**REVIEW ARTICLE**

**In and Around the Pineal Gland: A Neuroimaging Review**

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**ABBREVIATION KEY**

CSF - cerebrospinal fluid

CT - Computed Tomography

FLAIR - Fluid Attenuated Inversion Recovery

MRI - Magnetic Resonance Imaging

T1-WI - T1-weighted images

T2-WI - T2-weighted images

**INTRODUCTION**

The pineal gland (pineal body) is a pea-sized midline organ named for its shape resembling a pinecone (Latin *pinea*), projecting caudally from the posterior wall of the third ventricle into the quadrigeminal cistern, where it rests between the splenium of the corpus callosum superiorly, quadrigeminal plate inferiorly, and thalamic pulvinars laterally (Figure 1). Anteriorly, the pineal gland is attached to the posterior wall of the third ventricle by the pineal stalk composed of the habenular commissure forming its superior lamina, and the posterior commissure forming its inferior lamina. Looking from the lumen of the third ventricle the laminae of the pineal stalk outline an outpouching of its posterior wall known as the pineal recess. The pineal gland belongs anatomically to the diencephalon, and together with paired habenular nuclei, the habenular commissure and stria medullaris of the thalamus they form the epithalamus, which is the most caudal part of the diencephalon.1

It is important to note that the pineal gland is included amongst the circumventricular organs which demonstrate contrast enhancement as their normal imaging feature.2 However, unlike in the other circumventricular organs, pineal gland enhancement is considered secondary to a dense capillary network rather than incomplete blood-brain barrier or fenestrated vasculature.2 Another common feature of the pineal gland and the adjacent habenular commissure is calcification, the frequency of which increases with age – it is a matter of debate if calcification impairs the endocrine function of the gland, or if it is inconsequential, but its presence is not considered abnormal even in childhood.3

The pineal gland contains two cell types: pineocytes, which are the principle constituents of the parenchyma, and astrocytes.1,3,4 The biological function of the gland is not fully understood but it is regarded as a photosensitive neuroendocrine organ and a biological clock regulating the circadian rhythm by releasing melatonin and other neurochemicals.3

Lesions of the pineal region can originate from the pineal gland itself, where they may arise from both the pineocytes and glial cells, and from adjacent structures (Table 1). Clinical symptoms can be secondary to compression of the neighbouring brain structures, in particular the quadrigeminal (tectal) plate, as well as to disturbance of the neuroendocrine function of the gland. Compression of the tectum may lead to hydrocephalus caused by obstruction of the aqueduct of Sylvius,1,5 whereas compression of the vertical gaze centres and their connections that decussate in the posterior commissure leads to Parinaud syndrome (dorsal midbrain syndrome) - a constellation of vertical gaze palsy, convergence-retraction nystagmus, and pupillary light-near dissociation.6 Other neurological manifestations of midbrain compression such as cerebellar, corticospinal or sensory symptoms, are infrequent.1 Disturbance of the neuroendocrine function of the pineal gland does not usually affect the circadian rhythm but may affect the age of puberty owing to disruption of the inhibitory effect of melatonin on gonadal function – in particular, lesions that reduce melatonin production by destroying the normal architecture of the gland lead to precocious puberty, while tumours that produce melatonin cause delayed pubescence.1,5 Finally, some pineal masses such as germ cell tumours may exert hormonal effects by gonadotropin production.1

In the main part of this review we describe the commonly encountered non-neoplastic pineal cysts, tumours of the pineal region primary to the pineal gland, and germ cell tumours. Rare lesions of the pineal gland and lesions arising from adjacent structures are discussed in the Electronic Supplementary Material.

**PINEAL CYST**

Pineal cysts are the most common pineal gland lesions reported on 1.5-10.8% of standard brain MRIs. The highest prevalence in women in the third decade of life suggesting hormonal influence as a possible contributing factor.1,7,8 The origin of pineal cysts is not fully established but proposed mechanisms for their formation include enlargement of a remnant of the developmental embryonic pineal diverticulum, as well as ischaemic degeneration and necrosis of the gland.7 The cyst can either reside within the gland or completely replace the gland parenchyma.1

