Chapter 25
Management of Pineal Region Tumors

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Key Points

- Pineal region tumors account for around 1% of intracranial tumors in the general population.
- The most frequent histological types of pineal region tumors are germ cell tumors, pineal parenchymal tumors, gliomas, and meningiomas.
- No specific MRI feature helps to differentiate a single pineal tumor.

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- The clinical outcome in pineal region tumors heavily depend on the tumor entity and extent of surgical resection.
- Radiochemotherapy protocols for pineal tumors are in constant evolution and should be properly delivered.

25.1 Introduction

The pineal region (quadrigeminal cistern or posterior incisural space) is one of the most surgically challenging areas of the brain as it is surrounded by important structures such as the third ventricle, the corpus callosum, the thalamus, the quadrigeminal plate of the midbrain, the cerebellum, the deep venous system, and the choroidal arteries [1, 2]. Pineal region tumors account for around 1% of intracranial tumors in the general population, and 2.5–8.5% of pediatric intracranial tumors [3, 4]. The prevalence of pineal region tumors varies between geographical regions. Germ cell tumors (GCTs) are frequent lesions in Asian and American countries, while pineal parenchymal tumors (PPTs) seem more frequent in some European countries [3, 5–8]. PPTs, GCTs, gliomas, and meningiomas of the pineal region comprise most of pineal region tumors. However, hemangioblastomas, solitary fibrous tumor/hemangiopericytomas, ependymomas, epidermoid tumors, choroid plexus papillomas, metastatic tumors, among others, are also present in this region [9].

Over the years, various approaches have been developed for dealing with pineal lesions, all aimed at providing safe access to the region while minimizing neurovascular manipulation [1, 2, 10, 11]. After the first palliative operations in hopeless cases, using bitemporal or occipital decompression [12–14], a direct exposure of pineal lesions was reported by various authors (such as Horsley, Brunner, Schloffer, and Puusep) through infratentorial, supratentorial transcallosal, and temporal routes, but with quite unfavorable outcomes [1, 2].

In 1913, Oppenheim and Krause described the first successful removal of a pineal region tumor via the supracerebellar infratentorial route [15]. In 1921, Dandy published the first clinical experiences with the interhemispheric transcallosal approach to the pineal region that became the most used route, thanks to the good post-operative results [16, 17].

In 1931, Van Wagenen proposed a more invasive transcortical transventricular approach for pineal region lesion [18], that was subsequently used in a series of 19 cases by Suzuki and Iwabuchi [19]. In 1966, Poppen presented a modification of the occipital interhemispheric transtentorial approach, initially described by Horrax in 1937 [20, 21]. Later, with the introduction of the operating microscope, this approach was refined by Yasargil for dealing with vein of Galen malformations [22, 23].

Indeed, the introduction of the microsurgical technique, as well as advancements in neuroanesthesia, resulted in a marked improvement of postoperative results.

Stein refined the Krause's infratentorial supracerebellar approach [24, 25], which was later employed by Konovalov and Pitskhelauri for the resection of third ventricle colloid cysts [6].

Yasargil described the paramedian supracerebellar approach for dealing with superior cerebellar artery aneurysms [26]. Van den Bergh reported the lateral-paramedian infratentorial route for pineal lesions [27], which was refined by Ogata and Yonekawa for approaching upper brainstem and peduncular lesions [28].

A purely endoscopic fenestration of quadrigeminal region arachnoid cysts using a supracerebellar infratentorial corridor was first described by Ruge in 1996 [29], while Gore, in 2008, reported the first purely endoscopic pineal cyst removal through the same route [30–32].

Nowadays, a complete microsurgical removal still represents the mainstay for the treatment of benign pineal tumors. Moreover, in most of the cases, an extensive resection with an accurate histologic diagnosis also plays a key-role when dealing with malignant tumors for planning adjuvant therapies and, ultimately, for determining the final prognosis [3, 5, 7, 8, 33–35].

25.2 Anatomic Consideration

25.2.1 Pineal Gland Physiology

The primary function of the pineal gland is the synthesis and secretion of the hormone melatonin, which takes place in all vertebrates, investigated to date, during nighttime only [36, 37]. This rhythm in melatonin production is directed by efferent signals from the circadian master clock, residing in the hypothalamic suprachiasmatic nucleus (SCN). SCN signals reach the pineal gland by a multisynaptic pathway (Fig. 25.1), involving the paraventricular nucleus and intermediolateral cell column of the thoracic spinal cord, harboring the perikaria of postganglionic sympathetic fibres in the superior cervical ganglia, the so-called *nervi coronarii*, that project to the pineal gland [36, 37]. Central mediators of this pineal stimulation at nighttime are norepinephrine and neuropeptide-Y [38]. Activation of α_1 and β_1 adrenergic receptors in the pineal gland increases cAMP and Ca^{2+} concentrations in pinealocytes and activates the rate-limiting enzyme for melatonin synthesis, the aralkylamine *N*-acetyltransferase [39]. Elevated melatonin synthesis is readily inhibited by light during nighttime [40]. A notable feature exclusive to the human pineal gland is that it becomes calcified with age (acervulus, see Fig. 25.2) [41]. This process begins around the age of 16; its effects on function or developmental mechanisms are not well understood. Pineal calcification does not markedly interfere with the capacity of melatonin production, but it remains a prominent landmark in imaging techniques used to investigate the human brain [42].

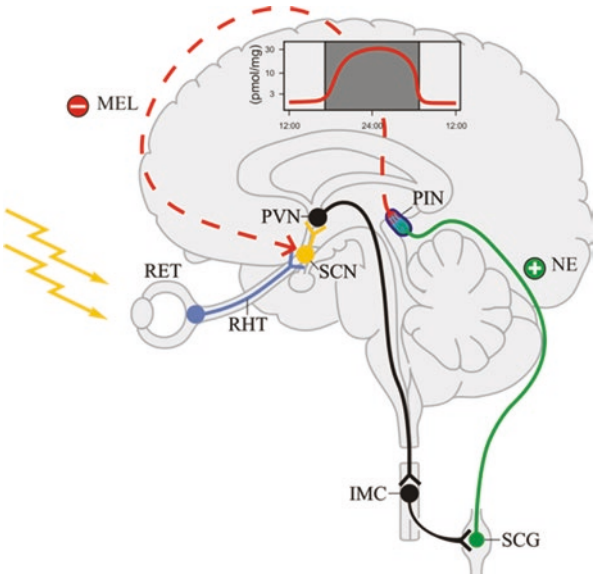

Fig. 25.1 The photoneuroendocrine system in the human. The photoneuroendocrine system consists of the retina (RET), which perceives environmental light information and the retinohypothalamic tract (RHT), which transmits light signals to the suprachiasmatic nuclei (SCN). The SCN constitutes the site of the endogenous circadian oscillator. SCN-efferent circadian cues are transmitted via the paraventricular nuclei (PVN) and the intermediolateral column of the spinal cord (IMC) to the superior cervical ganglia (SCG). Postganglionic sympathetic fibers stimulate the nocturnal increase in melatonin synthesis (MEL) through norepinephrine (NE). MEL can then provide feedback to the endogenous clock. The inset schematically shows dynamics of melatonin synthesis in the human pineal gland while the shaded area represents the night (modified from Stehle et al. 2011 [37])

25.2.2 Cellular Composition of the Pineal Gland

The pineal gland isnext to glial cells, predominantly composed of neuroendocrine cells, the pinealocytes *sensu strictu*. Thus, pineal tumors derive mainly from three cell types, namely from germ cells (most frequent tumor examples include germinoma, teratoma, choriocarcinoma, yolk sac tumor), pineal cells *sensu strictu* (pineocytoma, pineoblastoma, pineal tumor of intermediate differentiation) and differentiated astrocytes (rare e.g. astrocytoma) [33, 43]. Papillary tumors of the pineal region (PTPR) derive from ependymal cells of the subcommissural organ [44]. In addition, to these types the pineal gland contains small populations of other cell types including interstitial cells, perivascular phagocytes and endothelial cells [42].

25.2.3 Pineal Region and Vascular Relationships

Rhoton et al. performed an excellent summary of surgical interventional approaches to the pineal region [45–47]. The pineal region is surrounded by a roof, a floor as well as anterior and lateral walls (Fig. 25.3) [37]. The roof is formed by the lower

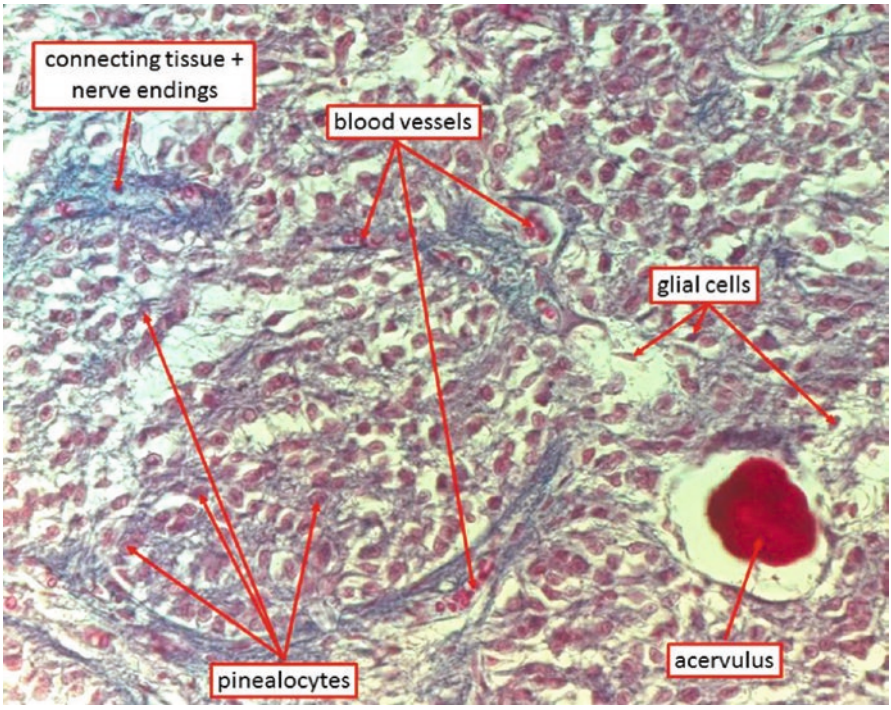

Fig. 25.2 Histology of the human pineal gland. Note that about 95% of all cells are neuroendocrine pinealocytes sensu strictu. Note the calcification products (acervulus)

