

PINEAL BODY TUMOR: AN OVERVIEW OF THE PATHOPHYSIOLOGY

ABSTRACT

The pineal gland is a pinecone, an endocrine gland that regulates the biological circadian rhythm in humans. It is responsible for melatonin production, also produced by parenchymal and glial cells. Tumors of the pineal region account for approximately 3–11% of pediatric brain neoplasms but fewer than 1% of brain neoplasms in adults. These tumors arise from the germ cells, pineal cells, and adjacent structures. It is fundamental for clinical and laboratory knowledge to differentiate and identify the various types of pineal gland tumors and thus facilitate accurate diagnosis with crafted therapeutic management of the pathology accompanying its incidence. There exist different histological subtypes of pineal body tumors and various management options like surgery, chemotherapy and radiotherapy. This review article is part of student's project on integrated learning, aim at understanding the pathophysiology of the pineal body tumor: a rare neoplasia with varying degrees of manifestations.

Keywords: Brain neoplasia, *Pineal body tumor*, *Pineoloma*, *Pineal gland*, *Pineocytoma*, *Melatonin*.

INTRODUCTION

Pineal body is part of the circumventricular organ of the brain that produce melatonin, an endocrine hormone which plays an important role in the regulation of sleep-wake pattern (Circadian rhythm) in humans. [1] In the pineal gland, information on environmental lighting conditions that is encoded by the retina is responsible for the synthesis of melatonin at night involving both biochemical and neuronal input. It is evident that pineal body may harbor neoplastic growth which can be primary or secondary (rare) metastatic lesions. Tumors are generally rare in the pineal gland. [1][2]

Pineal body tumor are rare brain tumor accounting for approximately 3–11% of pediatric brain neoplasms and approximately 1% of brain neoplasms in adults. They are mostly asymptomatic, but few symptomatic ones are usually mild and there are reported cases of aggressive subtypes.

The management of Pineal gland tumors are generally less discussed in most literatures because of the rarity. There exist few histopathological subtypes of primary pineal body tumors with varying level of differentiations, thus requiring a multi-disciplinary approaches in the management.[3][4] There are evidence of varying response to therapy depending on multiple factors with fairly good prognosis for some of the subtypes.[4][28]



EMBRYOLOGY AND ANATOMY

The pineal gland begins as an evagination in the diencephalic roof of the ventricle prenatally, flanked by posterior and habenular commissures below the splenium of the corpus callosum. It continues to grow after birth in response to rhythmic sympathetic innervation from the superior cervical ganglia. [1][2][3]

Anatomically, the pineal gland is described as a pinecone shaped, a neuroendocrine gland part of the thalamus. Connecting to the pineal and dorsal suprapineal recesses with anatomic boundaries that include the posterior wall of the third ventricle forming the gland's base, the splenium of the corpus callosum superiorly, and the thalamus surrounding both sides. [4] The gland calcifies with age, with most of its cells comprising pinealocytes.

In lower vertebrates, the pineal gland participates in the biological circadian rhythm by receiving information through its light-sensitive cells, with its primary responsibility being the production of Melatonin. However, in higher vertebrates, light is picked up by the eye's retinal cells, which transports this information to visual and non-visual areas of the brain, the pineal being one of such areas. The gland works in hand with the suprachiasmatic nucleus (SCN), which secretes GABA if the light signal is positive, inhibiting melatonin synthesis. When there is no light signal, the SCN secretes glutamate, driving paraventricular nucleus (PVN) transmission to the pineal gland. The PVN also communicates with the superior cervical ganglion that acts on the pineal gland through sympathetic fibers release norepinephrine (NE). The presence of NE is a major trigger for the pinealocytes to synthesize and secrete melatonin [5]. Studies show that in blind subjects, there is an independent rhythm of melatonin secretion [6]

The precursor of melatonin is tryptophan, which is hydroxylated inside the pinealocytes to 5-hydroxytryptophan. The aromatic L-amino corrosive decarboxylase then decarboxylates 5-hydroxytryptophan into serotonin. Serotonin then, at that point, gets changed into melatonin due to the methyltransferase-O-hydroxy-indole protein (HIOMT) [7,8]. This biochemical response chain suggests the presence of N,

PHYSIOLOGY



N-dimethyl-tryptamine (DMT) in pinealocytes.

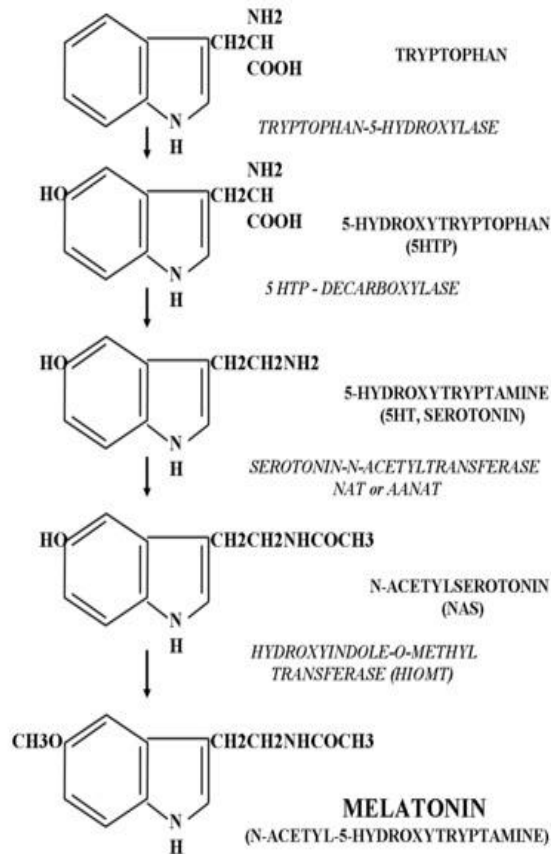


Figure 1. Melatonin biosynthesis.

Source: https://www.researchgate.net/figure/SYNTHESIS-OF-MELATONIN_fig1_6198068

PATHOLOGY

Pineal gland tumors are remarkably uncommon cancers, predominantly occurring as childhood malignancies representing 3–11% of all pediatric brain tumors compared to <1% of brain tumors in adults.[4] Tumors within the pineal region represent 1.5 to 8.5% of the pediatric brain tumors and 1.2% of all brain tumors [9]. On analysis of incidence in a 1973–2005 period, a study of 633 patients with pineal gland tumors showed a predominance in males at 3:1 and 11.8:1 for those with a germ cell tumor variant. The cohort's 5-year overall survival (OS) was $65\% \pm 2.1\%$. Those with germ cell tumors experienced the best survival (OS = $78.9\% \pm 2.3\%$), followed by those with gliomas (OS = $61\% \pm 9.3\%$), and those with pineal parenchymal tumors (OS = $47.2\% \pm 4.2\%$) [10].

The pineal gland tumors are classified as germ cell tumors (germinoma, choriocarcinoma, teratomas, yolk sac tumors), pineal parenchymal tumors (pineocytomas, pineoblastomas), and tumors derived from adjacent structures.