The majority of the pineal cysts are asymptomatic, although it is worth noting that the relation between the presence and size of the cysts and the clinical symptoms, and headache in particular, is not fully understood. Most studies reporting on the prevalence of pineal cysts consider lesions found in patients investigated for headache as non-causative based on the rationale that both conditions are common and their association is purely coincidental.7,9,10 On the other hand, there is evidence on higher incidence of headache in patients with pineal cysts suggesting a causative relationship, which appears independent of the presence of hydrocephalus, and does not correlate with the size of the cyst or compression of the adjacent structures.11 The aetiology of headache associated with non-hydrocephalic cysts is uncertain but it has been linked to reduced melatonin production11–13 and increased venous pressure in deep brain structures owing to compression of internal cerebral veins that pass between the cyst and the splenium of the corpus callosum (Figure 1).14,15 Some authors advocate surgical resection in patients with symptoms associated with non-hydrocephalic cysts,16 although identification of suitable candidates is difficult,17 and the treatment is controversial owing to limited evidence, surgical risks, and uncertain clinical benefit.7 Obstructive hydrocephalus, Parinaud syndrome and other compressive symptoms are rare and occur mainly with cysts larger than 15-20 mm.10,18 Interestingly, the size of the cyst has no direct correlation to symptoms and even large cysts can remain entirely asymptomatic.7

A typical pineal cyst has a round or elliptical shape with thin, regular and well-circumscribed walls histologically composed of inner gliotic and middle pineal parenchymal tissue surrounded by an outer leptomeningeal connective tissue layer (Figure 2). On MRI, the cystic content is usually homogenous and isointense to CSF but can be slightly hyperintense to CSF on both T1-weigthed (T1-WI) and T2-weighted (T2-WI) images.1,19 Variations in signal characteristics depend on the composition of the cyst content which may be watery, haemorrhagic or coagulated.1 Signal suppression on fluid-attenuated inversion recovery (FLAIR) images is typically incomplete and signal intensity on this sequence can vary over time owing to changes in protein content (Figure 3).1,19 A typical enhancement pattern is circumferential with a thin (less than 2 mm) and usually incomplete enhancing rim.1,19 On delayed imaging, gadolinium-based contrast agents may accumulate within the cystic component and appearances may be confused with a solid lesion; it is important to be aware of this potential pitfall and to perform imaging early after contrast injection.1,20

Less common imaging findings include fluid levels owing to intracystic haemorrhage (Figure 4) which may be asymptomatic but can also result in sudden increase in the cyst size with consequent hydrocephalus and acute neurological symptoms or even death (pineal apoplexy). 7,21 Findings such as irregular and non-ovoid shape, thin internal septations (Figure 4), rim thickness greater than 2 mm, or irregular enhancing nodularities are considered atypical imaging features, even though they are present in a relatively high proportion of pineal cysts.1,7,22 Atypical findings are not associated with a tendency of the cyst to increase in size or clinical symptoms but make differentiation between a non-tumoural pineal cyst and cystic pineal neoplasm more difficult.1,7 Nodular enhancement can be seen in 16% of cases, usually at the posterior aspect of the cyst and likely owing to adjacent vascularity or posteriorly displaced pineal tissue.1 Internal septations have been reported in 22% to 32% of cases 19,23 and are even more conspicuous on high resolution imaging using isotropic balanced steady state free precession sequences such as FIESTA24 or trueFISP,25 which in addition to trabeculations may reveal multiple small nodular cystic components. Overall, internal structure can be seen in 60% of cysts imaged using FIESTA,24 while trueFISP demonstrates atypical features such as irregular shape, internal septations or both in 41% of cases.25 Not surprisingly, high resolution MRI also demonstrates smaller cysts in a higher proportion of patients, approaching the incidence reported on autopsy series (25-40%).26 For example a combination of 1 mm isotropic T1-WI and T2-WI demonstrated pineal cysts as small as 2 mm (mean diameter 4.3 mm) in 23% of healthy volunteers aged 19-39 years sampled at random from a research imaging database, while cystic changes smaller than 2 mm were seen in an additional 13% of subjects.26 TruFISP demonstrated pineal cysts in 35% of a random patient cohort (­mean cyst diameter of 3.3 mm).25 With increasing availability and widespread use of MRI and introduction of high-resolution sequences into routine scanning protocols the incidence of small pineal cysts discovered incidentally in clinical practice is therefore likely to increase.

Despite the high prevalence of pineal cysts the data on the natural history of these lesions are relatively scarce. The available studies demonstrate that only a small proportion of cysts that have been followed up on imaging (5% on average, Table 2) shows increase in size, and in nearly all cases such the increase in size is not associated with any clinical symptoms. 7,9,10,15,18,19,21,22,24,27–30 The age distribution of cyst prevalence with a peak in the late childhood and early adulthood suggest that pineal cysts form in childhood and undergo a period of growth, then reach a period of quiescence and subsequently involute in older age.7,27 Thus, unless manifesting clinically, 31 an increase in the cyst size in the late childhood or early adulthood 7,27 or even in the first three decades of life21 should not be considered pathological as it may reflect the natural history of the lesion.7,27 Interval growth of pineal cysts occurs less frequently in older patients. 21,27 Large cysts are more likely to reduce in size than grow, and smaller cyst are most likely to remain stable.7

