sac tumor		9071/3
Choriocarcinoma		9100/3
Teratoma		9080/1
Mature teratoma		9080/0
Immature teratoma		9080/3
Teratoma with malignant transformation		9084/3
Mixed germ cell tumor		9085/3

WHO World Health Organization, *ICD-O* The International Classification of Diseases for Oncology

29.2 Germ Cell Tumors

GCTs are the most frequently encountered tumor type in the pineal region and comprise germinomas and non-germinomatous germ cell tumors (NGGCTs). NGGCTs include choriocarcinomas, endodermal sinus tumors, embryonal carcinomas, teratomas, and mixed tumors (Table 29.1). GCTs, both germinomas and NGGCTs, are sensitive to radiation and chemotherapy. Therefore, the role of surgical resection beyond diagnostic biopsy is controversial except in case of teratomas.

Owing to the high sensitivity to radiation, all germinoma patients were treated with craniospinal irradiation (CSI) alone until the early 1990s, which yielded a cure rate of over 90% [11, 12]. However, to reduce long-term toxicities such as neurocognitive insufficiency and endocrinopathy, combined treatment with primary chemotherapy and RT was used.

Since then, multicenter or international trials, such as the French SFOP (Société Française d'Oncologie Pédiatrique/French Pediatric Oncology Society) in 1990 [13], the Japanese Pediatric Brain Tumor Study Group trial in 1995 [14], the European SIOP (International Society of Paediatric Oncology) study in 1996 [15], and the North American COG (Children's Oncology Group) ACNS 0232/1123 [16], were conducted. Based on these trials, radiation dose and volume were reduced. Moreover, CSI is no longer prescribed for the treatment of localized germinoma, and thus the whole ventricular system provides the reference for RT target volume [16].

Currently, the European SIOP GCT CNS II protocol (NCT01424839) states that patients with localized germinoma are primarily treated with chemotherapy (two cycles of carboplatin and etoposide alternating with two cycles of ifosfamide and etoposide). And then, if there is a complete response at reassessment, whole ventricular irradiation (WVI) alone (24 Gy in 15 fractions) is added. If there is a partial response, WVI plus focal boost (16 Gy in 10 fractions) is administered. Or, if there is a stable disease, surgery followed by RT is recommended. As per the current ACNS 1123 protocol (NCT01602666), germinoma patients who present with a complete response after chemotherapy (four cycles of carboplatin and etoposide) receive WVI (18 Gy) and a boost to the primary tumor (12 Gy). In patients

with a partial response with residual tumor less than 1.5 cm, WVI (24 Gy) followed by a focal boost (12 Gy) is added without second-look surgery. According to the Japanese protocol [14], patients in the good prognosis group should be treated with 3 cycles of chemotherapy (carboplatin 450 mg/m^2 on day 1 and etoposide 150 mg/m^2 on day 1–3), followed by 23.4 Gy WVI. The response-based adjuvant chemotherapy (3 cycles of ICE, viz., ifosfamide 900 mg/m^2, cisplatin 20 mg/m^2 and etoposide 60 mg/m^2 on day 1–5) can be used for non-complete response patient group. Patients in the intermediate group should be treated with 3 cycles of chemotherapy (carboplatin 450 mg/m^2 on day 1 and etoposide 150 mg/m^2 on day 1–3), followed by 50.4 Gy WVI. In case of disseminated germinomas, patients are treated with the localized germinoma protocol, along with CSI and/or local boost RT.

NGGCTs are less radiosensitive than germinomas, and RT-alone treatment has provided both 5- and 10-year survival rates of 36% [17], whereas chemotherapy-alone treatment conferred poor outcome in these patients [18, 19]. Hence, NGGCTs are treated in combination with surgical resection, chemotherapy, and RT to obtain the best outcome. Especially for management of teratomas or tumors harboring teratoma components, surgery is preferred because of the resistant nature of these tumors to RT and chemotherapy [20]. In short, except for teratomas, localized NGGCTs are managed by multimodality therapy with chemotherapy followed by local RT [16].

The outcomes of management for GCTs varies across histological subtypes, where 10 year overall survival (OS) for germinomas is more than 90% [21–23], but that for NGGCTs remains 60–80% [23–25]. Considering the outcomes obtained from current management strategy, SRS would be the best option for treatment of resistant or recurrent tumors. Accordingly, most of the previous studies reported the utility of SRS as an adjuvant or salvage therapy rather than primary modality (Table 29.2) [26–34]. Better outcomes have been obtained in germinoma subtype as well as in the case of residual or recurrent tumors. In eight patients with germinomas, Kobayashi et al. observed 100% tumor control during 26-month follow-up, where patients were treated with conventional chemotherapy and fractionated RT followed by adjuvant SRS therapy [26]. In a study by Mori et al., 16 patients with germinoma who underwent SRS as a part of their management [30] showed local control in 82% of cases and progression-free survival (PFS) in 63% of cases, both at 5 years. Recently, Iorio-Morin et al. reported that 80% local control was obtained at 20 years for four patients with germinoma treated with SRS as an adjuvant boost following initial fractionated RT, but one patient with recurrence could not survive the disease [34].

Collectively, SRS can be considered a safe and effective adjuvant treatment for germinomas.

However, studies on NGGCTs suggest a relatively poor outcome compared with germinomas. Kobayashi et al. reported that in 13 patients with malignant GCTs, 50% local tumor control was obtained during 21-month mean follow-up, where patients were treated with SRS as an adjuvant therapy after the conventional treatment [26]. Hasegawa et al. observed 75% local control during 25-month mean follow-up in four patients with NGGCT, with death of one patient due to disease progression [27]. In the study by Mori et al. [30], 22 patients with NGGCT showed 5-year local control of 62% and 5-year PFS of 37%. In short, despite relatively poor outcomes in NGGCTs, SRS may offer a reasonable option in adjuvant or salvage settings, considering the aggressive nature of these tumors.

