Pineal Region Tumors

34

Gregory P. Lekovic and Andrew G. Shetter

Introduction and Background

The pineal gland is situated at the geographic center of the brain between the posterior and habenular commissures. Its central location, as well as its solitary nature in an organ comprised of paired structures, led early anatomists and physiologists to impart to it singular importance (e.g., famously asserting that the pineal was the seat of the human soul).

As cited by Baumgartner and Edwards [1], the first description of a lesion in the pineal region is attributed to Virchow in 1865. By the early twentieth century, neurosurgical pioneers had devised approaches to the pineal region, variants of which are still in use today, including the transcallosal approach of Dandy and Fedor Krause's supracerebellar infratentorial approach. These early experiences with surgery for pineal regions were highly morbid, a fact that is not surprising given the technological limitations of the time [2]. At the same time, the radiosensitivity of germinomas, the most common pineal region tumor, was beginning to be appreciated. Gradually, surgical approaches were given up in lieu of empiric treatment with radiotherapy. With the advent of the era of microneurosurgery, interest in the surgical management of pineal region tumors remerged, and empiric treatments with radiotherapy are now obsolete.

Most recently, the development of chemotherapy and radiosurgery has added additional variables to the treatment algorithm of these tumors. Chemotherapy has been used successfully to lower radiation doses used to treat patients with germinoma. This is especially important in the treatment of children, for whom whole brain irradiation carries significant morbidity. Gamma knife radiosurgery (GKRS) offers a similar advantage in providing highly conformal targeting with maximization of delivered dose to the therapeutic target and concomitant minimization of dose exposure to neighboring structures. Although the role of radiosurgery in the management of pineal region tumors is still evolving, it is safe to say that radiosurgery plays an important role in the multimodality management of these lesions.

G.P. Lekovic, M.D., Ph.D.
House Clinic, Good Samaritan Gama Knife Radiosurgery Center, 2100 West Third Street, Los Angeles, CA 90057, USA

A.G. Shetter, M.D. (✉)
Section of Functional Stereotactic Neurosurgery, Division of Neurological Surgery, Barrow Neurological Institute, St. Joseph's Hospital and Medical Center, 350 W. Thomas Road, Phoenix, AZ 85013, USA
e-mail: neuropub@dignitiyhealth.org

Anatomy

The pineal region is broadly defined as the region lying between the splenium of the corpus callosum and tela choroidea dorsally, and the quadrigeminal plate and tectum ventrally, and between the posterior third ventricle rostrally, and cerebellar vermis caudally. The pineal gland itself is situated between the habenula dorsally and posterior commissure anterior-inferiorly (Fig. 34.1).

The pineal region is notable in that it is a region rich in vasculature, especially the deep cerebral veins. The vascular supply to the pineal gland proper is predominantly from the medial posterior choroidal arteries, with contributions from the lateral posterior choroidal and quadrigeminal arteries as well [3]. However, the pineal is surrounded by the deep venous drainage of the brain on all sides—the velum interpositum, containing the internal cerebral veins, lies rostral and dorsal to the pineal gland (to which it is often attached to pineal region tumors by thick arachnoid adhesions) [4], the basal veins of Rosenthal are located at either flank, and the vein of Galen lies posterior and superior to it. For this reason, stereotactic biopsy of the pineal region is viewed with trepidation by some.

The cellular constituents of the pineal region include pinealocytes, astrocytes, and sympathetic nerves. The sympathetic innervation comes from the superior cervical ganglion. The physiological role of the pineal is thought to be concerned with the regulation of circadian rhythms.

L.S. Chin and W.F. Regine (eds.), *Principles and Practice of Stereotactic Radiosurgery*,
DOI 10.1007/978-1-4614-8363-2_34,

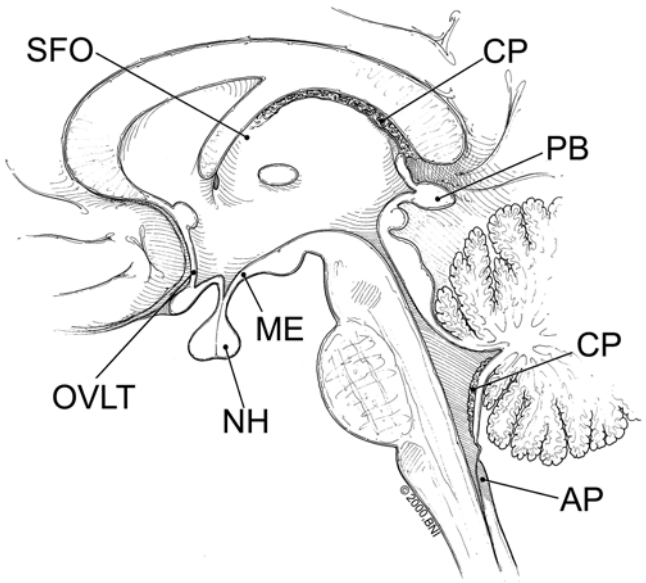

Fig. 34.1 Midsagittal section demonstrating the anatomy of the pineal region. Labeled structures include the pineal body (PB), the subfornical organ (SFO), choroid plexus (CP), area postrema (AP), neurohypophysis (NH), median eminence (ME), and organum vasculorum of the lamina terminalis (OVLT). Used with permission from Barrow Neurological Institute

Ontologically and embryologically the pineal is related to photoreceptor organs. Indeed, this role persists in certain reptiles where the pineal is known as the "parietal eye." Because of this shared evolutionary background, pineoblastomas are sometimes seen in association with retinoblastoma (so-called "trilateral retinoblastoma").

Pineal Region Tumor Presentation and Natural History

Although the physiological role of the pineal in humans is still somewhat obscure, it is an important locus of pathology. Broadly speaking, there are four categories of lesions occurring in the pineal region: germinoma (including pure germinoma, teratoma, and nongerminomatous germ cell tumors, NGCTs), pineal parenchymal tumors (pineocytoma and pineoblastoma), glial tumors, and miscellaneous tumors (including metastases, meningioma, and ependymoma).

Although pineal region tumors are relatively rare (accounting for less than 1 % of all intracranial neoplasms), they are much more common in Asia [5]. It is well known that there is a higher incidence of germ cell tumors (GCTs) in Asian populations than in North American or European populations. GCTs typically account for the majority of pineal region tumors, with pineal parenchymal tumors second and miscellaneous tumors third.