While symptomatic pineal cysts always warrant neurosurgical assessment, the management of incidentally discovered asymptomatic lesions remains controversial. Given the aforementioned natural history of pineal cysts, routine imaging follow-up of every asymptomatic patient appears to be of little benefit, and in view of the high prevalence can pose considerable burden on the imaging departments. Surveillance recommendations of asymptomatic cysts in the available literature vary widely from no routine imaging at all, through follow-up of selected lesions based on arbitrary size thresholds or suspicious imaging characteristics, to routine follow-up for many years (Table 3). As mentioned above, even though atypical features are seen in a relatively high proportion of simple non-neoplastic pineal cysts, the presence of thick (> 2 mm) or nodular wall enhancement raises a possibility of a cystic pineocytoma; on the other hand, pineocytoma appearing as a simple thin-walled cyst is extremely unlikely.20 Given the tendency of the majority of simple pineal cysts to remain stable or reduce in size, and the lack of direct correlation between the cysts size and development of clinical symptoms, exclusion of a pineal neoplasm rather than size monitoring is therefore considered a more important rationale for follow up by several authors.1,9,20 In the case of suspected pineal cyst found on computed tomography (CT) or unenhanced MRI, contrast-enhanced MRI should therefore always be performed to fully characterise the wall thickness of the lesion and guide the surveillance decisions.20

Recent management advice from a group of UK adult and paediatric neurosurgeons and a neuroradiologist takes into account all the aforementioned factors.32 The authors recommend the following pragmatic approach:

* simple pineal cysts less than 10 mm in diameter can be considered a normal variant and do not require any follow up
* adults with incidental pineal cysts regardless of size should be reassured and routine follow-up imaging is not usually required
* children with incidental pineal cysts should be monitored with interval follow-up MRI for 1-2 years as the cysts may enlarge and become symptomatic
* atypical pineal cysts (multiloculated, enhancing, with solid component) do not require long-term follow-up, but patients and clinicians may find it reassuring to undertake follow-up MRI at 1,3 and 5 years and germ cell tumour markers at diagnosis
* rare patients with suspected non-hydrocephalic symptomatic pineal cysts (with symptoms such as paroxysmal headache not typical of migraine, intermittent nausea and/or vomiting, visual disturbance, transient impaired conscious level, gait instability, hypersomnolence) are best referred for evaluation to specialist centres
* patients with pineal cysts causing hydrocephalus should be treated with combined endoscopic third ventriculostomy, endoscopic cyst drainage/fenestration and cyst wall biopsy if possible

**PINEAL TUMOURS**

In WHO 2021 classification the category of “pineal tumours” includes primary pineal neoplasms that originate from pineocytes or their precursors, but excludes other lesions that reside within the pineal gland but originate from different cells.33 These neoplasms account for 30% of pineal tumours and mainly affect children and young adults with no sex predilection.4,34,35 Primary pineal tumours show varying levels of malignancy, ranging from the benign pineocytoma (grade 1), through pineal parenchymal tumour of intermediate differentiation (PPTID, grade 2/3) to the highly malignant pineoblastoma (grade 4), with increasing cellularity, mitotic rate, nuclear atypia, propensity to metastatic spread via cerebrospinal fluid (CSF) and worsening survival.4,34,35 The reference standard for the diagnosis is pathology, with tumour grading guided by neurofilament protein expression, morphological features, and mitotic counts. On histopathologic examination, pineocytomas may demonstrate well-formed pineocytomatous rosettes and are well circumscribed with low mitotic counts, regular nuclei and sheet-like growth pattern, whereas pineoblastomas may form characteristic Homer-Wright or Flexner-Wintersteiner rosettes36 and exhibit small blue cells histology with a high nuclear/cytoplasmatic ratio resembling embryonal central nervous system tumours.34 On immunohistochemistry, these tumours demonstrate expression of neuronal markers (such as synaptophysin, neurofilament protein, and neuron-specific enolase) and photosensory markers (rhodopsin, S-arrestin, and cone-rod homeobox, CRX).37

Imaging plays little role in differentiating the particular type of pineal tumour owing to overlap in imaging features (Figures 5-7).35 As mentioned above, pineocytomas may appear similar to atypical pineal cysts with nodular wall enhancement,20 but more commonly are predominantly solid and share imaging characteristics with more aggressive tumours. Features that point to a higher grade lesion include young age of the patient, large size of the tumour, obstructive hydrocephalus and/or dorsal midbrain syndrome, 38 irregular margins,39,40 and “exploded” rather than peripheral pattern of calcification on CT, with calcification spread within the lesion.38 High proliferative index and cellularity in pineoblastoma results in hyperdensity on CT, as well as restricted diffusion and lower apparent diffusion coefficient (ADC) on MRI as compared to lower grade primary pineal tumours (Figure 7).39,41,42 The imaging protocol should include contrast-enhanced imaging of the entire spine owing to propensity for drop metastases.35