29.3 Pineal Parenchymal Tumors

The WHO classification in 2016 has categorized PPTs into three subtypes with up to four different grade categories: pineocytomas (grade I), PPTIDs (grade II or III), and pineoblastomas (grade IV) (Table 29.1) [35]. This classification was not changed from the 2007 WHO classification. Management and prognosis of patients are highly dependent on histological subtype and grade.

Pineocytomas are slowly growing tumors with favorable prognosis with 5-year survival of 64–91% [36]. Tumors cause symptoms by local

Table 29.2 Stereotactic radiosurgery for germ cell tumors

Author	Year	No. of cases treated with SRS (FU cases)	Median age in years (range)	Histology	SRS modality	Mean tumor vol. in cm^3 (range)	Median marginal dose in Gy (range)	Median maximal dose in Gy (range)	FU duration (mo)	Local tumor control (%)	Survival outcome	Complication
Kobayashi et al. [26]	2001	8 (7)	17 (13–22)	Germinoma	GK	ND	16.8	34.5	26.7 (10–36)	LTC 100% (CR2, PR5)	No death	ND
Kobayashi et al. [26]	2001	4 (3)	23.3 (16–41)	G + STGC	GK	ND	13.5	30.0	11 (10–12)	LTC 67% (PR2, PD1)	1 Death during FU	ND
Kobayashi et al. [26]	2001	13 (12)	24.8 (12–66)	Malignant GCT	GK	ND	15.7	30.8	21.4 (6–81)	LTC 50% (CR3, PR3, PD6)	5 Death during FU	ND
Hasegawa et al. [27]	2003	4	16.5 (9–21)	NGGCT	GK	10.5 (2.2–23.4)	14 (12–16)	28 (24–32)	25 (4–58)	LTC 75% (CR1, PR1, SD1, PD1)	1 Death during FU	None
Amendola et al. [28]	2005	13	21.8 (8–65)	GCT	GK	15.8 (0.52–52.1)	11.2 (8–13)		ND	ND	2 Death during FU	None
Amendola et al. [28]	2005	1	5	Teratoma	GK	0.1	10		ND	ND	No death	None
Lekovic et al. [29]	2007	1	13	NGGCT	GK	1.2	15	30	73	LTC 100% (CR1)	No death	None
Lekovic et al. [29]	2007	1	18	Malignant teratoma	GK	2.1	13	26	15	LTC 100% (PR1)	No death	None
Mori et al. [30]	2009	16	21 (8–66)	Germinoma	GK	3.3 (0.1–22)	15.5 (9.9–25.7)	27.4 (14.5–40)	49 (3–192)	LTC (3 yr) 82%, LTC (5 yr) 82%	PFS (3 yr) 79%, PFS (5 yr) 63%	ND

Mori et al. [30]	2009	22	21 (8–66)	NGGCT	GK	3.3 (0.1–22)	15.5 (9.9–25.7)	27.4 (14.5–40)	49 (3–192)	LTC (3 yr) 72%, LTC (5 yr) 62%)	PFS (3 yr) 43%, PFS (5 yr) 37%	ND
Yianni et al. [31]	2012	2	ND	Teratoma	GK	ND	15	ND	62.5 (6–240)	LTC 100%	PFS (1 yr) 100%	ND
Li et al. [33]	2015	40	14.4 (6–20)	GCT	GK	ND	ND	ND	ND	LTC (1 yr) 96.7%, LTC (3 yr) 88%, LTC (5 yr) 77.27%	No death	ND
Balossier A et al. [32]	2015	1	7	NGGCT	GK	1.9	18	ND	10	PD	No death	None
Balossier A et al. [32]	2015	1	18	Teratoma	GK	1.3	17	ND	ND	ND	No death	None
Iorio-Morin C et al. [34]	2017	5	36 (3.5–83)	Germinoma	GK	1.5 (1.3–9.8)	14 (13–18)	28 (26–36)	47 (4.6–260)	LTC (1 yr) 80%, LTC (3 yr) 80%, LTC (20 yr) 80%	OS (1 yr) 100%, OS (3 yr) 80%, OS (20 yr) 80%	ND
Iorio-Morin C et al. [34]	2017	1	9	NGGCT	GK	9.68	16	32	4	PD	1 Death during FU	ND
Iorio-Morin C et al. [34]	2017	2	36 (3.5–83)	Teratoma	GK	16.4 (9.3–23.4)	13 (12–14)	26 (24–28)	105.5 (58–153)	LTC (3 yr) 100%, LTC (5 yr) 50%	PFS (5 yr) 50%, OS (5 yr) 100%	ND

No Number, *SRS* Stereotactic radiosurgery, *FU* Follow-up, *Gy* Gray, *mo* Month, *GK* Gamma Knife radiosurgery, *ND* Data was not determined, *LTC* Local tumor control, *CR* Complete response, *PR* Partial response, *G + STGC* Germinoma with syncytiotrophoblastic giant cells, *PD* Progressive disease, *GCT* Germ cell tumors, *NGGCT* Non-germinomatous germ cell tumors, *SD* Stable disease, *yr* Year, *PFS* Progression-free survival, *OS* Overall survival

compression. Although complete surgical resection can be considered in a curative intention, the risk of operation-related complications is not negligible. Hence, SRS can be adopted either as primary or adjuvant treatment for residual or recurrent tumors (Table 29.3) [26, 27, 29–32, 34, 37–41]. In a retrospective study by Hasegawa et al., tumor control was observed during 69-month follow-up in all ten patients who underwent SRS as primary or adjuvant treatment for pineocytomas, except for one patient who succumbed to secondary leptomeningeal tumor spread [27]. Reyns et al. reported that of eight patients with pineocytoma, one showed complete and four showed partial regression, and two showed stable disease, following primary or adjuvant SRS treatment [38]. Tumor control was achieved in all patients without death during the mean follow-up of 32 months. Kano et al. also reported 100% tumor control in 13 patients, with complete tumor regression in 3, partial regression in 8, and stable status in 2 [39]. In addition, 5-year overall survival rate was 92.3%. In our own experience, all three patients showed sustained tumor control (one complete and two partial regression) during 99-month follow-up after SRS treatment (Fig. 29.1) [41]. Collectively, available data in the literature uniformly support high tumor control and patient survival rates, both up to 100% following SRS, indicating the role of SRS as an effective alternative or adjunct to surgical resection for management of pineocytomas.

