SIOP Europe
the European Society for Paediatric Oncology

BRAIN TUMOUR GROUP

European Reference Network
for rare or low prevalence complex diseases
Network Paediatric Cancer (ERN PaedCan)

CLINICAL PRACTICE RECOMMENDATIONS

PINEAL TUMOURS

as defined by 5th edition of WHO classification of CNS tumours

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Table of contents

1 BACKGROUND AND INCLUDED TUMOUR ENTITIES

1.1 General introduction

The pineal gland is situated in a deep-seated region of the brain in the area of the third ventricle between the posterior commissure at the top, and the tectal plate below.

Tumours occurring in this area pose a diagnostic and therapeutic challenge for clinicians. Pineal tumours represent less than 1% of all central nervous system tumours in adults and 2.8-11% of all brain tumours in children and adolescents.

The 2021 WHO classification of CNS tumours distinguishes tumours derived from the pineal parenchyma (pineal parenchymal tumours) and tumours specifically arising in the pineal region but originating from extra-pineal sources. Germ cell tumours which are the most common pineal region malignancy in the paediatric and adolescent population are considered separately.[1] (see differential diagnosis below)

This guideline includes the following tumour types:

1**) Pineal parenchymal tumours**

Pineoblastoma
Pineocytoma
Pineal parenchymal tumour of intermediate differentiation (PPTID)

2) **Other tumours specifically arising in the pineal region**

Papillary tumour of the pineal region (PTPR)
Desmoplastic myxoid tumour, *SMARCB1*-mutant

Pineal parenchymal tumours range from low-grade pineocytomas (CNS WHO grade 1) which are slow-growing and well-circumscribed to pineoblastomas (CNS WHO grade 4) which are aggressive poorly differentiated tumours. Pineal parenchymal tumours of intermediate differentiation (PPTID) have intermediate differentiation (CNS WHO grade 2 or 3) with associated risk of recurrence and spread. Papillary Tumour of the Pineal Region (PTPR) is a peculiar neoplasm with ependymal and epithelial features specifically arising in the pineal region and associated with a high risk of recurrence (CNS WHO grade 2 or 3). Therefore, making the correct diagnosis is important for prognosis and management.

In recent years, molecular diagnostics have acquired a central place in the diagnostic pathway and also play a significant part in acquiring prognostic information. For example, the recognition of pineoblastoma subtypes with distinct molecular and clinical features is useful for prognostication and management and the demonstration of *KBTBD4* in-frame insertions confirms the diagnosis of PPTID.

Pineal tumours can occur at any age but have different age distributions according to type. Pineoblastomas primarily occur in early childhood with a median age of presentation of 6 years (range 0-41 years). PPTID and PTPR have a median age of presentation of around 30 years, but both can rarely present in the paediatric age group. Pineocytomas mainly occur in adults with a median age of 44 years (range 1.1-85 years).

Pineoblastoma may arise based on a genetic predisposition in patients with familial retinoblastoma (*RB1* mutations) or *DICER1* mutations.

Due to the rarity of these tumours, there is limited evidence base as to optimal management. These guidelines aim to summarise the pathology and classification of these tumours and provide an approach to management of these patients based on the evidence available.

2 PRESENTATION, DIAGNOSIS AND STAGING

2.1 Clinical Presentation

Pineal region tumours generally present with signs and symptoms of hydrocephalus i.e., headache, vomiting, VI nerve palsy, papilledema and reduced consciousness. They can present with Parinaud syndrome (upward gaze palsy with impaired convergence, nystagmus, eyelid retraction and light-near dissociation of pupillary reaction) due to compression of the mesencephalic tectum. Focal motor or sensory deficits are rare but may be seen in cases of disease dissemination. Pineal tumours may also present incidentally on unrelated brain imaging although care should be taken to differentiate a tumour from a pineal cyst.

The initial evaluation should include a full patient history and physical examination with a complete neurological examination, detailing neurological deficits or evidence of increased intracranial pressure, as these patients may require prompt or even emergency intervention.

2.2 Diagnostic work-up and Staging

Basic information, differential diagnosis and staging

Magnetic resonance imaging (MRI) is the imaging modality of choice to characterise tumours of the pineal region although CT may have a role in identifying calcification within the tumour and for emergency assessment of a patient presenting with signs of raised intracranial pressure.