Treatment of pineocytoma is based on surgical resection with no adjuvant chemo- or radiotherapy; complete resection confers good prognosis with 84% overall survival.35 Given the risk of surgery and slow growth, suspected small pineocytomas may be initially monitored using MRI especially in cases of predominantly cystic lesions, which may represent simple cysts with atypical features.20 In contrast, pineoblastomas require timely multimodal therapy aimed at maximum surgical resection with adjuvant radiation (including spinal irradiation) and chemotherapy.34,38,43 Resection is usually combined with endoscopic third ventriculostomy to provide internal CSF diversion and avoid the need for a ventricular shunt.35 Overall prognosis is poor and worsens with younger age of the patient, incomplete tumour resection and CSF metastatic spread.34,38,43 A recent genomic analysis has identified four distinct molecular subgroups of pineoblastoma with vastly different patient demographics and clinical outcomes – alterations in microRNA processing pathways (PB-miRNA1 and 2) are seen in older children and young adolescents and confer intermediate or good prognosis (with 68% and 100% overall 5-year survival, respectively), whereas *MYC* amplification and *FOXR2* overexpression (PB-MYC/FOXR2) or *RB1* alteration (PB-RB1) occur in young children resulting in dismal survival figures (21% and 27%, respectively).34 Pineoblastoma associated with germline *RB1* mutations can manifest as trilateral retinoblastoma – bilateral retinoblastoma associated with pineoblastoma, usually diagnosed in children under 1 year of age, and with extremely poor prognosis.44 PPTID demonstrates a distinct genomic profile from pineoblastoma and occurs mainly in adults (median age of 33 years) with good prognosis (85% survival rate).34

Papillary tumour of the pineal region (PTPR, Figure 8) is a rare grade 2/3 neoplasm grouped together with pineocytoma, PPTID and pineoblastoma in the WHO classification but histopathologically distinct. It arises from the ependymal circumventricular subcommisural organ35 and demonstrates epithelial and papillary characteristics with immunoreactivity for cytokeratins (CK8/18), CD56, and GFAP (Figure 8) but unlike the other tumours from this group remains negative for neurofilament protein.45 PTPR affects patients of any age, with a slight female predilection.45,46 On MRI, intrinsic T1 hyperintensity owing to inclusion of secretory protein has been described as a characteristic feature47 but the tumours are usually indistinguishable from other pineal masses. Given its relatively recent description, optimal management strategies for PTPR are not yet established but are likely to be based on surgical resection with possible adjuvant chemotherapy; the role of radiation treatment in PTPR is not known yet.45

Desmoplastic myxoid tumour of the pineal region, *SMARCB1*-mutant is a new addition to WHO 2021 classification33 which shares the underlying mutation with a subtype of atypical teratoid/rhabdoid tumour affecting the infant population (see Electronic Supplementary Material).48 In contrast to its paediatric counterpart, the tumour occurs in adolescents and adults (with median age of 15-61 years), lacks histopathological signs of malignancy such as brisk mitotic activity or necrosis, and exclusively involves the pineal gland.49 On histopathology the tumour is composed of spindled and epithelioid cells embedded in desmoplastic stroma alternating with myxoid matrix, with loss of nuclear SMARCB1 expression, positive staining for CD34 and low proliferative index.49 Radiological accounts of the tumour are scarce and describe enhancing pineal mass with hydrocephalus,50 and a lesion slightly hyperdense on CT, with hyperintense T1 and mixed T2 signal initially suspected to be a germ cell tumour.51 Treatment attempted in the described cases included surgical resection, chemotherapy and radiotherapy resulting in intermediate prognosis.49

**GERM CELL TUMOURS**

Germ cell tumours (GCT) are the most common pineal region neoplasms accounting for 60% of pineal masses.35,52 GCTs arise from aberrant migration of primordial germ cells into the central nervous system during embryonic development. The peak incidence of GCTs is in the second decade of life with a strong male predominance 52,53 and is much higher in Japan and Taiwan (where they account for more than 15% of all brain tumours) compared with Europe and America (0.4-3.4%).52 In addition to the most common pineal location, 30-40% of GCTs involve the suprasellar region, 15-17% occur at both sites (bifocal location) and 4-10% occur in the basal ganglia.52 The suprasellar location is typically associated with diabetes insipidus and pituitary hormone deficiencies which may occur before the tumour is apparent on imaging.54 Thus, diabetes insipidus in a patient with a pineal mass should always prompt close evaluation of the pituitary gland for an evidence of bifocal tumours, which may only manifest as subtle thickening of the pituitary stalk or a loss of the normal posterior bright spot on T1-weighted images.54