PPTIDs share some features with both pineocytomas and pineoblastomas. Five-year survival rates for grade II and III tumors are estimated at 74% and 39%, respectively [32]. Pineoblastomas are considered malignant tumors with mean survival of around 2 years [42] and have a high rate of recurrence and metastasis. PPTIDs have histological features associated with an increased risk of recurrence and are commonly managed with surgical resection. However, the role of fractionated RT or SRS is not clearly elucidated to date. Most studies in the literature (Table 29.4) [31, 32, 34, 39, 41] did not opt for histological stratification, and the results for PPTIDs were pooled with those of pineoblastomas or pineocytomas, complicating a sound interpretation of the data. One recent study by Iorio-Morin et al. showed that patients with PPTID received SRS upfront or at recurrence and represented 5-year tumor control and survival rates of 50% and 56%, respectively [34]. In our own series of five patients with biopsy-confirmed PPTID, 100% local tumor control (two complete and three partial responses) and 100% survival were observed during 103-month follow-up following SRS (Fig. 29.2). With limited data available currently, the therapeutic role of SRS in PPTIDs needs to be further investigated, despite some promising outcomes in select cases.

Malignant pineoblastomas are managed with maximal surgical resection followed by fractionated RT and chemotherapy. SRS is usually reserved for treatment of recurrent tumors or as a local boost after primary therapy (Table 29.4) [31, 34, 39]. Reyns et al. reported 75% local control with complete or partial regression in three patients, although two patients succumbed to disease progression and death during 40-month follow-up [38]. Iorio-Morin et al. reported worse outcomes of 5-year tumor control and survival rates of 27% and 48%, respectively, where SRS was applied as a local boost or salvage. The utility of SRS appears to be limited in pineoblastomas, and it is usually indicated for recurrent tumors.

29.4 Papillary Tumors of the Pineal Region

The WHO introduced PTPRs, a rare grade II–III pineal lesion with specific histological and immunohistochemical features as a newer entity in 2007 [43]. These tumors present an immunohistochemical profile similar to that of choroid plexus tumors [43, 44].

However, they are morphologically less differentiated than choroid plexus papillomas and more differentiated than choroid plexus carcinomas. As a result, earlier PTPRs were frequently misdiagnosed as either ependymomas or choroid plexus tumors [45].

Table 29.3 Stereotactic radiosurgery for pineal parenchymal tumors (pineocytoma)

Author	Year	No. of cases treated with SRS (FU cases)	Median age in years (range)	Histology	SRS modality	Mean tumor vol. in cm^3 (range)	Median marginal dose in Gy (range)	Median maximal dose in Gy (range)	FU duration (mo)	Local tumor control (%)	Survival outcome	Complication
Kobayashi et al. [26]	2001	3	34.3 (11–69)	Pineocytoma	GK	ND	16.6	ND	21.7 (12–38)	LTC 100% (CR2, PR1)	No death	ND
Hasegawa et al. [27]	2003	10	38.3 (8–68)	Pineocytoma	GK	5.0 (0.9–14.2)	15.7 (12–20)	31.4 (24–40)	69.1 (14–108)	LTC 100% (CR2, PR7, SD1)	1 Death during FU	1 temporally upward gaze palsy
Deshmukh et al. [37]	2004	5	45 (24–63)	Pineocytoma	GK	6.4 (1.9–9.6)	14.8 (14–16)	ND	14.6 (6–31)	LTC 100% (PR5)	No death	None
Amendola et al. [28]	2005	1	37	Pineocytoma	GK	8.1	11	ND	ND	ND	No death	None
Reyns et al. [38]	2006	8 (7)	35.9 (13–74)	Pineocytoma	GK	ND	ND	28.8 (24–36)	32 (6–72)	LTC 100% (CR1, PR4, SD2)	No death	None
Lekovic et al. [29]	2007	8	49 (24–70)	Pineocytoma	GK	6.0 (1.9–12.4)	14.4 (13–16)	28.8 (26–32)	17 (1–57)	LTC 100% (PR4, SD4)	1 Death during FU	None
Mori et al. [30]	2009	5	21 (8–66)	Pineocytoma	GK	3.7 (0.3–23)	16.7 (12.5–20.3)	27.9 (17–40)	49 (3–192)	LTC (3 yr) 85%, LTC (5 yr) 85%	PFS (3 yr) 80%, PFS (5 yr) 80%	ND
Kano et al. [39]	2009	13	34 (3.5–68.4)	Pineocytoma	GK	4.4 (0.9–14.2)	15.2 (12–20)	30.4 (24–40)	51.6	LTC 100% (CR3, PR8, SD2)	OS (1 yr) 100%, OS (3 yr) 92.3%, OS (5 yr) 92.3%	4 ARE (1 ptosis, 2 upward gaze palsy, 1 asymptomatic edema)
Yianni et al. [31]	2012	6	ND	Pineocytoma	GK	3.8	20	ND	62.5 (6–240)	LTC 83% (PD1)	2 Deaths during FU, PFS (1 yr) 81%, PFS (5 yr) 77%	ND