In Western populations, GCTs account for 0.3–0.5 % of all primary intracranial neoplasms, but comprise approximately 3.0 % of those encountered in children. In contrast, in Asia, GCTs comprise at least 2.0 %, and up to 9–15 %, of all intracranial neoplasms and pediatric neoplasms, respectively. In Japanese and Korean populations, 80 % of pineal region tumors in patients aged 15–35 years of age are germinoma [6]. In contrast, out of 370 French patients undergoing stereotactic biopsy of pineal region tumors, only 51 % of patients under the age of 30 had radiosensitive tumors (germinoma + pineoblastoma) [7].

The most common presentation of pineal region tumors is from symptoms attributable to local mass effect, principally increased intracranial pressure related to aqueductal compression and/or to mass effect on the quadrigeminal plate (e.g., Parinaud's syndrome). The growth pattern of pineal region tumors tends to reflect the underlying histology, with benign, well-encapsulated tumors filling the posterior third ventricle, quadrigeminal cistern, and displacing the anterior cerebellum [4]. Malignant tumors are more likely to diffusely infiltrate the midbrain, thalamus, or other neighboring structures.

Importantly, there is tremendous variation in the natural history of pineal region tumors depending on their histology. The management of tumors of this region, therefore, is extremely dependent on an accurate diagnosis. In most cases, this necessitates a tissue diagnosis, whether through stereotactic, endoscopic, or open biopsy. This issue will be discussed in greater detail below.

Pathology

Germ Cell Tumors

Pure germinoma, the most common central nervous system GCT, consists of large undifferentiated cells arranged in monomorphous sheets. Nuclei are round and typically centrally positioned amidst abundant clear cytoplasm. Mitoses are common and necrosis uncommon. Some tumors may incite an inflammatory response that is evident on histology by the presence of either many lymphocytes or occasionally fibrous tissue. Immunohistochemical positivity for placental alkaline phosphatase is typical.

Nongerminomatous Germ Cell Tumors

The group of tumors that together comprise the nongerminomatous germ cell tumors (NGGCTs) include teratoma (mature and immature), yolk sac tumors, embryonal carcinoma, and choriocarcinoma. Only teratoma is commonly

encountered as a pure tumor type, with most NGGCTs having regional variations in histology suggestive of multiple tumor subtypes.

By definition, teratomas recapitulate somatic elements from endodermal, mesodermal, and ectodermal lines. Differentiated teratomas include well-formed, fully differentiated elements such as rests of skin, hair, teeth, or cysts of mucosal epithelia. Immature teratomas are much more common, and contain incompletely differentiated tissue. Occasionally, a carcinoma or sarcoma can arise from within a teratoma (so-called teratoma with malignant transformation).

Yolk sac tumors are characterized by a reticular epithelium set in a myxoid matrix; classically these may form papillae known as Schiller–Duvall bodies. Embryonal carcinoma is composed of sheets of large cells with prominent nucleoli, many mitoses, and abundant cytoplasm. Necrosis is common. Trophoblastic elements, such as syncytiotrophoblastic cells (which may be seen scattered with other CNS GCTs) indicate tumor trophoblastic differentiation and hence choriocarcinoma.

The immunohistochemistry of GCTs is helpful in differentiating tumor types. Typically, cell membranes and/or cytoplasm are positive for placental alkaline phosphatase in germinoma; beta-HCG and human placental lactogen in choriocarcinoma, and alpha-fetoprotein in yolk sac tumor and teratoma.

Pineal Parenchymal Tumor

Pineocytomas (aka, pinealocytoma) are slow growing neoplasms of the pineal gland composed of small uniform sized cells. Characteristically, the cells exhibit cytoplasmic processes that are said to resemble club-like endings. Unlike pineoblastomas, there is some preservation of the lobular architecture of the normal pineal gland.

Pineoblastomas are members of the family of small blue cell primitive neuroectodermal tumors, similar to medulloblastoma or retinoblastoma. Like these tumors, they are highly cellular neoplasms with a high nucleus to cytoplasm ratio, characterized by the presence of either Homer–Wright or Flexner–Wintersteiner rosettes, the latter being a mark of retinoblastic differentiation. True to the oncologic commonality between the pineal and photoreceptor organs, pineal parenchymal tumors stain positively for interphotoreceptor retinoid binding protein.

True intermediate tumor classification is relatively rare, with only about 8 % of pineal parenchymal tumors belonging to this category (WHO). These tumors are highly cellular with numerous mitoses and nuclear atypia, but without pineocytomatous rosettes. Even more rarely, a pineal parenchymal tumor may have within it areas of both pineocytomatous and pineoblastomatous differentiation.

Because many tumors of the pineal region are histologically heterogeneous (especially the NGGCTs), the ability of the surgeon to avoid sampling errors in obtaining tissue for histopathological examination is paramount. In general, this need for accurate histological diagnosis of disparate regions of tumor has been commonly cited as support for open or endoscopic biopsies, during which regions of tumor appearing grossly dissimilar can be biopsied separately.

Imaging

Magnetic resonance imaging (MRI) with and without gadolinium contrast enhancement is the diagnostic imaging modality of choice. Pineocytomas are typically hypointense on T1-weighted images, and hyperintense on T2-weighted sequences. Pineoblastomas are heterogeneous, and can be either hypo- to isointense on T1-weighted MRI. GCTs are typically well circumscribed, iso- to hyperdense relative to grey matter, and intensely enhancing. However, no certain method exists for differentiating pineal region tumors on the basis of imaging studies alone.

Tumors of the pineal region enhance variably, as does the normal pineal gland due to the absence of a blood–brain barrier. Incidental calcification of the pineal is common, although such calcifications are also associated with "brain sand" seen in pineocytomas. The diagnosis of GCT is suggested if the neoplasm appears to surround or engulf the normal pineal gland calcifications, whereas pineal parenchymal tumors are said to cause an "explosion" of pineal calcifications to the periphery of the lesion as the mass expands. On the other hand, hemorrhage (pineal apoplexy) is suggestive of choriocarcinoma. In general, tumors arising from the collicular plate are more likely to be of glial origin [1], and the presence of fat signal is characteristic of lipoma, mature teratoma, or dermoid tumors. The presence of mature teratomatous elements such as hair or teeth may also be evident on imaging studies.

Management of Pineal Region Tumors

Because of the varied natural history of pineal region tumors and the lack of diagnostic specificity of imaging studies, the importance of obtaining a tissue diagnosis cannot be overemphasized. Therefore, a biopsy, whether stereotactic, endoscopic, or open (see discussion below) should be obtained as the initial step in the management of tumors of this region in all cases, except where cerebrospinal fluid (CSF) is positive for markers of malignant germinoma (i.e., BHCG or alpha-fetoprotein), in the case of new metastatic lesions (where the tissue diagnosis is already known), or perhaps in patients who are too frail to undergo even a biopsy. As discussed in

more detail below, there is no role for empiric radiation therapy in the management of these tumors, at least not in occidental populations.