Different types of GCTs are derived from different stages of embryonic development.53 In Europe and North America, GCTs are classified into two prognostically distinct groups - germinoma or non-germinomatous GCTs (NGGCTs), according to their most malignant component.52 Germinoma is the most common type of GCTs with a favourable prognosis, whereas NGGCTs are a group of higher-risk tumours more resistant to treatment, such as embryonal carcinoma, yolk sac tumour, choriocarcinoma, and mixed germ cell tumour (Table 4). Teratoma, both mature and immature, contains tissues from all three of ectodermal, endodermal and mesodermal lineages with varying degrees of somatic differentiation. It is considered benign unless it includes a malignant component (termed “teratoma with malignant transformation”,52,53,55 and updated in the WHO 2021 classification to “teratoma with somatic-type malignancy”33).

Diagnosis of GCTs is aimed at identifying the most malignant component and initially relies on tumour markers. In Europe and North America the diagnosis of GCTs is based on the principle that minimal surgical intervention and biopsy should be avoided whenever possible.52 Choriocarcinoma and yolk sac tumour are diagnosed based on positive human chorionic gonadotropin (HCG) or alfa-fetoprotein (AFP), respectively, which must be measured both in the plasma and CSF.52 If the tumour markers are negative, biopsy is required for the diagnosis of germinoma or embryonic carcinoma. Diagnostic uncertainty may arise in case of some germinomas containing syncytiotrophoblastic cells that secrete low levels of HCG, which may lead to erroneous diagnosis of choriocarcinoma and overtreatment as there is no clear HCG threshold allowing differentiation between the two GCT types.52,53 Immature teratomas containing liver or gastrointestinal tissue may secrete AFP, which may also lead to diagnosis of yolk sac tumour and overtreatment. 52 Novel biomarkers such as microRNAs have shown promising results in confirming the diagnosis of GCTs,56 and in the future specific microRNAs could be used to distinguish specific GCT subtypes.

Similar to primary pineal tumours, imaging plays only a limited role in the diagnosis but is essential for biopsy planning and establishing their metastatic spread. Imaging of the spinal cord with contrast-enhanced MRI is required in all cases, although in Europe craniospinal irradiation is instigated based on positive CSF cytology even if spinal MRI appears negative.52 MRI appearances of GCTs are in general indistinguishable from other pineal tumours (Figure 9). Similar to other high-grade lesions GCTs may demonstrate restricted diffusion owing to their high cellularity, although the degree of diffusion restriction is lower than in pineoblastoma.39,42 Bifocal tumour location with involvement of the pineal gland and suprasellar region in the absence of AFP elevation is almost always associated with germinoma,52 although it is not pathognomonic.57 Presence of fat signal and calcifications suggest teratoma, either in isolation (Figure 10) or as a component of a mixed tumour (which may be associated with germinoma, NGGCT or other brain neoplasms). However, a teratoma component may be occult on imaging prior to treatment and only becomes evident as a residual tumour after radio- and chemotherapy, given its resistance to these treatments.52

GCTs are primarily treated using a combination of radiotherapy and chemotherapy. Germinomas are highly radiosensitive and curable with radiotherapy only but adjunctive chemotherapy allows reduction of radiation dose and limiting of long term neurological and cognitive sequelae of treatment.52 Small residual lesions after treatment of germinoma does not require resection unless there is suspicion of a teratoma component that should be removed surgically. NGGCTs are less radiosensitive than germinoma and require more intensive treatment regimens including surgical removal of any remnant following chemo- and radiotherapy; such remnant may reveal a teratoma component or necrotic residual tumour. In some cases the teratoma component of a mixed GCTs (which may not be known about on initial diagnosis) may demonstrate significant increase in size during treatment despite progressive normalisation of tumour markers. This phenomenon is known as intracranial growing teratoma syndrome.58,59 It is important to recognise that the paradoxical growth does not signify malignant tumour progression as the high grade component is responding to treatment, and the newly formed tumour is composed of mature teratoma.58 The proposed mechanisms of this phenomenon include induction of differentiation of immature to mature teratoma by chemotherapy or radiation, or favourable conditions for uninhibited growth of teratoma arising upon shrinkage of the treatment-sensitive malignant component.59 Intracranial growing teratoma syndrome occurs in 5% of patients with GCTs and most often involves the pineal location,58 but can also be seen in other intracranial and spinal locations.59 Imaging appearances are characteristic with honeycomb-shaped multicystic growth pattern on MRI.58 Timely recognition is essential to enable early surgery which increases the chances of total resection;58 if resection is not possible, cell cycle inhibitors have shown early promising results.52 Therefore, regular imaging plays a key role in treatment follow-up of GCTs and should continue even if tumour markers are decreasing or have normalised.58 GCTs diagnosed initially as teratoma are treated primarily by surgical resection with no role for adjunctive chemo- or radiotherapy if malignant component is absent.52

