Pineal Region Tumors

92

Nir Shimony, Asim F. Choudhri, John T. Lucas Jr., and Paul Klimo Jr.

Contents

N. Shimony
Institute of Brain Protection Sciences, Johns Hopkins University and Medicine, Johns Hopkins All Children's Hospital, St. Petersburg, FL, USA
e-mail: nshimon1@jhmi.edu; nirsh8@gmail.com

A. F. Choudhri
Department of Radiology, Le Bonheur Children's Hospital, University of Tennessee Health Science Center, Memphis, TN, USA
e-mail: achoudhri@uthsc.edu; asim@mac.com

J. T. Lucas Jr.
Department of Radiation Oncology, St. Jude Children's Research Hospital, Memphis, TN, USA
e-mail: john.lucas@stjude.org

P. Klimo Jr. (✉)
Semmes Murphey, Memphis, TN, USA
e-mail: pklimo@semmes-murphey.com

© Springer Nature Switzerland AG 2020
C. Di Rocco et al. (eds.), *Textbook of Pediatric Neurosurgery*,
https://doi.org/10.1007/978-3-319-72168-2_88

Introduction

The pineal gland is a diencephalic structure, also known as the epithalamus, and is the center of a busy neuroanatomical region of the brain (Fig. 1). The splenium of the corpus callosum is located superiorly, the quadrigeminal plate inferiorly, and the quadrigeminal plate cistern and superior surface of the vermis posteriorly. The gland is attached to the posterior wall of the third ventricle by the superior and inferior leaflets of the pineal stalk. From a superior to inferior direction, the posterior wall of the third ventricle consists of the suprapineal recess, the habenular commissure, the pineal body, the pineal recess, the posterior commissure, and the aqueduct of Sylvius. The stria medullaris thalami extend along the superomedial border of each thalamus from the foramen of Monro to the habenular commissure. The posterior roof of the third ventricle is composed of the forniceal crura and hippocampal commissure, followed by the superior layer of the tela choroidea, which is derived from the pia. In between the superior and inferior layers of the tela choroidea is the velum interpositum, a vascular-rich region containing the paired internal cerebral veins and the medial posterior choroidal arteries. Veins dominate the pineal region. The internal cerebral veins, basal veins of Rosenthal, superior cerebellar veins, and posterior splenial veins all drain into the vein of Galen under the splenium within the quadrigeminal cistern.

Pineal tumors account for 0.5% of all central nervous system (CNS) tumors in adults, 1% in

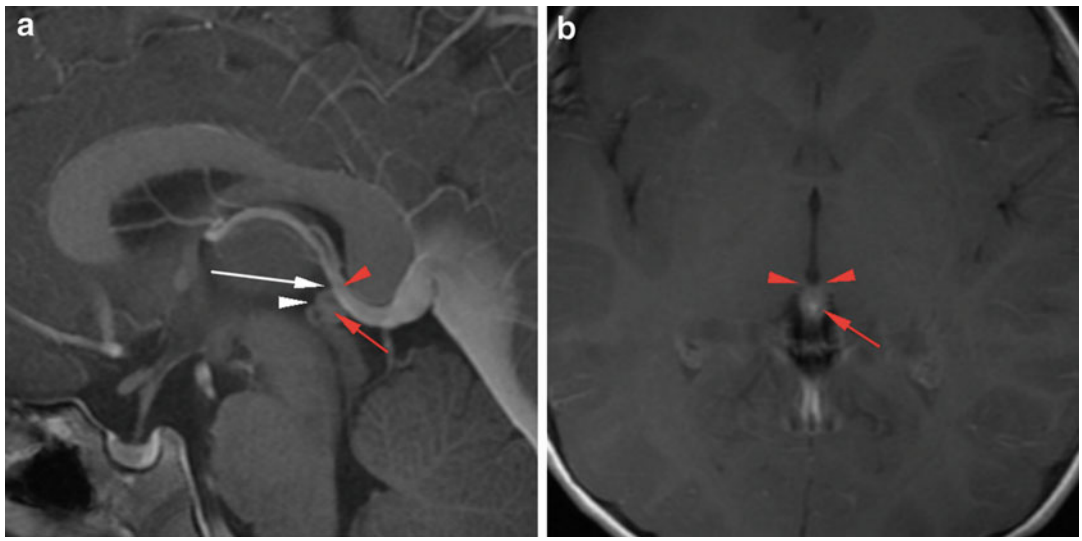

Fig. 1 Normal pineal anatomy. (**a**) Sagittal T1-weighted with contrast image of the pineal region in a 5-year-old male with no prior or subsequent history of pineal abnormalities shows a normal appearing pineal gland (red arrow) along the inferior margin of the internal cerebral veins (red arrowhead). The gland demarcates the pineal recess (white arrowhead) and suprapineal recess (white arrow) of the third ventricle. (**b**) Axial T1-weighted with contrast image shows a normal sized pineal gland (red arrow), which demonstrates post-contrast enhancement. The gland is posterior and medial to the habenulae (red arrowheads), which appear as focal protrusions along the posterior aspect of the medial margin of the thalami

Table 1 Most common tumors of the pineal region (grade)

Germ cell origin
Germinoma (IV)
Embryonal carcinoma (IV)
Yolk sac tumor (IV)
Choriocarcinoma (IV)
Teratoma
Mature (I)
Immature teratoma (N/A)
Teratoma with malignant transformation (IV)
Mixed germ cell tumor
Tumors of pineal parenchymal cells
Pineocytoma (I)
Pineal parenchymal tumor of intermediate differentiation (II or III)
Pineoblastoma (IV)
Papillary tumor of the pineal region (II or III)
Embryonal tumor
Atypical teratoid/rhabdoid tumor (IV)
Embryonal tumor with multilayered rosettes (IV)
Tumors arising from adjacent structures
Ependymoma (II or III)
Glioma (I–IV)
Meningioma (I–III)
Choroid plexus tumors (I–III)

young adults (aged 20–34 years), and 2.7% in children (aged 1–12 years). Using the new 2016 World Health Organization (WHO) Classification of Tumors of the Central Nervous System, there are a large number of distinctly unique histological types of neoplasms that arise from the pineal region (Table 1) (Louis et al. 2016). In this chapter, we will take the reader through the workup and management of a child with a newly diagnosed pineal region tumor, starting with presentation, imaging, management of hydrocephalus, analysis of CSF, and surgical management.

Clinical Presentation

The surrounding neuroanatomy dictates the clinical presentation of pineal tumors. Mass effect from direct compression or dilation of the third ventricle causes the more common signs and symptoms. Owing to the proximity of the aqueduct of Sylvius, the most common presentation of pineal tumors is hydrocephalus – more specifically, triventricular hydrocephalus. Symptoms include headache, nausea, vomiting (particularly at night or morning), decreased activity, drowsiness or lethargy, and visual disturbances (i.e., double vision or blurred vision). Papilledema is a common ophthalmologic finding. With larger tumors or with tumors that have internally hemorrhaged or infarcted (pineal apoplexy), a number of unique ophthalmologic disturbances may occur, collectively known as Parinaud's syndrome. These include upgaze palsy, convergence-retraction nystagmus, light-near pupillary dissociation (pseudo-Argyll Robertson pupil), lid retraction (Collier's sign, from involvement of posterior commissure levator inhibitory fibers), and sun setting eyes, which is combination of upgaze palsy and lid retraction, resulting in preferential downgaze that is coupled with exposure of the sclera. Parinaud's syndrome, known also as dorsal midbrain syndrome, can be found in 50–75% of pineal tumor patients. Diplopia can be caused by palsies of the fourth or sixth cranial nerves due to the child's hydrocephalus or compression of the dorsal midbrain. The fourth or trochlear nerve innervates the superior oblique muscle, which intorts, depresses, and adducts the eye. Therefore, a palsy of this nerve will cause vertical and oblique diplopia that is worse in downgaze and gaze away from the affected eye, resulting in difficulty reading and walking downstairs. Patients, especially younger children, will adopt a characteristic head tilt away from their affected eye to reduce their diplopia, which is called the Bielschowsky sign. The sixth or abducens nerve abducts the eye by innervating the lateral rectus. Weakness of this nerve results in a lateral gaze palsy and horizontal diplopia that is worse with gaze toward the affected eye.