Brain and spine MRI according to SIOP-E Imaging Guidelines[2] at the time of diagnosis is mandatory in all patients. If the patient's condition allows, spinal imaging should be performed before any surgical intervention to prevent diagnostic uncertainties due to postoperative changes.

There is a wide differential of pineal region masses. Tumours directly arising from the pineal region include germ cell tumours (>50%) and pineal tumours as described in this guideline (14-27%). The remaining 25% of pineal region lesions include those expanding from adjacent anatomical structures and include Low-Grade Glioma (LGG), embryonal tumour with multilayered rosettes (ETMR), atypical teratoid/rhabdoid tumour (AT/RT), diffuse midline glioma (DMG) and ependymoma[3].

The most common tumours in this region are intracranial germ cell tumours (GCT), so tumour markers (AFP and β-HCG) must be assessed both in the serum and cerebrospinal fluid (CSF). Ideally this should be done before biopsy as positive markers are sufficient to make a diagnosis of secreting GCT without the need for biopsy. However, a lumbar puncture should not be performed in case of elevated intracranial pressure. In the event of hydrocephalus and need for urgent CSF diversion, collection of CSF for markers and cytology should be performed within this intervention and biopsy may be considered depending on neurosurgical opinion. In cases where diagnosis cannot be made based on tumour markers, biopsy is mandatory.

(For further details on the management of suspected GCT see the SIOP-E ESCP guideline for Childhood Intracranial GCT)[4].

Pineal cysts which are not tumours can also be seen in the pineal gland but generally have a characteristic radiological appearance of a benign cyst that does not require intervention. (see 3.6 Pineal cysts)

In patients with hereditary retinoblastoma, the identification of an asymptomatic solid pineoblastoma is important. The European Retinoblastoma Imaging Collaboration Group (ERIC) has published size ranges for the normal (solid and cystic) pineal gland [5,6].

Staging:

There is no dedicated staging system and the Chang staging system is applied with respect to metastatic disease:

- M0 – No evidence of gross subarachnoid or haematogenous metastasis
- M1 – Microscopic tumour cells found in CSF
- M2 – Gross nodular seeding demonstrated in the cerebellar/cerebral subarachnoid space or in the third or lateral ventricles
- M3 – Gross nodular seeding in the spinal subarachnoid space
- M4 – Metastasis outside the cerebrospinal axis

The CSF should be collected 14 days post-op via a lumbar puncture and sent for cytopathology.

The identification of metastatic disease is an important part of the diagnostic process as it has consistently been shown to be a prognostic factor and guides radiotherapy dose.

A post-operative MRI scan should be performed within 48 hours of surgery to assess and document extent of resection. Spinal imaging with contrast should be undertaken if not performed pre-operatively although post-operative changes can make interpretation difficult.

2.3 Surgical considerations

As described above, if serum/plasma AFP/ß-HCG is positive for a secreting Germ Cell Tumour, there is no need for biopsy per se, but waiting for these results should not delay the urgent treatment of hydrocephalus if this is required.

The following surgical strategy should be used in the approach to managing pineal tumours:

i) Treat hydrocephalus if present.

- Obtain CSF intraoperatively for cytology and germ cell tumour markers (AFP, HCG). CSF should be collected before commencing endoscopic irrigation and proceeding to the diversion itself.
- An endoscopic third ventriculostomy (ETV), where feasible, is the favoured surgical intervention for obstructive hydrocephalus[4].
- Inspect ventricles for small metastatic deposits which may not be visible on MRI.
- Consider an endoscopic biopsy of the tumour as part of the same procedure (see below). This should be done after ETV as bleeding can make ETV more difficult.
- If ETV is not possible, consider an external ventricular drain (EVD) or ventriculo-peritoneal shunt

ii) Biopsy

- Endoscopic biopsy (see above) has the advantage of being taken under direct vision. Yield is likely to be 70-90% but specimens are small. There is a theoretical risk of blocking the ETV although in practice this does not seem to be higher if a biopsy is performed.
- Stereotactic biopsy (using frame or image guidance) should be considered if endoscopy is not appropriate. This has yields greater than 95% and has been associated with low complication rates although specimens will still be small and there is concern due to the proximity of the major veins.