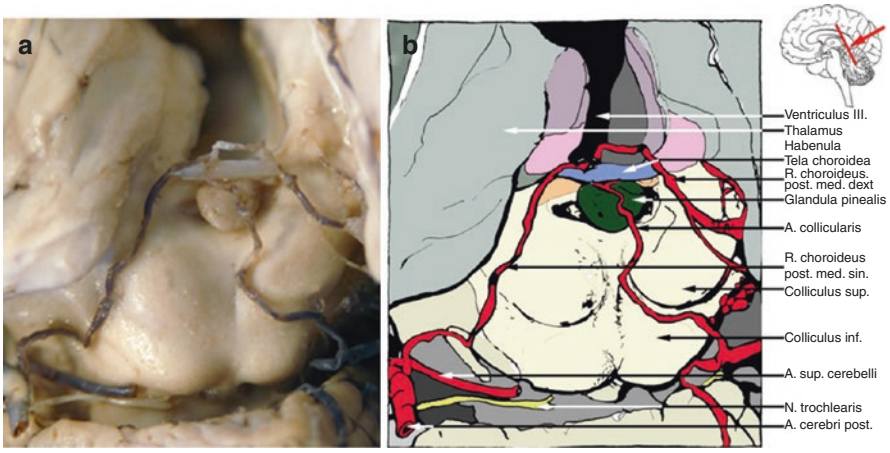

Fig. 25.3 Topographic anatomy and vascularisation of the human pineal gland (*glandula pinealis*). (**a**) Photographic picture of an unfixed and unstained human brain, demonstrating in situ the topographic localization of the pineal gland and neighbouring vascularisation as seen from the dorsal aspect. (**b**) Corresponding drawing of the image shown in (**a**) with visible structures indicated and named. Red arrow in the schematically drawn whole brain image shown in the upper right corner indicates the direction of inspection. For better visualisation of the human pineal gland, parts of the brain have been removed. Anatomical denominations were done according to the *Nomina anatomica* (Modified from Stehle et al. 2011 [37])

surface of the splenium, the terminal part of the crura of the fornices and the hippocampal commissure. The floor consists of the vermian culmen medially and the cerebellar lobules laterally. The anterior wall is shaped by the pineal body superiorly, the quadrigeminal plate centrally and the vermian lingula and cerebellar peduncles inferiorly. The posterior portion of the third ventricle and the cerebral aqueduct run ventral to the anterior wall of the pineal region.

Particularly, the survey of the dense vasculature surrounding the pineal gland underscores the neuroendocrine function of this structure, readily releasing melatonin upon synthesis into the blood stream, rather than storing the hormone. The quadrigeminal cistern contains the neurovascular structures of the pineal region, of which main arterial structures are formed by the posterior cerebral artery (PCA) and the superior cerebellar artery (SCA). The P3 segment of the PCA crosses the pineal region to bifurcate into the calcarine and parietooccipital arteries, whereas medial posterior choroidal arteries run aside the pineal body to enter the velum interpositum to supply the choroid plexus. The lateral posterior choroidal arteries pass around the posteromedial surface of the pulvinar to enter the choroidal fissure. Lastly, the SCA runs into the pineal region in the cerebello-mesencephalic fissure to supply the superior cerebellar surface. A separate entity is formed by the tentorial arteries: The arteries of Bernasconi and Cassinari from the meningohypophyseal trunk, the marginal tentorial artery from the inferolateral trunk, which runs laterally to the abducens nerve and then superior-posteriorly to the trochlear nerve prior to terminating in the tentorial edge. The meningeal branch of the SCA and the tentorial branch of the proximal PCA arising as a long, circumflex artery and running around the brainstem to access the tentorium at is apex complete the group of tentorial arteries [48]. Venous structures of the pineal region include the internal cerebral veins, the basal veins, the vein of Galen, the precentral and vermian veins, and the internal occipital veins. These vessels drain the pineal body into the straight sinus. After the internal cerebral veins exit the velum interpositum and the basal veins exit the ambient cistern, they receive flow from the occipital veins draining the medial surfaces of the occipital lobes as well as the precentral and vermian veins and small tributaries from the pineal region walls.

25.3 Surgical Indications of Pineal Region Tumors

The role of surgical resection of pineal tumors has largely increased in the last decades due to the value of accurate tissue diagnosis combined with the improvement in microsurgical techniques [2, 6, 9, 49]. The pineal region is one of the most complex areas of the brain regarding pathological types. Therefore, requiring proper histological diagnosis for planning of further optimal treatment.

Previously during the pre-microsurgical era, a non-surgical conservative management with empiric radiation was favored, this was mainly due to the high radiotherapy response of some tumors and due to the relative high morbidity after surgical resection [50]. However, this approach of “empiric and blind radiation” led to

unnecessary and potentially harmful radiation exposure to patients harboring benign or radiation-resistant tumors. Currently, management of pineal tumors incorporates surgical resection in the majority of cases with data supporting better outcomes after resection [2, 6, 9, 51–53]. Moreover, treatment strategies require tumor tissue for adequate tailoring of co-adjuvant therapies, prognosis and follow-up plans.

Strategies available for patients with pineal region lesions include: 1) confirm diagnosis, 2) manage associated symptoms like hydrocephalus or mass effect, and 3) cytoreduction or tumor debulking. These treatment strategies should be tailored according to patients' clinical condition, tumor markers, dissemination, age and general clinical condition [49, 54–56]. An important aspect for the surgical management of pineal regions lesions is to rule out the presence of pineal cysts, since these lesions are benign, normal variants of the gland and generally asymptomatic and do not require treatment unless clear surgical indications [57, 58].

25.3.1 Biomarkers for Pineal Region Tumors

The presence of alpha-fetoprotein (AFP), beta-human chorionic gonadotrophin (HCG), and placental alkaline phosphatase measurable in CSF or serum is pathognomonic of malignant germ cells elements and it precludes the needs of surgical resection [4, 59–61]. These three clinical tumor markers are helpful to neurosurgeons while establishing a postoperative baseline for further follow-up and tumor recurrence detection. More importantly, they reliably indicate the presence of a GCT, allowing the patients primary radiation and chemotherapy. No available biomarkers currently exist for the management of pineal parenchymal tumors. However, melatonin tests may be useful for monitoring response to treatment [43].

25.3.2 Hydrocephalus in Pineal Region Tumors

Patients suffering of obstructive hydrocephalus can be managed in several ways: a) Mildly asymptomatic or slowly progressive hydrocephalus often resolves without requiring CSF diversion procedures following resection of the pineal mass and the aqueductal compression is relieved, since the third ventricle communicates with the fourth ventricle through the cerebral aqueduct. The aqueductal compression is relieved; b) Slightly symptomatic patients in whose total gross resection is anticipated, would benefit of placing an external ventricular drainage during the surgical resection [4, 49]. Acute symptomatic hydrocephalus may require CSF diversion procedures such as: endoscopic third ventriculostomy or placement of a shunt. An endoscopic third ventriculostomy is preferred in this group of patients, since it reduces the risk of shunt-associated complications such as infection, peritoneal seeding, or over shunting among others [4, 56].

25.3.3 Surgical Removal of Pineal Region Tumors

As mentioned before, tissue diagnosis is necessary to optimize a treatment plan given the histological diversity of this region [4, 62]. Tissue diagnosis can be obtained through biopsy or open surgical resection. Surgeons should take careful considerations of patient's clinical condition, tumor radiological characteristics and surgical experience with lesions around this area while considering one procedure or another.

Patients with known primary systemic tumors, multiple lesions, and presence of previous diseases which would increase surgical risks are good candidates for stereotactic biopsy [4, 49]. Stereotactic biopsy has the advantages of short surgical time, minimal risk of complications, minimal anesthesia and less complexity procedures. However, the risk of bleeding remains high after injury of the deep venous system or presence of highly vascularized tumors [63]. Lately, neuroendoscopic biopsy has become an alternative option to stereotactic biopsy, with flexible endoscopes available for biopsy and third ventriculostomies [55, 56, 64]. Open microsurgical resection has the advantages of providing larger amounts of tissue sample and to achieve further cytoreduction or tumor debulking. Surgical resection is usually complete and curative for tumors that are benign. Patients with malignant tumors benefit for a more radical resection when possible to enhance the response adjuvant therapy [6, 52, 53].

25.4 Imaging Features

The high variation of pineal region tumors contrasts with the low predictive value of magnetic resonance imaging (MRI) studies. Currently, no specific MRI feature helps to differentiate a single pineal tumor [65–68].

25.4.1 Pineal Parenchyma Lesions

25.4.1.1 Pineocytomas

Pineocytomas are composed of well-differentiated pineocytes and are considered slow-growing tumors (Grade I) based on the WHO classification [62]. Due to the well-differentiated nature, pineocytomas are difficult to distinguish from the normal pineal gland parenchyma. They are well circumscribed and unencapsulated tumors that arise and expand from the normal pineal gland. Additionally, these lesions show the characteristic "explosion" of the pineal calcifications towards the periphery [69]. On MRI, pineocytomas show low to intermediate signal on TI-weighted images (TIWI), and high to intermediate signal on T2-weitgthed images (T2WI) (Fig. 25.4) [70]. Pineocytomas typically express prominent contrast enhancement, and occasionally, cystic components demonstrating internal or nodular wall enhancement on post-contrast imaging [71].

