Tumors of the Pineal Region

14

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Contents

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14.1 Epidemiology

The term "pineal region tumors" includes both the neoplasms originating from the pineal body and those originating from the adjacent anatomical structures, such as the thalamus, the dorsal midbrain, and the falcotentorium. The term "pineal tumors" indicates the former. Glial tumors originating from the tectum and meningiomas originating from the falcotentorial junction are not a true pineal tumor. Primary pineal tumors are mainly composed of two categories of brain neoplasms, pineal parenchymal tumors and germ cell tumors (Table 14.1).

Each of them is a rare neoplasm in the central nervous system (CNS) and predominantly occurs in the pediatric population. Pineoblastomas and teratomas are often found in very young children. The Brain Tumor Registry of Japan [29] recorded 966 pineal region tumors (806 male patients and 160 female patients) in 2003; there were 585 germinomas (60.6%), 80 pineocytomas (8.3%), 56 teratomas (5.8%), 49 pineoblastomas (5.1%), 50 malignant teratomas (5.2%), and others. A clear male predominance was observed in each histological type of germ cell tumor, where the male to female ratio was approximately 10:1. Pineal parenchymal tumors, however, show no gender difference for incidence [18, 22]. It is well known that the incidence of pineal tumors is higher in Asia than in Europe. This is attributed to a significantly higher incidence of germ cell tumors in Far-East Asia than in the Western countries. It should be noted that germinoma is the most common type of pineal origin neoplasm both in Asian and Western countries. Pineal mature teratomas occasionally present as congenital tumors in newborns.

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Table 14.1 WHO classification (2007) of tumors primarily originating from the pineal gland

Tumors of the pineal region
Pineocytoma
Pineal parenchymal tumor of intermediate differentiation
Pineoblastoma
Papillary tumor of the pineal region
Germ cell tumors
Germinoma
Embryonal carcinoma teratoma
Yolk-sac tumor
Choriocarcinoma
Teratoma
Mature
Immature
Teratoma with malignant transformation
Mixed germ cell tumors

14.2 Genetics of Pineal Tumors

Because of their rarity, limited information is available on the genetic alterations and the molecular pathways involved in the pathogenesis of pineal tumors. Intracranial germ cell tumors mainly occur in the pineal body and the neurohypophysis. Extragonadal location of germ cell tumors including in the CNS is thought to arise from ectopic migration and homing of germ cells during embryogenesis. This notion is supported by imprinting studies showing a methylation pattern in gonadal and extragonadal germ cell tumor similar to that of early stages of germ cell development [27]. Moreover, the histological appearance of the whole spectrum of gonadal and intracranial germ cell tumors is undistinguishable, making it likely, although not certain, that these tumors in fact share a common underlying genetic alteration [13, 27]. One landmark cytogenetic anomaly of testicular germ cell tumors is the gain of chromosome 12p, most frequently in the form of an isochromosome, which is present in the vast majority of these tumors [16]. Several genes mapped to this chromosome arm are involved in pluripotency and self-renewal (NANOG and STELLAR), but also in cell cycle control (CCND2), or are known oncogenes (KRAS2) and suppressors of apoptosis (EKI1). Other genetic alterations are found at a lower frequency such as 4q12, 17q21.3, 22q11.23, Xq22 gain and 5q33, 11q12.1, 16q22.3, 22q11 loss [16]. One recent study has found isochromosome 12p in a majority of intracranial germ cell tumors. A comparison with a parallel metaanalysis of 116 germ cell tumors conducted in the same study concluded that central nervous system germ cell tumors are genetically indistinguishable from other germ cell gonadal or extragonadal tumors [13, 27]. The KIT gene located at 4q12 is amplified and overexpressed in some seminomas, and recent studies have found a robust expression of c-KIT in pineal germ cell tumors, with a mutation of c-KIT gene in some cases [19]. These findings are important as c-KIT, which is tyrosine kinase receptor, is a major target of imatinib mesylate, which is used very successfully in chronic myelogenous leukemia and gastrointestinal stromal tumors.