Table 29.3 (continued)

Author	Year	No. of cases treated with SRS (FU cases)	Median age in years (range)	Histology	SRS modality	Mean tumor vol. in cm^3 (range)	Median marginal dose in Gy (range)	Median maximal dose in Gy (range)	FU duration (mo)	Local tumor control (%)	Survival outcome	Complication
Author	Year	No. of cases treated with SRS (FU cases)	Median age in years (range)	Histology	SRS modality	Mean tumor vol. in cm^3 (range)	Median marginal dose in Gy (range)	Median maximal dose in Gy (range)	FU duration (mo)	Local tumor control (%)	Survival outcome	Complication
Wilson et al. [40]	2012	5	43.6 (24–57)	Pineocytoma	GK	2.6 (1.9–9.7)	14.6 (14–16)	29.2 (28–32)	64.8	LTC 100% (CR2, PR1 SD2)	No death	None
Park et al. [41]	2015	3 (GK:1, CK:2)	49 (44–53)	Pineocytoma	GK/CK	8.2 (3.6–13.4)	GK:12/ CK:36	ND	99 (32–223)	LTC 100% (CR1, PR2)	No death	1 Temporary memory impairment
Balossier A et al. [32]	2015	3	61 (57–64)	Pineocytoma	GK	4.3 (1.8–8.7)	15 (12–17)	30 (24–34)	42 (15–72)	LTC 100% (CR1, PR1, SD1)	No death	None
Iorio-Morin et al. [34]	2017	26	36 (3.5–83)	Pineocytoma	GK	3.3 (0.89–14.2)	16 (12–20)	32 (21–50)	47 (4.6–260)	LTC (1 yr) 100%, LTC (3 yr), 100%, LTC (20 yr) 80%	OS (1 yr) 100%, OS (20 yr) 80%	ND

No Number, SRS Stereotactic radiosurgery, *FU* Follow-up, *Gy* Gray, *mo* Month, *GK* Gamma Knife radiosurgery, *ND* Data was not determined, *LTC* Local tumor control, *CR* Complete response, *PR* Partial response, *SD* Stable disease, *yr* Year, *PFS* Progression-free survival, *OS* Overall survival, *PD* Progressive disease, *CK* CyberKnife radiosurgery

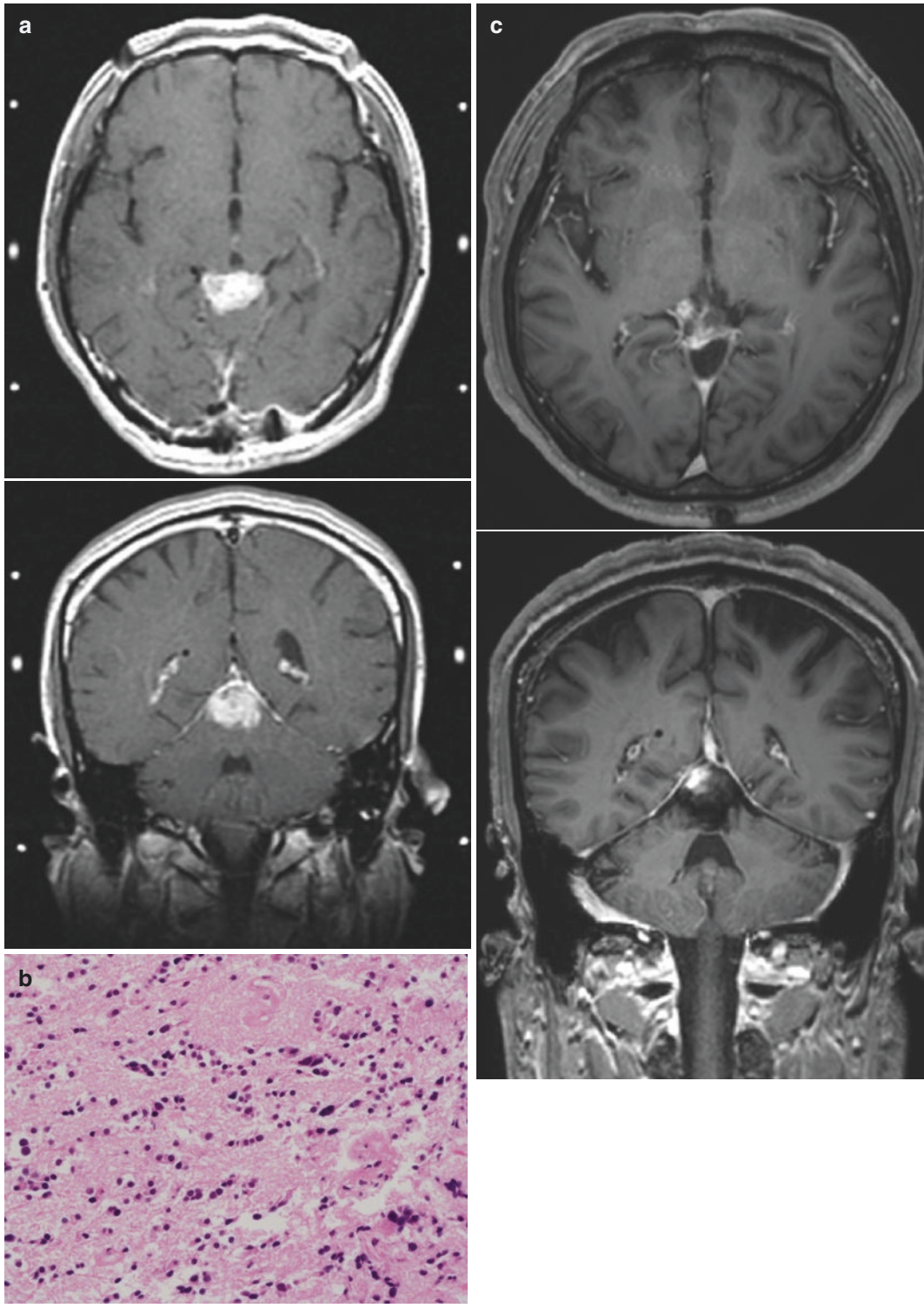

Fig. 29.1 A 44-year-old man with a pineocytoma. Gadolinium-enhanced magnetic resonance images at the time of Gamma Knife (GK) treatment (**a**). Tumor consists of relatively small, uniform, mature cells resembling normal pineocytes, and cell-free spaces filled with cell processes are forming vague rosettes (**b**). After GK treatment with marginal dose of 12 Gy, he achieved durable tumor response with more than 18 years of follow-up (**c**)