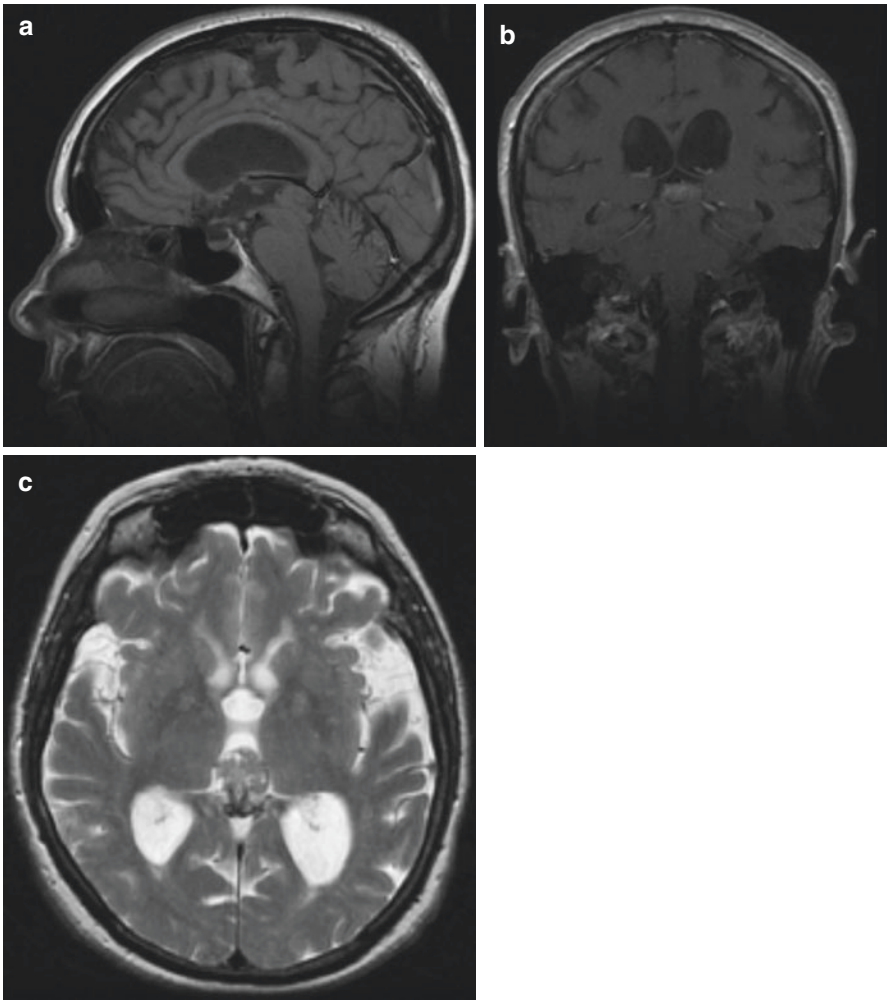

Fig. 25.4 Pineocytoma in TIWI (**a**), T1WI with contrast (**b**), and T2WI (**c**) MRI sequences

25.4.1.2 Pineal Parenchyma Tumour of Intermediate Differentiation

Pineal parenchymal tumors of intermediate differentiation (PPTIDs) have similar characteristics as pineocytomas or pineoblastomas, since they contain diffuse sheets or lobules of cells. Additionally, the cells show mild to moderate nuclear atypia and low to moderate mitotic activity [62]. PPTIDs often show intermediate to high signal on T2WI, typically show contrast enhancement and may contain cystic areas, however, no specific MRI findings distinguish PPTIDs from pineocytomas or pineoblastomas (Fig. 25.5) [62, 70, 71].

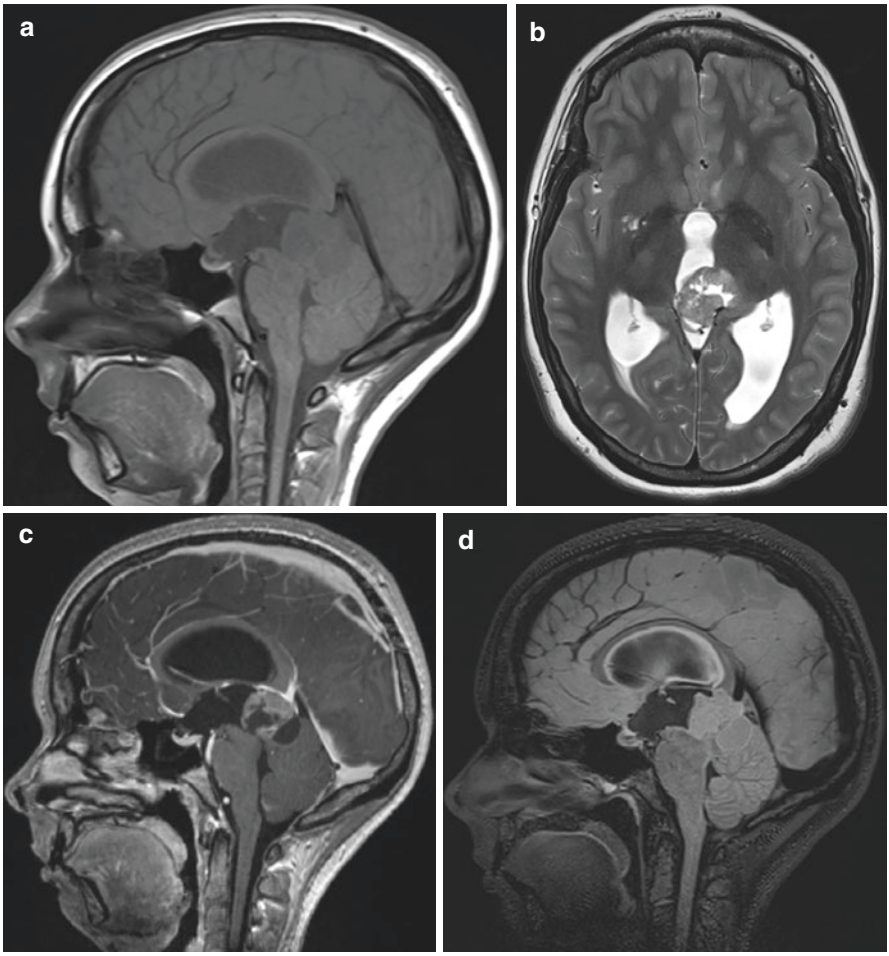

Fig. 25.5 PPTID in TIWI (**a**), T2WI (**b**), T1WI with contrast (**c**), and FLAIR (**d**) MRI sequences

25.4.1.3 Pineoblastomas

On MRI, pineoblastomas usually appear as large, lobulated and enhanced lesions [71]. Pineoblastomas show low to intermediate signal on T1WI and intermediate to high signal on T2WI (Fig. 25.6) [72]. Due to their aggressive and malignant nature, it is not uncommon to find hemorrhage or necrosis inside the lesion. A helpful aspect to differentiate pineoblastomas among other pineal region neoplasms is the occasional infiltration into adjacent structures with CSF seeding and dissemination into the subarachnoid space [69]. Additionally, these tumors have restricted diffusion on diffusion-weighted images and low minimum apparent diffusion coefficient (ADC). On magnetic resonance spectroscopy, pineoblastomas show elevated choline and decreased N-acetylaspartate values, as well as slightly elevated glutamate and taurine peaks [70].

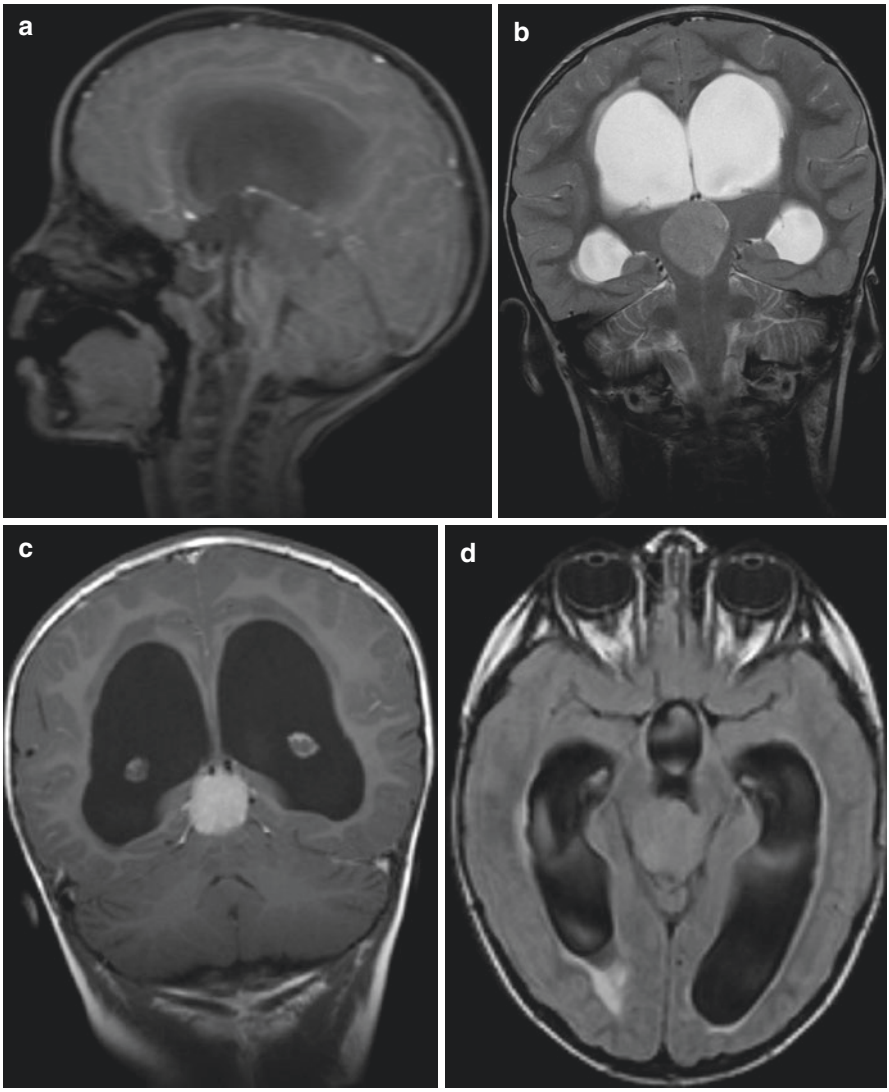

Fig. 25.6 Pineoblastoma in TIWI (**a**), T2WI (**b**), T1WI with contrast (**c**), and FLAIR (**d**) MRI sequences