Pineal parenchymal tumors including pineoblastomas may exhibit differentiation features of photoreceptor cells, such as the expression of retinal S-antigen, and they also share histopathological characteristics with retinoblastoma, such as Flexner-Wintersteiner rosettes [21]. This is in concordance with the embryological development of the pineal gland, which exhibits features of a photoreceptor organ with photosensory cells and neuroendocrine differentiation. Moreover, pineoblastomas can be associated with sporadic or hereditary retinoblastomas, a condition known as trilateral retinoblastoma [4]. The RB1 gene is therefore probably a prominent player in the development of pineoblastomas associated with retinoblastomas. It is, however, not known whether alteration of RB1 signaling by direct RB1 mutation, epigenetic mechanisms, or functional alteration of the RB1 pathway is present in sporadic pineoblastomas or familial pineoblastomas without association with retinoblastoma. The cytogenetic abnormalities in pineocytomas are inconsistent as some studies reported loss of chromosomes 22, 11, and 1, whereas other studies did not find chromosomal alterations at all in these tumors. Reported genetic anomalies in pineoblastomas include monosomy of chromosome 20 and 22, gains of chromosomes 1q, 5p and q, 6p and 14 q [8]. In pineoblastomas, gene expression studies have found high expression of genes also associated with other tumors such as UBEC2, PRAME, and CD24 or with defined developmental as well as tumor-associated functions, such as SOX4 (self-renewal and neural development), TERT and TEP1(telomerase activity), HOXD13 (homeobox gene), and POU4F2 (also expressed in retinal ganglion cells). Pineocytomas showed a gene expression profile associated with phototransduction

in the retina (OPN4, RGS16, and CRB3) and overexpression of TPH and HIOMT, genes involved in melatonin synthesis [15].

14.3 Symptoms and Clinical Signs

Pineal region tumors generally present symptoms of increased intracranial pressure because of obstructive hydrocephalus and/or impairment of ocular movements such as Parinaud's syndrome (upward gaze palsy). The obstructive hydrocephalus is mostly chronic and gradually progressive, presenting with headache, inattention, mental deterioration, double vision, gait imbalance, vomiting, emaciation, and finally disturbance of consciousness.

The clinical course depends on the histological nature of the neoplasm. The patients with aggressive tumors may show acute and severe aggravation of neurological symptoms, whereas the patients with pineocytoma, mature teratoma, and pineal cyst may have a long history of chronic headache. Certain mature teratomas and pineocytomas are indolent tumors. They may present asymptomatic arrested hydrocephalus and be stable for years without progression. Slowly progressive hydrocephalus may cause symptoms of normal pressure hydrocephalus, such as mild mental deterioration (cognitive dysfunction), gait disturbance without limb ataxia, urinary incontinence, and chronic headache.

The disturbance in vertical eye movements is related to three main neuronal structures near the pineal gland, i.e., the posterior commissure, the rostral interstitial nucleus of the medial longitudinal fasciculus, and the interstitial nucleus of Cajal in the midbrain. Among a variety of disease processes that affect the posterior commissure, pineal tumors are the most representative disorder to produce Parinaud's syndrome. A pineal tumor induces Parinaud's syndrome either by direct compression on the posterior commissure or by causing an obstructive hydrocephalus. Hydrocephalus alone produces this syndrome by enlarging the aqueduct, the third ventricle, and the suprapineal recess, thereby stretching or compressing the posterior commissure. A pineal tumor occasionally causes dorsal midbrain syndrome, which includes disturbance of horizontal eye movements, especially convergence. A large benign cystic tumor can compress the trochlear nerve, resulting in minor double vision. Chronic increased intracranial pressure due to hydrocephalus may lead to abducens palsy.

Neurosurgeons who operate on pineal neoplasms should be aware of these anatomical structures and neuro-ophthalmological physiology. In particular, the superior colliculus and the posterior commissure can be easily injured by a radical procedure during tumor resection. Acquaintance with these fragile and important neuronal structures may alter the strategy of neurosurgical intervention to treat pineal tumors, especially germinomas and pineoblastomas, which frequently invade the surrounding neuronal structures, including the periaquedactal white matter.

It is notable that pineal germ cell tumors occasionally involve both the pineal and hypothalamic/pituitary sites and may present with diabetes insipidus as its initial manifestation. Germ cell tumors that exhibit elevated levels of serum human chorionic gonadotropin (HCG)-beta may cause precocious puberty, mainly in young children aged below 10 years.

Pineal tumors also, but infrequently, present with cerebellar ataxia due to a compression of the superior cerebellar peduncle and pyramidal tract signs. Though it is rare, a large tumor causes peduncular hallucinosis, which is characterized by complex visual hallucination. Malignant tumors disseminating through the subarachnoid pathways produce meningeal signs, back pain, radiculopathy, or other diverse neurological symptoms depending on the site of metastasis.

14.4 Diagnosis

Although they are essential tools for the diagnosis of pineal tumors, MRI and CT do not permit a differential diagnosis between pineal parenchymal tumors and germ cell tumors. A craniotomy offers an exact histological diagnosis, and a stereotactic biopsy is feasible for large tumors. Endoscopic technique through the third ventricle is also applied to obtain a biopsy sample and to treat hydrocephalus by a third ventriculostomy.