A number of less common clinical manifestations may occur. Larger tumors may extend into the posterior fossa, compressing the superior vermis and the superior cerebellar peduncles, resulting in ataxia and horizontal nystagmus. Compression of the midbrain tegmentum can result in weakness (due to cerebral peduncles), depressed level of arousal (reticular activating system), ophthalmoparesis, mydriasis, anisocoria, and ptosis (all due to primary and accessory [Edinger-Westphal] oculomotor nuclei). Tumor

infiltration, although rare, can invade the dorsal thalamus and internal capsule resulting in relevant motor and sensory deficits. Diffuse spinal leptomeningeal disease may cause generalized or spinal pain in older children or unremitting irritability in infants. Diabetes insipidus is a rare presenting phenomenon, but if present, it may be due to direct spread of tumor to the hypothalamus or synchronous dual site germ cell tumor of the pineal and suprasellar regions.

Imaging

Imaging plays an important role in the diagnosis and management of pineal region tumors. CT and MRI are the imaging techniques most important in the evaluation of pineal region tumors. Because many children with pineal tumors and symptoms of mass effect and obstructive hydrocephalus initially present in the emergency department, these lesions typically are initially identified with CT. CT is rapidly performed and widely available and typically does not require sedation. It is also sensitive enough to find calcifications within the primary tumor and signs of acute hemorrhagic changes. MRI is usually performed for much greater soft tissue characterization, as opposed to CT. Imaging evaluation of newly diagnosed pineal region tumors has several goals, including tumor characterization, tumor localization, detection of metastatic disease, and aiding in surgical planning.

MRI has multiple imaging sequences that are important for tumor characterization. Conventional T1-weighted (T1W) and T2-weighted (T2W) images are the mainstay of MR examinations, and each has a role in lesion characterization. T1-weighted hyperintense signal within a lesion can be a sign of methemoglobin from subacute hemorrhage or fat, which can be found in mature teratomas. CT can be a useful adjunct in helping differentiate these entities, with fat having a low density, approximately between 0 and −100 Hounsfield units (HU). Post-contrast T1-weighted imaging is the standard method of evaluating for metastatic disease. A normal pineal gland will demonstrate post-contrast enhancement since there is no intact blood-brain barrier (i.e., circumventricular organ). T2-weighted hypointense signal can be seen with some blood products and with calcifications. Susceptibility-weighted imaging (SWI) is an MRI technique that can help detect hemorrhage and/or calcifications. Diffusion-weighted imaging (DWI) is a technique that can evaluate microstructural features of a lesion and – with the apparent diffusion coefficient (ADC) value inversely correlating with tumor cellularity – tumor grade (Dumrongpisutikul et al. 2012; Choudhri et al. 2015). MR perfusion techniques are used to detect lesions with increased blood flow and blood volume, which are features that tend to correspond with high-grade lesions (Pillai et al. 2010). MR venography can be performed to evaluate the position and patency of the internal cerebral veins, which are superiorly and laterally displaced by large pineal masses; however, the position of the internal cerebral veins can typically be characterized by the hypointense flow voids on T2-weighted imaging and also by their hyperintense appearance on post-contrast T1-weighted imaging.

Fluid attenuation inversion recovery (FLAIR) imaging can aid in determining whether the cystic components of a pineal region lesion contain CSF-like contents, which will have central suppressed signal characteristics, or proteinaceous fluid, which will have incomplete suppression. FLAIR can also be a means of detecting periventricular interstitial edema, which is a sign that can help differentiate ventriculomegaly from hydrocephalus. Post-contrast FLAIR imaging is a technique that some studies suggest may be highly sensitive to detecting subtle leptomeningeal metastatic disease (Ercan et al. 2004).

Balanced steady-state free precession imaging, which typically goes by proprietary names such as fast imaging employing steady-state acquisition (FIESTA) or constructive interference into steady-state (CISS), can provide high-resolution characterization of CSF spaces, including patency of the aqueduct of Sylvius, morphology of the third ventricle for endoscopic third ventriculostomy (ETV) planning, and patency of ETVs. These techniques can also be used to identify the trochlear nerve (Blitz et al. 2014a, b).

While imaging alone cannot predict the exact histology of tumors, there are imaging patterns of particular tumors that can aid in narrowing differential diagnoses. Key features of the lesions are presented below, with tumors grouped into pineal origin tumors, germ cell tumors, and other entities.

Pineal Origin Tumors

Pineoblastoma. Pineoblastoma is a high-grade tumor that can grow to be large (sometimes in excess of 5 cm) and is diffusely enhancing with some internal cystic areas. There are often calcifications that are spread throughout the lesion, sometimes referred to as "exploded" calcifications. This pattern of calcifications, as opposed to a focal area of peripherally displaced calcifications, suggests the tumor is of pineal cell origin. These tumors are highly cellular, often have mitoses, and therefore have a restricted diffusion. Pineoblastomas have a propensity for CSF dissemination, and careful evaluation of the entire neuraxis for possible metastatic disease is warranted. These lesions tend to have diffusivity of less than 800×10^{-6} mm^2/sec. In patients with germline mutations in the retinoblastoma gene (Rb, chromosome 13), a pineal tumor histologically related to pineoblastoma can occur. This is presumably due to primitive light-detecting features of the pineal gland, and when present, it is referred to as "trilateral" retinoblastoma (Fig. 2).

Pineocytoma. Pineocytoma is a low-grade pineal cell tumor that typically appears to be an enlarged pineal gland and is more circumscribed than a pineoblastoma. These lesions will rarely hemorrhage, are less cellular than pineoblastomas, and therefore have greater diffusivity, in the 1200×10^{-6} mm^2/sec range. At times it can be difficult to identify this definitively as a tumor and not an enlarged pineal gland, and follow-up with thin-section imaging may be required to evaluate for subtle changes over time.

Pineal parenchymal tumor of indeterminate differentiation (PPTID). As the name suggests, PPTID is an intermediate-grade tumor that has features of both pineoblastoma and pineocytoma. These lesions may be more heterogeneous and multilobulated than pineocytomas; however, they will be less likely to have internal hemorrhage or a very large size, like pineoblastomas. Specific imaging prediction of this histologic diagnosis is not typically possible, because it can overlap with a large pineocytoma and also with a small pineoblastoma.

Papillary tumor of the pineal region (PTPR). PTPR is a rare tumor of the pineal gland that tends to have multiple internal cysts, with post-contrast enhancement of the solid portions and the cyst walls. There are few imaging features that can offer specific prediction of this histologic diagnosis. While histologically distinct entities, the imaging features can be similar to that of PPTID.

Germ Cell Tumors

Germinoma. Germinomas tend to be predominantly solid tumors of the pineal region that can have some internal cystic areas. There is often a focal displaced or engulfed pineal calcification. The solid portions of the lesion tend to be high density on CT and enhance on post-contrast T1-weighted imaging. Pineal region germinomas do not typically restrict diffusion and have a mean diffusivity of approximately 1500×10^{-6} mm^2/sec (Dumrongpisutikul et al. 2012; Choudhri et al. 2015). Germinomas of the pineal region are much more common in males than females, unlike suprasellar germinomas, which are seen slightly more commonly in females (Fig. 3).