25.4.2 Papillary Tumor of the Pineal Region

The PTPR is the most recently identified type of pineal tumor [62]. Histologically, PTPRs contain epithelial-like growth patterns and fibrovascular papillae associated with a well-defined secretory function [33, 44]. PTPRs present as

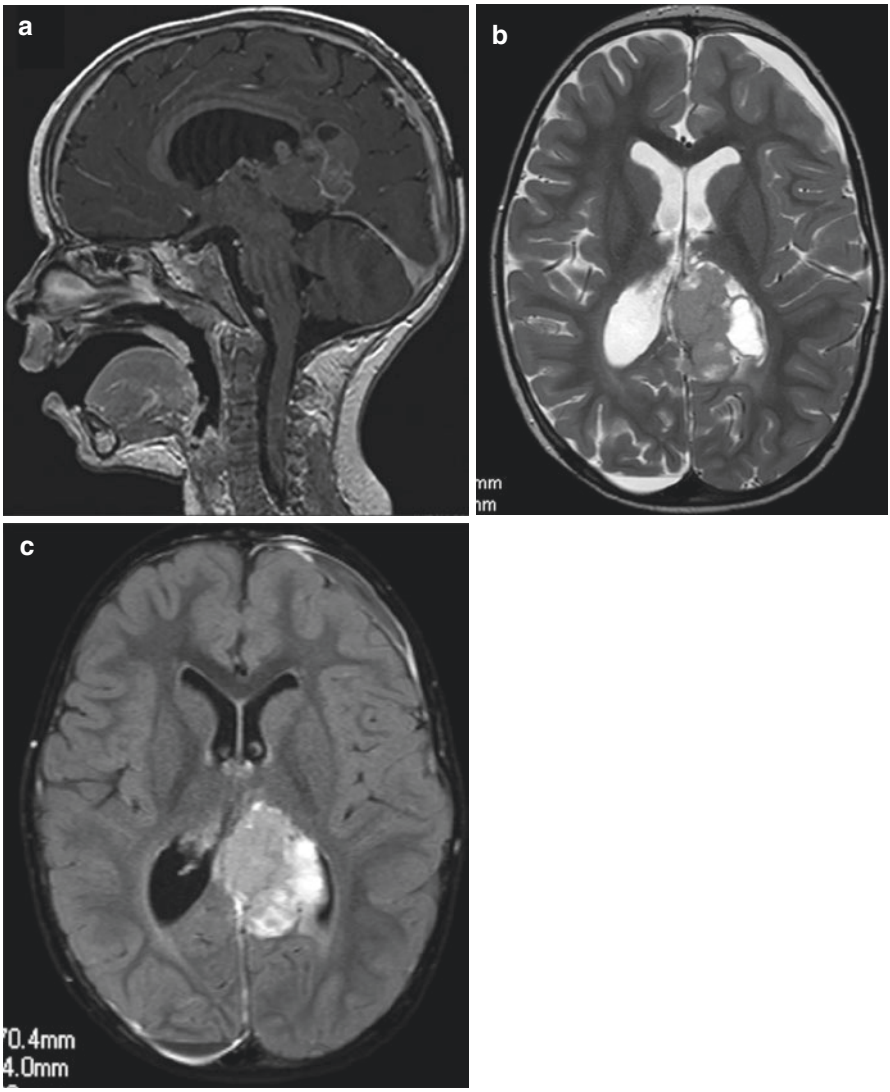

Fig. 25.7 PTPR in T1WI with contrast (**a**), T2WI (**b**), and FLAIR (**c**) MRI sequences

well-circumscribed lesions and tend to be larger than other pineal tumors. On MRI, they show variable signal intensities on T1WI and T2WI with heterogenous contrast enhancement. PTPRs can contain single or multiple cysts, as well as show hyperintense foci on T1WI due to the inclusion of proteins (Fig. 25.7). MRI spectroscopy findings have not been yet standardized, however, in two case reports, increased choline and N-acetyl-aspartate, and a discrete lactate peak have been identified [44, 73].

25.4.3 Germ Cell Tumors

25.4.3.1 Germinomas

Germinomas are malignant tumors that are composed of undifferentiated large germ cells and resemble primordial germinal elements [62]. Germinomas can appear on MRI as solid masses with intermediate to high signal compare to brain parenchyma on T1WI and T2WI. These tumors tend to present contrast enhancement (Fig. 25.8). Approximately 20–52% of germinomas present cystic components on MRI and when the region of interest shows both solid and cystic components ADC values are higher than those of the more densely cellular

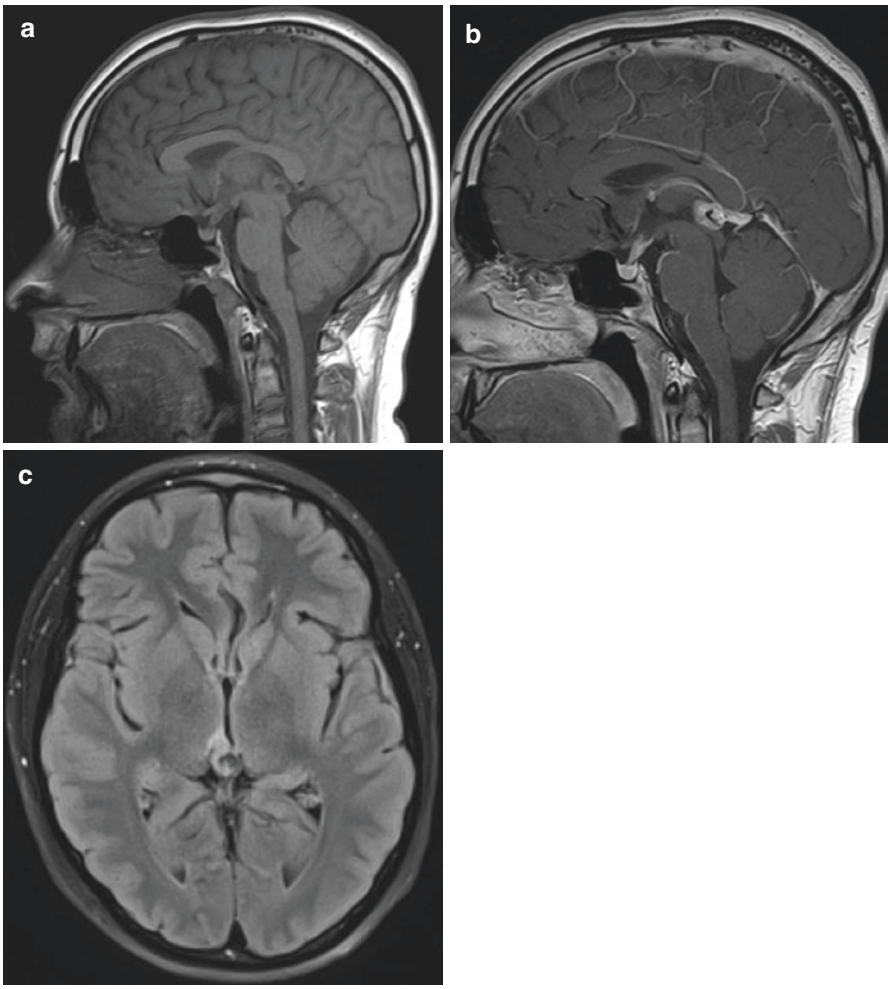

Fig. 25.8 Germinoma in T1WI (**a**) T1WI with contrast (**b**), and FLAIR (**c**) MRI sequences

pineal cell tumours such as pineoblastomas. To differentiate germinomas among other pineal regions tumors, several authors described the following radiographic features: a) Butterfly sign (sensitivity 43%), b) Bi-thalamic extension of the tumor (76% sensitivity), and c) cardioid-shape (100% specificity) [6, 74, 75].

25.4.3.2 Teratomas

Teratomas are tumors derived from pluri-potential cells from at least two embryological layers (endoderm, mesoderm and ectoderm) [62, 69]. On MRI, teratomas are seen as multi-loculated and lobulated lesions with mixed signal, including regions of high-signal intensity in T1WI due to the presence of fat, and areas of low-signal intensity from calcifications (Fig. 25.9). Teratomas tend to be hypo or isointense compare to brain parenchyma on T2WI. Moreover, soft tissue inside teratomas can show postcontrast enhancement [69].

25.4.4 Pineal Region Meningioma

Pineal meningiomas arise from cells within the tela choroidea, velum interpositum or falcotentorial junction. Meningiomas show vivid enhancement on postcontrast MRI images. Moreover, meningiomas express low to intermediate signal on T1WI and intermediate to slight-high signal on T2WI (Fig. 25.10) [76].