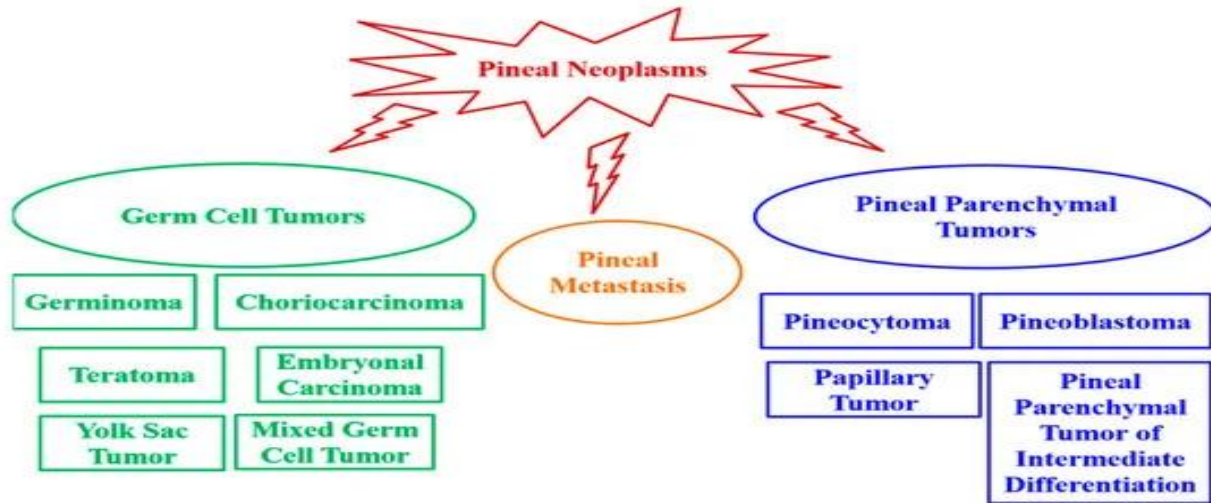


Figure 2: Pineal Tumor Classification.

Source: <https://www.mdpi.com/2072-6694/13/7/1547/htm>

Practically speaking, the determination of pineal gland neoplasms depends on the clinical show, imaging, and pathology results. Serum and cerebrospinal liquid (CSF) biomarkers supplement these standard indicative strategies by giving extra information before intrusive techniques are performed. This review will explore the features and clinical relevance of the main pineal gland tumors, highlighting the importance of triggering causes of the masses and effective primary diagnosis with subsequent, correct treatment and management.

Germ cell tumor

Germ cell tumors are derived from primordial germ cells that, although developed primarily in the gonads, can migrate to the mediastinum, pineal gland, and brain. These tumors are commonly

found in male patients and account for about 50% of intracranial germ cell tumors, seemingly more common in Asian populations [11]. There are six types of germ cell tumors: germinomas, choriocarcinomas, teratomas, embryonal carcinomas, yolk sac tumors, and mixed germ cell tumors.



Germinoma

Germinomas are the most common pineal type, representing almost 50% of tumors in Europe, the United States, and Japan.

Germinomas are not encapsulated and find it easy to invade adjacent brain structures while also disseminating along the brain surface through the CSF. Histology reveals homogenous germinoma cells with large round nuclei, prominent nucleoli, clear cytoplasm with connective tissue septal bands and capillaries, lymphocytes, and, infrequently, granulomas [11,12].

Germinomas show heterogeneous features on imaging, often presenting as solid or solid/cystic masses with engulfed calcifications. Imaging alone is not sufficient in distinguishing between the tumors; therefore, a complete evaluation is needed. Germinomas are diagnosed using serum and CSF markers with the expression of oncoproteins, e.g., alpha-fetoprotein, lactate dehydrogenase, and beta-human chorionic gonadotropin [13].

Furthermore, corticosteroid treatment seems to be able to modify the patient's immunological defense, empowering the immune system to suppress cancer.

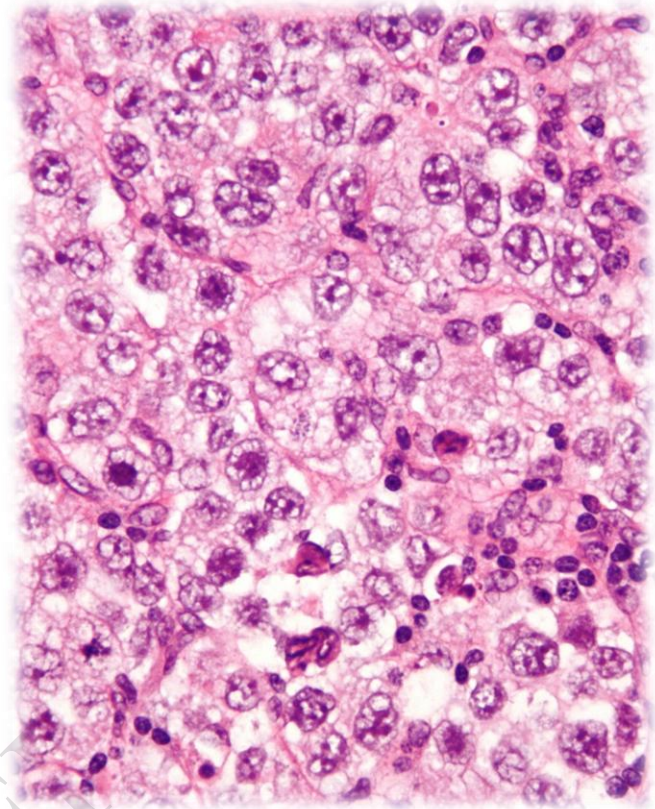


Figure 3: Histology of Germinoma
Source: [Germinoma - Wikipedia](#)

Choriocarcinoma

Choriocarcinomas are relatively uncommon neoplasms, they have the most aggressive form of gestational trophoblastic disease. They have a very poor prognosis concerning other germ cell tumors.

Young men (3–22 years old) with premature puberty are more likely to develop primary cerebral choriocarcinoma. Although these tumors do not cause any symptoms, those with choriocarcinoma have mainly reported headaches, vomiting, nausea, visual



impairment, polydipsia, polyuria, and endocrinologic alterations [14,15]. Intimately related syncytiotrophoblasts and cytotrophoblasts characterize histology without forming definite placental type villi. On imaging, choriocarcinomas appear as ovoid, heterogenous, and slightly hyperdense masses. Choriocarcinomas can be linked with elevated plasma and CSF human chorionic gonadotropin levels.

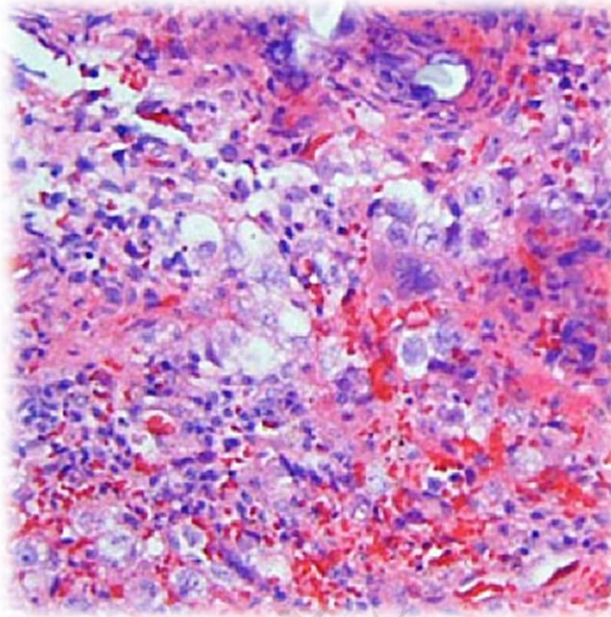


Figure 4: Choriocarcinoma H&E Stains showing syncytiotrophoblasts (large, multinuclear cells in the central portion of the illustration).