- If an endoscopic or stereotactic biopsy is not feasible, or the result is indeterminate, in the context of negative tumour markers, an open biopsy may be required. This is carried out through an appropriate craniotomy, with a plan to obtain a histological diagnosis early in the procedure. If the frozen section or smear are consistent with germinoma, further resection should not be pursued.

iii) Resection

- On confirmation of most non-germ cell pineal tumours, surgical resection is required, with **maximal safe resection** as the principal surgical objective. Understanding that gross total resection may have an impact on overall management is important but should be balanced by predicted surgical morbidity. It is important to recognise that in most cases pineoblastoma is chemotherapy-sensitive. Therefore, post-operative induction chemotherapy may be used to treat residual tumour or facilitating more complete second surgery.
- Surgery should be tailored to the individual case. The route to the tumour should consider individual anatomy (such as the position of the torcula and the angle of the tentorium), the growth pattern of the lesion and the likely position of the important venous structures in this region. The best chance of maximal safe resection is at the first attempt, so surgery should by performed by an appropriately experienced surgeon. All adjuncts available to optimise surgical resection, such as the use of intra-operative MRI, should be considered.
- A post-operative baseline scan should be performed within 48 hours of surgery to assess and document the extent of resection.

Appropriate surgery in this region can achieve high gross total resection rates and whilst the risk of damage to the veins exists, complications of surgery in experienced centres are low. If the patient is being treated in a centre without adequate expertise, referral to a more expert centre should be considered. Where available we recommend contacting the national reference structures for advice. Otherwise, the neurosurgical members of the writing group for this ESCP guideline may be contacted for further information.

2.4 Neuropathological diagnosis and differential diagnosis

Neuropathological diagnosis should be based on the criteria mentioned within the WHO classification of CNS tumours[1]. This includes the combination of morphological and molecular criteria into an integrated diagnosis.

The initial diagnostic approach is mainly based on standard histological analysis on H&E sections and immunohistochemistry. Molecular studies as far as possible should also be performed as they can be very valuable for example in defining pineoblastoma subgroups and distinguishing between pineoblastoma and PPTID.

On small specimens (especially endoscopic biopsies), the diagnosis may be more challenging. Where tumoural tissue is limited, one of the main goals is to ascertain the tumoural type (germ cell tumours versus pineal parenchymal tumours versus gliomas versus PTPR). The morphological analysis usually needs to be confirmed by a carefully chosen panel of antibodies so that the diagnosis is reached using a minimal amount of tumoural tissue.

Specific diagnostic approaches and diagnostic criteria for the different tumour types are mentioned in the chapters below.

2.5 Germline predisposition

Most pineoblastomas occur sporadically, but a few can also occur in the context of cancer predisposition syndromes, the main ones being *DICER1* and *RB1* constitutional pathogenic variations. These pathogenic variants appear to be found specifically, depending on the gene involved, in some of the five consensually defined pineal tumour subtypes: PB-miRNA1, PB-miRNA2, PB-*MYC/FOXR2*, PB-*RB1* and PPTID[7,8].

There is a common predisposition between retinoblastoma and pineoblastoma, which is explained by the fact that pinealocytes and retinal receptor cells share a common embryonic origin in humans[9]. When it occurs in a rare disease called "trilateral retinoblastoma syndrome", pineoblastoma is associated with concomitant bilateral (or very rarely unilateral) retinoblastoma. This tumour association, explained by a genetic predisposition with an underlying *RB1* constitutional pathogenic variant[10-12] is found exclusively in the PB-*RB1* subtype, characterized molecularly by somatic *RB1* alterations[7,8,13]. Of note, PB-*RB1* can also occur sporadically without presence of a constitutional RB1 pathogenic variant (see 3.1.1 Pineoblastoma Introduction). The European Retinoblastoma Imaging Collaboration has developed recommendations on screening for pineoblastoma in patients with hereditary retinoblastoma[5,6]. Further information on the European Retinoblastoma Group can be found on the respective website: www.eurbg.org.