As germ cell tumors consist of embryonic-type cells, they produce a variety of embryonic proteins, which are recognized as tumor markers. Serological examinations for alpha-fetoprotein (AFP) and HCG-beta will assist in defining their malignancy. In addition to being a useful diagnostic aid, AFP and HCG-beta can be used for monitoring the efficacy of treatment, assessing activity

of a residual disease, and detecting a recurrence. Using immunohistochemistry, placental alkaline phosphatase (PLAP) is positive in most germinomas. The germ cell tumors that show elevations of AFP levels are yolk-sac tumor, embryonal carcinoma, immature teratoma, and mixed germ cell tumors. An AFP level of more than 1,000 ng/mL is characteristically a hallmark of the presence of the yolk-sac tumor component. Serum HCG-beta is elevated in all cases of choriocarcinoma, and also some embryonal carcinomas and mixed germ cell tumors. Almost all germinomas produce a very low level of HCG-beta in serum and CSF.

Pineocytomas are well-circumscribed masses that remain locally confined, whereas pineoblastomas demonstrate local invasion as well as distant spread through the CSF space. Biopsy is necessary to distinguish pineal parenchymal tumors from other pineal tumors. The imaging appearance of pineocytoma, pineal parenchymal tumor of intermediate differentiation (PPTID), and pineoblastoma overlaps considerably [11], although pineocytomas tend to be smaller, round, and homogeneous, while pineoblastomas tend to be larger, lobulated, and heterogeneous. Pineocytomas occasionally appear entirely cystic, similar to a pineal cyst. The peripheral rim-like calcification surrounding a pineal region mass is characteristic of pineal parenchymal tumors, especially pineocytomas. More than half of pineocytomas have either central or peripheral calcifications, and pineoblastomas may also have similar calcifications, but less frequently. The MR appearance of pineal parenchymal tumors is nonspecific; they are usually iso- to hypointense on T1-weighted images, either isointense, hyperintense, or mixed-intense on T2-weighted images, and homogeneously or heterogeneously enhanced on contrast-enhanced T1-weighted images.

Large pineal cysts, a non-neoplastic pineal mass, cause a slight impression on the superior colliculi. The contents of the pineal cyst are homogeneous and are either isointense or slightly hyperintense to CSF on all pulse sequences. After intravenous contrast administration, the thin rim of the cyst is typically partially enhanced.

Pineal germinoma is usually an oval or lobulated solid mass, which is isointense or slightly hypointense on T1-weighted images and isointense or slightly hyperintense on T2-weighted images. Its enhancement pattern is homogeneous and usually well marginated. Multiple cystic areas exist, and a small intratumoral hemorrhage may be seen as well. Pineal germinomas have a propensity to invade the midbrain and thalamus, causing thalamic edema that appears as a hyperintense area on T2-weighted images. On CT, a calcified pineal gland is commonly seen as being surrounded and engulfed by the tumor tissue. A pineal calcification seen in children less than 6 years old is considered "premature calcification" and is often associated with a germ cell tumor or a pineal parenchymal tumor.

Both on CT and MRI, pineal teratomas are extremely heterogeneous masses with an irregular, lobulated outline. They have a solid component, multiple cysts, and calcifications. Fatty components are frequent constituents, and a small intratumoral hemorrhage may be found. Enhancement following contrast administration is observed in the majority of cases, but is absent in some cases. CT is essential in detecting unusual calcifications and adipose tissue of teratomas. Teratomas often include a component of epidermoid cyst, which typically shows high signal intensity on diffusion-weighted MR images. Distinction of mature teratomas, immature teratomas, or other mixed types is impossible on imaging studies alone.

A striking feature of pineal choriocarcinoma, an extremely rare neoplasm, is intratumoral hemorrhage. A massive hemorrhage within a pineal tumor found in a child or young adult is suggestive of a choriocarcinoma. Patterns of focal hyperintensity on T1-weighted images may differentiate choriocarcinomas or teratoma from other pineal tumors. Angiography usually shows pronounced tumor vascularity. The imaging features of yolk-sac tumor and embryonal carcinoma are nonspecific. These tumors often occur as a part of mixed germ cell tumors including an immature teratoma component. They usually appear as a slightly high-density mass on CT and show marked enhancement either homogeneously or heterogeneously after contrast administration. Mixed germ cell tumors, any combination of the above-mentioned histological types, may occur, and any findings on images are not predictive of a detailed histology of these germ cell tumors.

14.5 Staging and Classification

Because each histological type of primary pineal tumor is rare and little is known regarding their clinical behavior, no prospective study to elucidate a proper staging has been reported in the literature. Furthermore, the similarity of the clinical presentation and radiological

findings among the pineal tumors with different histological malignancies makes their management complex and prediction of prognosis difficult.