Whether it is better to perform an open biopsy, coincident with attempted gross total resection or cytoreductive surgery, or to perform a minimally invasive (i.e., stereotactic or endoscopic biopsy) is controversial. Proponents of open biopsy cite the relative safety and low morbidity of approaches to the pineal region given modern instrumentation and microsurgical technique. Because of the histopathologic heterogeneity common to tumors of this region, the ability to minimize sampling errors with open biopsy may yield more accurate specimens for diagnosis. Benign tumors may be completely respectable; therefore, an open approach offers the potential for cure of these lesions. Moreover, even malignant tumors and radiation sensitive tumors may benefit from cytoreduction.

On the other hand, minimally invasive approaches avoid the risks of craniotomy, and have high diagnostic yield. Because of the pineal region's proximity to the deep cerebral veins, some authors argue that stereotactic biopsy of this region is a relatively higher risk. However, Regis et al. [7] reviewed 370 stereotactic biopsies of the pineal region from 15 Fr neurosurgical centers. They reported a 1.3 % mortality and 0.8 % severe neurological morbidity attributable to stereotactic biopsy. This was believed not to reflect an increased risk of death or neurologic injury over other intracranial sites. Overall, diagnostic tissue was obtained in 94 % of patients. However, 2.3 % of biopsied patients underwent repeat biopsy or subsequent open surgery and were found to have been initially misdiagnosed. Sampling errors were felt to contribute to about half of these cases (i.e., about 1 % diagnostic error due to sampling errors).

The endoscopic approach to the pineal region for the purposes of biopsy was first described by Fukushima [8, 9]. The advantages of an endoscopic approach include direct visualization of the biopsy site which could lessen sampling errors and lead to greater diagnostic accuracy [10]. In addition, because many patients with pineal region tumors either present with, or are at high risk of hydrocephalus, a CSF diversionary procedure may be required. An endoscopic biopsy affords the possibility of simultaneously performing an endoscopic third ventriculostomy at the same operative sitting. Oi et al. reported their experience with 20 consecutive patients followed prospectively who underwent endoscopic biopsy in the initial management of their pineal region tumors [11]. Importantly, they reported the endoscopic detection of spread of tumor not visualized in preoperative neuroimaging. This suggests that endoscopy may have benefit as a diagnostic tool per se. Nevertheless, the proper role of the endoscope in the management of pineal region lesions remains controversial.

The Role of Surgery

Pineal region tumors can be successfully resected with microsurgical techniques at tolerable levels of morbidity and mortality. Approaches to the pineal region include both supratentorial (interhemispheric transcallosal and occipital transtentorial) and infratentorial (supracerebellar infratentorial approach, Fig. 34.2). Bruce and Stein [12] described their experience with 160 pineal region tumors. They achieved a gross total resection in 46/53 benign pineal region tumors, with overall mortality and morbidity of 4 % and 3 %, respectively. Their results are comparable to other major surgical series for whom mortality rates range from 2 to 11 % and serious morbidity from 3 to nearly 30 % (for a recent review, see [13]).

The role of surgery for maximal debulking and/or resection is best established for benign lesions, where gross total resection may be curative. Conversely, these are also the lesions best suited to radiosurgical treatment. The argument for surgery for benign pineal region tumors is that gross total resection is often possible, and that this may afford a permanent cure and obviate the need for CSF diversion.

Whether surgical resection or debulking plays a significant role in the management of malignant tumors is much more hotly debated. Aggressive malignancies, especially those that on preoperative imaging are seen to invade the brainstem or other neighboring structures, are unlikely to be amenable to complete resection. Nevertheless, some studies have shown benefit of cytoreduction even in these cases, although these data have not reached statistical significance [14, 15]

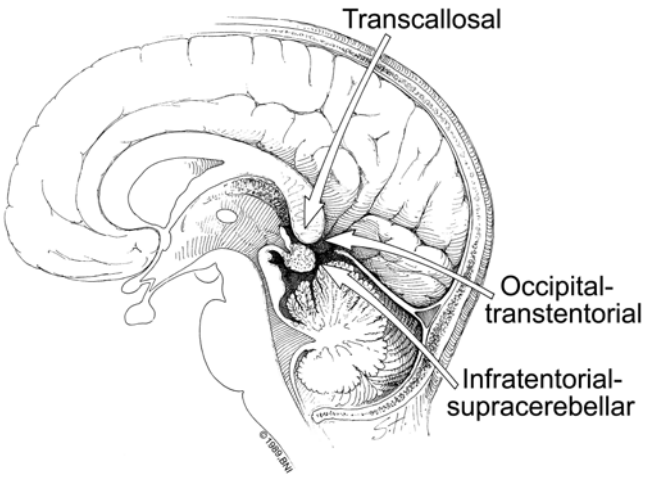

Fig. 34.2 Surgical approaches to the pineal region. Midsagittal section of the human brain demonstrating the surgical corridors to the pineal region, the transcallosal, occipital transtentorial, and the supracerebellar infratentorial. Used with permission from Barrow Neurological Institute

Finally, some centers advocate "second-look" surgery if imaging abnormalities persist after initial treatment of NGGCTs with chemotherapy and radiation [13]. The majority of these surgeries find either necrosis or, in the case of mixed NGGCTs, rests of mature teratoma.

Role of Radiation

It has been known for decades that radiation is curative for intracranial germinoma [16], with 5-year survival rates of up to 95 % reported for pure germinoma and up to 76 % for NGGCTs. Indeed, radiation remains the mainstay of treatment of most pineal region tumors, whether as primary treatment modality or as adjuvant therapy. Nevertheless, radiation has significant morbidity. Efforts at reducing radiation exposure have included avoiding whole brain and prophylactic craniospinal irradiation, the use of chemotherapy, and radiosurgery.

Traditionally, germinoma was treated with craniospinal irradiation, given estimates of spinal cord metastasis or seeding after surgery range of 13–40 %. However, as the sequelae of prophylactic craniospinal irradiation have become more appreciated, efforts have been made to delay or avoid spinal irradiation, and to limit cranial irradiation from whole brain to local field. The effectiveness of partial brain fields comprising tumor plus a 2-cm margin was shown initially by Dattoli and Newall in 1990 [17]. In this retrospective study, 12 patients were treated with partial brain irradiation, consisting of either fields comprising tumor plus a 2-cm margin ($n=10$), or fields comprising the ventricular system with a boost to the tumor ($n=2$). Nine out of ten patients treated with partial brain irradiation were complete responders; however, one patient relapsed and ultimately succumbed to the disease. This patient, however, also received a reduced dose of less than 40 Gy. Thus, the authors concluded that whole neuraxis radiation could be safely avoided in the majority of patients, provided that sufficient tumoricidal doses of radiation were delivered.