Over the last ten years, constitutional alterations in *DICER1* have been identified in patients with pineoblastoma[14,15]. More recently, constitutional *DICER1* alterations have also been reported in association with pineal parenchymal tumours of intermediate differentiation (PPTID)[16,17] but it should be noted that the diagnosis of PPTID in these case reports has not been molecularly confirmed and so it is possible that these cases were pineoblastoma given the histological overlap between the two entities.

Mutational inactivation of the *DICER1* gene causes aberrant micro-RNA maturation, which can affect post-transcriptional regulation of gene expression, thereby contributing to tumour formation in various organs. Initially associated with embryonic tumours such as pleuropulmonary blastoma (PPB) in infants[18], DICER1 syndrome, due to constitutional *DICER1* pathogenic variants, is a pleiotropic condition with an increased risk of various neoplastic conditions. This cancer predisposition syndrome has been progressively enriched over the years with cystic nephroma, ovarian sex cord-stromal tumours (especially Sertoli-Leydig cell tumour), embryonal rhabdomyosarcoma of the uterine cervix, and benign (multinodular goitre) or malignant thyroid disorders. The penetrance of *DICER1* pathogenic variants is generally low and is higher in females than in males[19].

Only a few pineoblastoma patients with a heterozygous constitutional *DICER1* pathogenic variant have been reported[8,15,20]. De Kock et al. first described constitutional *DICER1* pathogenic variants in six patients affected with pineoblastoma with age at diagnosis between 2 and 24 years; all of the pathogenic variants were loss-of-function mutations that inactivated one allele of *DICER1*[15]. In the largest study recently published, six patients with constitutional *DICER1* pathogenic variants were identified out of 12 patients with available germline data, they were only found in PB-miRNA1 and PB-miRNA2 molecular subgroups[8]. In contrast to what is seen in other *DICER1*-related tumours, which typically harbour biallelic inactivating *DICER1* alterations, LOH of the *DICER1* locus is the most frequent second somatic event in pineoblastomas[14,15,21].

The data available to date do not allow us to assess the true impact of the underlying constitutional *DICER1* pathogenic variant on the outcome of patients affected with a pineoblastoma. International studies are needed to determine whether the treatment of patients with pineoblastoma should take this genetic factor into account. Because of the lifelong oncological risk associated with constitutional *DICER1* pathogenic variants, family genetic counselling is necessary. Updated recommendations for carrier patients' surveillance have been recently published, taking into account the lower penetrance of *DICER1* mutations

than initially suspected[19], mainly based on pleuropulmonary blastoma monitoring in newborns followed by abdominal and thyroid ultrasound from childhood to adulthood[22].

One publication reported the case of a patient harbouring a constitutional *APC* pathogenic variant who was first diagnosed with pineoblastoma and then developed thyroid papillary carcinoma and multiple colonic polyps[23]. Further explorations are needed to validate the possibility of *APC* or other genes as potential cancer predisposition genes for pineoblastomas.

3 TYPE-SPECIFIC DIAGNOSTICS AND TREATMENT

Pineal parenchymal tumours

3.1 Pineoblastoma

3.1.1 Introduction

Pineoblastoma is a rare embryonal tumour and the main histological type of pineal parenchymal tumours in childhood[24]. Pineoblastoma mainly affects young children and infants below four years of age[25] with an overall median age at diagnosis of 5-6 years[26,27]. It is a highly aggressive tumour, classified as CNS WHO grade 4[28] with a tendency to disseminate along the cranio-spinal axis[27,29] and is often associated with a poor outcome, especially for younger children[27,30,31]. Molecular characteristics of pineoblastoma described in recent studies[7,8,13] have been incorporated in the newest 2021 version of the WHO classification of Tumours of the Central Nervous System[1].

Based on genome-wide methylation profiling, four distinct molecular subtypes of pineoblastoma can be distinguished:

- **Pineoblastoma, miRNA processing-altered 1 (PB-miRNA1)**
- **Pineoblastoma, miRNA processing-altered 2 (PB-miRNA2)**
- **Pineoblastoma, *MYC/FOXR2*-altered (PB-*MYC/FOXR2*)**
- **Pineoblastoma, *RB1*-altered (PB-*RB1*)**[8].

These molecular subtypes are associated with differing demographics, like age distribution and outcome, as well as with specific genetic alterations[7,8,13,26,32].