A number of pineal parenchymal tumors do not fit precisely into either pineocytoma or pineoblastoma and have been termed "pineal parenchymal tumors of intermediate differentiation (PPTID)" by WHO, "mixed pineocytoma/pineoblastoma," or "pineocytoma with anaplasia."

The category of PPTID raises the most problematic issue, both in terms of histological definition and treatment selection. Jouvet et al. proposed a new prognostic classification scheme comprising four grades: grade I for pineocytoma, grade II for pineal parenchymal tumor with fewer than six mitoses and positive immunostaining for neurofilaments, grade III for pineal parenchymal tumor with six or more mitoses but without immunostaining for neurofilaments, and grade IV for pineoblastoma [18]. Older age is clearly associated with low-grade tumors that are less malignant [22]. Fauchon et al. reported that the mean patient ages were 13, 27, 40, and 47 years in patients with pineoblastoma, PPTID (grade III), PPTID (grade II), and pineocytoma, respectively [14]. In addition to the histological grading, an initial clinical staging should include examination of the CSF and MRI of the whole neuraxis because the extent of disease at diagnosis is an important prognostic factor for malignant pineal parenchymal tumors [10, 18, 22].

The histopathological entity "germ cell tumor" encompasses a number of histological subtypes whose prognoses and responses to adjuvant therapy are extremely diverse. For selecting a therapeutic regimen, CNS germ cell tumors have been traditionally divided into two major groups, germinomas and nongerminomatous germ cell tumors, as a simple extrapolation from gonadal germ cell tumors. However, considering the prognoses and to select a treatment plan, CNS germ cell tumors can be grossly divided into three categories, namely, good, intermediate, and poor prognostic groups [24]. Solitary germinoma and mature teratoma are highly curable and classified into the good prognostic group. Embryonal carcinoma, yolk-sac tumor, choriocarcinoma, teratoma with malignant transformation, and mixed GCT including a component of cancer or sarcoma leave patients with a dismal prognosis. Between these good and poor prognostic groups, there are other types of germ cell tumors with an intermediate prognosis, such as immature teratoma, mixed germ cell tumors composed of teratoma and germinoma, and disseminated germinoma.

14.6 Treatment

Planning of the neurosurgical management greatly depends on the biological nature of the individual neoplasm and should be determined by evaluating preoperative radiological findings, levels of serum/CSF tumor markers, and an intraoperative histological diagnosis using frozen sections, as well as the surgeon's experience. Germinoma, which is the most common tumor originating from the pineal body, can be cured by low-dose radiotherapy in combination with chemotherapy, and nowadays needs only to be biopsied (Fig. 14.1). On the other hand, mature teratomas, pineocytomas, and meningiomas can be cured only by a radical surgical resection. Other tumors, such as malignant teratomas, pineoblastomas, embryonal carcinomas, choriocarcinomas, and yolk-sac tumors need a sophisticated combination therapy that includes surgery, craniospinal radiation therapy, and intensive chemotherapy. For such tumors, neurosurgeons have to recognize that a surgical resection is only part of the combination therapy. For instance, an application of an appropriate neoadjuvant therapy prior to radical surgical removal will remarkably reduce the surgical risk for a complete resection of a highly malignant, large pineal neoplasm, in particular yolk-sac tumors.

The goal of treatment should be tightly focused on the reduction of post-treatment sequelae including surgical morbidity, but not on a complete microsurgical resection itself. Both the occipital transtentorial approach and the infratentorial supracerebellar approach have become safe surgical procedures in the experienced neurosurgeon's hands. Recently, a vast majority of neurosurgeons prefer the occipital tentorial approach to the infratentorial route, although small tumors located in a confined area of the midline quadrigeminal cistern and the posterior third ventricle are safely removed by the infratentorial approach.

14.6.1 Surgery

Approximately one third of pineal region tumors are benign, including pineocytomas, mature teratomas, falcotentorial meningiomas, neurocytomas, hemangioblastomas, cavernous hemangiomas, gangliogliomas, and symptomatic pineal cysts. For these, microsurgery