Table 29.4 Stereotactic radiosurgery for pineal parenchymal tumors of intermediate differentiation (PPTIDs) and pineoblastoma

Author	Year	No. of cases treated with SRS (FU cases)	Median age in years (range)	Histology	SRS modality	Mean tumor vol. in cm^3 (range)	Median marginal dose in Gy (range)	Median maximal dose in Gy (range)	FU duration (mo)	Local tumor control (%)	Survival outcome	Complication
Kobayashi et al. [26]	2001	3	22.5 (3–42)	Pineoblastoma	GK	ND	16.6	ND	21.7 (12–38)	LTC 100% (CR2, PR1)	No death	ND
Hasegawa et al. [27]	2003	6	34.8 (3–66)	2PPTID + 4Pineoblastoma	GK	5.0 (0.9–14.2)	14.5 (13–16)	29 (26–32)	23 (7–47)	LTC 100% (CR2, PR1, SD1, 2 cases of no image)	4 Death during FU	1 upward And downward gaze palsies and ataxia
Reyns et al. [38]	2006	5 (8 lesions)	28 (10–45)	Pineoblastoma	GK	ND	ND	33.6 (28–50)	40.6 (10–88)	LTC 75% (CR4 PR2, PD2)	2 Death during FU	None
Lekovic et al. [29]	2007	1	22	Pineoblastoma	GK	23	14	28	45	SD1	No death	None
Mori et al. [30]	2009	3	21 (8–66)	1PPTID + 2Pineoblastoma	GK	3.7 (0.3–23)	16.7 (12.5–20.3)	27.9 (17–40)	49 (3–192)	LTC (2 yr) 30%	PFS (2 yr) 33%	ND
Kano et al. [39]	2009	7	34 (3.5–68.4)	2 Mixed PPTs + 5pineoblastoma	GK	4.4 (0.9–14.2)	15.2 (12–20)	30.4 (24–40)	54.1	LTC 66.7% (CR2, PR1, NC1, PD2, f/u loss 1)	4 Death during FU, PFS (1 yr) 100% PFS (3 yr) 66.7%	None
Yianni et al. [31]	2012	5	ND	3PPTID + 2Pineoblastoma	GK	ND	20	ND	62.5 (6–240)	LTC 80% (PD1)	1 Death during FU, PFS (1 yr) 81%, PFS (5 yr) 77%	ND
Park et al. [41]	2015	5 (GK2, CK3)	37.4 (31–50)	PPTID	GK/CK	7.18 (3.8–11.9)	GK14 (12–16) /CK30	ND	77.6 (14–213)	LTC 100% (CR2, PR3)	No death	None
Balossier A et al. [32]	2015	6	59.3 (45–73)	PPTID	GK	3.1 (1.16–5.2)	15.5 (14–18)	31 (28–36)	24.2 (5–76)	LTC 100% (SD5, f/u loss 1)	No death	None
Iorio-Morin et al. [34]	2017	20	36 (3.5–83)	7PPTID + 13Pineoblastoma	GK	PPTID 2.6 (0.61–38.3) /PB 3.3 (0.78–10.5	PPTID 17 (10–20) /PB 15 (12–18)	PPTID 34 (20–40) /PB 30 (21.54–36)	47 (4.6–260)	PPTID LTC (5 yr) 50% /PB LTC (5 yr) 27%	PPTID OS (5 yr) 56% /PB OS (5 yr) 48%	ND

No Number, *SRS* Stereotactic radiosurgery, *FU* Follow-up, *Gy* Gray, *mo* Month, *GK* Gamma Knife radiosurgery, *ND* Data was not determined, *LTC* Local tumor control, *CR* Complete response, *PR* Partial response, *PPTID* Pineal parenchymal tumors of intermediate differentiation, *SD* Stable disease, *PD* Progressive disease, *yr* Year, *PFS* Progression-free survival, *PPTs* Pineal parenchymal tumors, *CK* CyberKnife radiosurgery, *PB* Pineoblastoma, *OS* Overall survival