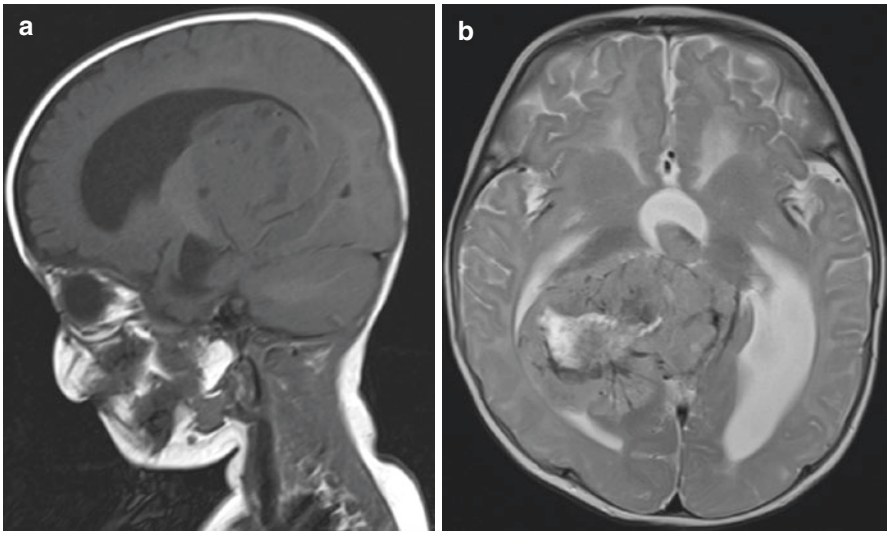

Fig. 25.9 Teratoma in T1WI (**a**), and T2WI (**b**) MRI sequences

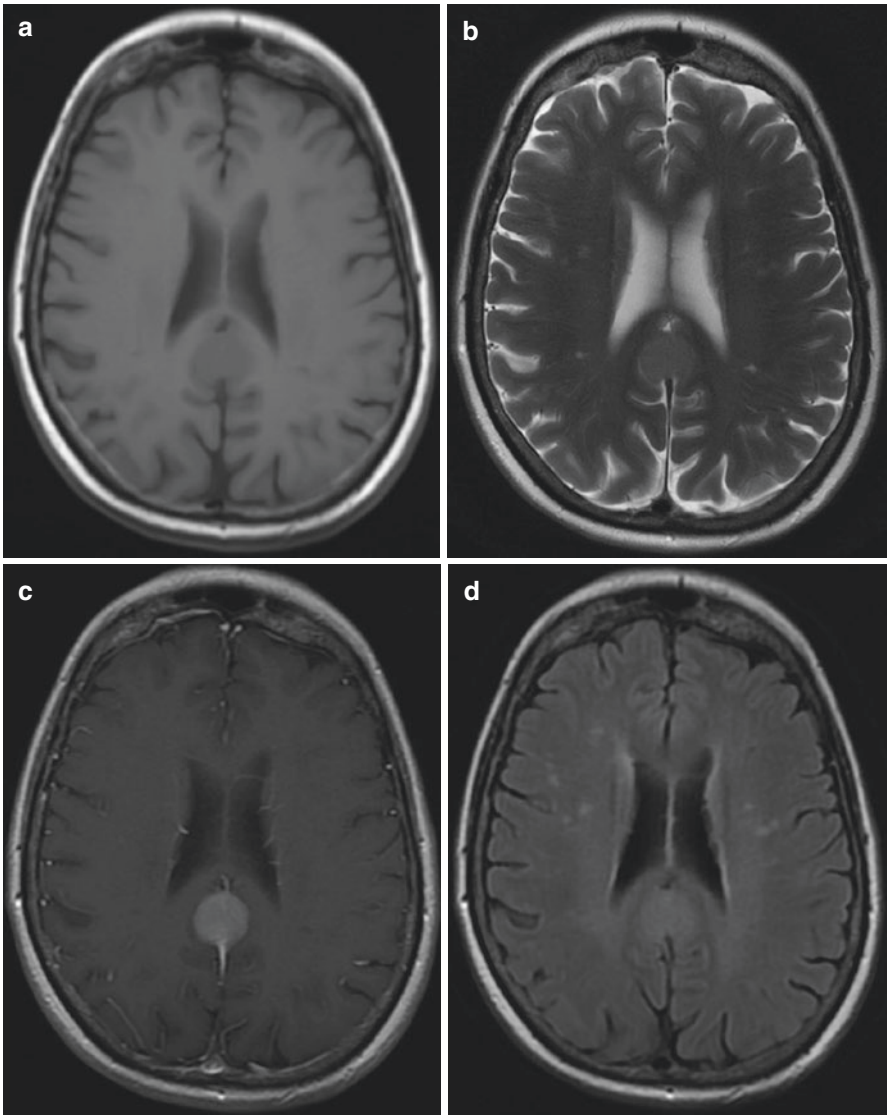

Fig. 25.10 Falcotentorial meningioma in TIWI (**a**), T2WI (**b**), T1WI with contrast (**c**), and FLAIR (**d**) MRI sequences

25.4.5 Gliomas of the Pineal Region

Pineal region gliomas share similar MRI features than their hemispheric counterpart. However, the wide imaging variation among low- and high-grade gliomas remains a limitation for the predictive value of MRI in clinical practice [77]. Figure 25.11 represents the MRI features of a pilocytic astrocytoma of the pineal region.

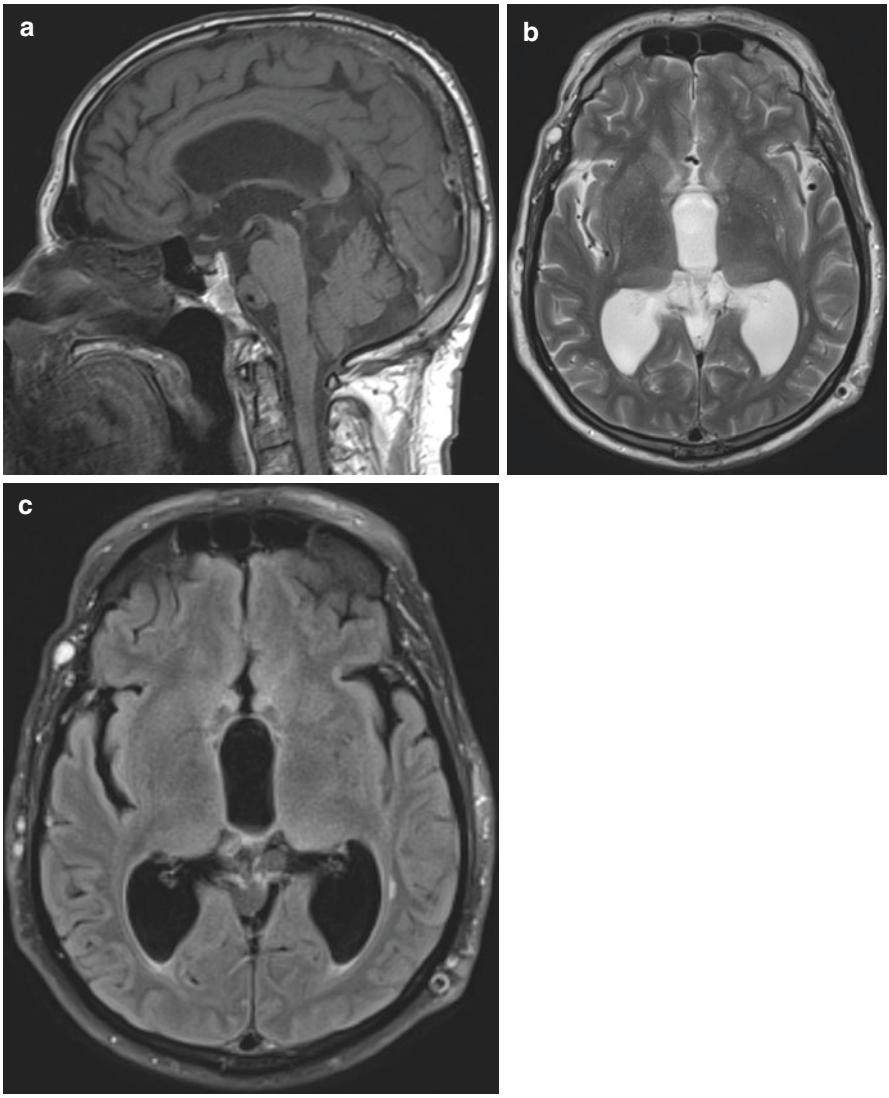

Fig. 25.11 Pilocytic astrocytoma in TIWI (**a**), T2WI (**b**), and FLAIR (**c**) MRI sequences

25.5 Pineal Region Microneurosurgery

Pineal region surgery comprises pre-microsurgical and microsurgical stages, both of them following an adequate protocol of anesthesia. The pre-microsurgical stage comprises of positioning, prepping, draping, and an effective approach to the pineal region, all of them allowing an optimal microneurosurgery.

In most of high specialized centers, the sitting position and the supracerebellar infratentorial approach are common procedures for pineal region surgery [7, 9, 10,

78, 79]. General exclusion criteria for the sitting position include history of cerebral ischemia, old age patients, patent foramen ovale, right atrial pressure greater than left atrial pressure, severe congestive heart failure, uncontrolled previous hypertension, and ventriculoatrial shunt [78, 80]. Prone, concorde, park bench, and three quarter prone positions are also employed in pineal region surgery [81].

A modified sitting praying position developed by Hernesniemi et al. offers an ergonomic position for the surgeon, allows gravity effect on posterior fossa structures, and reduces the risk of severe venous air embolism [78–80, 82, 83]. The ergonomic position of the patient, the use of antigravity trousers, optimal anesthetic considerations, and a proper team work are essential variables for a correct management of pineal region surgery in sitting position [78, 79]. In the following sections, we describe the microsurgical style developed by professor Hernesniemi.

25.5.1 Anesthetic Considerations

The main objective of neuroanesthesia is to maintain optimal perfusion and oxygen delivery to the central nervous system during the treatment. Anesthetic considerations for pineal region surgery in sitting position involve: a) conventional use of fentanyl, thiopental propofol and rocuronium or vecuronium; b) intravenous delivery of Ringer's acetate or hydroxyethyl starch before the positioning of the patient; c) target mean arterial pressure in adults at minimum of 60 mmHg with minimal systolic arterial pressure of 100 mmHg; d) placement of a precordial Doppler ultrasonography; e) normoventilation with 100% inspired oxygen without positive end-expiratory pressure [target $PaCO_2$ = 4.4–5.0 kPa (33.0–37.5 mmHg)]; and g) regular assessment of arterial blood gases. Peripheral venous access instead of central venous access, a urinary catheter, G-suit trousers—tied elastic bandages in kids—are set before positioning of the patient [78–80].