Source: [The ISPN Guide to Pediatric Neurosurgery](#)

Teratomas

Intracranial Teratomas (ICTs) account for up to 50% of fetal brain neoplasms; in neonates, they comprise 33% of intracranial tumors, but they comprise only 2%–4% of intracranial tumors in patients aged <15 years [16]. Teratomas are histologically classified as mature, immature, and teratomas with malignant transformation. This tumor is characterized by multipotential cells that revert to normal organ-producing mechanisms, usually producing tissues that showcase a combination of two or more layers of the ectoderm, mesoderm, and endoderm. Teratomas can be encapsulated or unencapsulated (invasive) [17]. These pineal tumors present foci of fat, calcification, and cystic regions on imaging.

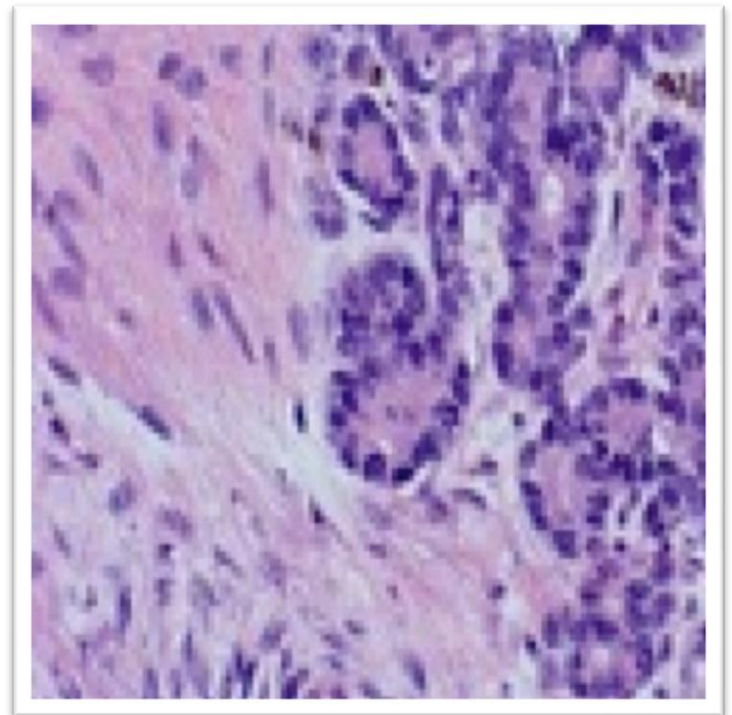


Figure 5: Mature Teratoma on H&E stain showing rosettes of neuroepithelial tissue. Source: [The ISPN Guide to Pediatric Neurosurgery](#)

solid, sometimes with focal areas of cystic change, gray, well-circumscribed mass with or without hemorrhage [20]. Pineocytomas may arise at all ages but are more frequent in adults aged 30-60 years.

Pineal Parenchyma Tumors

Pineal parenchymal tumors are neuroepithelial-derived neoplasms emerging from pinealocytes. These growths are phenomenal, representing less than 1% of all primitive central nervous system cancers and comprising 15% to 30% of pineal gland tumors. These tumors present with different features, grades, and levels of invasiveness. The World Health Organization (WHO) recognizes pineal parenchymal tumors in four distinct categories: pineocytomas, pineoblastomas, papillary pineal tumors, and pineal parenchyma tumors of intermediate differentiation. [18]

Pineal parenchyma tumors are highest in children with no sexual predominance [19]. PPTs are negative for the three most commonly evaluated tumor markers (AFP, b-HCG, ALP).

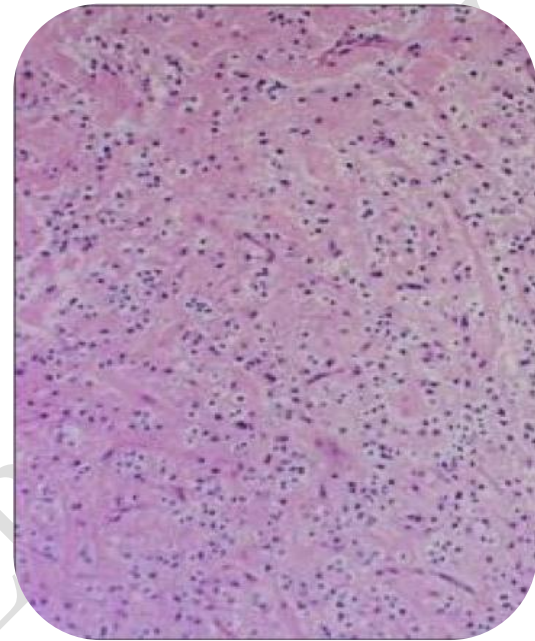


Figure 6: Pineocytoma H&E stain showing moderate cellularity with low mitotic rate and pseudo rosettes.

Source: [The ISPN Guide to Pediatric Neurosurgery](#)

Pineocytomas

Pineocytomas are slow-growing grade I neoplasms that are histologically characterized by benign-appearing cells (uniform size and intact membrane) and the presence of neurocytic rosette. On gross pathology, pineocytoma is characterized by

Pineoblastomas

Pineoblastomas are aggressive, grade IV neoplasms derived from the neuroectoderm. They are undifferentiated embryonal tumors with poor prognosis and sometimes aggressive clinical behavior due to the frequent invasion of adjacent structures and CSF dissemination [21]. Incidence is highest in children under two years, where



retinoblastomas can also be combined with pineoblastomas [22].

During the evaluation, synaptophysin and chromogranin are markers of primitive neuroendocrine tumors that may be expressed in pineoblastomas and detectable in the serum or CSF [4]. Pineoblastomas are histologically characterized by hypercellular appearance, packed small round blue cells (which indicates a high nucleus to cytoplasm ratio), Homer-Wright rosettes, and oval, angulated nuclei with atypia. Gross pathology reveals solid, large, poorly defined masses.