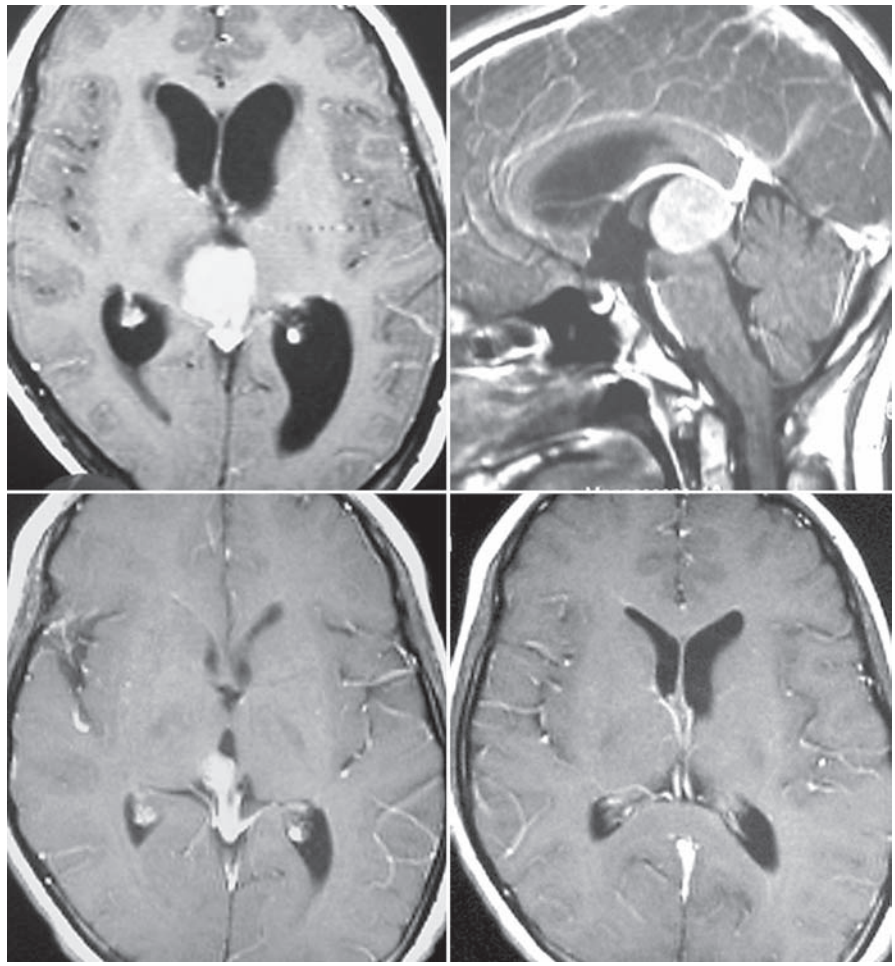

Fig. 14.1 (**a, b**) A large pineal tumor occurring in a 12-year-old girl presenting with Parinaud's syndrome, vomiting, and bilateral abducens palsy. Germinoma was verified by a biopsy using a CT-guided stereotactic procedure. (**c**) Two weeks after the initiation of the first course of a cisplatin-based chemotherapy, the tumor shrunk remarkably in size, and the hydrocephalus was resolved with symptoms. During the chemotherapy, the hydrocephalus was controlled by a ventricular drainage placed during the biopsy. Shunting surgery is not necessary in cases of germinoma. (**d**) After three courses of chemotherapy and before radiation therapy, the germinoma completely disappeared on MR image

alone can be curative. These tumors are the target of surgical eradication.

Although in general a greater resection of the malignant neoplasm is associated with a better prognosis for patients, a radical surgical resection of invasive tumor in the pineal region carries a significant risk of operative morbidity. The primary goal of surgery for pineal germinomas should be to obtain a sufficient volume of tumor tissue for an accurate histological examination. If preoperative radiological studies indicated a strong suspicion of germinoma, biopsy samples should be obtained by a craniotomy, stereotactic, or endoscopic procedure. Especially endoscopic surgery is less invasive and allows both biopsy and third ventriculostomy to solve obstructive hydrocephalus. When an intraoperative histological diagnosis of germinoma was made during craniotomy, no risk should be taken in continuing the resection, because near the end of tumor resection, we often encounter a residual mass invading the posterior commissure, the periaqueductal white matter, the superior colliculus, and the posterior thalamus. Stopping the procedure at this point will reduce the complication rate significantly without reducing the cure rate of this unique neoplasm.

There are two major surgical approaches to the pineal tumors: the infratentorial supracerebellar approach and the occipital transtentorial approach [25]. Krause was the first to use the infratentorial supracerebellar approach to the quadrigeminal plate, and by the 1920s he had successfully treated three cases. Using microsurgical techniques, Stein developed this approach further during the 1970s. Poppen experimented with the right suboccipital approach in one case; he lifted the occipital lobe after having introduced a catheter into the ventricle to drain the cerebrospinal fluid. Jamieson modified this approach by mobilizing the occipital pole laterally rather than

using an approach below it. With increasing experience and developed technique, the occipital transtentorial approach is allowing the resection of almost all pineal tumors.