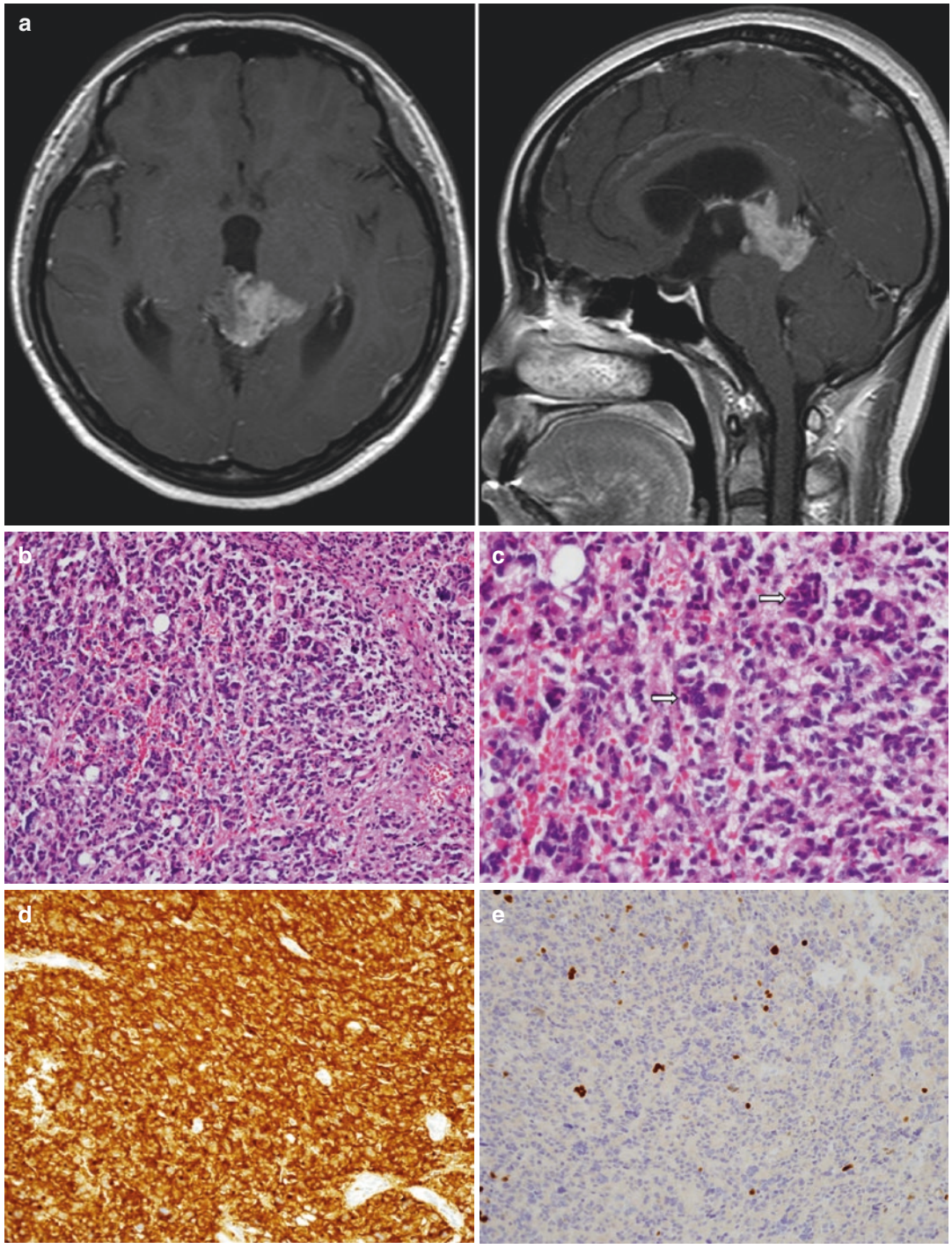

Fig. 29.2 A 34-year-old woman with pineal parenchymal tumor of intermediate differentiation. Gadolinium-enhanced magnetic resonance images showing a 3.2 × 2.4 × 2.0 cm sized tumor in the pineal region with obstructive hydrocephalus (**a**). Tumor shows diffusely high cellularity and tumor cell nuclei are pleomorphic (**b**). Multinucleated giant tumor cells are frequently seen (**c**, arrows). Tumor cells are diffusely immunoreactive for synaptophysin (**d**). Proliferation activity assessed by MIB-1 is low (**e**). She received 5-fraction CyberKnife (CK) treatment with marginal dose of 30 Gy (**f**). Tumor completely disappeared in 9 months after CK, and no evidence of disease was seen at the last follow-up of 5 years (**g**)