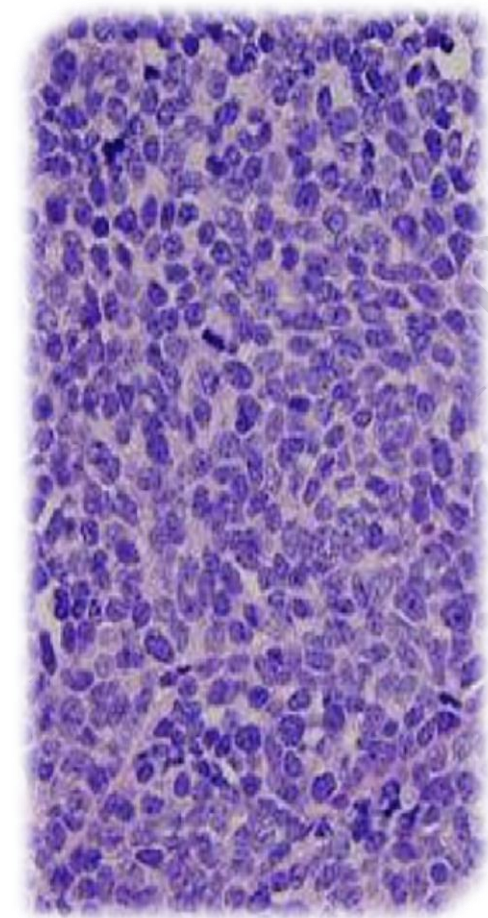


Figure 7: Pineoblastoma H&E stain showing a sheet of small round blue cells tightly packed with nuclear atypic and frequent mitotic figures.

Source: [The ISPN Guide to Pediatric Neurosurgery](#)

Papillary Tumors

Pineal papillary tumors are rare grade I or II neoplasms that occur within a broad spectrum of patients with the age of patients presenting with papillary tumors ranging from 15 months to 67 years with a mild female prevalence [23]. The main symptom presented by patients with this condition is headaches related to obstructive hydrocephalus. Histological examination shows distinct solid papillary growth patterns with a lining of the papillae by multi-layered cuboidal to columnar cells, prominent perivascular rosette, and focal true ependymal rosette formation. Cells may have moderate amounts of eosinophilic, non-fibrillary cytoplasm, and indistinct borders, with large pleomorphic nuclei displaying a dense chromatin pattern and occasionally prominent nucleolus. A lot of apoptotic figures can also be seen. [24,25]



Pineal papillary tumors often present increased proliferative activity (Ki67/MIB1 proliferation index) [26], which is correlated with a worse prognosis.

Immunohistochemically, papillary tumors are also positive for S100, CAM 5.2, and prealbumin.

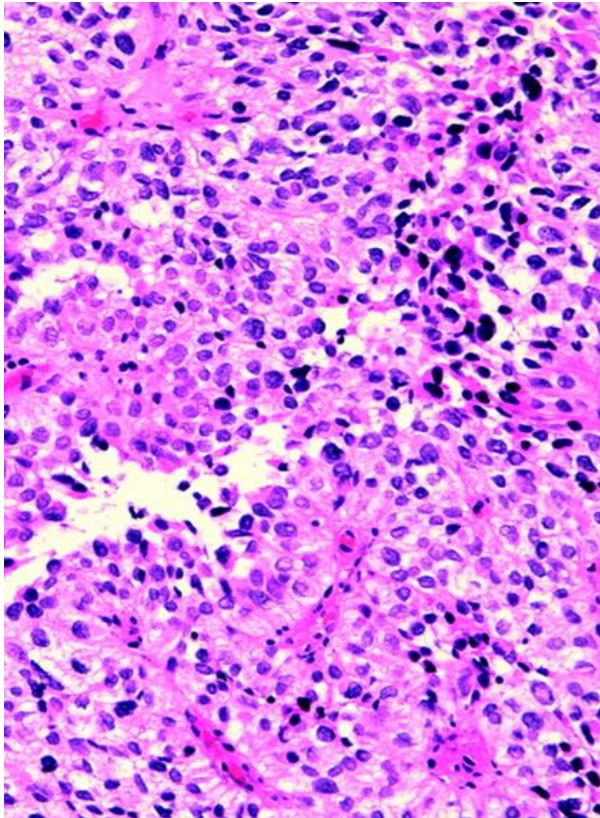


Figure 8: Epithelial-appearing tumor with papillary features.

Source: Papillary tumor of the pineal region.

Alejandro et al. Neurology Aug 2009, 73 (6) 486;

Pineal Parenchymal Tumors of Intermediate Differentiation [PPTIDs]

These are rare tumors that present features found in pineocytomas and pineoblastomas [27]. It can occur at any age and is more common in women, teenagers, and middle-aged patients. Pineal parenchymal tumors of intermediate differentiation are often considered to be not a single disease but a spectrum of grade II and III pineal parenchymal tumors [27]. Although there is yet to be a grading criterion for differentiating PPTIDs, the WHO classification of CNS tumors considers that an approach to stratification employed by Jouvett et al. relied mainly on two criteria, proliferative activity (mitoses) and immunoreactivity for neurofilament protein, the latter being sparse in higher grade examples [28].

PPTIDs show moderate cellularity, mild-moderate atypical nuclei, low-moderate mitosis, occasional Homer Wright rosettes, lack of small, primitive appearance, and necrosis.



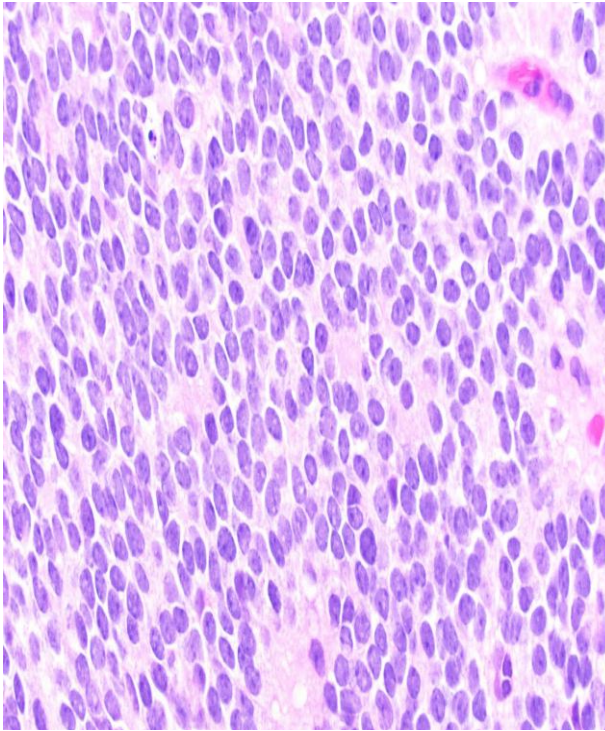


Figure 9: Pineal Parenchymal Tumor of Intermediate Differentiation, WHO grade II-III with the presence of small rosettes.

Source: [Pineal Parenchymal Tumor of Intermediate Differentiation, WHO grade II-III](#)

Pineal Metastasis

Metastatic cancer of the pineal gland is highly uncommon and is almost always associated with lung carcinoma. This usually occurs in end-stage disease features, and treatment of pineal gland metastases varies due to the type of tumor, systemic conditions, and presenting neurological symptoms.