**CONCLUSION**

The pineal gland occupies a key anatomical position between the third ventricle, the quadrigeminal plate and the splenium of the corpus callosum. The most common non-tumoural lesion of the pineal gland, a pineal cyst, is usually incidental and asymptomatic but often prompts follow up studies. Recent practical recommendations based on consensus neurosurgical-neuroradiological opinion suggest that asymptomatic simple pineal cysts less than 10 mm in diameter should be considered normal variation of the pineal gland, and that routine follow-up is not usually required in adults regardless of the cyst size. The diagnostic role of imaging in the case of solid pineal tumours, such as primary pineal and germ cell tumours, is usually limited owing to significant overlap in their imaging features. However, contrast-enhanced MRI of the brain is required for surgical planning, and imaging of the entire neuraxis should always be performed for detection of drop metastases. MRI also plays a key role in treatment response monitoring and post-treatment surveillance. Less common pineal masses and tumours arising external to the pineal gland are described in the Electronic Supplementary Material.

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**TABLES**

**Table 1.** Non-tumoural pineal lesions (in italics) and pineal tumours (WHO 2021 categories)

|  |  |
| --- | --- |
| ***Non-tumoural cysts*** | *Pineal cyst* |
| **Pineal tumours** | PineocytomaPineal parenchymal tumour of intermediate differentiation PineoblastomaPapillary tumour of the pineal regionDesmoplastic myxoid tumour of the pineal region, *SMARCB1*-mutant |
| **Germ cell tumours** | GerminomaEmbryonal carcinomaYolk sac tumourChoriocarcinomaTeratoma – mature and immatureTeratoma with somatic-type malignancy Mixed germ cell tumour  |
| **Diffuse gliomas (adult and paediatric types)** | GlioblastomaAstrocytomaOligodendrogliomaDiffuse midline glioma H3K27M-altered |
|  | Pilocytic astrocytomaPleomorphic xanthoastrocytomaSubependymal giant cell astrocytoma |
| **Glioneuronal and neuronal tumours** | GangliogliomaRosette-forming glioneuronal tumourMalignant epithelioid glioneuronal tumour (\*) |
| **Embryonal tumours** | Atypical teratoid/rhabdoid tumourMedulloblastoma |
| **Meningiomas** | Meningioma |
| **Metastases to the CNS** | Metastases to the brain and spinal cord parenchyma |
| **Mesenchymal non-meningothelial tumours** | Lipoma |
| ***Congenital inclusion cysts*** | *Epidermoid cyst**Dermoid cyst* |

(\*) not currently included in WHO 2021 classification

**Table 2.** Studies on the natural history of pineal cysts

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Author** | **Age (years)** | **Cyst size** | **Follow-up duration** | **No of cysts**  | **stable** | **Increased** | **Reduced** |
| Al-Holou et al. 2010 27 | < 25 (mean 11.7) | mean 9.9 ± 4.5 mm | mean 3 years | 106 | 99 | 6 | 1 |
| Al-Holou et al. 2011 7 | > 19 (mean 40.1) | mean 9.7± 3.8 mm | 6 months -13 years (mean 3.4 years) | 151 | 124 | 4 | 23 |
| Barboriak et al. 2001 28 | 0.7-67 (mean 22.9) | 5-22 mm | 6 months - 9 years (mean 3.7 years) | 32 | 24 | 3 | 5 |
| Gokce & Beyhan 2018 19 | 5-61 (mean 31.3) | 5-19.7 (mean 11.2 mm)  | 2 months - 7.8 years (mean 2.5 years) | 18 | 18 | 0 | 0 |
| Golzarian et al. 1993 29 | 1-59 (mean 37) | 5-17 mm | 1 year | 12 | 12 | 0 | 0 |
| Jussila et al. 2017 9 | 1-16 (mean 8.6) | > 10 mm (mean 12.8 mm) | 3 months - 12.1 years (median 10 months) | 79 | 70 | 9 | 0 |
| Majovsky & Benes 2018 21 | 7-62 (mean 31.1) | 7-35 mm (mean 12.7 mm) | 1-3 years | 133 | 116 | 7 | 10 |
| Mandera et al. 2003 18 | 4-18 | > 5 mm (5 cysts > 20 mm) | 2-5 years (mean 3.2 years) | 24 | 23 | 1 | 0 |
| Nevins et al. 2016 10 | 16-84 (median 38) | 2-28 mm (median 10 mm) | 1 month - 5.7 years (median 6 months) | 181 | 170 | 7 | 4 |
| Pastel et al. 2009 24 | 1-64 (mean 28) | 6-30 mm (mean 12.7) | 1-25 months (mean 10 months) | 23 | 22 | 1 | 0 |
| Sawamura et al. 1995 30 | 21-80 | mean 11.2 ± 7.9 mm | median 18 months | 20 | 20 | 0 | 0 |
| Tamaki et al. 1989 15 | 8-69 | not stated | 3 months - 4 years | 32 | 29 | 1 | 2 |
| Whitehead et al. 2013 22 | 0-17 (mean 6.8) | 1.5-16 mm (mean 4.2 mm) | 1.5-5 years | 17 | 12 | 2 | 3 |
| **Total** |  |  |  | **828** | **738** | **41** | **48** |
|  |  |  |  |  | **89%** | **5%** | **6%** |