Because gonadal GCTs respond well to chemotherapy, chemotherapy has been advocated as a means to further reduce the amount of radiation necessary to obtain control of the tumor. In this regard, the rationale for chemotherapy anticipates the argument made for radiosurgery. Balmaceda et al. [18] enrolled 71 patients with GCTs (including both pure and NGGCTs) in an international cooperative study comprising 31 institutions in 6 countries, and demonstrated that chemotherapy could not be used alone for the treatment of GCTs. They employed a high-dose regimen of carboplatin, etoposide, and bleomycin. Although 41 of the 71 patients were successfully managed with chemotherapy alone initially, 35 patients showed evidence of recurrence or progression. Furthermore, 7 of 71 patients treated died of chemotherapy related toxicity.

In contrast, Buckner et al. [19] reported the results of a Phase II trial of primary chemotherapy followed by reduced-dose radiation for the treatment of CNS GCT in which the partial brain dose was reduced to 30 from 54 Gy. All patients were alive without progression at 51-month mean follow-up. One patient relapsed distally (spinal cord) and was salvaged with spinal irradiation. Thus, the prevailing paradigm at the present time is to use chemotherapy as an adjuvant therapy in combination with reduced-dose radiation. Spinal irradiation should be reserved for those cases presenting with disseminated disease or in the case of relapse.

The Role of Radiosurgery

The role of radiosurgery in the management of pineal region tumors remains controversial. Traditionally, pineal region tumors have either been approached surgically with the goal of gross total resection and cure (if benign), or with conventional radiation if the tumor is of a histology known to be radiosensitive and/or malignant. Radiosurgery, on the other hand, has the potential to be used either as a "boost" modality in conjunction with conventional radiotherapy, or even as an alternative to radiotherapy and/or surgery altogether.

Table 34.1 summarizes the results of reports in the English language literature, including three from our institution, on the use of stereotactic radiosurgery in the treatment of pineal region tumors. Several factors, however, make it difficult to draw easy comparisons or conclusions from these studies, including relatively small sample sizes and because of the heterogeneity of diagnoses included within individual series.

Backlund et al. [20] first reported the treatment of two cases of pineocytoma with GKRS in 1974. The patients were treated with peak dose of 50 Gy. At 13 and 36 months follow-up neither patient had displayed evidence of tumor progression. Subach et al. [21] included eight patients with pineocytoma (out of 14), with three tumors demonstrating a complete response to GKRS, three a partial response, and two no change. GKRS mean marginal doses for all tumor types treated were 15.4 Gy, and all tumors were treated to the 50 % isodose line. Hasegawa et al. [22], however, reported a distant recurrence of pineocytoma after GKRS, although 100 % local control was achieved. A complete response of pineoblastoma to GKRS was demonstrated by Manera et al. [23] in one patient and a partial response in another. However, Hasegawa et al. [22] experienced three distant failures following GKRS for pineoblastoma treated with a mean marginal dose of 15.3 Gy to the 50 % isodose line. Kano et al. retrospectively reviewed 13 patients with pineocytoma treated with a median marginal dose of 15 Gy [24].

Table 34.1 Summary of pineal region tumors in literature

Reference	No. and diagnosis	Biopsy	Mean follow-up (months)	Prior treatment	Radiological results	Dosimetry	Progression	Complication
Backlund et al. (1974) [20]	2 pineocytoma	2 SB	13 and 36	None	Regression of tumor	GKRS 50 Gy	None	None
Dempsey and Lunsford (1992) [32]	4 meningioma, 2 anaplastic astrocytoma, 1 ependymoma, 1 craniopharyngioma, 1 pineocytoma	4 SB, 5 OB	20.7 (3–32)	4 primary, 5 OR, 4 with previous WBRT, 1 chemotherapy	6 partial or complete responses, 3 no change (all meningioma)	GKRS mean marginal dose of 16.6 Gy (10–2- Gy) at 50–60 % isodose line	None	3 new neurological deficits
Manera et al. (1996) [23]	1 pineocytoma, 1 astrocytoma, 2 germinoma, 2 pinealoblastoma, 3 meningioma	7 SB, 4 NO	12.3 (2–34)	1 OR	3 complete responses (1pinealoblastoma, 2 germinoma), 5 partial, 2 no change, 1 insufficient follow-up	GKRS mean marginal dose = 9.3 Gy (6–20), 40–50 % isodose line	None	None
Subach et al. (1998) [21]	8 pineocytoma, 2pineoblastoma, 2 germinoma, 2 NGGCT	9 SB, 2 OB, 3 NO	Mean imaging follow-up 21	1 55 Gy EBRT, 1 subtotal OR, 2 chemotherapy	4 complete responses (3 pineocytoma and 1 pineoblastoma), 6 partial (3 pineocytoma, 1 pineoblastoma, 2 germinoma)	GKRS marginal doses 15.4 (12–20), all treated to 50 % isodose line mean volume 6.4 cm^3	1 (embryonal carcinoma)	1 new Parinaud's, 3 deaths (only 1 attributed to progression)
Kobayashi et al. (2001) [26]	8 germinoma, 4 STGC, 13 malignant GCT, 3 pineocytoma, 2 pineoblastoma, 2 unknown	11 NO	N/A	Germinoma: 8 chemotherapy, 5 OR malignant GCT: 10 OR, chemotherapy 10, EBRT 8	8 complete response, overall response rate = 73.3 %, For germinoma and pineocytoma 100 % control rate	GKRS marginal dose = 16.8 Gy for germinoma, 13.4 Gy for malignant GCT, 17.5 Gy for PPT and others	8	7 deaths attributable to progression
Hasegawa et al. (2002) [22][a]	10 pineocytoma, 2 mixed histology, 4 pineoblastomas	10 SB, 4 OB	52	4 OR, 4 EBRT (2 as boost and 2 after recurrence)	4 complete response, 8 partial, 2 no change, 2 no imaging follow-up, local control = 100 %	GKRS mean marginal dose = 15.3 Gy at 50 % isodose line	4 distant treatment failure (1 pineocytoma, 3 pineoblastomas)	2 new deficits, 5 deaths (4 attributable to progression)
Hasegawa et al. (2003) [28][a]	4 NGGCT	1 SB, 2 OB, 1 CSF	25	2 OR	2 partial, 1 no change, 1 progression	12–16 Gy marginal dose to 50 % isodose line	1 (death)	None