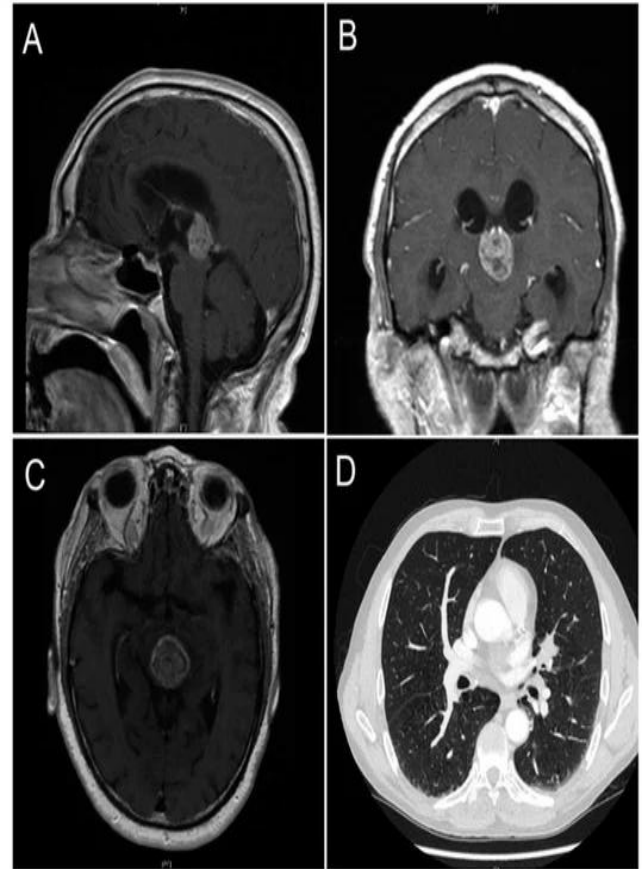


Figure 10. Pineal metastasis from lung adenocarcinoma. Brain MRI sagittal (A), coronal (B), and transverse (C) sections show the pineal gland metastatic mass. Computed tomography shows a lung nodule over the left hilar region in the lower right corner (D). Image from Abdallah et al. (2020)-Ochsner Journal.

CLINICAL MANIFESTATIONS

The clinical complications resulting from pineal region tumors are related to the normal pineal gland anatomy and histology.



Migraines, nausea, and vomiting caused by compression of the aqueduct of Sylvius and resultant obstructive hydrocephalus with raised ICP, if left untreated, hydrocephalus may lead progressively to lethargy, obtundation, and death. Visual changes occur due to the involvement of the rectal region (a region responsible for dictating eye movements). Diplopia is a common feature, along with difficulty in accommodation.

Parinaud Syndrome :compression of the superior colliculus and pretectal area, either through direct compression or tumor invasion, results in a syndrome of vertical gaze palsy associated with pupillary or oculomotor nerve paresis, pupillary light-near dissociation, lid retraction, and convergence-retraction nystagmus (Collier's sign).[29]

Motor impairment, such as ataxia and dysmetria, results from compression of the cerebellar efferent fibers within the superior cerebellar peduncle.

Pseudo precocious puberty caused by beta-human chorionic gonadotropin (b-HCG) can be observed with germ cell tumors in either the pineal or suprasellar region.

Pineal apoplexy (bleeding into the tumor area of the pineal gland) is a rare but possible manifestation.

Hormonal disturbances lead to secondary amenorrhea and growth arrest. Children with pineal region tumors can present with endocrine malfunctions. Hydrocephalus or concurrent suprasellar tumors can cause diabetes insipidus [30]

The relative 5-year survival rate for pineal region tumors is 69.5% but know that many factors can affect prognosis. Includes the tumor grade and type, cancer traits, the person's age and health when diagnosed, and how they respond to treatment. Talk to your doctor if you want to understand your prognosis. [28][37]

DIAGNOSTIC MODALITIES

Diagnosis of pineal region neoplasms is based on the following:

Clinical presentations (as has been outlined in presenting signs and symptoms).

Magnetic Resonant Imaging study (MRI)

Excisional biopsy and molecular/histopathological analysis.

Serum and CSF biomarkers complement the above standard diagnostic techniques by providing additional data points before invasive procedures.

Pineal mass workup presently entails imaging followed by serum and CSF laboratory workup for germ cell tumor markers like alpha-fetoprotein, β -hCG, and placental alkaline phosphatase. These markers are somewhat helpful for diagnosis but are more helpful for monitoring response to treatment. Serum and CSF biomarkers, in conjunction with clinical and radiographic evidence of a pineal region mass, can inform the decision to undertake stereotactic biopsy or surgical excision or whether to proceed straight to medical treatment [38].



Comparing CSF and serum β -hCG levels is a crucial step in the workup of a pineal mass, as patients with metastatic disease do not benefit from resection of the primary tumor. Moreover, the combination of a typical tumorous lesion of the pineal region and the laboratory findings of elevated alpha-fetoprotein (AFP) and beta-human chorionadotropin (β -HCG) in either serum or cerebrospinal fluid establishes the diagnosis of a secreting germ cell tumor [39]. Endoscopic biopsy offers another means of obtaining tissue for diagnosis without open resection and can be used as an alternative to stereotactic biopsy, depending on the surgeon's judgment and experience [40, 41, 42, 43, 44]. Endoscopic tumor biopsies are safe as a minimally invasive and highly effective strategy for the initial management of pineal body tumors. It addresses the issue of tissue diagnosis and offers a solution for the associated hydrocephalus frequently encountered in patients [45].

Primary surgical resection without biopsy would expose many patients to unnecessary risk. Because less than a third of patients need primary surgical resection once the histological diagnosis is confirmed, a primary biopsy of pineal lesions should precede attempted surgical resection in children. Problems with the endoscopic technique are its limited ability to control bleeding and limited tissue sampling. Some series have reported up to 94% yield, although many patients require a second procedure [41]. Performing an endoscopic third ventriculostomy and an endoscopic

biopsy of the pineal region with one burr hole is usually impossible because of anatomic considerations.

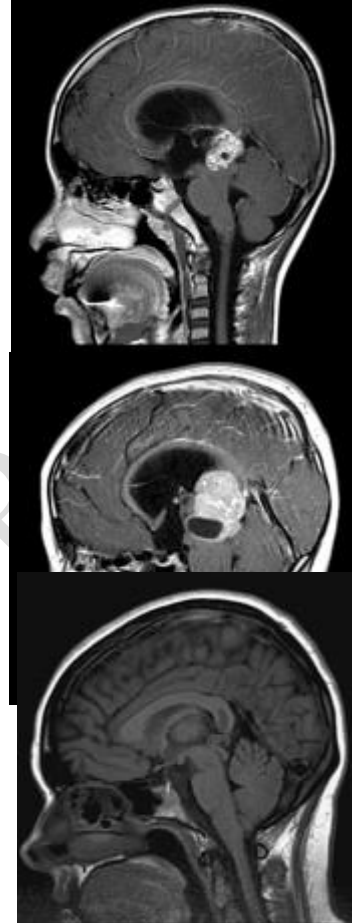


Figure 11. MRI scans showing different pineal tumors (A) Sagittal T1 of Pineocytoma (B) Sagittal T1 view of Pineal Germ cell body tumor [non-germinomatous] (C) Sagittal T1 view of Pineal germinoma

Source: [Radiopedia](https://radiopaedia.org)



MANAGEMENT

Tumor resection

Apart from germ cell tumors, microsurgical excision is still the basis of treatment for most pineal area malignancies today [42]. Surgical management of pineal region tumors comprises various microsurgical and endoscopic options. Benign pineal tumors should be cured with surgery alone.