On the way to the pineal body, the prominent obstacle is the Galenic venous system (Fig. 14.2). The vein of Galen gathers several important tributaries. The superior vermian vein and the precentral cerebellar vein run in the midline and into a dorsocaudal part of the great vein of Galen. The internal cerebral veins and the pineal veins join ventrally. With pineal tumors, the posterior portion of the internal cerebral veins is always elevated superiorly, and the veins are occasionally separated from each other. On the lateral aspect of the great vein, the medial occipital veins, the third segment of the basal veins of Rosenthal, and the posterior mesencephalic veins join. The pineal veins, which are the draining veins of pineal tumors, drain into either the posterior portion of the internal cerebral veins or directly into the vein of Galen. The superior vermian vein, the precentral cerebellar vein, and the pineal veins can be sacrificed, but all the other veins must be preserved. An injury to the basal vein or the internal cerebral vein will yield serious complications, and a transection of a major medial occipital vein may cause homonymous hemianopsia or visual seizures.

The choice of approach will depend on the angle of the straight sinus, the size and location of the tumor, the presence or absence of obstructive hydrocephalus, and in particular the direction of displacement of the quadrigeminal plate (Fig. 14.3).

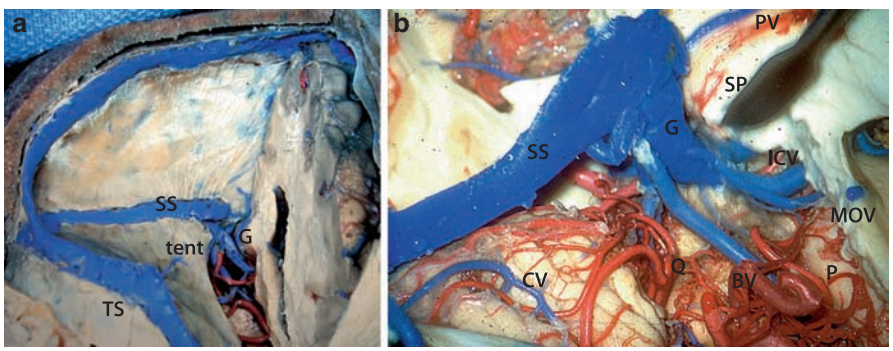

Fig. 14.2 (**a, b**) Overview of the pineal region through the right occipital area. The occipital lobes, the falx, the tentorium, and the arachnoid membranes have been removed. *BV* Basal vein of Rosenthal, *CV* cerebellar vermis, *G* great vein of Galen, *ICV* internal cerebral vein, *MOV* medial occipital vein, *P* pulvinar, *PV* pericallosal vein, *Q* quadrigeminal plate, *Sp* splenium, *SS* straight sinus, *TS* transverse sinus

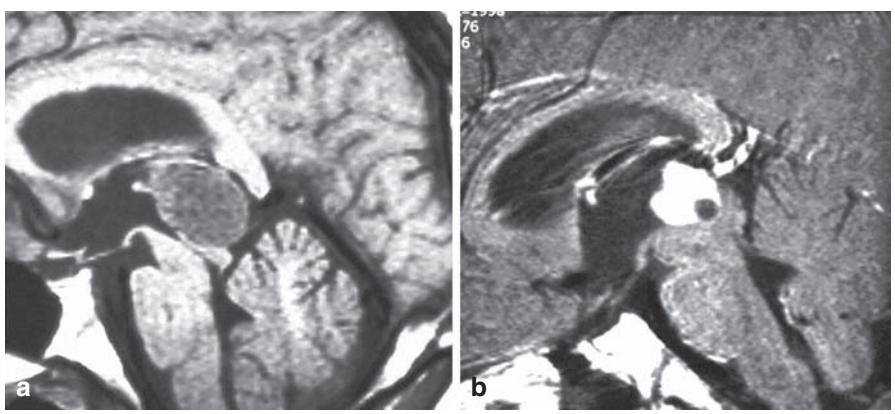

Fig. 14.3 (**a**) An embryonal carcinoma in a 19-year-old man. A pineal tumor like this, lying strictly in the midline and in the posterior part of the third ventricle and compressing the quadrigeminal plate caudally, can be approached infratentorially. (**b**) A pineal germinoma in a 9-year-old boy. When a tumor lies more caudally and pushes the quadrigeminal plate dorsally, the occipital approach is more appropriate. Pineal tumors often extend into the supratentorial segment of the aqueduct

The angle of the straight sinus is quite variable from one patient to another. When we apply the infratentorial approach, a very steep angle of the straight sinus makes it necessary to retract the cerebellum downwards rather extensively. Lateral exposure of the surgical space is also restricted for a large tumor, although this is not a problem in the case of a small tumor. In cases with a steep angle of the straight sinus, the occipital transtentorial approach is preferable.