Patients with **PB-miRNA1** tumours have a median age at diagnosis of 8.5 years. The 5-year overall survival rate is 70.3%. More than half of the cases with this subtype harbour mutually exclusive alterations in crucial genes of the miRNA processing pathway, namely *DICER1* (26%), *DROSHA* (23-25%) or *DGCR8* (7-8%). Frame-shifting/truncating variants (FTV) and/or focal chromosomal losses of the gene lead to impaired function of the respective protein[8].

Patients of the **PB-miRNA2** subtype are slightly older with a median age at diagnosis of 11.8 years and have a better outcome (5-year overall survival rate in the so far characterised cohorts 100%). Alterations in *DICER1* (52%) and *DROSHA* (29%) but no alterations in *DGCR8* are also the main molecular characteristics of this subtype. Furthermore, the co-occurrence of loss of chromosome 14q together with *DICER1* loss-of-function mutations, presumably leads to complete inactivation of *DICER1* in *DICER1*-altered cases of this subtype[8].

In both miRNA-altered pineoblastoma subtypes, *DICER1* constitutional pathogenic variants are described[8].

In contrast, the **PB-*MYC/FOXR2*** subtype mainly occurs in infants (median age at diagnosis of 1.4 years) and is associated with the poorest prognosis (5-year overall survival rate of 23.8%). Alterations of the *MYC* gene, like focal amplification or gain of chromosome 8q including *MYC,* were observed in approximately a quarter of cases. Furthermore, this subtype features an elevated RNA expression of the proto-oncogene *FOXR2*. However, no recurrent distinct driver mutation could be identified in this subtype[8].

Subtype **PB-*RB1*** also affects mainly younger children with a median age at diagnosis of 2.1 years. Notably, metastatic status at diagnosis is most frequent in this subtype and the outcome is comparably dismal (5-year overall survival rate of 29.8%). The main molecular characteristics of this subtype are alterations in the *RB1* gene (81%), like FTV and/or focal deletions. The similarity of this subtype with retinoblastoma is underlined by the frequent occurrence of similar chromosomal changes, like chromosome 16 loss and chromosome 1q and 6p gain[33,34]. The PB-*RB1* subtype includes cases with clinical diagnosis of trilateral retinoblastoma[8,35].

3.1.2 Neuropathological diagnosis

Definition

Pineoblastoma is a CNS WHO grade 4 embryonal tumour of the pineal gland[1]. On H&E sections, pineoblastoma shows an embryonal morphology characterized by diffuse sheets of densely packed undifferentiated neoplastic cells[36,37]. Homer Wright pseudorosettes may be seen. The tumoural cells exhibit a high nuclear to cytoplasmic ratio, scant cytoplasm, and atypical round to angular hyperchromatic nuclei. Mitotic activity is high and necrosis common. The resulting appearances may thus be similar to classic medulloblastoma.

Diagnostic criteria according to the 2021 WHO classification

Essential diagnostic criteria:

Pineal region location + histopathological features of an embryonal tumour + high proliferative/mitotic activity

Desirable diagnostic criteria:

Retained nuclear SMARCB1/INI1 staining and/or DNA methylation profile of pineoblastoma

Recommended diagnostic work-up:

The diagnosis of pineoblastoma is based on standard histology, which is usually supplemented by immunohistochemical and molecular analyses. In most cases, pineoblastoma can be easily distinguished from low-grade gliomas (pilocytic astrocytoma), germ cell tumours, and papillary tumour of the pineal region. Histologically, the differentiation between pineoblastoma and PPTID may be more challenging. An undifferentiated pineoblastoma-like morphology may also be observed in AT/RT, ETMR, or small cell glioblastoma.

Synaptophysin is the most reliable marker of neuronal differentiation in pineoblastoma. Neurofilament immunopositivity is usually negative or weak and is mostly found in more differentiated pineal parenchymal tumours such as pineocytoma and PPTID. In contrast to gliomas, glial markers (GFAP, OLIG2) are negative. Nuclear SMARCB1/INI1 immunostaining is retained and should be performed to rule out the possibility of AT/RT, especially in infants. Unlike ETMR, LIN28A immunoexpression is negative. Strong expression of CRX, a transcription factor of the pineal and retinal lineages, is a very useful addition to the immunohistochemical work-up[38].