Non-germinomatous germ cell tumors. This group of rare lesions, including embryonal carcinomas, yolk sac tumors, and choriocarcinomas, has a wide variety of imaging presentations. Suspicion of this class of lesions is typically known based upon germ cell marker analysis.

Teratoma. Teratomas tend to be mixed solid and cystic, with areas of calcification occurring as often as internal macroscopic areas of fat. Fat will be hyperintense on T1-weighted imaging and can be differentiated from methemoglobin by employing T1-weighted imaging with fat suppression and also by performing a CT scan and

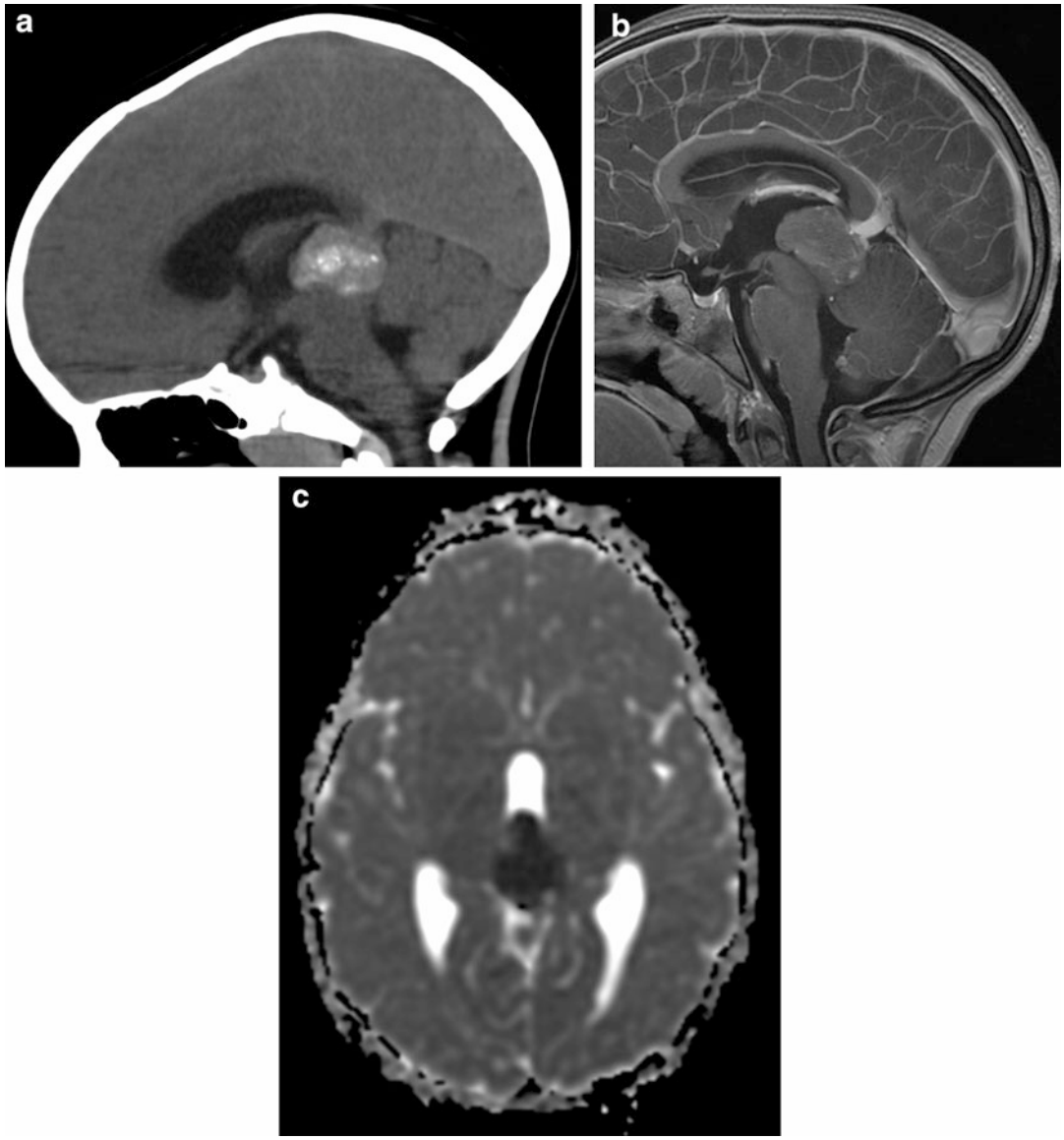

Fig. 2 **Pineoblastoma**. (**a**) Sagittal CT image in a 3-year-old female shows a large pineal region mass with heterogeneous internal areas of calcification throughout the lesion. (**b**) Sagittal T1-weighted with contrast image shows post-contrast enhancement within the mass, which effaces the aqueduct of Sylvius. (**c**) Axial apparent diffusion coefficient (ADC) map showing hypointense signal within this lesion, with quantitative analysis confirming restricted diffusion with a diffusivity of approximately 480 × 10–6 mm2/sec. This was confirmed to be a pineoblastoma

looking for material with a density of less than 0 HU (Fig. 4).

Mixed germ cell tumors. Mixed germ cell tumors can have a variety of imaging appearances and do not have any specific features that define them without other indicators, such as germ cell markers or biopsy. Fat within the lesion is likely to be an indication of a teratoma component. A mixed germ cell tumor leaves behind a teratoma component that may subsequently start growing after treatment with chemotherapy (for non-germinomatous tumors) or radiation (for

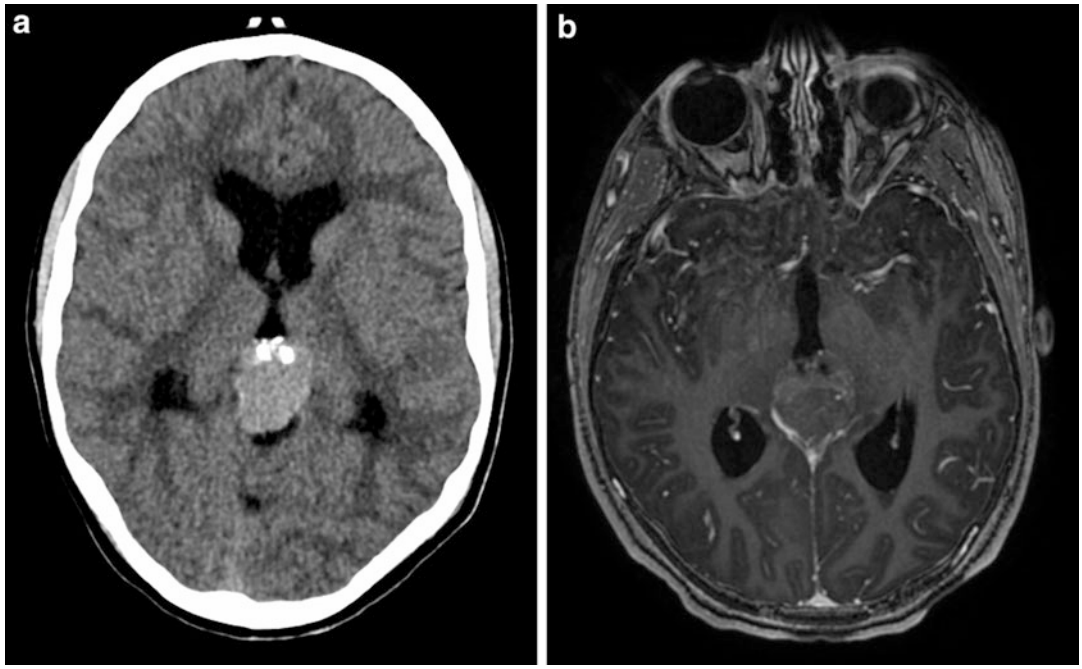

Fig. 3 **Germinoma**. (**a**) Axial CT image in an 11-year-old male shows a large pineal mass with focal calcifications within the anterior aspect of the lesion. (**b**) Axial T1-weighted with contrast image shows mild diffuse post-contrast enhancement within the mass, with focal hypointense non-enhancing areas anteriorly corresponding to the calcifications. This was confirmed by biopsy to represent a germinoma

germinoma). This posttreatment growth of the teratoma component is referred to as the "growing teratoma syndrome," which will be discussed further below (O'Callaghan et al. 1997).