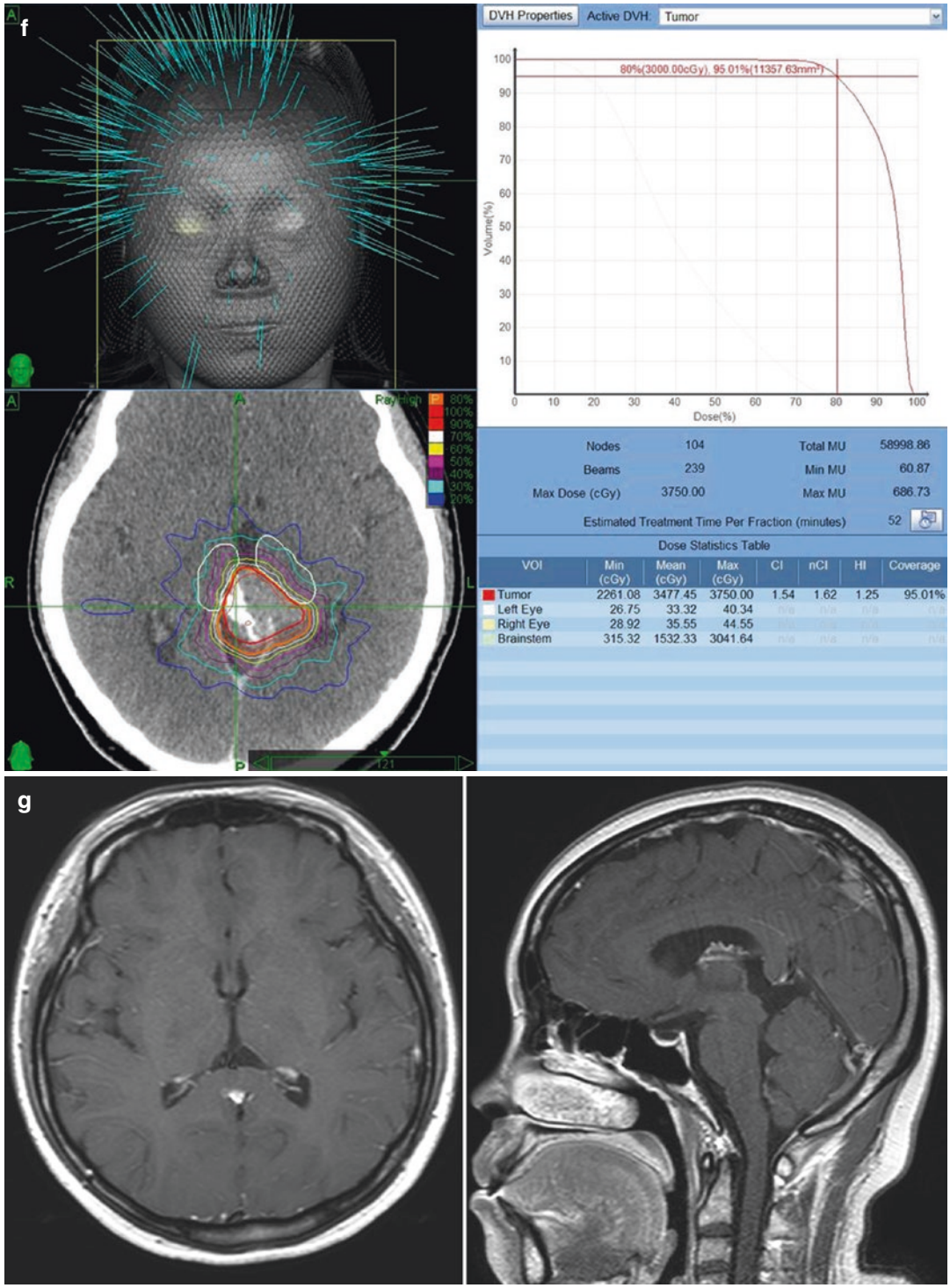

Fig. 29.2 (continued)

Optimal management remains debatable, and upfront RT or chemotherapy have not led to reduction in the risk of recurrence [46].

Focusing on the high potential for local recurrence [47], several groups are investigating the role of SRS in the treatment of PTPRs (Table 29.5) [32, 34, 46, 48–50]. In a retrospective study by Fauchon et al., out of 43 patients with PTPR, only 2 patients opted for SRS following partial resection, but both showed tumor recurrence and 1 succumbed to death [46].

Iorio-Morin et al. reported that five patients with histologically confirmed PTPR opted for SRS as an initial management and another one patient was treated for recurrence after gross total resection (GTR). Among them, five patients experienced local recurrence yielding 5-year tumor control and survival rates of 33% and 100%, respectively. All patients with recurrent tumors underwent repeat SRS and prolonged local control was achieved in four patients [34]. Fernandez-Mateos et al. reported that treatment of two patients with PTPR using SRS following biopsy showed excellent outcomes without recurrence during 15-year follow-up [50]. SRS therefore appears to be a viable option as primary or adjuvant treatment for residual or recurrent PTPRs.

29.5 Pineal Glioma and Miscellaneous Tumors

Pineal region gliomas arise either from the pineal region itself or from the adjacent structures such as the thalamus or the midbrain. Various glial histologies including pilocytic astrocytomas, fibrillary astrocytomas, anaplastic astrocytomas, glioblastomas, oligodendrogliomas, and ependymomas have been reported [4].

In general, maximal safe resection is applied for the management of pineal gliomas. But, the success rate to achieve GTR varies from 21 to 88% depending on the surgeon's skill and experience [51]. Adjuvant RT and chemotherapy are used for treatment of malignant gliomas based on the histology. Although scarce data are available (Table 29.6) [28, 29, 31], SRS appears to be useful for local tumor control with less radiation toxicity than conventional RT. However, detailed analyses on more clinical data are needed to define the role of SRS in the treatment of pineal gliomas.

Various other tumor types such as meningiomas, choroid plexus papillomas, and metastatic tumors may arise in the pineal region. Although the number of cases are limited, these tumors have been treated using SRS, representing similarly fair outcomes (Table 29.6) [29, 31].

In certain clinical situations, obtaining patient tumor tissue is not possible due to various reasons such as patient comorbidities, refusal for surgery, or limited available tissue despite surgery. Li et al. reported a large cohort consisting of 147 patients who underwent SRS for pineal lesions based on imaging and clinical diagnosis alone [33]. They observed regression of the initial tumor in 69% of the cases, with local control rates of 97%, 94%, and 91% after 1, 3, and 5 years, respectively, following SRS. In addition, patient survival rates were 80%, 72%, and 67% after 1, 3, and 5 years of follow-up respectively. Iorio-Morin et al. opted for SRS in 10 patients based on imaging diagnosis without histological confirmation and obtained 5-year tumor control and survival rates of 61% and 67%, respectively, which were similar to the aggregate results of their entire series [34].

These observations support the utility of SRS in selected patients even in the absence of histopathological confirmation [26, 30, 31, 33, 34].

29.6 The Role of SRS for Pineal Region Tumors

Given the limited number of reports, it is difficult to draw a clear conclusion on the utility of SRS for the treatment of pineal region tumors. The authors had to combine various histological subgroups of tumors due to insufficient cohort size, complicating the analyses on tumor control and survival outcomes. Recently, Iorio-Morin et al. tried to overcome this hurdle by performing histology-stratified analyses to provide better quality data to guide patient management.