Deshmukh et al. (2004) [33]	5 pineocytoma	5 OR	14.6	5 OR	4/5 partial response 100 % local control	GKRS marginal dose 14–16 Gy	None	None
Casentini et al. (1990) [25]	6 germinoma	5 yes	27.6 (1–58)	"Inverse boost" paradigm with extended field radiotherapy: mean 31 Gy, range 24–36)	Complete response	Varian LINAC (marginal dose 10–11 Gy, peak doses 10–12.5)	None	1 periprocedural death (unrelated)
Kano et al. (2009) [24]	13 pineocytoma, 5 pineoblastoma, 2 mixed histology	20 with OB or SB	54.1	6 OR, 3 EBRT, 3 chemotherapy, 2 EBRT and chemotherapy	26 % complete, 47 % partial, 11 % "stable," 11 % local progression	GKRS mean marginal dose 15 Gy	6 deaths, 5-year progression-free survival 89 %	No permanent morbidity
Mori et al. (2009) [27]	38 germ cell tumor, 9 PPT, 2 unknown	Biopsy in 13 germ cell tumors, OB in 9 PPT	33.5	13 OR, 20 EBRT, 27 chemotherapy	NR	Mean marginal dose 15.5 Gy	Progression-free survival at 10 years 68 % for germ cell tumors, 67 % for PPTs	1 optic neuropathy
Wilson et al. (2012) [30]	14 pineocytoma	12 OB, 2 EB	53	12 OR, 5 with gross total excision	5 complete resection, 9 residual tumors postoperatively	Mean marginal dose of 14.6 Gy with GKRS in 5 patients	Progression in 3 patients with subtotal excision, none in patients with gross total excision or GKRS	None for GKRS
Yianni et al. (2012) [31]	11 PPT, 2 germ cell tumors, 2 papillary epithelial tumors, 9 gliomas, 20 with no histologic diagnosis	16 SB, 11 EB, 17 OB	62.5	17 OR, 10 EBRT, 4 chemotherapy	NR	Mean marginal dose 18 Gy	8 deaths, progression-free survival 27 % at 5 years	None

Used with permission from Barrow Neurological Institute

GKRS Gamma knife radiosurgery, *NR* not reported, *NGGCT* nongerminomatous germ cell tumor, *SB* stereotactic biopsy, *OB* open biopsy (craniotomy), *EB* endoscopic biopsy, *STGC* germinoma with syncytiotrophoblastic giant cells, *OR* surgery, *EBRT* external beam radiation therapy, *PPT* pineal parenchymal tumor

[a]Patients partially included in previous reports

Overall survival after GKRS was 92.3 % at 5 years, with 23 % of tumors treated demonstrating a complete radiographic response.

Although germinoma is highly curable by external beam irradiation, efforts to reduce the dose of EBRT radiation have gained momentum because of concerns of the toxicity of even partial brain irradiation (especially in children). In 1990, Casentini et al. [25] reported their results using Varian LINAC radiosurgery as an "inverse boost" paradigm for the treatment of germinoma, with all six patients so treated demonstrating a complete response. Kobayashi et al. [26] included eight patients with the diagnosis of germinoma who were treated with chemotherapy prior to GKRS. They obtained a 100 % control rate for these tumors with a marginal dose of 16.8 Gy. Mori et al. [27] treated 18 germinomas with GKRS, the largest case series to date. Marginal doses ranged from 9.9 to 25.7 Gy, and all but one patient received fractionated external beams radiation therapy as well. The progression-free survival rate at 5 years was 63 %. The single patient who received GKRS as the initial therapy experienced CSF dissemination at 15 months.

Increasingly, GKRS is being reported in the treatment of NGGCTs. The number of reported cases is now well over 50. However, due to the heterogeneity of diagnoses in the reported series it is difficult to draw comparisons. Nevertheless, it is clear that NGGCTs are less responsive to GKRS than are germinoma or pineocytoma. Mori et al. [27] used adjuvant GKRS for 16 NGGCTs with marginal doses similar to those for GCTs. The progression-free survival rate at 5 years was 37 % [27]. Neither of the two NGGCTs reported by Subach et al. [21] demonstrated a response to GKRS. Hasegawa et al. [28] treated four NGGCTs with between 12 and 16 Gy at the 50 % isodose line. At a mean follow-up of 25 months, one tumor progressed, one demonstrated no change, and two tumors partially responded. Kobayashi et al. [26] reported the results of 13 malignant GCTs treated with GKRS. Follow-up data was obtained in 12 patients, of whom 3 demonstrated a complete response, 3 a partial response, and 6 had progressed. Five patients were deceased at a mean follow-up of 12.6 months.

Barrow Neurological Institute GKRS Experience

We recently reported our experience with GKRS for pineal region tumors in 17 patients with non-metastatic tumors of the pineal region [29]. Diagnoses included pineocytoma ($n=8$), as well as choroid plexus papilloma, neurocytoma, anaplastic astrocytoma, PNET, low-grade astrocytoma, pineoblastoma, NGGCT, malignant teratoma, and pineal parenchymal tumor of intermediate differentiation ($n=1$ each).

All patients were treated using Leksell Gamma Plan treatment planning software, with a mean marginal dose of 14.06 Gy (range 12–18 Gy). All doses were prescribed to the 50 % isodose line. Seven to 27 isocenters (mean 11.4) were used to treat a mean target volume of 7.42 cm^3 (range 1.2–32.5 cm^3).

Fourteen patients were treated with GKS as either the primary radiation modality or as a salvage treatment for a recurrence after conventional EBRT failed. Two patients, one with an NGGCT and another with an anaplastic astrocytoma, were administered a 15- and 12-Gy GKS boost to the pineal region after receiving reduced-dose craniospinal radiation therapy (3,600 cGy).

There were no complications attributable to GKRS. There were three mortalities after GKRS. One patient died 6 days after radiosurgery (this patient was excluded from further analysis), one died 2 months after radiosurgery, and the third died after developing widespread metastatic disease. These latter two patients demonstrated local control of tumor, despite of their clinical progression. Upon latest follow-up imaging, local control was established in 100 % of the patients.

Wilson et al. examined a subset of 15 patients with histologically proven pineocytomas treated at the BNI over a 12-year interval [30]. The mean clinical and radiographic follow-ups were 44 and 53 months, respectively. Gross total tumor excisions were achieved in five patients with no known recurrences, although two of those patients were lost to radiographic follow-up. Of the nine patients who underwent subtotal tumor excisions or endoscopic biopsy, three received initial GKRS and six were observed. None of the patients treated with "up-front" radiosurgery recurred. The remaining six patients demonstrated recurrence at varying intervals. Four received subsequent radiosurgery and developed no further signs of tumor progression. The authors concluded that adjuvant GKRS is an effective treatment for pineocytomas when complete surgical excision is not feasible, and that radiosurgery can be successful in controlling recurrent disease. Their data also suggests that subtotal pineocytoma excision plus radiosurgery may yield results equivalent to gross total surgical excision, although greater patient numbers and larger follow-ups will be needed before this finding can be stated with certainty.