Other Lesions

Tectal glioma. Gliomas of the tectal plate can be confused for a pineal tumor; however, after careful analysis, the upwardly displaced pineal gland is easy to identify, which will typically be intrinsically normal. Accurately differentiating this type of tumor from a pineal origin tumor is critical because tectal gliomas are rarely resected due to resultant morbidity. These lesions are often histologically pilocytic astrocytomas and have a variety of imaging appearances, including T2 hyperintense non-enhancing enlargement of the tectum and a focal heterogeneously enhancing lesion with internal microcystic changes (Fig. 5).

Thalamic/habenular glioma. Similar to tectal gliomas, focal tumors of the medial thalamus and/or habenula can be mistaken for a pineal tumor. Thalamic tumors will result in displacement of the pineal gland, often either to the contralateral side or posteriorly. Any pineal region tumor that is off-midline should raise suspicion for a thalamic tumor.

Mimicking Conditions

While CT and MRI are excellent at detecting and characterizing pineal tumors, they can also detect nonneoplastic mimicking conditions, such as physiologic pineal calcifications and pineal cysts. Calcifications are a physiologic finding within the pineal gland, which is present in approximately 50% of individuals by early adolescence and nearly 100% of individuals by adulthood. With modern thin-section imaging, calcifications have been identified in asymptomatic patients as young as 3 years of age, with an incidence that increases throughout childhood. Therefore, pineal calcifications alone – without

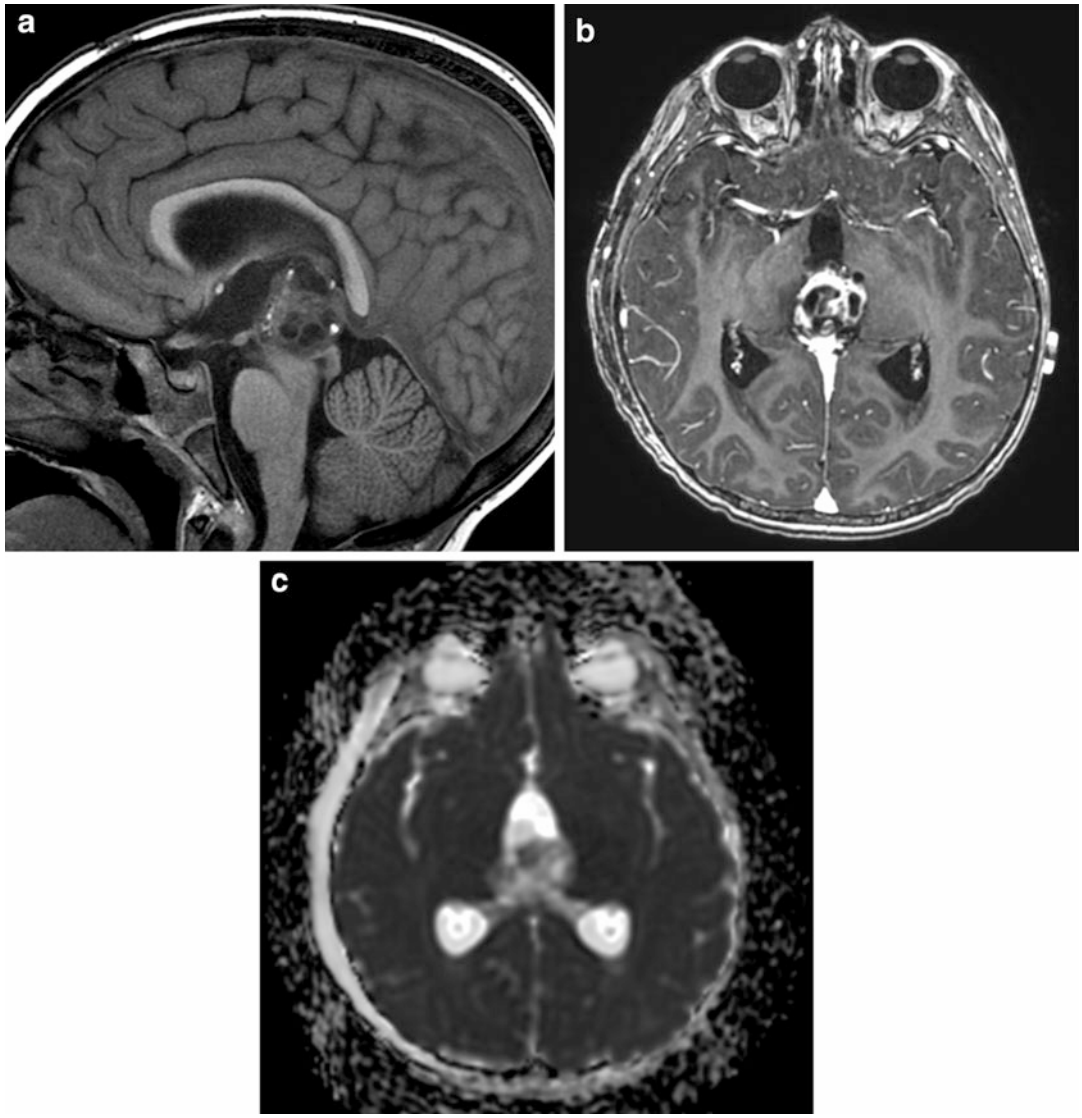

Fig. 4 **Teratoma**. (**a**) Axial T1-weighted with contrast image in a 4-year-old male shows a multicystic pineal lesion. (**b**) Axial apparent diffusion coefficient (ADC) map showing hyperintense signal within this lesion, with quantitative analysis confirming relative facilitated diffusion with a diffusivity of approximately 1450 × 10–6 mm2/sec. This was confirmed to be a teratoma

signs of an associated mass – are doubtful to be indicative of a pineal tumor, unless the patient is younger than 3 years of age (Zimmerman and Bilaniuk 1982; Whitehead et al. 2015; Galluzzi et al. 2016).

Cysts of the pineal gland can also be a cause of uncertainty; however, with modern high-resolution imaging, pineal cysts have been detected in greater than 50% of asymptomatic patients with scans being performed for unrelated issues (Whitehead et al. 2013; Sirin et al. 2016). Cysts of the pineal gland are, therefore, typically a physiologic finding also, even when larger than 10 mm. Without associated solid tissue and/or mural irregularities, these are unlikely to be indicative of a pineal tumor. Clinical and/or imaging