Table 29.5 Stereotactic radiosurgery for papillary tumors of the pineal region (PTPR)

Author	Year	No. of cases treated with SRS (FU cases)	Median age in years (range)	Histology	SRS modality	Mean tumor vol. in cm^3 (range)	Median marginal dose in Gy (range)	Median maximal dose in Gy (range)	FU duration (mo)	Local tumor control (%)	Survival outcome	Complication
Fauchon et al. [46]	2013	2	52.5 (52–53)	PTPR	GK	ND	12	ND	63.5 (36–91)	ND	No death	None
Riis et al. [48]	2013	1	20	PTPR	GK	12.3	12	24	50	LTC 100% (PR1)	No death	None
Shakir et al. [49]	2015	1	31	PTPR	GK	4.2	18	36	9 yr	LTC 100% (PR1)	No death	None
Balossier et al. [32]	2015	1	27	PTPR	GK	1.1	15	30	6	LTC 100% (SD1)	No death	None
Iorio-Morin et al. [34]	2017	6	36 (3.5–83)	PTPR	GK	2.2 (0.42–4.97)	16 (14–18)	32 (26.67–36)	47 (4.6–260)	LTC 16% (5PD) LTC (5 yr) 33%	No death	ND
Fernandez-Mateos et al. [50]	2018	2	36.5 (27–46)	PTPR	GK	8.5(4.1–13)	11(10–12)	20	17.5 yr. (15–20 yr)	LTC 100% (PR2)	No death	None

No Number, *SRS* Stereotactic radiosurgery, *FU* Follow-up, *Gy* Gray, *mo* Month, *PTPR* Papillary tumors of the pineal region, *GK* Gamma Knife radiosurgery, *ND* Data was not determined, *LTC* Local tumor control, *PR* Partial response, *SD* Stable disease, *PD* Progressive disease, *yr* Year

Table 29.6 Stereotactic radiosurgery for miscellaneous tumors of the pineal region

Author	Year	No. of cases treated with SRS (FU cases)	Median age in years (range)	Histology	SRS modality	Mean tumor vol. in cm^3 (range)	Median marginal dose in Gy (range)	Median maximal dose in Gy (range)	FU duration (mo)	Local tumor control (%)	Survival outcome	Complication
Lekovic et al. [29]	2007	1	55	Choroid plexus adenoma	GK	3.9	16	32	96	LTC 100% (PR1)	No death	None
Lekovic et al. [29]	2007	1	54	Neurocytoma	GK	1.4	18	36	54	LTC 100% (PR1)	No death	None
Lekovic et al. [29]	2007	1	29	Anaplastic astrocytoma	GK	3.9	12	24	8	PD1	1 Death during FU	None
Lekovic et al. [29]	2007	1	55	PNET	GK	8.3	12	24	44	LTC 100% (PR1)	No death	None
Lekovic et al. [29]	2007	1	27	Low-grade astrocytoma	GK	1.6	14	28	21	LTC 100% (CR1)	No death	None
Mori et al. [30]	2009	2	21 (8–66)	Unknown	GK	ND	ND	ND	26 (22–30)	LTC 100%	No death	ND
Yianni et al. [31]	2012	11		Astrocytoma	GK		17.3		62.5 (6–240)		PFS (1 yr) 100%, PFS (5 yr) 100%	None
Yianni et al. [31]	2012	6		Ependymoma	GK		16.5		62.5 (6–240)		PFS(1 yr) 67%, PFS (5 yr) 67%	None
Yianni et al. [31]	2012	1		Choroid plexus papilloma	GK		?18		62.5 (6–240)		PFS(1 yr) 95%, PFS (5 yr) 81%	None
Yianni et al. [31]	2012	1		Meningioma	GK		?18		62.5 (6–240)		PFS(1 yr) 95%, PFS (5 yr) 81%	None
Yianni et al. [31]	2012	5		Unknown	GK		?18		62.5 (6–240)		PFS(1 yr) 95%, PFS (5 yr) 81%	None
Iorio-Morin et al. [34]	2017	10	36 (3.5–83)	Unknown	GK	2.2 (0.58–7.14)	15 (13–17)	30 (26–35)	47 (4.6–260)	LTC (2 yr) 61%	OS (2 yr) 67%	ND

No Number, *SRS* Stereotactic radiosurgery, *FU* Follow-up, *Gy* Gray, *mo* Month, *GK* Gamma Knife radiosurgery, *LTC* Local tumor control, *PR*: Partial response, *PD* Progressive disease, *CR* Complete response, *ND* Data was not determined, *PFS* Progression-free survival, *yr* Year

Overall, currently available data in the literature supports that SRS can be a useful treatment option for select patients with pineal region tumors. In germinomas, SRS can be used as a focal radiation boost to the tumor bed serving as an alternative to fractionated RT, or as salvage for recurrence. For NGGCTs, SRS can be used as a focal boost to residual tumor following surgical resection or as a salvage after recurrence, itself alone or in combination with fractionated RT and/or chemotherapy. Similar strategy could be an option for pineoblastomas.

In pineocytomas, SRS appears to provide long-term tumor control and patient survival, suggesting upfront SRS as a viable alternative to surgical resection. Although this idea may be applied to PPTIDs as well, cautions are required to interpret the results of studies with these tumors merged with pineocytomas or pineoblastomas. Finally, SRS may serve as a reasonable primary or adjuvant option for patients with PTPRs given their high propensity for local recurrence even in case of GTR.

In most studies, SRS dose to tumor margin varied from 10 to 20 Gy, and the optimal dosage could not be formulated given the rarity of available data. Since SRS is frequently used as an adjunct or as salvage after previous fractionated RT, careful dose adjustment is recommended accordingly, with application of dose constraints to critical structures such as the diencephalon and the brainstem.

29.7 Conclusions

Evidence on the role of SRS to guide the management of pineal region tumors is still insufficient. However, SRS may be useful as an effective and safe modality in different tumor types based on histological verification. In pineocytomas and PTPRs, it can be used as an alternative to surgery for primary treatment or as an adjunct/salvage for residual/recurrent disease. In case of GCTs and pineoblastomas, SRS helps as a part of multimodality management or as a salvage option for recurrence.

Further clinical studies are needed to elucidate more clearly the role of SRS in the treatment of tumors in this particular region.

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