 |  |  |  |  |  |  |  |

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| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  |  |  |
| **Table 3.** Summary ofimaging follow-up recommendations for pineal cysts |  |  |  |  |  |  |  |
|

|  |  |
| --- | --- |
| **Author** | **Imaging follow up recommendation (\*)**  |
| Barboriak et al. 2001 28 | follow-up on clinical basis alone |
| Golzarian et al. 1993 29 | cyst in the absence of symptoms should be considered a normal variant |
| Pastel et al. 2009 24 | no follow-up unless new or worsening symptoms |
| Jussila et al. 2017 9 | follow-up not necessary in the absence of unusual characteristics or clinical symptoms |
| Al.-Holou et al. 201027 and 20117 | follow-up imaging and neurosurgical evaluation merely optional  |
| Pu et al. 2007 26 | further work-up or imaging follow-up is unwarranted for small and asymptomatic cysts in adults |
| Storey et al. 2020 60 | adult pineal cysts without clinical symptoms, haemorrhage, indistinct borders or hydrocephalus do not require follow-up |
| Jenkinson D et al. 32 | no imaging for required for simple cysts < 10 mm in size and adult cysts regardless of size; required for paediatric cysts; optional for atypical cysts +/- germ cell tumour markers – the most recent UK recommendation |
| Nevins et al. 2016 10 | diagnosis made by experienced neurosurgeon or neuroradiologist, single follow-up in 12 months, discharge if stable; optional in patients > 60 years and small cysts; no recommendation for atypical cysts |
| Whitehead et al. 2013 22 | imaging follow-up if atypical features (soft tissue nodularity, wall >2 mm) or unrelenting or progressive symptoms; clinical follow-up alone for other asymptomatic lesions irrespective of size |
| Fakhran and Escott, 2008 20 | no imaging follow-up required in the absence of atypical features (wall < 2 mm, no nodularity) |
| Marquez and Rivero, 2011 61 | imaging at 1 and 3 years - discharge if stable, otherwise monitor annually until the size is stable |
| Woernle et al.. 2019 62 | follow-up of asymptomatic cysts if size +/- 2 cm |
| West Midlands Cancer Alliance 2018 63 | follow-up at 6 months, 1 and 2 years |
| Mandera et al.. 2003 18 | follow up for many years |

 |  |  |  |  |  |  |  |

 (\*) sorted according to increasing suggested imaging follow up frequency

**Table 4.** Classification, markers and prognosis of germ cell tumours (GCTs)

|  |  |  |
| --- | --- | --- |
| **GCT type** | **Tumour markers** | **Survival** |
| HCG | AFP |
| Germinoma | -/+1 | - | 90% |
| NGGCTs |  |  |  |
|  Embryonal carcinoma (EC) Yolk sac tumour (YST) Choriocarcinoma (CHC)  Teratoma - immature  Teratoma - mature Mixed germ cell tumour  | --+-- -/+ | -+-- /+2--/+ | 60-70%60-70%60-70%33-71%87-100%component-dependent |

1 low level HCG secretion possible in germinomas containing syncytiotrophoblastic cells

2 low level AFP secretion possible in immature teratoma containing immature liver and/or gastrointestinal tissues

**FIGURE LEGENDS**

**Figure 1.** Anatomy of the pineal gland region. The pineal gland (PG) lies above the quadrigeminal plate (QP) and splenium of the corpus callosum (CC), attached to the posterior wall of the third ventricle by the pineal stalk comprising habenular commissure (HC) and posterior commissure (PC). Internal cerebral veins (ICV) lie immediately superior to the pineal gland. PR – pineal recess, ST/TT – stria terminalis / taenia thalami, F – fornix, AoS – aqueduct of Sylvius, M – midbrain tegmentum, 4V – fourth ventricle, VOG- vein of Galen.