The G-suit trousers (Trousers ANTIG, NATO No 8475991300180, Beaufort, Belfast, UK) maintain a proper preload of the patient in the sitting position. Thus, elevation of the lower limbs of the patient is unnecessary. Thanks to their side zippers, G-suit trousers easily allow the lower limbs of the patient to be inflated up to a pressure of 40 mmHg. Potential injuries of peripheral nerves and/or blood vessels are prevented by the anatomic configuration of the trousers and by the flexible positioning of lower extremities' joints. However, effective blood gas testing, hemodynamic monitoring, and precordial Doppler ultrasound are mandatory [78, 80, 84].

25.5.2 Prepping and Draping of the Patient

Adequate prepping and draping of the patient must provide the anesthesiologist free access to compress both jugular veins in case of VAE. The incision site is shaved with an electric razor before being finished with a fine manual razor shaving. The hair is combed back away. Antisepsis of the operative field is performed repeatedly

using swabs soaked in 80% alcohol. The incision is drawn with aseptic markers and the wound is infiltrated with 20 ml of a vasoactive solution of ropivacaine and lidocaine with adrenaline. The incision area is isolated by large abdominal swabs. The prepping is attached to the Mayfield head frame by a large adhesive film to prevent the surgical dress from sliding over the surgical field during the surgery. The surgical draping of the patient has also a systematic sequence in which the adhesive borders of a light single-use "Leg U" surgical drape are attached to the prepping. Then, both elements—including drainage bag—are fixed with multiple adhesive films [79].

25.5.3 Protocol for a Praying-Sitting Positioning

Preliminary evaluation of the microscope (balance, optics, and mouthpiece) and the preoperative images is imperative before the procedure starts. Under deep anesthesia, the surgeon fixes the Mayfield-Kees head clamp (Integra lifesciences, Plainsboro, New Jersey, USA) and stays holding the patient's head through the head frame throughout the procedure. The patient´s hips are located at the level of the surgical table-flexing place with some pillows below the knees, and the shoulders are placed 10–15 cm from the cranial edge of the table. The table and the upper torso of the patient are bent around 90°–100°. The neck and the head of the patient are slightly flexed 20°–30° beyond the projection of the anterior wall of the thorax preserving a distance between the chin and sternum. The Mayfield head frame is fixed to the surgical table with a special system called trapeze. The patient´s head maintains slight flexion with or without minimal lateral rotation. Thus, an optimal surgical access without cervical cord damage is ensured. Three elements: a safety belt around the pelvis, a suction cushion wrapping the patient, and a flat board against the feet will prevent any accidental movement of the patient when the table position is changed forwards during the surgery. The arms are supported by pillows over the patient´s legs. Precordial doppler and the endotracheal tube are secured. Finally, the correct positioning of the head is once more revised. The surgical table keeps parallel to the floor as low as possible and will be modified by the anesthesiologist according to the neurosurgeon (Fig. 25.12).

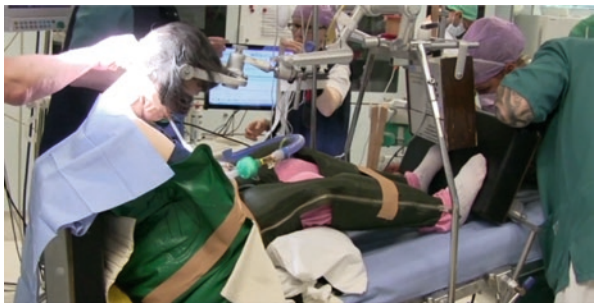

Fig. 25.12 Praying sitting position for pineal region surgery

25.5.4 Surgical Approach to the Pineal Region

Surgical approaches to the pineal region may be classified as anterior approaches, posterior supracerebellar approaches, posterior infratentorial approaches, and posterior combined approaches. Among all of them, the occipital interhemispheric and the supracerebellar infratentorial approaches are the most frequent ones [20, 26, 85, 86]. The experience of the neurosurgeon associated with the proper analysis of the preoperative imaging determines the best approach to the pineal region. Tumors with large supratentorial components above and behind the deep venous structures are more suitable for supracerebellar interhemispheric approaches. Infratentorial components running under the deep venous system are better accessed by the infratentorial approach. Large lateral tumors with ventricular extension and hydrocephalus are suitable for transcortical transventricular approaches. Large pineal tumors with inferior extension to the fourth ventricle may require telovelar approaches. Finally, tumors with anterior extension to the third ventricle may require posterior or anterior transcallosal approaches [9, 81].

The supracerebellar infratentorial paramedian approach is a safer and more efficient variant of the midline infratentorial approach. A simplified one burr-hole paramedian supracerebellar infratentorial approach was developed by Hernesniemi et al. and successfully used in pineal surgery (Fig. 25.13). A single layer skin-muscle incision and a one burr-hole craniotomy are followed by a lateral opening of the dura under the microscope to access the lateral recess of the quadrigeminal cistern. Complete microsurgical resection of the tumor is performed with minimal manipulation of the deep venous structures [10, 26, 28, 87].

25.5.5 Microsurgical Technique

A careful evaluation of the preoperative imaging helps to determine some cleavage plane between the tumor and surrounding structures for adequate microsurgical dissection. Opposite to diffuse infiltrative gliomas, most of the pineal region tumors prevent aggressive microscopic infiltration of the surrounding parenchymal structures. Thus, allowing a safe complete removal. Once the craniotomy is performed, the dura may require a transverse sinus-based opening or a superior sagittal sinus-based opening according to the selected infratentorial or interhemispheric approach. Strong retraction of the dura provides optimal microscopic view. Along the access CSF is constantly released. Thin lateral bridging veins may be coagulated and cut during the supracerebellar access. However, large bridging veins are always preserved. Preoperative spinal catheter or opening of the cisterna magna are often unnecessary, and occipital ventriculostomy might rarely performed. The quadrigeminal cistern is often recognized as a dark tight membrane at the end of the supracerebellar access. On the other hand, the occipital interhemispheric approach may allow to recognize directly the pineal tumor following the falx towards the

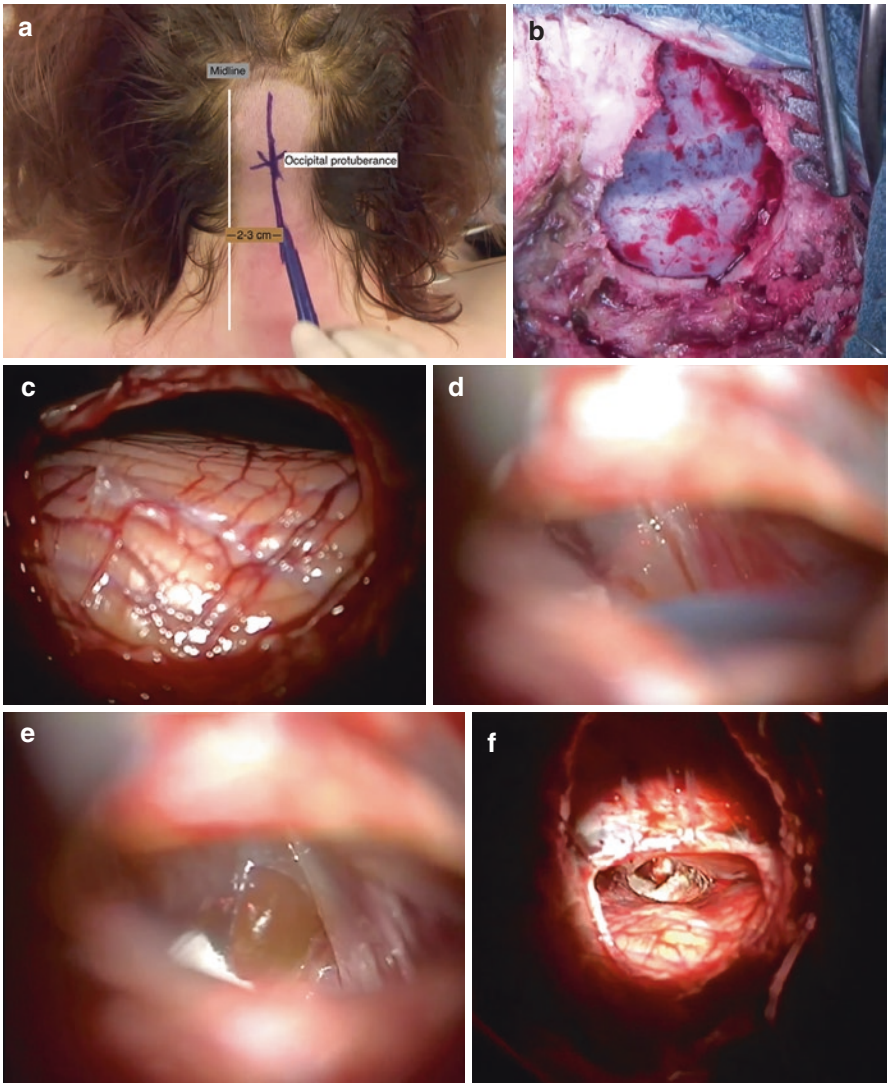

Fig. 25.13 Right paramedian supracerebellar infratentorial approach. Skin incision 2–3 cm lateral from the midline (**a**) is followed by a one burr-hole craniotomy (**b**) to access the pineal region by a lateral supracerebellar route (**c**). The tumor is removed under high magnification (**d**–**f**)

splenium. During the intradural stage, it is essential to recognize the deeply located veins from the dark blue-colored cisterns [2, 9, 33–35].

Initially, an immediate sample tissue is obtained for immediate and definitive histological study. Medium size and large tumors deserve internal decompression with bipolar forceps or ring microforceps under thumb regulated aspiration. Ultrasound aspiration is difficult to apply into this deep surgical location following

less invasive approaches. Lateral dissection through the cleavage plane requires conventional microsurgical technique with soft and continuous traction, water dissection and cotton dissection. The inferior pole, which is usually hidden under conventional microscopy deserves special care since small bleedings occlude the cerebral aqueduct with serious consequences. Endoscopic vision or the use of a microsurgical mirror help to discover residual tumors in this hidden area [88–94].