The benefits of complete tumor resection are best surmised by tumor type and histology. Evidence suggests that surgical debulking may improve the response to postoperative adjuvant therapy in patients with malignant tumor components. Gross complete tumor excision also offers the neuropathologist adequate tissue specimens for diagnosis. This avoids the concerns of sampling mistakes and incorrect diagnosis that stereotactic biopsy can cause due to the little volume of tissue available.

Patients presenting with hydrocephalus and radiographic evidence of a malignant pineal region tumor may have their hydrocephalus treated with a third ventriculostomy or ventriculoperitoneal (VP) shunt before biopsy or resection. The staged procedure allows for definitive control of the hydrocephalus before surgical resection of lesions suspected of being malignant.

Radiotherapy

Radiotherapy is being used to treat malignant pineal area tumors in children over three years. Early clinical trials of radiation patients revealed considerable mortality. Even low doses of radiation can have significant long-term effects on a child's cognitive development. Radiation-induced deficits are an important consideration because many children with pineal region tumors enjoy prolonged survival [30] [46].

Although the advent of more sophisticated surgical procedures inspires a periodic renewal of enthusiasm for extirpation, radiotherapy remains the approved primary care treatment for pinealoma and ectopic pinealoma [43]. In most published series, germinomas are among the most radiosensitive cancers, with patient response rates and long-term tumor-free survival rates above 90%. Conventional radiation therapy alone can cure pure germinomas, which are highly radiosensitive. Malignant tumors should be treated with aggressive resection followed by irradiation and chemotherapy [44].

Equally complex are the treatment options with microsurgery as the standard modality, but stereotactic radiosurgery, an alternative and adjunctive treatment to surgery for selected cases, also holds promise. After surgery, patients with malignant and/or residual grade II or grade III tumor benefit



from adjuvant therapy. Intensive multimodal adjuvant therapy is recommended for patients with evidence of neuraxial dissemination, and prophylactic multimodal adjuvant therapy is recommended for all patients with PB and PPTIDs with adverse features such as subtotal resection and large cell morphology [45]

Surgical therapy

The literature has thoroughly argued the pros and cons of performing a biopsy versus an open operation for a pineal tumor. While the ultimate choice of procedure is based upon the surgeon's personal bias and experience, some distinct advantages and disadvantages exist for each procedure.

Chemotherapy

Chemotherapy has emerged as a promising way to adequately reduce the amount of radiation required to treat children with pineal tumors. Chemotherapy response for patients with pineal area tumors varies according to tumor histology, just like radiation. Pineal cell cancers have traditionally been more resistant to chemotherapy than germ cell tumors.

Patients with pineal gland tumor can be given platinum-based regimens, where response rates for germinomas and non-germinomatous germ cell cancers have

ranged from 80 to 100%. Patients with extracranial nongerminomatous germ cell tumors respond well to treatment with various chemotherapeutic agents.

Some regimens have shown response rates as high as 78 percent in patients with intracranial nongerminomatous germ cell tumors. The Einhorn regimen, which comprises cisplatin, vinblastine, and bleomycin and later swapped VP-16 for vinblastine and bleomycin, has shown some promise. Several studies are underway to determine the best adjuvant therapy sequence for children with non-germinomatous germ cell tumors. These children are now undergoing chemotherapy before receiving radiation treatment.

The dramatic success of radiotherapy in treating germinoma children has precluded extensive consideration of chemotherapy as a first-line treatment in older children. Chemotherapy should be considered a first-line treatment only in very young children [47]. Some authors advocate treating children with chemotherapy before radiation to reduce radiation exposure and associated morbidity.

Patients with recurring or metastatic germinomas, most clinicians now recommend a variant of the Einhorn regimen as an alternate treatment. After diagnosing nongerminomatous germ cell tumors, some doctors recommend chemotherapy and radiotherapy. Children with nongerminomatous germ cell tumors who were treated with radiation alone had a 5-



year survival rate of 30-65%, which prompted the introduction of chemotherapy to these patients. [47]

The effectiveness of chemotherapy treatments for children with pineal cell tumors has only been described in anecdotal case reports and small series of patients. No dominant agent has evolved as the drug of choice, and treatment regimens have included various combinations of vincristine, lomustine, cisplatin, etoposide, cyclophosphamide, actinomycin D, and methotrexate.

High-dose cyclophosphamide has been advocated as a single-agent protocol for treating pineoblastomas children. While on the program, children treated with high-dose cyclophosphamide had a stable or declining illness, according to Ashley and colleagues. The adverse consequences were pulmonary dysfunction and thrombocytopenia.

COMPLICATIONS

The most common complications following pineal region surgery, regardless of the approach, are extraocular movement dysfunction, ataxia, and altered mental status [48]. Many of these neurologic symptoms, such as extraocular movement dysfunction and ataxia, are present before surgery and progressively worsen before

improving or resolving completely. Prior radiation treatment, significant preoperative neurologic deficit, malignant tumor pathology, and invasive tumor features are all factors that are linked to an increased risk of surgical complications.

The most devastating complication of pineal region tumor surgery is postoperative hemorrhage into a sub resected tumor bed. The hemorrhage may be delayed for several days and is most associated with vascular tumors, such as pineal cell tumors. Another serious consequence is venous infarction, which can occur with or without bleeding. Shunt malfunction, hemorrhage during the third ventriculostomy following fenestration of the third ventricle floor, ventriculostomy closure, and aseptic meningitis are less common postoperative complications. Seizures, hemianopsia, and hemiparesis are possible side effects of supratentorial methods.

Potential complications include hypothalamic and endocrine dysfunction, cerebral necrosis, secondary tumorigenesis, and disease progression. Since 1953, at least 35 cases of radiation-induced meningioma have been reported in children after radiotherapy for pineal region tumors. Standard radiotherapy protocols for children with malignant pineal cell tumors use 4000 cGy of whole-brain radiation followed by 1500 cGy to the pineal region. The dose is administered in 180-cGy daily fractions.

Whole-brain radiation can cause significant morbidity in prepubescent patients, limiting



the recommended initial extended field to 2500-3000 cGy. An additional dose directed at the tumor bed can be administered subsequently. Several studies show that individuals who receive less than 5000 cGy are more likely to have a recurrence, implying this is the ideal total dose of radiation. The typical treatment for children with malignant germ cell tumors is focused irradiation followed by ventricular field radiation. The histology of the tumor being treated determines how radiation is used. [28][49]

The use of prophylactic spinal irradiation is controversial. Reports demonstrating that drop metastases in the spine are generally low have precluded early recommendations for postoperative spinal irradiation. The likelihood of a pineal tumor metastasizing to the spine varies depending on the tumor's histology. Estimates of the incidence of spinal seeding with pineal cell tumors are 10-20%, with significantly higher rates noted for pineoblastoma compared with pineocytoma.

CONCLUSION

Pineal body tumors are rare group of brain tumors commoner in children with varying degrees of manifestations. Confirmation of the definitive diagnosis of pineal body tumors often involve multiple investigative procedures employed over the years.