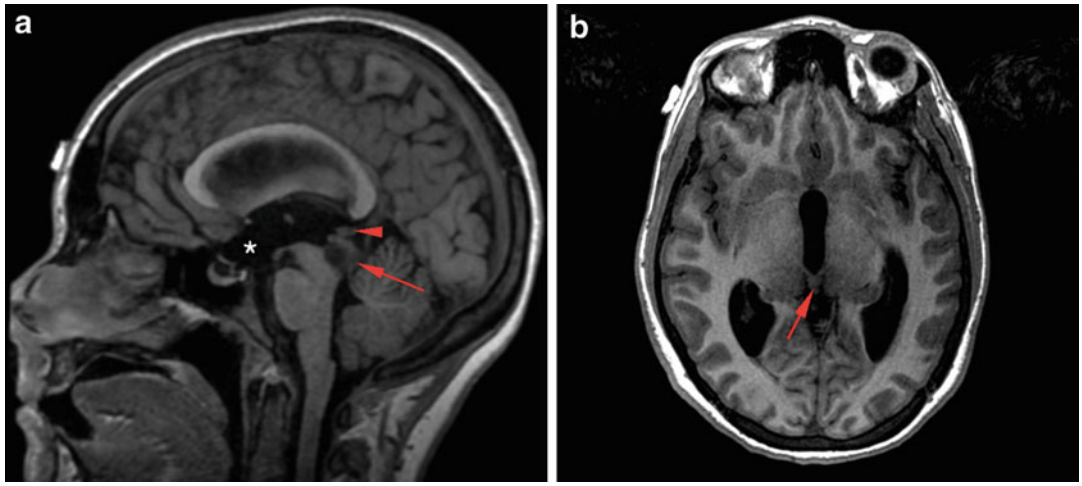

Fig. 5 Tectal glioma. (**a**) Sagittal T1-weighted image in an 18-year-old female demonstrates a pineal region mass (red arrow). Close evaluation confirms that the pineal gland is separate from the lesion (red arrow) and the lesion is centered in the tectum and tegmentum. There are also signs of third ventricular distention (*), including anterior bowing of the lamina terminalis, inferior bowing of the floor of the third ventricle, and splaying of the chiasmatic and infundibular recesses of the third ventricle, related to obstruction of the aqueduct of Sylvius. (**b**) Axial T1-weighted image shows a normal appearing pineal gland (red arrow). There is also enlargement of the imaged portions of the lateral and third ventricles, consistent with triventricular obstructive hydrocephalus

follow-up in the case of larger pineal cysts without suspicious features is likely more relevant with regard to mass effect than neoplastic potential.

Management of Hydrocephalus

For many children with a brain tumor and hydrocephalus, removal of the former can treat the latter. Pineal tumors are unique because information obtained from CSF or tissue analysis will dictate further treatment, which may not necessarily be resection of the mass. Thus, management of hydrocephalus and determination of tumor type are interrelated, but essentially different separate objectives. Hydrocephalus in the setting of pineal mass can be treated either by a temporary external ventricular drain (EVD), a shunt, or ETV.

Patients who present in extremis from severe hydrocephalus may require emergent placement of an EVD. This gets the child out of immediate danger of herniation and allows further evaluation to proceed in a controlled setting. CSF can now be sent for germ cell markers (see below) and cytology. Eventually, the EVD will have to be removed, if the child's hydrocephalus has been treated with resection of the mass or replaced by a shunt or, if hydrocephalus persists, an ETV.

We generally avoid placing a shunt up front in a child with a newly diagnosed pineal tumor, but we will, if resection is not immediately indicated or the ETV fails. The treatment of choice is ETV as it allows the surgeon to achieve three goals: treat the hydrocephalus, obtain CSF, and biopsy the tumor, particularly if the tumor extends into the anterior part of the third ventricle (see below) (Morgenstern and Souweidane 2013; Pettorini et al. 2013). Of the three goals, the first two are of higher priority than the third. The third ventriculostomy is always performed first before the biopsy because if bleeding ensues from the biopsy, it will obscure visualization for the third ventriculostomy. Because the CSF germ cell marker results do not rapidly return, ETV and tumor biopsy is typically done at the same operation. Thus, the surgeon should approach the biopsy portion of the procedure with some trepidation, if there is intraoperative or radiographic evidence of a hypervascular tumor. For these cases,

we consider neoadjuvant chemotherapy before proceeding with a resection (see below). We routinely leave an Ommaya reservoir in place as a safety (i.e., therapeutic) and diagnostic device, if the ETV was to fail or one needed to know the opening pressure or obtain CSF for analysis, respectively.

The ETV Success Score was developed to help surgeons determine the likelihood of ETV succeeding in a particular child, taking into consideration age, hydrocephalus etiology, and whether or not the child currently has a shunt (Kulkarni et al. 2009). Infants (<2 years) and children with CSF dissemination are at high risk for ETV failure and need careful monitoring. There are a number of clinical and radiographic findings that indicate the ETV has not worked. These include recurrence or persistence of the child's hydrocephalus symptoms, increasing ventricular size, development and expansion of a subdural hygroma, a pseudomeningocele (particularly with a CSF-cutaneous fistula), and an elevated pressure with tapping of an Ommaya, if present.

CSF Analysis and Need for Tissue

CSF analysis for germ cell markers is a critical early step in the management of a newly diagnosed pineal tumor. Non-germinomatous germ cell tumors may produce elevated levels of beta-human chorionic gonadotropin (β-hCG, choriocarcinoma), alpha-fetoprotein (α-FP, endodermal sinus, or yolk sac tumor), or both (embryonal cell carcinoma). Elevated placental alkaline phosphatase (PLAP) is classically specific for germinoma, but this test is often not available. Mature teratomas do not express tumor markers, but immature teratomas may have mildly elevated β-hCG or α-FP. Although we continue to routinely measure β-hCG from both serum and CSF, a recent study from our institution suggested that serum α-FP may be sufficient in some cases, whereas β-hCG requires both (Qaddoumi et al. 2012). As mentioned previously, CSF may be obtained from an EVD or at the time of an ETV but also from a lumbar puncture, if there is no obstructive hydrocephalus.

Elevation of β-hCG or α-FP is diagnostic for a non-germinomatous germ cell tumor, whether pure or mixed with other germ cell tumor type. In these cases, no tissue confirmation is required. These patients may still require resection, if their markers have normalized after chemotherapy, but they have a persistent and possibly increasing mass due to the teratomatous component of their mixed tumor, a phenomenon known as growing teratoma syndrome (Kim et al. 2011). The literature regarding treating non-germinomatous germ cell tumor is diverse, whether sending the patient for radical resection and then complete the treatment with adjuvant chemotherapy or, like we prefer, postponing the surgery for resection, at least initially, and use chemotherapy as neoadjuvant or even as stand-alone treatment.

Lack of elevation of β-hCG or α-FP would suggest a germinoma or other non-germ cell tumor, such as a pineoblastoma or atypical teratoid rhabdoid tumor (ATRT). In these patients, tissue confirmation is necessary. In our practice, tissue can be obtained endoscopically or through a craniotomy, but we generally do not perform stereotactic needle biopsy because of the risk of bleeding – either from the tumor or surrounding vasculature – and sampling error. Sampling error is a notable issue in the case of mixed germ cell tumors, which comprise 30–40% of intracranial germ cell tumors. Both sampling error and bleeding can certainly occur with an endoscopic biopsy, but the surgeon has the advantage of selecting an area of the tumor that is relatively avascular and having the tactile and visual feedback to determine how much tissue to grasp and remove with some abilities to stop bleeding, if it occurs (Ahmed et al. 2015). Furthermore, the surgeon can carefully inspect the ependyma of the ventricle for "sugar coating" tumor spread, which may not be evident on MRI (Oi et al. 2000, 2001; Roth and Constantini 2015). As endoscopic tumor biopsy is often done at the same time as the third ventriculostomy, technical nuances have been proposed to achieve both. We prefer the use of a rigid endoscope placed through a single burr hole approximately 3 cm off-midline and 1–2 cm anterior to the coronal suture for both procedures. Others have advocated for a 2-burr-hole approach, with a standard burr hole for the

ETV followed by a second anterior burr hole, which allows for a more posteriorly directed trajectory to the posterior third ventricle and pineal region (Veto et al. 1997; Oi et al. 2001; Oppido et al. 2011). More recently, Roth and Constantini have merged the two techniques by using a flexible and rigid scope through the same burr hole. The rigid endoscope, with its superior optics, is used to make the third ventriculostomy, whereas the flexible scope is used to reach posteriorly for the biopsy (Roth and Constantini 2015).