Tumor attachment to the deep venous system especially to the internal cerebral veins should be carefully dissected aiming to prevent immediate or delayed complications. Often, some adherence and infiltration of the tumor into external layers of the veins is observed. Water dissection technique, cotton dissection, microscissors, and bipolar microforceps are useful in these instances [9, 35]. Meningiomas of the pineal region requires extreme cautious dissection from the surrounding arterial and venous vessels. Accurate hemostasis under continuous saline irrigation and a patient prevent postoperative hemorrhagic events.

Four positive aspects are related with the wound closure under the microscope: such a closure a) looks beneficial for a better hemostasis; b) allows a precise wound margin approximation; c) permits an atraumatic handling of tissues; and d) helps to improve the surgical dexterity. The dura is tightly closed with running suture, and a synthetic dural graft might be rarely used in case of a large dural defect. The bone flap is firmly fixed with titanium clamp systems. The suboccipital muscles and the epicranial aponeurosis are tightly and properly sutured in multiple layers [95].

25.6 Adjuvant Radiochemotherapy

Radiochemotherapy protocols for intracranial tumors renew continuously. Table 25.1 summarize the adjuvant radiochemotherapy protocols for pineal region tumors in Helsinki University Hospital between 1997 and 2015 [9].

Table 25.1 Radiochemotherapy protocols for pineal region tumors at Helsinki University Hospital

Tumor	Radiotherapy	Chemotherapy
Glioblastoma multiforme	• 54 Gy of EBRT	• Temozolomide 150 mg/m^2
Pineoblastoma	• EBRT: 36 Gy craniospinal radiation + 18 Gy boost of radiation on the tumoral bed after gross total resection.	• Medulloblastoma protocol: initially, vincristine 1.5 mg/m^2 once a week for 6 weeks is set. Six weeks after this initial treatment, a new scheme of chemotherapy is administrated every 6 weeks with eight cycles of lomustine: 75 mg/m^2 × 1; cisplatino: 75 mg/m^2 × 1; and vincristine: 1.5 mg/m^2 × 3 on days 0, 7, and 14. • It is employed for children and patients with high risk of metastases such as incomplete resection or tumor recurrences.

(continued)

Table 25.1 (continued)

Tumor	Radiotherapy	Chemotherapy
Grade II-III PPTID	• EBRT: 36 Gy craniospinal radiation + 18 Gy boost in: a) high grade PPTID with pleomorphic histology including pineoblastoma features, b) after partial resection of the lesion, and c) after recurrence of the tumor at the follow up. • Brachytherapy with iodine-125 seeds (a case).	• Recommend in pediatric presentation or high risk of recurrence.
PTPR	• 36 Gy craniospinal radiation + 18 Gy boost.	• High grade ependymoma protocol: cisplatin-cyclophosphamide-vincristine-etoposide, delivered in four intravenous cycles, each lasting 21 days: 1) days 1, 8, and 15 for the first three cycles: vincristine, 1.5 mg/m^2, 2) days 1, 2, 3: etoposide, 100 mg/m^2, 3) day 1: cisplatin, 100 mg/m^2, and 4) days 2, 3: cyclophosphamide, 1000 mg/m^2.
Ependymoma	• 36 Gy craniospinal radiation + 18 Gy boost for residual tumor.	• Recommended in high grade ependymomas as mentioned above.
Germinoma	• Currently, EBRT: 45 Gy (30.6 ventricular area + 14.4 sGy boost to the hypophysis-pineal region).	• Post radiation chemotherapy with etoposide 100 mg/m^2 days 1–5, cisplatin 20 mg/m^2 days 1–5, and bleomycin 30,000 IU days 1, 8, and 15.
Mixed germ cell tumors	• EBRT: Craniospinal radiotherapy or whole-ventricular radiation therapy are applied according to the poor or intermediate prognosis of the lesion (poor: yolk sac tumor-choriocarcinoma-embryonal carcinoma; intermediate: germinoma-teratoma) and serum markers (poor >2000 UI) of α-fetoprotein and β-human chorionic gonadotropin.	• Chemotherapy after gross total resection based on the above etoposide-cisplatin-bleomycin protocol.
Immature teratoma	• Requires radiochemotherapy. However, the unique case in our series had a bad neurological outcome and did not receive any complementary treatment.	
Microcellular metastases	• 30 Gy of whole brain external radiation therapy.	• Chemotherapy according to the primary tumor.
Small recurrent meningiomas or pilocytic astrocytomas	• Focal external radiation therapy/ stereotactic radiosurgery.	

Adapted from Choque-Velasquez et al. 2019 [9].
EBRT external beam radiotherapy, *PPTID* pineal parenchymal tumors of intermediate differentiation, *PTPR* papillary tumor of the pineal region.

25.7 Complications: Resolve and Avoid

A careful hemostasis in pineal region surgery is paramount, in particular with highly vascular lesion, in order to avoid intra- or post-operative hemorrhage, that may also present before surgery ("pineal apoplexy") or following stereotactic biopsy [10, 11, 96, 97].

The risks of severe venous air embolism and hypotension while operating in the sitting position may be efficiently prevented by some essential anesthetic considerations in order to maintain stable hemodynamics, the use of antigravity trousers, precordial Doppler ultrasonography and end-tidal carbon dioxide levels monitoring, as well as by a skillful neurosurgery and an imperative proper teamwork [10, 78–80, 82, 98–101].

When hydrocephalus is present, the incidence of cortical collapse following tumor removal and consequent subdural hygromas may be lowered by pre-operative ventricular drainage or third ventriculostomy. Nonetheless, post-operative subdural hygromas gradually resolve without clinical sequelae, and extremely rarely a subdural shunting is required [6, 8, 10, 79].

An adequate brain relaxation (by the opening of subarachnoid cisterns for drainage of cerebrospinal fluid or by osmotic agents), together with a gentle support of the cerebral parenchyma, may be helpful to reduce retraction injuries, which are reported more frequently with the interhemispheric approach (transient contralateral sensory or stereognostic deficits due to parietal lobe retraction) than with the occipital transtentorial approach (visual field deficits caused by occipital lobe retraction) [6, 8, 10, 11, 96]. Moreover, the retraction of cerebral lobes may determine hemiparesis, which are usually transient. This complication has been also associated with bridging vein injuries [6, 8, 10]. In this regard, the squeeze maneuver may be useful to regain the blood flow of stretched and/or occluded veins [10, 102]. When performing a supracerebellar infratentorial approach, a paramedian route, as compared to the classic median one, may decrease the need for venous sacrifice of bridging veins and of vein of Galen tributaries, and demand less cerebellar retraction [10, 103].

Most of the patients experience some post-operative extraocular movements deficits, in particular of upward gaze and convergence, as well as pupillary impairments with difficulty focusing. Their improvement rates and magnitude are directly linked to their extent preoperatively and, ultimately, to the degree of quadrigeminal region invasion [5–8].

Manipulation of the walls of the third ventricle may jeopardize different cerebral functions, such as memory, visual acuity, and level of consciousness [6, 11]. Cognitive impairment, as well as akinetic mutism may be determined by brainstem manipulation [6, 8]. Disconnection syndromes have been rarely reported with corpus callosum incisions [6, 8]. Postoperative ataxia, when present, usually resolves in few days [6, 8].

Previous radiation therapy, progressively worsening pre-operative symptoms, and invasive tumors are associated with a greater risk and severity of post-operative deficits [6, 8].

Shunt or third ventriculostomy malfunction is reported in about 20% of the cases at the follow-up [5, 8].

25.8 Advances in Technologies

Pineal region tumors are a heterogeneous group of a wide range of histological tumor entities. The management of pineal these tumors is challenging because of their critical location and often-aggressive nature of the tumor. The standard diagnostic tools include clinical neurological evaluation, serum and CSF biomarker and cranial contrast enhanced MRI scan. Stereotactic or endoscopic biopsy (with ETV in case of hydrocephalus) are established methods for the tissue diagnostic. The traditional management of these tumors includes open surgical resection followed by a fractionated radiation and chemotherapy in selected cases. Here, we discuss recent advances in diagnostic and treatment of pineal region tumors.

25.8.1 Advances in Diagnostics

Workup of a pineal mass currently entails imaging with MRI scan followed by serum and CSF laboratory workup for germ cell tumor markers alpha-fetoprotein, β-hCG, and placental alkaline phosphatase. These tumor markers are helpful for diagnosis, but they are more useful for monitoring response to treatment. A pineal mass that is negative for all three markers may be a germ cell tumor that is negative for markers or a pineal parenchymal cell tumor. There are no established biomarkers for pineal parenchymal tumors for clinical use. Reduced melatonin in pineal parenchymal tumors is not specific enough for clinical use. Elevated serum or CSF levels of synaptophysin and chromogranin in pineoblastoma still need further validation [104].

25.8.2 Advances in Radiosurgery

Stereotactic radiosurgery (SRS) to treat pineal region tumors has been reported in a limited number of cases. However, due to rarity of these tumors, the level of evidence to treat with stereotactic radiosurgery is low. The existing limited data suggest that SRS seems to be a safe option, but its effectiveness heavily depends on the tumor entity and histological grade. SRS could be a possible alternative to surgery in pineocytomas and papillary pineal tumors. In case of germ cell tumors and pineoblastomas SRS can be used in recurrent cases or as a boost allowing the reduction of dose of fractionated radiation [105].