Conclusions

Although tumors in this region are relatively rare, the pineal region is an important site of a wide range of pathological processes. Because of the wide variation in natural history of these tumors depending on this histological heterogeneity, obtaining a tissue diagnosis prior to instituting definitive therapy is paramount. Exceptions to this rule may be in met-

astatic disease (where the presumptive tissue diagnosis is already known) and in patients that are truly too poor surgical candidates. In our experience, open craniotomy with attempted resection or at least debulking of tumor with biopsy has been the favored approach to obtaining a diagnosis. Endoscopic biopsy potentially spares the patient the risk of craniotomy if the tumor is found to be radiosensitive. In addition, endoscopy does afford the theoretical advantage of being able to perform an endoscopic third ventriculostomy at the same surgery as that for obtaining a biopsy; however, in our series all patients' third ventriculostomies eventually failed, ultimately requiring ventriculoperitoneal shunting. Other centers have reported good results using stereotactic biopsy to obtain a histologic diagnosis [7, 31].

The role of radiosurgery in the management of pineal region tumors remains controversial. We have found it helpful to dichotomize our approach to the appropriateness of pineal region tumors based on the grade of tumor involved. For benign lesions, i.e., those with an indolent natural history, that are relatively radioresistant, and curable with gross total surgical resection, radiosurgery competes with conventional surgery in the treatment options. Despite advances in microsurgical approaches to the pineal region, surgical extirpation of tumors occurring in this region is often impossible. Moreover, the sensitivity of pineal region tumors to radiation tends to weigh against surgical aggressiveness. Nevertheless, because surgery does offer at least the potential for cure, we believe radiosurgery may be reserved in these cases for poor surgical candidates or for the treatment of residual or recurrent disease. For malignant lesions, the role of radiosurgery is perhaps less well defined. Many malignant lesions are surgically incurable, and likely treatable with radiotherapy and chemotherapy alone. Nevertheless, like surgery, radiotherapy has significant morbidity that may be ameliorated by using radiosurgery as either a boost modality or as an alternative treatment altogether. The rationale for radiosurgery for radiation sensitive tumors is therefore analogous to that of chemotherapy (i.e., to avoid, delay, or at a minimum to reduce the dose of, conventional external beam radiation therapy). However, enthusiasm for the role of radiosurgery in malignant disease must be tempered, in our experience, by the fact that we have found that Gamma knife as a primary radiation modality in the treatment of malignant disease may lead to distal failure. Of course, in this case the possibility of salvage with either repeat radiosurgery or radiotherapy remains. In such case, radiosurgery may still be of value in delaying the exposure to whole brain external beam radiation therapy.

Case Examples

Patient #1

A 12-year-old boy presenting with progressive headache, nausea, and vomiting for 5 days underwent computed tomography (CT) of the head revealing a pineal region mass with hydrocephalus at an outside institution and was subsequently transferred to the our institution for definitive care. The patient had a prior history of strabismus but was otherwise previously healthy. On admission examination, the patient was awake, alert, and fully oriented. He complained of diplopia but his extraocular movements were intact to examination except for some divergence of gaze looking upwards. There were no other cranial nerve findings, and motor examination revealed 5/5 motor strength throughout without drift. Imaging revealed a pineal region tumor with hydrocephalus. Serum markers were positive for an elevated alpha-fetoprotein of 213, although CSF markers were absent.

The patient underwent stereotactic wand-guided endoscopic biopsy and third ventriculostomy. However, endoscopic biopsy material was nondiagnostic, and so the patient subsequently underwent a suboccipital craniotomy for supracerebellar infratentorial approach for biopsy and tumor debulking 2 days later. Despite third ventriculostomy, the patient developed recurrent symptoms of hydrocephalus and eventually required ventriculoperitoneal shunting. Pathological examination was consistent with a malignant mixed GCT.

After surgery, the patient was begun on induction chemotherapy with a 3-day course of VePesid, carboplatin, cytotaxin, and bleomycin followed by high-dose Neupogen and Procrit. He returned for subsequent cycles of chemotherapy every 3 weeks for a total of four cycles. Repeat imaging demonstrated persistent disease.

The patient then underwent craniospinal irradiation with planned Gamma knife boost to the pineal region. The brain was treated with shaped-opposed 6 MV photon beams with dose calculated at midplane. The brain was treated to 3,600 cGy in 20 fractions. The spine was treated with two separate fields, one including the cervical and thoracic spines primarily, and the other comprising the lumbar region. Both fields were treated to a depth of 4.5 cm to 3,600 cGy.

(continued)

(continued)

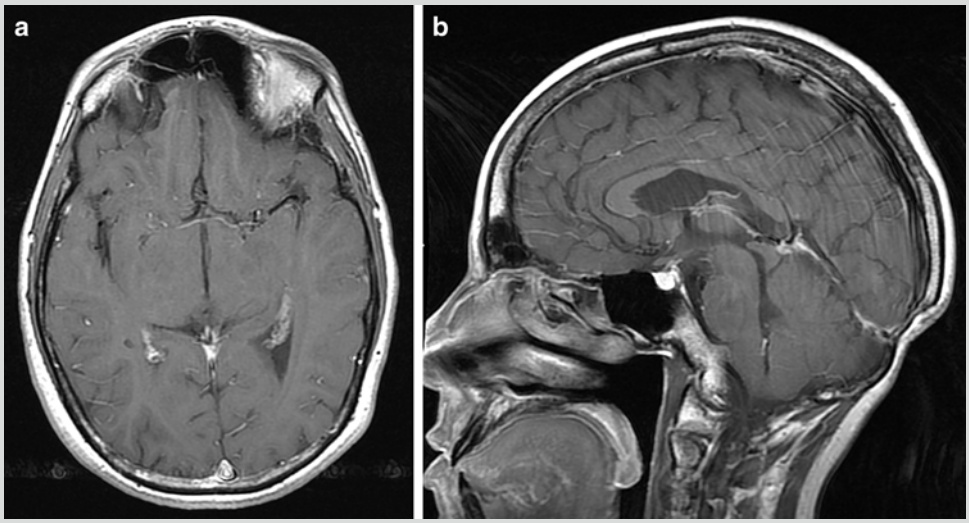

Fig. 34.3 A 12-year-old boy presented with hydrocephalus secondary to pineal region NGGCT. Axial (**a**) and sagittal (**b**) gadolinium-enhanced MRI demonstrating complete of response of pineal region NGGCT 6 years after GKRS boost to craniospinal irradiation

The patient tolerated both chemotherapy and craniospinal irradiation well and was felt to be an excellent candidate for GKRS boost to the pineal. Two days after the completion of his course of craniospinal irradiation, the patient underwent GKRS. The prescription dose was 15 Gy prescribed at the 50 % isodose line. The target volume was 1.2 cm^3, and was covered in a single matrix with two 4-mm collimator isocenters and 6 8 mm isocenters.