A recent report showed improved diagnostic accuracy with stereotactic biopsy with low morbidity compared with endoscopy (Balossier et al. 2016). Balossier et al. compared an endoscopic series with a stereotactic one and found that, with endoscopy, the diagnostic rate was 81% with a perioperative morbidity of 25%, whereas, with stereotactic biopsy, the diagnostic rate was 99% with a perioperative morbidity of 6.4%. Figure 6 is a flow diagram algorithm that provides a step-by-step workup and management of a newly diagnosed pineal region mass, similar to one in a recent publication by Zaazoue and Goumnerova (2016).

Molecular subtyping harbors promise for better tailoring the treatment options. Recent cellular and molecular evidence in the molecular characterization of intracranial germ cell tumors suggests the roles of CCND2, RB1, and PRDM14 in their pathogenesis and identifies several cellular pathways with potential therapeutic utilities, such as KIT/RAS and AKT1/mTOR pathways (Terashima et al. 2014; Huang et al. 2016). The activation of the MAPK pathway by KIT or RAS mutations plays a role in the pathogenesis of germinomas (Sakuma et al. 2004; Fukushima et al. 2014). This will potentially allow using molecular targeting agents, such as imatinib, for those specific tumors and avoid the well-known long-term complications associated with radiotherapy in the pediatric population.

Surgical Management

Surgical resection is indicated for all marker-negative tumors, with one exception – germinoma. Germinomas respond so readily and rapidly with radiation that resection is not needed, and so the surgeon's objectives in these patients are to treat the hydrocephalus and obtain tissue for diagnosis. A diagnostic trial of chemotherapy or radiation for suspected cases of germinoma with the hope of sparing the patient surgery should be relegated to history and has no role today (Choi et al. 1998).

For larger or vascular appearing pineal tumors, which are typically pineoblastomas or ATRTs, we have found neoadjuvant chemotherapy to be invaluable in helping achieve a complete resection. The chemotherapy regimen consists of two rounds of carboplatin, cyclophosphamide, and etoposide, each taking approximately 1 month from start to full hematologic recovery (Van Poppel et al. 2011). Chemotherapy converts the tumor from one that is soft, friable, and easily aspirated but bloody to one that is markedly less vascular, but more firm with a well-developed tumor capsule. Sometimes there is no significant decrease in the overall volume of the tumor, but there may be cystic changes and decreased enhancement. The tumor capsule now helps with the dissection of the tumor away from adjacent neurovascular structures.

Surgery of the pineal region and posterior third ventricle remains one of the most challenging cases for pediatric neurosurgeons. The history of pineal and posterior third ventricular surgery is filled with the names of well-known and familiar neurosurgeons, including Dandy, Horrax, Poppen, Krause, Stein, and Jamieson (Zülch 1981). Various operative approaches have been described, each with its advantages and disadvantages (Hart et al. 2013; Sonabend et al. 2016). Surgical approaches can broadly be divided into supratentorial or infratentorial. There are two primary supratentorial approaches, both of which are midline and interhemispheric approaches – posterior-transcallosal and occipital-transtentorial. The classic infratentorial approach is the supracerebellar-infratentorial, which is most commonly performed as a midline approach but can also be done off-midline (Kulwin et al. 2016). There are also combined supra-infratentorial approaches for large masses (Ziyal et al. 1998). The selection of the operative approach is dependent on a number of factors, including the goal of surgery (e.g., biopsy only, reestablishment of CSF flow, or complete

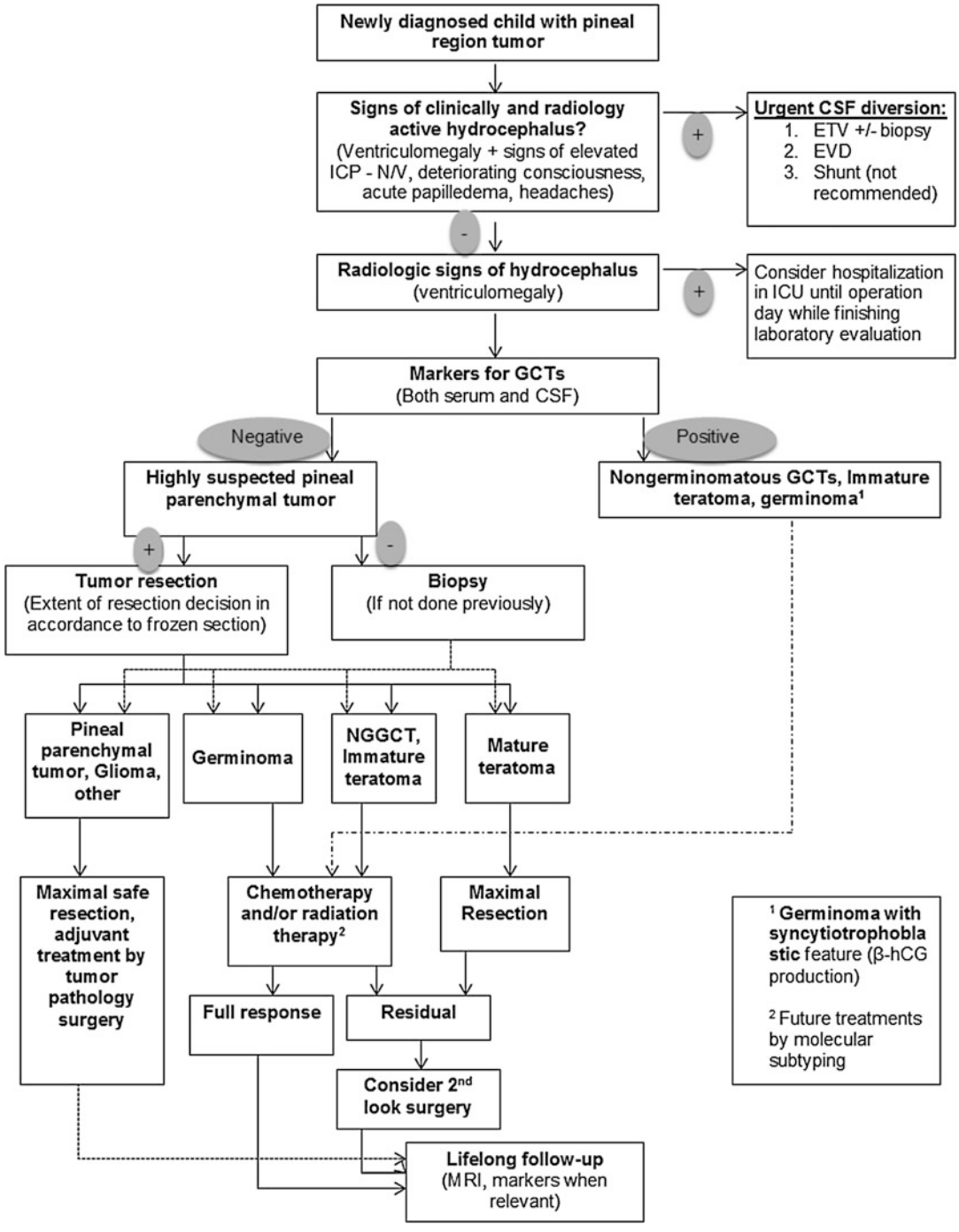

Fig. 6 Flow diagram summarizing the workup and management of a newly diagnosed pineal region mass

surgical extirpation), tumor size, location, displacement or invasion of the surrounding neurovascular structures by the lesion, and finally – but probably most importantly – the surgeon's experience and comfort level with various approaches. There have been recent publications on purely endoscopic or

endoscopically assisted resection of pineal tumors. This new technique is still in its infancy, but we anticipate it gaining more traction in the coming years (Shahinian and Ra 2013; Zaidi et al. 2015; Felbaum et al. 2016; Gu et al. 2016; Liu 2016).