Proliferative and mitotic activity should be assessed by mitotic count and Ki67/MIB1 proliferation index, respectively. In pineoblastoma, the mean proliferation index is usually higher than 30% while in PPTID, the mean proliferation index is typically around 10%[39].

Molecular testing of pineoblastoma is highly recommended. This may be achieved by a combination of various techniques including DNA methylation profiling, NGS or Sanger sequencing. We strongly recommend DNA methylation profiling of pineoblastoma (for example, EPIC array and classification by the Heidelberg brain tumour classifier (www.molecularneuropathology.org)).

DNA methylation profiling not only allows for classification of pineoblastoma into one of the four molecular groups defined by the 2021 WHO classification (PB-miRNA1, PB-miRNA2, PB-*RB,* or PB-*MYC/FOXR2*)[8,13,26], but also has the advantage of a copy number variant (CNV) profile that can be generated from intensity values and may provide useful additional information regarding gene loci involved in the pathobiology of pineoblastoma, i.e. deletion of *DICER1* (14q32.13), *DROSHA* (5p13.3)[32], *DGCR8* (22q11.21), or *RB1* (13q14.2), gain of miR-17/92 cluster (13q31.3) as well gain/amplification of *MYC* (8q24.21). CNV may also be separately analyzed by CGH or SNP array. Sequencing of *DICER1*, *DROSHA*, *DGCR8*, and/or *RB1* should be performed. The choice of the genes to be analysed is ideally guided by the molecular group and/or the CNV profile. However, this analysis may also be performed as part of a NGS panel, independently of other molecular tests. Demonstration of *KBTBD4* in-frame insertions typically encountered in PPTID aids to exclude the diagnosis of pineoblastoma in challenging cases[8,21].

Of note, rare cases of pineal region tumours are histologically and biologically similar to WNT-activated medulloblastomas, all showing an embryonal appearance, nuclear accumulation of beta-catenin by immunohistochemistry, and mutation in exon 3 of *CTNNB1*. These cases may probably be regarded as 'ectopic' medulloblastomas[40].

Pineal anlage tumours

Pineal anlage tumour is an extremely rare neoplasm of the pineal region, currently classified as a very peculiar variant of pineoblastoma in the 2021 WHO classification[1]. They typically affect infants and young children and behave aggressively, some of them showing leptomeningeal dissemination.

Pineal anlage tumour is histologically characterized by a variable combination of:

- *Neuroepithelial elements* that includes an immature pineoblastoma-like cell population, clusters of melanin-containing epithelioid cells, and fibrillary areas of more differentiated glial and neuronal cells
- *Ectomesenchymal elements* that includes striated muscle fibres, rhabdomyoblasts, cartilage islands, and chondroid matrix

By definition, no endodermal derivatives are seen.

Because of the rarity of this tumour, it is currently not possible to draw firm conclusions regarding the best treatment options. As they seem to follow an aggressive course, they are usually treated as pineoblastoma. Considering the lack of clear data regarding the management of these tumours, discussion with the advisory group is recommended.

3.1.3 Clinical features and available evidence for treatment of pineoblastoma

I) Available evidence for patients younger than 3-5 years at diagnosis, or ineligible for upfront craniospinal irradiation (CSI)

Pineoblastoma in younger children usually show a molecularly distinct profile compared to older children. Most tumours belong to the methylation groups *MYC/FOXR2*-altered (PB-*MYC/FOXR2*) and pineoblastoma, RB1-altered (PB-*RB1*). Patients with PB-*RB1* may carry inherited alterations of *RB1* and pineoblastoma may arise in the context of trilateral retinoblastoma. It is known that PB-*MYC/FOXR2* and PB-*RB1* have a particularly poor outcome compared to PB-miRNA1 and PB-miRNA2 groups that tend to occur in older children.

It is assumed that most of the children treated with radiation-sparing treatment strategies probably belonged to these two molecular groups. However, methylation-based classification is mostly unknown in historical series and conversely for many biologically informed series, details on therapy are missing.