Follow up imaging studies demonstrated the complete response of the tumor to treatment at 1 year of follow-up. Six years after GKRS, the patient's MRI scan continues to show no evidence of tumor (Fig. 34.3). He is performing in high school at his grade level, and he has been off treatment for 5 years, although he continues to require pituitary replacement therapy.

Patient #2

A 20-year-old man presented with 3 weeks of persistent headache, dizziness, and diplopia. CT demonstrated an enhancing pineal region mass. The patient underwent a suboccipital craniotomy for supracerebellar infratentorial approach for resection of the mass. Pathological examination was consistent with pineoblastoma. The patient subsequently underwent ventriculoperitoneal shunting.

The patient was begun on emergent whole brain radiotherapy, and an initial response was found after seven treatments. The patient was therefore administered craniospinal irradiation, with 3,600 cGy prescribed to the brain and spine with an IMRT boost to the pineal, for a total of 5,580 cGy to this location. In addition, the patient underwent GKRS to the residual tumor, with a prescription dose of 14 at the 50 % isodose line. The defined target volume was 23.00 cm^3, and 22.00 cm^3 were covered within the dose matrix with a combination of three 8-mm collimator isocenters and twelve 18-mm collimator isocenters.

The patient tolerated craniospinal irradiation and GKRS well. There were no treatment-related complications. The patient has been followed with serial imaging which at 4.5 years post GKRS demonstrate stable tumor with loss of central enhancement and without evidence of growth (Fig. 34.4). Clinically, the patient has a KPS of 100 and has returned to work full-time.

(continued)

(continued)

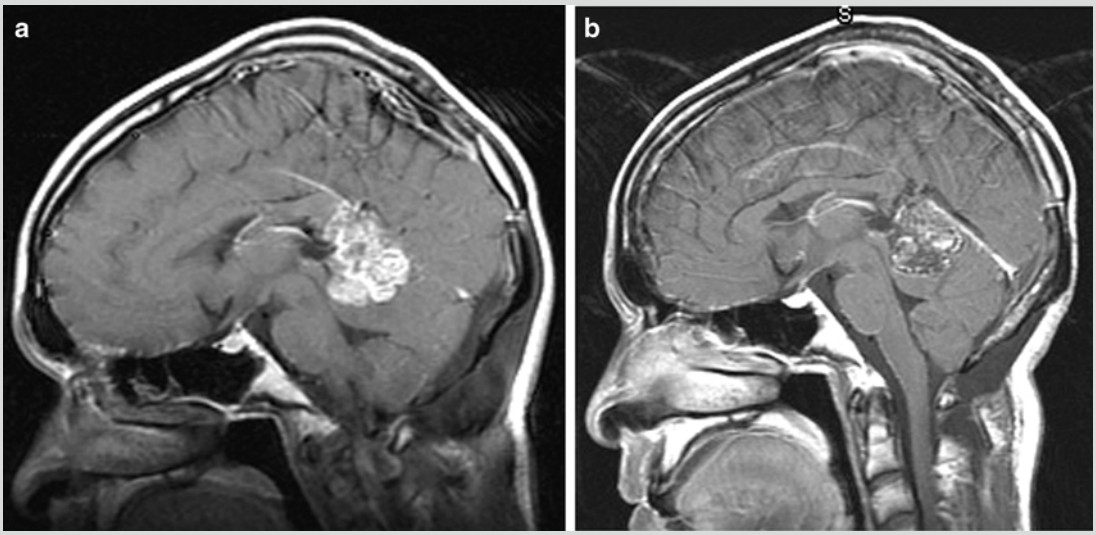

Fig. 34.4 A 20-year-old man presented with pineoblastoma, treated with GKRS boost after craniospinal irradiation. Sagittal gadolinium-enhanced MRI at the time of GKRS (**a**), compared to that on follow-up imaging (**b**) demonstrates stable tumor size with a prominent loss of central enhancement

Patient #3

A 52-year-old woman, a nursing home resident with severe psychiatric disease, was found to have a diminishing level of consciousness and incontinence of bowel and bladder. She denied headache and her neurological exam was nonfocal. Imaging studies revealed a large (>5 cm) contrast enhancing lesion in the pineal region. The patient underwent endoscopic third ventriculostomy and biopsy. Pathological examination demonstrated a low-grade appearing lesion with preserved pineal glandular architecture; the MIB labeling index was less than 0.1 %. Because of the benign pathological appearance of the tumor, the patient was taken back to the operating room for resection of the tumor via a suboccipital craniotomy and supracerebellar infratentorial approach. In addition, she eventually required ventriculoperitoneal shunting after failure of her third ventriculostomy.

After surgery, the patient was evaluated for GKRS to residual tumor. The defined target volume was 7.33 cm^3. The prescription dose was 14 Gy to the 50 % isodose line. The target dose volume histogram volume was 7.22 cm^3; the treatment plan included five 8 mm and five 14-mm collimator isocenters. The patient tolerated the treatment well and there were no treatment-related complications.

After treatment, the patient returned to her care facility in her usual state of health. On 25-month follow-up, MR imaging demonstrated slight shrinkage of the tumor (Fig. 34.5).

(continued)

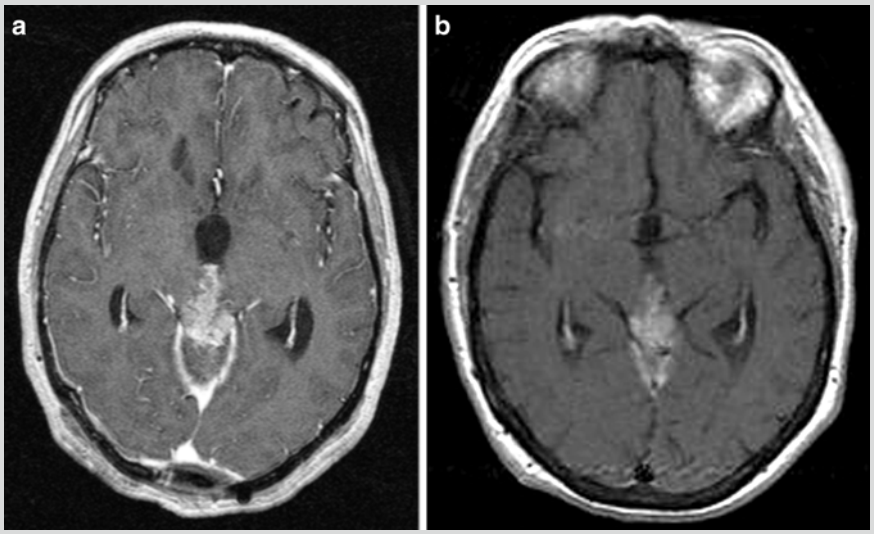

Fig. 34.5 A 52-year-old woman presented with a large (>5 cm) pineocytoma. The patient underwent subtotal resection with treatment of 7.3 cm^3 of residual tumor with GKRS (**a**). Two years after treatment, axial MRI with contrast through the pineal demonstrates stable appearance of the lesion (**b**)