25.8.3 Advances in Surgical Techniques

Microscopic microsurgical tumor removal through supracerebellar infratentorial approach in prone, sitting or semi-sitting position is the established procedure in most of the neurosurgical centers. This technique is time consuming and has some

morbidity. Moreover, the approach is narrow through the culmen limiting the exposure of the posterior tentorium incisura, and deep for debulking large tumors which raise into the supratentorial space. Recently, endoscope has been introduced in the pineal region surgery that provide excellent possibility to perform the surgery through ventricular or supracerebellar infratentorial route using a single burr hole or very small craniotomy. Prone or lateral oblique position are the preferable positions for endoscopic pineal region surgery [106, 107]. These positions reduce the risk of air embolism compared to sitting position. In addition to reduction in surgical trauma, endoscope aid visualization of hidden remnants and deep neurovascular structures and surrounding tissue adequately. However, there are still some limitations including limited and a predefined small surgical corridor, difficult intraoperative orientation and insufficiency of available micro-instruments [107]. Utilization of operating microscope in sitting position is uncomfortable due to its long focal distance and the surgeon has to operate on with arms outstretched. This difficult and awkward position leads to fatigue surgeon that may affect negatively on the surgical outcome.

Any technology or device that provide high magnification and illumination of operative field but also allows surgeon a comfortable position could be beneficial. Taking the surgeon's comfort into account, two-dimensional and three-dimensional exoscopes (Fig. 25.14) [108] have been introduced in cranial surgery. However, only few cases of pineal region tumors operated with exoscope have been reported [108–110]. Exoscope provides excellent magnification and illumination of the surgical field in the pineal region and it is more comfortable for the surgeon to operate

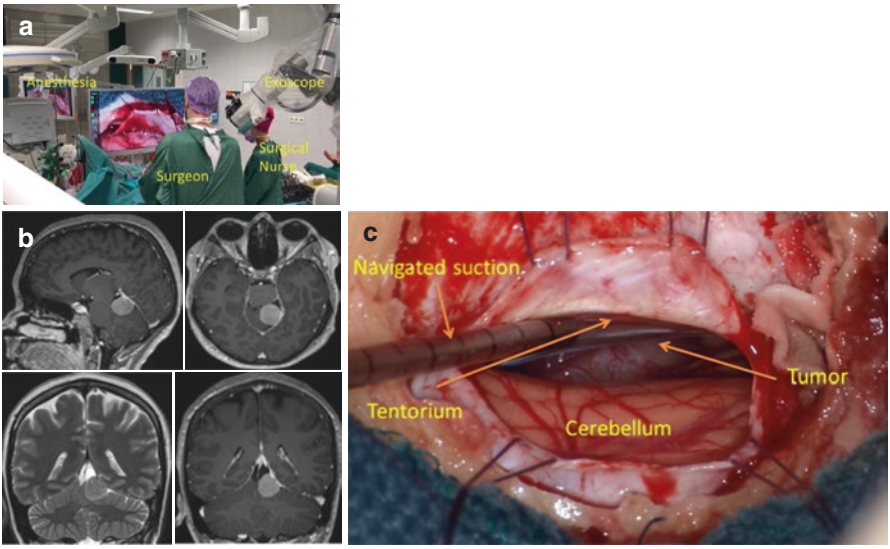

Fig. 25.14 Operative set-up for pineal region tumor surgery. Position of surgeon, exoscope, anesthesia and surgical nurse (**a**). Pre-operative MRI scans (**b**) and intra-operative view of a tentorial meningioma (**c**) nearly reaching pineal region (Taken from Muhammad et al. 2019 [108])

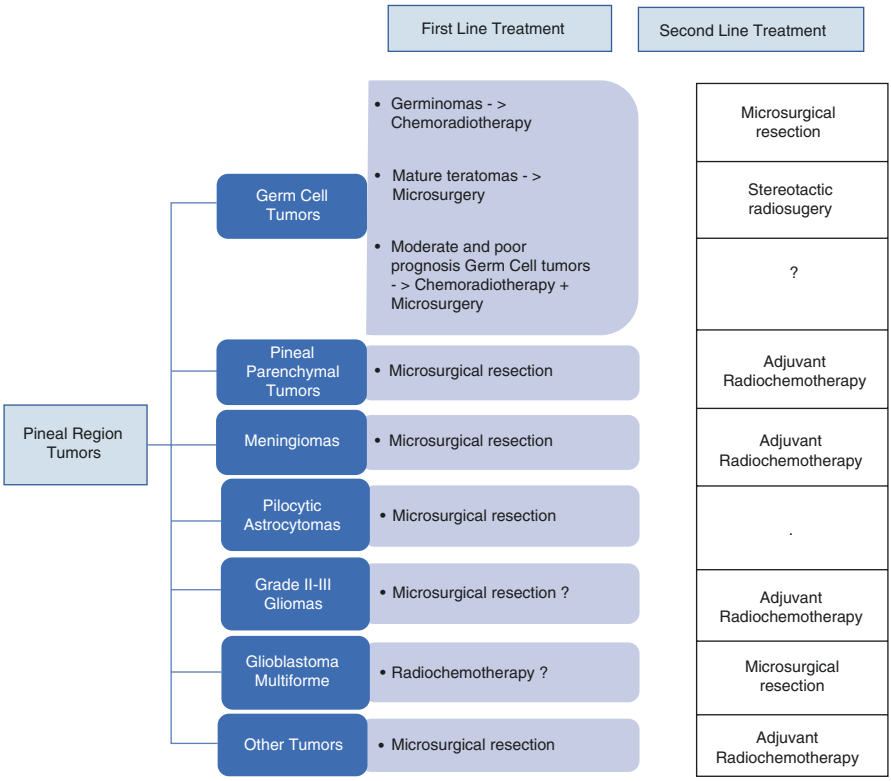

Fig. 25.15 First- and second-line treatment modalities for pineal region tumors

on with the exoscope. However, depth perception especially with 2D exoscope is lower than a standard microscope. Hence, intensive training to adopt the exoscope is necessary before its clinical use.

25.9 Surgical Decision-Making Algorithm

Figure 25.15 represents the first- and second-line treatment modalities for the different pineal region tumors. First line treatment of diffuse grade II-IV gliomas is still not well established since microsurgical resection seems not to offer benefit in the long term outcome [9, 111]. Figure 25.16 was developed for the doctoral thesis (in press) of the first author J.CH. It summarizes a decision-making algorithm for the management of pineal region tumors [9].

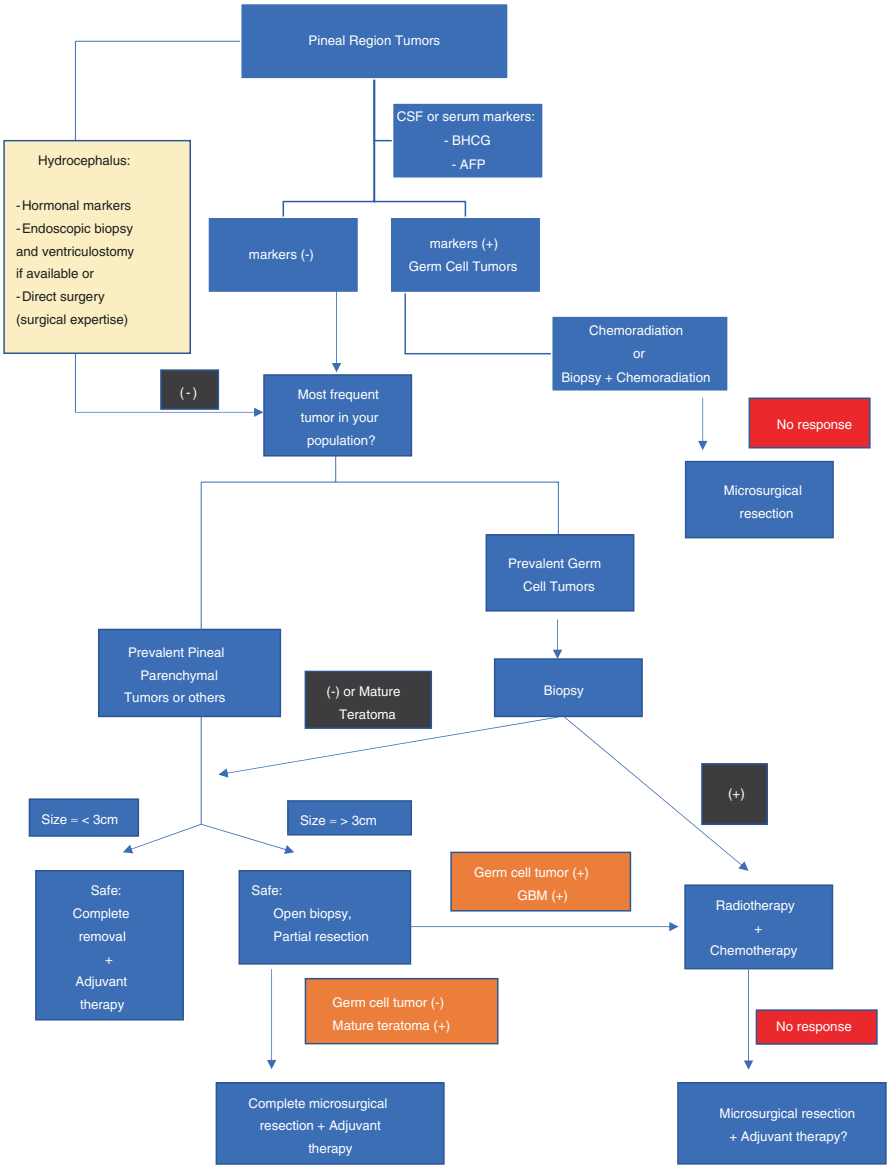

Fig. 25.16 Surgical decision-making algorithm for the management of pineal region tumors

25.10 Conclusion

Pineal region lesions are very heterogeneous, ranging from pineal cysts to pineal gliomas. These tumors are challenging to treat surgically due to their deep location surrounded by important microvascular and brain structures. Tissue biopsy and tumor markers including β-HCG and AFP help to decide the treatment modality. Surgery is the preferred treatment modality in β-HCG/AFP negative tumors. The surgical approach depends on the tumor size and location in relation to tentorium. Most preferred approaches are the supracerebellar infratentorial or interhemispheric in the sitting or semi sitting position. The clinical outcome in pineal region tumors heavily depend on the tumor entity and extent of surgery.

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