The technical aspects of each open approach are beyond the scope of this chapter, but we provide a discussion on some of the advantages and disadvantages of the three main approaches – supracerebellar-infratentorial, occipital-transtentorial, and posterior-transcallosal. The supracerebellar-infratentorial approach allows a midline approach to pineal region pathology, but it may be difficult to reach tumors that have significant components laterally, anteriorly into the third ventricle, or above the tentorial incisura (Kalani et al. 2016). The angle of the approach is dictated by the angle of the tentorium, thereby making this approach difficult, if the torcula is low with a steep tentorium. At least one or more bridging cerebellar veins (i.e., precentral) need to be sacrificed, and the cerebellum may need to be retracted, but retraction can be limited if the child is in a seated position. Ergonomically, it can be a long and uncomfortable reach for the surgeon, with the internal cerebral veins often being at the farthest point along the operative corridor. Although the sitting position helps with cerebellar retraction, there are a number of disadvantages, most notably venous air embolism, and it is not commonly used in children.

The occipital-transtentorial approach is best suited for midline pineal pathology directed predominantly in the anteroposterior axis – particularly tumors with significant subsplenial or retrosplenial portions – and does not require sacrifice of any bridging veins. However, the initial operative window is small and often requires sectioning of the tentorium (which may harbor venous lakes), contralateral access may be limited by the falx cerebri, and homonymous hemianopsia may occur as a result of brain retraction (Clark and Spetzler 2013). Gravity may assist in brain retraction, if the patient is positioned laterally or in the ¾ prone position, but this may make it more difficult for an assistant to participate compared with the prone position where the primary surgeon and assistant can work across from each other (180°) using "four-hand technique" (Ausman et al. 1988; Brotchi et al. 1991; Sonabend et al. 2016).

The posterior-transcallosal approach is the least well-known of the three approaches. It allows wide access to all three dimensions (anterior-posterior, superior-inferior, lateral) while gaining early identification and control of the internal cerebral veins, which are always displaced superiorly with pineal pathology. These factors are especially important for fibrous tumors (i.e., teratomas) and vascular tumors that require more expanded operative working angles. The patient is positioned supine with the head flexed so the drawbacks of the prone position are avoided. However, disadvantages include the possible need to sacrifice one or more bridging cortical veins in order to gain access to the interhemispheric corridor, retraction of eloquent cortex (supplementary motor cortex or primary motor cortex), disconnection syndrome as a result of incising the posterior corpus callosum, and short-term memory deficit due to the interforniceal working corridor.

Adjuvant Therapy

The main chemotherapy agents used for pineoblastoma and germ cell tumors – both pure germinoma and mixed germ cell tumors – are cisplatin, carboplatin, etoposide (VP 16), ifosfamide, cyclophosphamide, and bleomycin, the latter falling out of favor due to pulmonary toxicity. In general, the patient undergoes four to six cycles of chemotherapy.

Tumors originating from the pineal region have varied propensities for recurrence and patterns of dissemination and as such require customized application of radiotherapy dose, volume, and treatment techniques to maximize the therapeutic ratio in children and adolescents. While pineoblastoma and mixed germ cell tumors uniformly require craniospinal radiotherapy, germinomas require more customized treatment strategies that may include regional (whole ventricular radiotherapy) or craniospinal radiotherapy in combination with focal radiation (Parikh et al.

2017; Chintagumpala et al. 2009; Merchant et al. 1998; Merchant et al. 2000; Aoyama et al. 2002). PPTID has varied metastatic potential, and as such decision-making surrounding the use of craniospinal versus focal radiotherapy is often made after taking into account complete staging information and thorough review of tumor grade. PTPR may require conformal radiotherapy, but the optimal clinical conditions remain poorly defined for achieving the best clinical outcomes given the rarity of this disease (Fauchon et al. 2013). Tectal gliomas are frequently candidates for observation given the low risk for progression, and radiotherapy is infrequently applied only after recurrence following other therapy (Kershenovich et al. 2016).

Outcome

The outcomes of all the potential tumors within the pineal region are beyond the scope of this chapter, but here we provide some generalizations for the more common pediatric pathologies. Pathology, age, and extent of disease are the main determinants of survival. As previously mentioned, patients with germinoma – even metastatic germinoma – have excellent long-term survival but less so with non-germinomatous germ cell tumors. Mature teratomas, whether alone or as part of a growing teratoma syndrome, are purely a surgical disease, and therefore all efforts should be directed at achieving a gross total resection. Immature teratomas require multimodal therapy, of which maximal resection is integral. Embryonal tumors (i.e., ATRT, pineoblastoma, and embryonal tumor with multilayered rosettes) should also be approached with the goal being complete resection, particularly in nonmetastatic cases, but will also require further therapy.

Conclusion

Pineal tumors remain a very challenging entity for pediatric neurosurgeons. The three main tasks before the neurosurgeon are to manage hydrocephalus, make a diagnosis, and resect the tumor, if necessary. There is a wide spectrum of pineal tumors, which can be categorized as germ cell, pineal parenchymal, embryonal, and all others. ETV is the initial treatment of choice as it allows treatment of hydrocephalus, CSF for germ cell markers, and possible tumor biopsy. Non-germinomatous germ cell tumors and germinomas are nonsurgical neoplasms, but all others will require resection. Each surgical approach has advantages and disadvantages and needs to be carefully selected based on the goal of surgery and one of the features of the tumor and surrounding neurovascular structures.

References

Ahmed AI, Zaben MJ, Mathad NV et al (2015) Endoscopic biopsy and third ventriculostomy for the management of pineal region tumors. World Neurosurg 83:543–547

Aoyama H, Shirato H, Ikeda J et al (2002) Induction chemotherapy followed by low-dose involved-field radiotherapy for intracranial germ cell tumors. J Clin Oncol 20(3):857–865

Ausman JI, Malik GM, Dujovny M et al (1988) Three-quarter prone approach to the pineal-tentorial region. Surg Neurol 29:298–306

Balossier A, Blond S, Reyns N (2016) Endoscopic versus stereotactic procedure for pineal tumor biopsies: focus on overall efficacy rate. World Neurosurg 92:223–228

Blitz AM, Choudhri AF, Chonka ZD et al (2014a) Anatomic considerations, nomenclature, and advanced cross-sectional imaging techniques for visualization of the cranial nerve segments by MR imaging. Neuroimaging Clin N Am 24:1–15

Blitz AM, Macedo LL, Chonka ZD et al (2014b) High-resolution CISS MR imaging with and without contrast for evaluation of the upper cranial nerves: segmental anatomy and selected pathologic conditions of the cisternal through extraforaminal segments. Neuroimaging Clin N Am 24:17–34

Brotchi J, Levivier M, Raftopoulos C et al (1991) Three-quarter prone approach to the pineal-tentorial region. Report of seven cases. Acta Neurochir Suppl (Wien) 53:144–147

Chintagumpala M, Hassall T, Palmer S et al (2009) A pilot study of risk-adapted radiotherapy and chemotherapy in patients with supratentorial PNET. Neuro-Oncology 11(1):33–40

Choi JU, Kim DS, Chung SS et al (1998) Treatment of germ cell tumors in the pineal region. Childs Nerv Syst 14:41–48

Choudhri AF, Whitehead MT, Siddiqui A et al (2015) Diffusion characteristics of pediatric pineal tumors. Neuroradiol J 28:209–216

Clark JC, Spetzler RF (2013) Defining the limits of the occipital transtentorial keyhole approach. World Neurosurg 80:62–63

Dumrongpisutikul N, Intrapiromkul J, Yousem DM (2012) Distinguishing between germinomas and pineal cell tumors on MR imaging. AJNR Am J Neuroradiol 33:550–555