References

1. Baumgartner JE, Edwards MS. Pineal tumors. Neurosurg Clin N Am. 1992;3:853–62.
2. Bruce JN. Pineal tumors Historical perspective. In: Winn HR, editor. Youman's neurologica surgery. Philadelphia: Elsevier; 2005. p. 1–6.
3. Yamamoto I, Kageyama N. Microsurgical anatomy of the pineal region. J Neurosurg. 1980;53:205–21.
4. Stein BM. Supracerebellar-infratentorial approach to pineal tumors. Surg Neurol. 1979;11:331–7.
5. Knierim DS, Yamada S. Pineal tumors and associated lesions: the effect of ethnicity on tumor type and treatment. Pediatr Neurosurg. 2003;38:307–23.
6. Oi S, Matsumoto S. Controversy pertaining to therapeutic modalities for tumors of the pineal region: a worldwide survey of different patient populations. Childs Nerv Syst. 1992;8:332–6.
7. Regis J, Bouillot P, Rouby-Volot F, et al. Pineal region tumors and the role of stereotactic biopsy: review of the mortality, morbidity, and diagnostic rates in 370 cases. Neurosurgery. 1996;39:907–12.
8. Fukushima T. Endoscopic biopsy of intraventricular tumors with the use of a ventriculofiberscope. Neurosurgery. 1978;2:110–3.
9. Fukushima T, Ishijima B, Hirakawa K, et al. Ventriculofiberscope: a new technique for endoscopic diagnosis and operation. Technical note J Neurosurg. 1973;38:251–6.
10. Robinson S, Cohen AR. The role of neuroendoscopy in the treatment of pineal region tumors. Surg Neurol. 1997;48:360–5.
11. Oi S, Shibata M, Tominaga J, et al. Efficacy of neuroendoscopic procedures in minimally invasive preferential management of pineal region tumors: a prospective study. J Neurosurg. 2000;93:245–53.
12. Bruce JN, Stein BM. Surgical management of pineal region tumors. Acta Neurochir (Wien). 1995;134:130–5.
13. Bruce JN, Ogden AT. Surgical strategies for treating patients with pineal region tumors. J Neurooncol. 2004;69:221–36.
14. Matsutani M, Sano K, Takakura K, et al. Primary intracranial germ cell tumors: a clinical analysis of 153 histologically verified cases. J Neurosurg. 1997;86:446–55.
15. Weiner HL, Finlay JL. Surgery in the management of primary intracranial germ cell tumors. Childs Nerv Syst. 1999;15:770–3.
16. Sung DI, Harisiadis L, Chang CH. Midline pineal tumors and suprasellar germinomas: highly curable by irradiation. Radiology. 1978;128:745–51.
17. Dattoli MJ, Newall J. Radiation therapy for intracranial germinoma: the case for limited volume treatment. Int J Radiat Oncol Biol Phys. 1990;19:429–33.
18. Balmaceda C, Heller G, Rosenblum M, et al. Chemotherapy without irradiation—a novel approach for newly diagnosed CNS germ cell tumors: results of an international cooperative trial. The First International Central Nervous System Germ Cell Tumor Study. J Clin Oncol. 1996;14:2908–15.
19. Buckner JC, Peethambaram PP, Smithson WA, et al. Phase II trial of primary chemotherapy followed by reduced-dose radiation for CNS germ cell tumors. J Clin Oncol. 1999;17:933–40.
20. Backlund EO, Rahn T, Sarby B. Treatment of pinealomas by stereotaxic radiation surgery. Acta Radiol Ther Phys Biol. 1974;13:368–76.

21. Subach BR, Lunsford LD, Kondziolka D. Stereotactic radiosurgery in the treatment of pineal region tumors. Prog Neurol Surg. 1998;14:175–94.
22. Hasegawa T, Kondziolka D, Hadjipanayis CG, et al. The role of radiosurgery for the treatment of pineal parenchymal tumors. Neurosurgery. 2002;51:880–9.
23. Manera L, Regis J, Chinot O, et al. Pineal region tumors: the role of stereotactic radiosurgery. Stereotact Funct Neurosurg. 1996;66 Suppl 1:164–73.
24. Kano H, Niranjan A, Kondziolka D, et al. Role of stereotactic radiosurgery in the management of pineal parenchymal tumors. Prog Neurol Surg. 2009;23:44–58.
25. Casentini L, Colombo F, Pozza F, et al. Combined radiosurgery and external radiotherapy of intracranial germinomas. Surg Neurol. 1990;34:79–86.
26. Kobayashi T, Kida Y, Mori Y. Stereotactic gamma radiosurgery for pineal and related tumors. J Neurooncol. 2001;54:301–9.
27. Mori Y, Kobayashi T, Hasegawa T, et al. Stereotactic radiosurgery for pineal and related tumors. Prog Neurol Surg. 2009;23:106–18.
28. Hasegawa T, Kondziolka D, Hadjipanayis CG, et al. Stereotactic radiosurgery for CNS nongerminomatous germ cell tumors. Report of four cases. Pediatr Neurosurg. 2003;38:329–33.
29. Lekovic GP, Gonzalez LF, Shetter AG, et al. Role of Gamma Knife surgery in the management of pineal region tumors. Neurosurg Focus. 2007;23:E12.
30. Wilson DA, Awad AW, Brachman D, et al. Long-term radiosurgical control of subtotally resected adult pineocytomas. J Neurosurg. 2012;117:212–7.
31. Yianni J, Rowe J, Khandanpour N, et al. Stereotactic radiosurgery for pineal tumours. Br J Neurosurg. 2012;26:361–6.
32. Dempsey PK, Lunsford LD. Stereotactic radiosurgery for pineal region tumors. Neurosurg Clin N Am. 1992;3:245–53.
33. Deshmukh VR, Smith KA, Rekate HL, et al. Diagnosis and management of pineocytomas. Neurosurgery. 2004;55:349–55.