**Figure 2.**  Pineal cyst. (A) Pathological specimen of a pineal cyst showing compressed pineal parenchymal layer (PL) surrounding inner hypocellular gliotic tissue layer (GL) containing Rosenthal fibres (arrow in the magnified image on the right); the outer leptomeningeal connective tissue layer is not seen here. (B-E) Appearances of a typical pineal cyst on T2-WI (B), FIESTA (C), unenhanced T1-WI (D) and contrast-enhanced T1-WI (E). The cyst is slightly hyperintense to CSF on T2, hypointense to CSF on FIESTA, and slightly hyperintense on T1 with a thin rim of enhancement.

**Figure 3.** Pineal cyst associated with hydrocephalus. A large pineal cyst slightly hyperintense to CSF on T2-WI (A), FLAIR (B), and T1-WI (C) with minor contrast enhancement posteriorly (arrow in D). The tectal plate is displaced inferiorly causing narrowing of the aqueduct of Sylvius and obstructive hydrocephalus with no periventricular interstitial edema suggestive of longstanding duration. (E) Images from a different patient showing changes in FLAIR signal with reduction in signal intensity on 6 month follow up (6m) which subsequently remained stable; there was no change in size of the cyst or development of symptoms.

**Figure 4.** Less common imaging findings in pineal cysts. (A) Two-compartmental pineal cyst with FLAIR-hyperintense anterior locule (arrowhead) and fluid level due to haemorrhage in the posterior locule (arrow) in an asymptomatic patient. (B) Pineal apoplexy due to intracystic haemorrhage as shown by a fluid level (arrow) with acute hydrocephalus with periventricular signal change (arrowheads). (C) Lobulated shape and (D) thin internal septation are considered atypical features.

**Figure 5**. Pineocytoma. Axial T2-WI (A), T1-WI (B), and axial (C) and sagittal (D) contrast-enhanced T1-WI in a 62-year old female patient show a predominantly solid pineal mass with a small non-enhancing cystic component (arrow in D).

**Figure 6**. Pineal parenchymal tumour of intermediate differentiation (PPTID). Axial T2-WI (A), contrast-enhanced axial (B) and sagittal (C) T1-WI in 14-year old female patient demonstrate a complex solid-cystic mass with homogenous enhancement within the posterior solid component. Histologically (D) the tumour is composed of sheets of small monotonous neoplastic cells with mild pleomorphism.

**Figure 7**. Pineoblastoma. Axial T2-WI (A), axial FLAIR (B), and contrast-enhanced sagittal T1-WI (C), axial DWI (D) and unenhanced CT (E) in a 5-year old male patient demonstrate a large pineal mass extending anteriorly and superiorly with compression of the tectum and acute hydrocephalus. The lesion demonstrates restricted diffusion (D) and hyperdensity on CT (E) in keeping with high cellularity as confirmed by the pathological correlation (F) which shows sheets of closely packed cells with a high nuclear to cytoplasmic ratio and hyperchromatic pleomorphic nuclei (small round blue cell tumour).

**Figure 8**. Papillary tumour of the pineal region (PPTR). Axial T2-WI (A), sagittal FLAIR (B), and axial contrast-enhanced T1-WI (C) demonstrate a uniformly enhancing pineal mass in 45-year old male patient. (D) Histopathology shows characteristic staining for cytokeratins (CK8/18) and neuronal cell adhesion molecule (NCAM, CD56).

**Figure 9.** Germinoma. Sagittal T2-WI (A), axial FLAIR (B), and contrast-enhanced T1-WI demonstrated a uniformly enhancing pineal mass in 26-year old male patient, subsequently diagnosed as germinoma. Similar to pineoblastoma, these tumours may demonstrate increased signal on DWI (D) owing to high cellularity. Histopathology demonstrates large pleomorphic neoplastic cells and abundant lymphoid tissue; neoplastic cells show nuclear expression of the germ cell marker OCT3/4. (F) An example of bifocal tumour in a different patient involving the pineal and suprasellar region. Coupled with negative tumour markers this radiological picture is almost always consistent with a germinoma, although not pathognomonic.

**Figure 10.**  Teratoma. Axial T2-WI (A), axial FLAIR (B) and axial unenhanced T1-WI (C) demonstrate a pineal mass containing fat signal component anteriorly (arrows in A-C). The solid part of the tumour demonstrates patchy contrast enhancement (D) and there is evidence of punctate calcification on CT (E). Histopathology slide (F) demonstrates nodules of squamous epithelium (black arrow) and glandular gastrointestinal type epithelium (white arrow).