Ercan N, Gultekin S, Celik H et al (2004) Diagnostic value of contrast-enhanced fluid-attenuated inversion recovery MR imaging of intracranial metastases. AJNR Am J Neuroradiol 25:761–765

Fauchon F, Hasselblatt M, Jouvet A et al (2013) Role of surgery, radiotherapy and chemotherapy in papillary tumors of the pineal region: a multicenter study. J Neuro-Oncol 112(2):223–231

Felbaum D, Syed HR, Ryan JE et al (2016) Endoscope-assisted combined Supracerebellar Infratentorial and endoscopic Transventricular approach to the pineal region: a technical note. Cureus 8:e520

Fukushima S, Otsuka A, Suzuki T et al (2014) Mutually exclusive mutations of KIT and RAS are associated with KIT mRNA expression and chromosomal instability in primary intracranial pure germinomas. Acta Neuropathol 127:911–925

Galluzzi P, de Jong MC, Sirin S et al (2016) MRI-based assessment of the pineal gland in a large population of children aged 0-5 years and comparison with pineoblastoma: part I, the solid gland. Neuroradiology 58:705–712

Gu Y, Hu F, Zhang X (2016) Purely endoscopic resection of pineal region tumors using infratentorial supracerebellar approach: how I do it. Acta Neurochir 158:2155

Hart MG, Santarius T, Kirollos RW (2013) How I do it – pineal surgery: supracerebellar infratentorial versus occipital transtentorial. Acta Neurochir 155:463–467

Huang X, Zhang R, Mao Y et al (2016) Recent advances in molecular biology and treatment strategies for intracranial germ cell tumors. World J Pediatr 12:275–282

Kalani MY, Martirosyan NL, Nakaji P et al (2016) The supracerebellar infratentorial approach to the dorsal midbrain. Neurosurg Focus 40(Video Suppl 1):2016. 2011 FocusVid 15462

Kershenovich A, Silman Z, de Rungs D et al (2016) Tectal lesions in children: a long-term follow-up volumetric tumor growth analysis in surgical and nonsurgical cases. Pediatr Neurosurg 51(2):69–78

Kim CY, Choi JW, Lee JY et al (2011) Intracranial growing teratoma syndrome: clinical characteristics and treatment strategy. J Neuro-Oncol 101:109–115

Kulkarni AV, Drake JM, Mallucci CL et al (2009) Endoscopic third ventriculostomy in the treatment of childhood hydrocephalus. J Pediatr 155:254–259 e251

Kulwin C, Matsushima K, Malekpour M et al (2016) Lateral supracerebellar infratentorial approach for microsurgical resection of large midline pineal region tumors: techniques to expand the operative corridor. J Neurosurg 124:269–276

Liu JK (2016) Endoscopic-assisted interhemispheric parieto-occipital transtentorial approach for microsurgical resection of a pineal region tumor: operative video and technical nuances. Neurosurg Focus 40(Video Suppl 1):2016. 2011 FocusVid 15450

Louis DN, Perry A, Reifenberger G et al (2016) The 2016 World Health Organization classification of Tumors of the central nervous system: a summary. Acta Neuropathol 131:803–820

Merchant TE, Davis BJ, Sheldon JM et al (1998) Radiation therapy for relapsed CNS germinoma after primary chemotherapy. J Clin Oncol 16(1):204–209

Merchant TE, Sherwood SH, Mulhern RK et al (2000) CNS germinoma: disease control and long-term functional outcome for 12 children treated with craniospinal irradiation. Int J Radiat Oncol Biol Phys 46(5):1171–1176

Morgenstern PF, Souweidane MM (2013) Pineal region tumors: simultaneous endoscopic third ventriculostomy and tumor biopsy. World Neurosurg 79(S18):e19–e13

O'Callaghan AM, Katapodis O, Ellison DW et al (1997) The growing teratoma syndrome in a non-germinomatous germ cell tumor of the pineal gland: a case report and review. Cancer 80:942–947

Oi S, Shibata M, Tominaga J et al (2000) Efficacy of neuroendoscopic procedures in minimally invasive preferential management of pineal region tumors: a prospective study. J Neurosurg 93:245–253

Oi S, Kamio M, Joki T et al (2001) Neuroendoscopic anatomy and surgery in pineal region tumors: role of neuroendoscopic procedure in the 'minimally-invasive preferential' management. J Neuro-Oncol 54:277–286

Oppido PA, Fiorindi A, Benvenuti L et al (2011) Neuroendoscopic biopsy of ventricular tumors: a multicentric experience. Neurosurg Focus 30:E2

Parikh KA, Venable GT, Orr BA et al (2017) Pineoblastoma-the experience at St. Jude Children's Research Hospital. Neurosurgery 81(1):120–128

Pettorini BL, Al-Mahfoud R, Jenkinson MD et al (2013) Surgical pathway and management of pineal region tumours in children. Childs Nerv Syst 29:433–439

Pillai J, Zaca D, Choudhri A (2010) Clinical impact of integrated physiologic brain tumor imaging. Technol Cancer Res Treat 9:359–380

Qaddoumi I, Sane M, Li S et al (2012) Diagnostic utility and correlation of tumor markers in the serum and cerebrospinal fluid of children with intracranial germ cell tumors. Childs Nerv Syst 28:1017–1024

Roth J, Constantini S (2015) Combined rigid and flexible endoscopy for tumors in the posterior third ventricle. J Neurosurg 122:1341–1346

Sakuma Y, Sakurai S, Oguni S et al (2004) c-kit gene mutations in intracranial germinomas. Cancer Sci 95:716–720

Shahinian H, Ra Y (2013) Fully endoscopic resection of pineal region tumors. J Neurol Surg B Skull Base 74:114–117

Sirin S, de Jong MC, Galluzzi P et al (2016) MRI-based assessment of the pineal gland in a large population of children aged 0-5 years and comparison with pineoblastoma: part II, the cystic gland. Neuroradiology 58:713–721

Sonabend AM, Bowden S, Bruce JN (2016) Microsurgical resection of pineal region tumors. J Neuro-Oncol 130:351

Terashima K, Yu A, Chow WY et al (2014) Genome-wide analysis of DNA copy number alterations and loss of heterozygosity in intracranial germ cell tumors. Pediatr Blood Cancer 61:593–600

Van Poppel M, Klimo P Jr, Dewire M et al (2011) Resection of infantile brain tumors after neoadjuvant chemotherapy: the St. Jude experience. J Neurosurg Pediatr 8:251–256

Veto F, Horvath Z, Doczi T (1997) Biportal endoscopic management of third ventricle tumors in patients with occlusive hydrocephalus: technical note. Neurosurgery 40:871–875; discussion 875–877

Whitehead MT, Oh CC, Choudhri AF (2013) Incidental pineal cysts in children who undergo 3-T MRI. Pediatr Radiol 43:1577–1583

Whitehead MT, Oh C, Raju A et al (2015) Physiologic pineal region, choroid plexus, and dural calcifications in the first decade of life. AJNR Am J Neuroradiol 36:575–580

Zaazoue MA, Goumnerova LC (2016) Pineal region tumors: a simplified management scheme. Childs Nerv Syst 32:2041

Zaidi HA, Elhadi AM, Lei T et al (2015) Minimally invasive endoscopic Supracerebellar-Infratentorial surgery of the pineal region: anatomical comparison of four variant approaches. World Neurosurg 84:257–266

Zimmerman RA, Bilaniuk LT (1982) Age-related incidence of pineal calcification detected by computed tomography. Radiology 142:659–662

Ziyal IM, Sekhar LN, Salas E et al (1998) Combined supra/infratentorial-transsinus approach to large pineal region tumors. J Neurosurg 88:1050–1057

Zülch K (1981) Reflections on the surgery of the pineal gland (a glimpse into the past). Neurosurg Rev 4:159–163