A pineal tumor may lie more or less ventrally in the pineal area. Its relationship with the quadrigeminal plate, the splenium of the corpus callosum, and the venous system varies. The tumors lying strictly in the midline and in the posterior part of the third ventricle anterior to the pineal gland, and compressing the tectum of the midbrain caudally, can be approached infratentorially because this approach will allow direct access and symmetrical exposure of the walls of the third ventricle and the internal cerebral veins on both sides. This approach, however, requires a sacrifice of the veins bridging the straight sinus, the cerebellum, and the tentorium, such as the superior vermian vein and the precentral cerebellar vein. It may occasionally cause venous infarction and postsurgical ataxia. Given these drawbacks, we have recently been using the occipital transtentorial approach alone.

Pineal tumors often extend into the supratentorial segment of the aqueduct, and as a consequence the tumors depress the quadrigeminal plate dorsally. In such cases, the infratentorial approach is not applicable, because the colliculi definitely obstruct the tumor. A large tumor compressing or invading the pulvinar thalami is approached by the occipital transtentorial route, which gives a wider lateral exposure than the infratentorial route does.

Obstructive hydrocephalus is frequently present, but no preoperative shunting should be performed before craniotomy. Indeed, taping the lateral ventricle at the beginning of operation makes retraction of the occipital lobe extremely easy and opens a highway to the pineal area. However, if there is no hydrocephalus or if shunting was placed previously, the retraction of the occipital lobe may be somewhat difficult. In such cases, CSF can be aspirated from the quadrigerminal or supracerebellar cistern by retracting the occipital lobe gently. Shunting should be avoided in cases of germinomas or other malignant neoplasms because of the potential for peritoneal metastasis through the shunt.

Infiltrative tumors may invade the posterior commissure and the periaqueductal neuronal tissue. In such cases, extremely careful observation is necessary in order to keep these neuronal tissues intact during a tumor resection; otherwise, postsurgical gaze palsy will remain permanently.

Double vision may be minor, but is the most frequent postsurgical morbidity. Potential complications of the infratentorial approach are transient or permanent ataxia due to cerebellar vermis infarction caused by excessive down retraction of the cerebellum and sacrifice of bridging veins over the superior surface of the cerebellum. The complications of the occipital approach are mainly hemianopsia, visual seizures, or metamorphopsia due to excessive retraction of the occipital lobe or injury of the internal occipital veins. Usually no significant surface bridging veins are present in the occipital area, but in cases they are, their sacrifice can lead to hemorrhagic infarction of the occipital lobe. Care also should be taken to minimize CSF draining from the ventricle. A lethal complication may occur as a result of an injury to the great vein of Galen, an uncontrollable arterial bleeding in the ambient cistern, or an air embolism while the patient is in the sitting position. Major complications are induced by impairment of venous circulation through the deep major veins, in particular the internal cerebral veins or the basal veins, whose injury will cause venous infarction in the areas including the thalamus, the diencephalon, the mesial temporal lobe, and/or the internal capsule.

14.6.2 Radiotherapy and Chemotherapy

Pineocytomas are usually curable by a total surgical resection or a partial surgical resection with adjuvant radiation therapy. Some pineocytomas in the pediatric population, however, are aggressive, with a high propensity for leptomeningeal dissemination [12]. However, all patients with pineoblastoma should be treated with intensive adjuvant therapy. PPTID also requires postsurgical adjuvant therapy. For these malignant pineal parenchymal tumors, the median total dose administered to the pineal region was approximately 54 Gy [22, 26]. Pineoblastomas that frequently disseminate through the CSF pathway require craniospinal irradiation, as the CCG-921 trial

report suggested that craniospinal irradiation has a significant impact on survival with a 3-year event-free survival of 61% in children [17]. In the literature, various chemotherapeutic agents and response to chemotherapy are also documented only in pediatric series. No standard regimen, however, has been established for young children with malignant pineal parenchymal tumors [14, 17].

A complete surgical removal alone inevitably causes an early relapse of the germinoma. It is, therefore, clear that a radical resection of pineal germinoma offers no benefit over biopsy [23]. Germinomas are so radiosensitive that they occasionally show regression even after the radiation for diagnostic angiography. Tumor regression after a very small dose of radiation is suggestive of germinoma. Germinomas tend to be treated with a lower dose of irradiation than those used with conventional radiotherapy of 40–55 Gy [6]. Bayens et al. suggested that the outcomes of patients with germinoma treated with a dose of 30 Gy were comparable to those of patients with testicular germinoma treated with a similar dose [7].