However, it is established that in order to confirm the incidence of pineal body tumor inclusion of the patient's clinical presentations combined with investigations like MRI, CT scans, and pathological biopsy are essential. An elevated alpha-fetoprotein (AFP) and Beta human chorionic gonadotropin hormone in either serum or CSF will aid the diagnosis of a secreting tumor. It is advisable that once the histological diagnosis is confirmed with a primary biopsy of pineal lesions in children surgical resection should follow. [30][42][49]

We have established that endoscopic tumor biopsies are considered safe and minimally invasive, thus an effective strategy for the initial management of pineal gland tumors. [48] Furthermore, benign pineal tumors can be cured with surgery alone, while irradiation and chemotherapy will be effective for malignant pineal tumors.

REFERENCES

1. Horsburgh A, Massoud TF. The circumventricular organs of the brain: conspicuity on clinical 3T MRI and a review of functional anatomy. *Surg Radiol Anat.* 2013 May. 35(4):343-9. [\[OxMD MEDLINE Link\]](#).
2. Maronde E, Stehle JH. The mammalian pineal gland: known facts, unknown facets. *Trends Endocrinol Metab.* 2007; 18: 142-149. pmid:17374488 [View Article](#)
3. Yamazaki S, Yoshikawa T, Biscoe EW, Numano R, Gallaspy LM, Soulsby S, et al. Ontogeny of



- circadian organization in the rat. *J Biol Rhythms*. 2009;24: 55–63. Pmid: 19150929
4. Carr, C.; O'Neill, B.E.; Hochhalter, C.B.; Strong, M.J.; Ware, M.L. Biomarkers of pineal region tumors: A review. *Ochsner J*. **2019**, 19, 26–31.
5. Cipolla-Neto J, Amaral FGD. Melatonin as a Hormone: New Physiological and Clinical Insights. *Endocr Rev*. 2018; 39(6):990–1028. [[PubMed](#)]
6. Smith JA, O'Hara J, Schiff AA. Altered diurnal serum melatonin rhythm in blind men. *Lancet*. 1981; 2:933.
7. Macchi MM, Bruce JN. Human pineal physiology and functional significance of melatonin. *Front Neuroendocrinol*. 2004; 25:177–195.
8. Ostrin LA. Ocular and systemic melatonin and the influence of light exposure. *Clin Exp Optom*. 2019; 102:99–108.
9. Abbassy, M.; Aref, K.; Farhoud, A.; Hekal, A. Outcome of single-trajectory rigid endoscopic third ventriculostomy and biopsy in the management algorithm of pineal region tumors: A case series and review of the literature. *Childs Nerv. Syst*. **2018**, 34, 1335–1344.
10. Al-Hussaini, M., Sultan, I., Abuirmileh, N., Jaradat, I. and Qaddoumi, I., 2009. Pineal gland tumors: experience from the SEER database. *Journal of neuro-oncology*, 94(3), pp.351-358.
11. Nagasawa DT, Lagman C, Sun M, Yew A, Chung LK, Lee SJ, Bui TT, Ooi YC, Robison RA, Zada G, Yang I. Pineal germ cell tumors: Two cases with review of histopathologies and biomarkers. *J Clin Neurosci*. 2017 Apr; 38:23-31. Doi: 10.1016/j.jocn.2016.12.024. Epub 2017 February 8. PMID: 28189312; PMCID: PMC8908809.
12. Tan, G.C.; Sallapan, S.; Haworth, K.; Finlay, J.; Boue, D.R.; Pierson, C.R. CNS germinoma with extensive calcification: An unusual histologic finding. *Malays. J. Pathol*. **2019**, 41, 71–73.
13. Reiter, R.J.; Tan, D.X.; Fuentes-Broto, L. Melatonin: A multitasking molecule. *Prog. Brain Res*. **2010**, 181, 127–151. Causalusil, L.D.; Ames, R.; Paul, P.; Castillo, M. Adult brain tumors and pseudotumors: Interesting (Bizarre) cases. *Neuroimaging Clin. N. Am*. **2016**, 26, 667–689.
14. Lv, X.F.; Qiu, Y.W.; Zhang, X.L.; Han, L.J.; Qiu, S.J.; Xiong, W.; Wen, G.; Zhang, Y.Z.; Zhang, J. Primary intracranial choriocarcinoma: MR imaging findings. *AJNR Am. J. Neuroradiol*. **2010**, 31, 1994–1998.
15. Peterson, C.M.; Buckley, C.; Holley, S.; Menias, C.O. Teratomas: A multimodality review. *Curr. Probl. Diagn. Radiol*. **2012**, 41, 210–219. Smirniotopoulos, J.G., Rushing, E.J. and Mena, H., 1992. Pineal region masses: differential diagnosis. *Radiographics*, 12(3), pp.577-596.
16. Louis, D.N.; Perry, A.; Reifenberger, G.; von Deimling, A.; Figarella-Branger, D.; Cavenee, W.K.; Ohgaki, H.; Wiestler, O.D.; Kleihues, P.; Ellison, D.W. The 2016 World Health Organization classification of tumors of the central nervous system: A summary. *Acta Neuropathol*
17. Tamrazi, B.; Nelson, M.; Blüml, S. Pineal region masses in pediatric patients. *Neuroimaging Clin. N. Am*. **2017**, 27, 85–97. [Gross description of pineocytoma. Pathology Outlines 2015.](#)



18. Villano, J.L.; Propp, J.M.; Porter, K.R.; Stewart, A.K.; Valyi-Nagy, T.; Li, X.; Engelhard, H.H.; McCarthy, B.J. Malignant pineal germ-cell tumors: An analysis of cases from three tumor registries. *Neuro Oncol.* **2008**, *10*, 121–130.
19. De Jong, M.C.; Kors, W.A.; de Graaf, P.; Castelijns, J.A.; Kivelä, T.; Moll, A.C. Trilateral retinoblastoma: A systematic review and meta-analysis. *Lancet Oncol.* **2014**, *15*, 1157–1167.
20. Alkhotani, A.; Bilbao, J.M.; Mainprize, T.G. A 49-year-old woman with a pineal mass. *Brain Pathol.* **2014**, *24*, 191–192.
21. Boco, T., Aalaei, S., Musacchio, M., Byrne, R. and Cochran, E. (2008), Papillary tumor of the pineal region. *Neuropathology*, *28*: 87-92.
[\[CrossRef\]](#) **Papillary tumor of the pineal region.** Poulain, Katherine, et al. *Journal of Clinical Neuroscience*, Volume 18, Issue 8, 1007 - 1017
22. Fernández-Mateos, C.; Martínez, R.; Vaquero, J. Long-term follow-up after radiosurgery of papillary tumor of pineal region: 2 case reports and review of literature. *World Neurosurg.* **2018**, *116*, 190–193.
23. Bando, T.; Ueno, Y.; Shinoda, N.; Imai, Y.; Ichikawa, K.; Kuramoto, Y.; Kuroyama, T.; Shimo, D.; Mikami, K.; Hori, S.; et al. Therapeutic strategy for pineal parenchymal tumor of intermediate differentiation (PPTID): Case report of PPTID with malignant transformation to pineocytoma with leptomeningeal dissemination 6 years after surgery. *J. Neurosurg.* **2018**, *1–7*. Scheithauer, B.W.; Fuller, G.N.; Vandenberg, S.R. 2007 WHO classification of tumors of the nervous system: Controversies in surgical neuropathology. *Brain Pathol.* **2008**, *18*, 307–316, Erratum in *Brain Pathol.* **2008**, *18*, 640.
24. Le, Tao, and Vikas Bhushan. *First Aid for the USMLE Step 1 2015. 25th-anniversary edition.* New York: McGraw-Hill Medical, 2015.
25. Jeffrey N Bruce, M. D. (2022, March 3). *Pineal Tumors Clinical Presentation: Complications.* Retrieved April 12, 2022. Westpahl M. & Emami P. (2015) Pineal lesions: A multidisciplinary challenge. *Adv Tech Stand Neurosurg*;42:79-102.
26. Epari, S., Verma, A., Bakiratharajan, D., Sahay, A., Goel, N., Chinnaswamy, G. et al. (2019). Primary pineal tumors – Unraveling histological challenges and certain clinical myths. *Neurology India*, *67*(2), 491. doi: 10.4103/0028-3886.258045
27. Chaturvedi, S., & Suri, V. (2019). Pineal tumors: Rare but challenging entity. *Neurology India*, *67*(2), 503. doi: 10.4103/0028-3886.2023
28. Görgün, Ö., Koç, B., Kebudi, R., Wolff, J., Kebudi, A., & Darendeliler, E. (2021). Clinical characteristics, late effects, and outcomes in pineoblastomas in children: a single center experience. *The Turkish Journal Of Pediatrics*, *63*(6), 955. doi: 10.24953/turkjped.06.002
29. Mottolese, C., Szathmari, A. & Beuriat, P. (2015). Incidence of pineal tumours. A review of the literature. *Neurochirurgie*, *61*(2-3), 65-69. doi: 10.1016/j.neuchi.2014.01.005
30. Jooma, R., & Kendall, B. (1983). Diagnosis and management of pineal tumors. *Journal Of Neurosurgery*, *58*(5), 654-665. doi: 10.3171/jns.1983.58.5.0654 .Pineal Region Tumors Diagnosis and Treatment. *National Cancer Institute at the National Institutes of Health.* July 21, 2021. <https://www.cancer.gov/rare-brain-spine-tumor/tumors/pineal-region-tumors>
31. Gaillard, F. (2022). Pineal region mass | *Radiology Reference Article* | Radiopaedia.org. Retrieved April 12 2022, from <https://radiopaedia.org/articles/pineal-region-mass>



32. Carr, C., O'Neill, B., Hochhalter, C., Strong, M., & Ware, M. (2019). Biomarkers of Pineal Region Tumors: A Review. *Ochsner Journal*, 19(1), 26-31. doi: 10.31486/toj.18.011 Ferrer E, Santamarta D, Garcia-Fructuoso G, et al. (1997). Neuroendoscopic management of pineal region tumours. *Acta Neurochir (Wien)*. 139(1):12-20; discussion 20-1. [QxMD MEDLINE Link].
33. Pople I.K., Athanasiou T.C., Sandeman D.R. & Coakham H.B. (2001) The role of endoscopic biopsy and third ventriculostomy in the management of pineal region tumours. *Br J Neurosurg*. August 15 (4):305-11. [QxMD MEDLINE Link].
34. Gangemi M., Maiuri F., Colella G. & Buonamassa S. (2001) Endoscopic surgery for pineal region tumors. *Minim Invasive Neurosurg*. Jun. 44(2):70-3. [QxMD MEDLINE Link].
35. Oi S., Kamio M., Joki T. & Abe T. (2001) Neuroendoscopic anatomy and surgery in pineal region tumors: role of neuroendoscopic procedure in the 'minimally-invasive preferential' management. *J Neurooncol*. Sep. 54(3):277-86. [QxMD MEDLINE Link].
36. Takeda J., Nonaka M., Li Y., Komori Y., Kamei T., Iwata R., et al. (2017) 5-ALA fluorescence-guided endoscopic surgery for mixed germ cell tumors. *J Neurooncol*. Aug. 134 (1):119-124. [QxMD MEDLINE Link].
37. Calaminus G., Andreussi L., Garre M. L., Kortmann R.D., Schober R., Gobel U. (1997) Secreting germ cell tumors of the central nervous system (CNS). First results of the cooperative German/Italian pilot study (CNS site). *Klin Paediatr* 209:222-227
38. Bruce J. F. & Housepian E. M. (2017) Pineal Tumors Treatment & Management Updated: October 19 Medscape; *Neurosurgery: Drugs and diseases*. <https://emedicine.medscape.com/article/249945-treatment#d9>
39. Ashley D. M., Longee D., Tien R., et al. (1996) Treatment of patients with pineoblastoma with high dose cyclophosphamide. *Med Pediatr Oncol*. June 26 (6):387-92. [QxMD MEDLINE Link].
40. Abecassis I. J., Hanak B., Barber J., Mortazavi M. & Ellenbogen R.G.(2017) A Single-Institution Experience with Pineal Region Tumors: 50 Tumors Over 1 Preoperative Details Decade. *Oper Neurosurg (Hagerstown)*. October 1. 13 (5):566-575. [QxMD MEDLINE Link].
41. Azab, W., Nasim, K., & Salaheddin, W. (2014). An overview of the current surgical options for pineal region tumors. *Surgical Neurology International*, 5(1), 39. DOI: 10.4103/2152-7806.129430
42. Schulz, M., Afshar-Bakshloo, M., Koch, A., Capper, D., Driever, P., Tietze, A. et al. (2020). Management of pineal region tumors in a pediatric case series. *Neurosurgical Review*, 44(3), 1417



43. Radovanovic I., Dizdarevic K., Tribolet N., Masic T. & Muminagic S. (2009) Pineal region tumors-neurosurgical review. *Med Arh*;63:171-3 xiii
44. Mincer, F., Meltzer, J., & Botstein, C. (1976). Pinealoma. A report of twelve irradiated cases. *Cancer*, 37(6), 2713-2718. DOI: 10.1002/1090142(197606)37:6<2713:aid-cnrcr2820370622>3.0.co; 2-a
45. Konovalov, A., & Pitskhelauri, D. (2003). Principles of treatment of the pineal region tumors. *Surgical Neurology*, 59(4), 252-270. DOI: 10.1016/s0090-3019(03)00080
46. Raleigh D. R., Solomon D.A., Llyod S. A., Lazar A., Garcia M. A., Sneed P. K., et al. (2017) Histopathology review of pineal parenchymal tumors identifies novel morphologic subtypes and prognostic factors for outcomes. *Neuro Oncol*; 19:78-88.
47. Fuller B. G., Kapp D. S., and Cox R. (1994) Radiation therapy of pineal region tumors: 25 new cases and a review of 208 previously reported cases. *Int J Radiat Oncol Biol Phys*. January 1. 28(1):229-45. [QxMD MEDLINE Link].
48. Manera L, Regis J, Chinot O, et al. (1996) Pineal region tumors: the role of stereotactic radiosurgery. *Stereotact Funct Neurosurg*. . 66 Suppl 1:164-73. [QxMD MEDLINE Link].
49. Regis J, Bouillot P, Rouby-Volot F, et al. (1996) Pineal region tumors and the role of stereotactic biopsy: a review of the mortality, morbidity, and diagnostic rates in 370 cases. *Neurosurgery*. Nov. 39(5):907-12; discussion 912-4. [QxMD MEDLINE Link].