Preirradiation chemotherapy has been advocated as an adjuvant therapy to further decrease the total volume of irradiation [2]. It is known that germinomas are highly chemosensitive tumors, and the agents that have been examined in previous clinical studies are bleomycin, carboplatin, cisplatin, cyclophosphamide, etoposide, ifosfamide, and vinblastine [1–3, 5, 9]. The most common combination in chemotherapeutic regimens includes carboplatin/cisplatin plus etoposide. A European study has suggested that preirradiation chemotherapy followed by 30–40 Gy of irradiation may be adequate for treating germinomas [9]. Aoyama et al. reported the results of an induction chemotherapy followed by 24 Gy of irradiation in 12 fractions to the involved field. With a mean follow-up duration of 58 months, 6 of 27 patients with germinoma had a relapse [3]. This high relapse rate is attributed to the small radiation field that they employed. The whole ventricle is recommended as the smallest target volume for germinoma [28].

Biopsy failure of a mixed GCT may be not rare. If a mixed GCT is mistakenly interpreted as "pure germinoma" after a biopsy, at least the germinoma component can be eradicated by an adjuvant therapy, and other components, such as epidermoid cyst or immature teratoma, may remain. After that, a second-look surgery is feasible to resect the residual tumor that was resistant to the adjuvant therapy. For the highly malignant germ cell tumors, no standard chemotherapeutic regimen has been established. They, as well as pineoblastomas, are treated by craniospinal irradiation with local boost and intensive chemotherapy. Neoadjuvant therapy, including chemotherapy and radiation therapy, has recently been advocated in the treatment of large and malignant pineal tumors, in particular AFP-producing germ cell tumors [20]. After giving an effective neoadjuvant therapy and obtaining visible tumor-bulk reduction on neuroimaging, a safer and complete surgical resection can be performed.

14.7 Prognosis/Quality of Life

Pineocytomas are found in older individuals than pineoblastomas and show better prognosis after surgery. Except for certain pediatric cases, a complete removal usually yields long-term control or cure. In contrast, pineoblastomas and PPTID have a poor prognosis like malignant neoplasms. Fauchon et al. reported a series of 76 patients with pineal parenchymal tumors in which the 5-year survival was 91%, 74%, 39%, and 10% for grades I, II, III, and IV tumors, respectively. Histology and tumor volume were significant prognostic factors, but the extent of surgery and radiotherapy had no clear influence on survival [14].

In a multicenter, large, retrospective study reported by Lutterbach et al. [22], the median survival of 101 patients at least 18 years of age who received radiation therapy for a malignant pineal parenchymal tumor was 100 months, and the 10-year survival rate was 41%. In their study, the variables that significantly influenced the survival were the extent of disease at diagnosis (localized vs disseminated), histological differentiation (PPTID vs pineoblastoma), and residual disease after initial treatment (no residual vs major residual). Late relapses were common, and the median overall survival in patients with local or spinal failure was only 15 months.

The prognosis for each subtype of germ cell tumor is diverse. Sawamura et al. have analyzed the records of 109 patients undergoing treatment mainly with radiation therapy [24]. With a median follow-up duration of over 6 years, the probability of surviving 5 years was better than 90% for patients with a pure germinoma or mature teratoma. The 5-year overall survival rate in patients

with an immature teratoma with or without a germinoma component was approximately 65%. Patients with germ cell tumors that included a highly malignant component, such as an embryonal carcinoma or yolk-sac tumor, exhibited a poor prognosis with an approximately 40% chance of 5-year survival.

Quality of life of long-term survivors depends on the severity of the initial manifestation and densities of treatments, including surgical intervention, dosage of radiation therapy, and intensity of chemotherapy. Although no data were available in the literature concerning the quality of life, at least the delayed toxicity of craniospinal irradiation has to be considered before selecting an initial treatment plan, especially in young children whose CNS are vulnerable to radiation therapy. The CCG-921 trial reported that all 12 children aged 9 years or less who received craniospinal radiation therapy for malignant pineal tumor had significant neurocognitive deficits [17].

14.8 Follow-Up/Specific Problems and Measures

Malignant pineal tumors often disseminate from the pineal region by direct infiltration or spread along the CSF pathways. Treatment failure is found both in the pineal region and distant sites with evidence of relapse. An adequate neurological examination and craniospinal MRI scans are, therefore, necessary for patient follow-up. For germ cell tumors, monitoring of the levels of HCG-beta and AFP has proven useful for the early detection of tumor recurrence or relapse. Measurement of the tumor markers often serves for more sensitive detection of the recurring disease than does MRI of the whole neuraxis.

14.9 Future Perspectives

Curability and quality of life in patients with a benign pineal tumor have been dramatically improved along with the development of modern neurosurgery. In contrast, many fundamental issues regarding the therapeutic management of malignant pineal tumors remain to be investigated, such as the prognostic effect of the extent of resection, the curative radiation dosages, and the role of chemotherapy. These issues need to be clarified in future prospective trials, although the low incidences of each pineal tumor may make the trial design difficult.

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