Overall, the data indicate that radiation-sparing approaches are associated with a high risk of relapse. Many protocols today use intensive chemotherapy in conjunction with marrow-ablative chemotherapy and autologous stem cell rescue but despite this, outcomes remain poor. The prognostic impact of clinical staging is largely unknown as most patients progressed after radiation-sparing regimens irrespective of the clinical stage and most died from their disease[27].

For these young patients, most published series describe the use of different combinations of chemotherapy, some including marrow-ablative chemotherapy with autologous stem cell support[41], intraventricular methotrexate[42] or a combination of both[43].

Progression-free survival and CSI-free survival were poor in all series, however there were a small number of survivors who did not receive radiotherapy[31].

Given the small number of patients, it is not possible to compare the outcome of different regimens.

Response to initial chemotherapy has been observed in several patients while progression on subsequent intensive chemotherapy can nevertheless occur[41].

Summary of published original trial series:

Publication	Therapy	Nr. of pts.	Outcome	Risk factors/conclusions
Abdelbaki , 2020 PBC[41]	HS1/HS2/HS3	23	5yPFS 9.7% 5yOS 13%	Use of CSI was important risk factor
Liu, 2020 Acta Neuropathol[26]	SJYC07	12	14% (intermediate risk n= 7) 0% (high risk n=5)	Young children are biologically different from older children, CSI associated with better outcomes
Friedrich, 2013, Neuro Oncol[42]	HIT-SKK or Carboplatin/ Etoposide -based induction followed by HDCT	8	5 DOD 3 alive at last FU	Intensified chemo might be more effective Use of CSI effective
Hinkes, 2007, J Neurooncol[44]	HIT-SKK92 or HIT-SKK 87	5	5 DOD	Poor outcomes in young children
Hansford , 2020, Neuroonc Adv[31]	Australian and COG trials (Meta-analysis)	49	5y-PFs 13.5 ± 5.1% 5y-OS 16.2 ± 5.3%	3/7 survivors had received HDCT without CSI 4/7 survivors had received CSI
Mynarek, 2017, Neuro-Oncology[27]	SIOP and HS (meta-analysis)	57	5y-PFS 11 ± 4% 5y-OS 12 ± 4%	CSI important risk factor Salvage CSI only occasionally effective Focal RT in M0 patients might play a role

Table 1. Summary of the published literature on treatment series for patients with pineoblastoma, younger than 3-5 years of age at diagnosis. Abbreviations: CSI, craniospinal irradiation; DOD, death of disease; FU, follow-up; GTR, gross total resection; HDCT, high-dose chemotherapy; HS, Head Start

Work not included:

Parikh K. 2017, Neurosurgery[30]	Focus on neurosurgery, no detailed description of postoperative management, probably overlapping with Liu 2020.[26]
Liu APY, 2021, Acta Neuropathol[8]	Age as influencing factor reported, no details on treatment.

Table 2. Publications not included in the description of evidence on treatment.

II) Available evidence for older patients, eligible for CSI

Pineoblastoma in older children differs in molecular profile from pineoblastoma that occur in younger children.

Most tumours in older children belong to the group of pineoblastoma, miRNA processing altered (PB-miRNA). More rarely, PB-*MYC/FOXR2* occur in children older than 3 years at diagnosis, while PB-*RB-1* have only been reported in children younger than 4 years at diagnosis[7,8,13]. A tabulated summary of available evidence for treatment and outcome of older patients with pineoblastoma is given below.

Clinical risk factors:

- **Age:**

In several series, it has been shown that survival rates for pineoblastoma patients older than 3 to 5 years at diagnosis were superior than the survival rates for younger children[27,31,45,46]. Given the strong prognostic effect of radiotherapy treatment in different treatment series, it has been speculated that the regular use of CSI in the older patients may be one relevant factor that leads to this difference[27,46]. In addition, the differential age specific occurrence of the pineoblastoma subtypes is assumed to play a major role in the prognostic difference between the age groups[7,8]. (see above)

- **Metastases:**

The clinical staging at presentation also differs between the different molecular subtypes. The lowest reported frequency of metastases at presentation was 16% in the group of patients with PB-miRNA2. Higher frequencies were observed in the cohorts of patients with PB-miRNA1 and PB-*MYC/FOXR2* with a frequency of about 40% in each group[7,8]. In molecularly not characterized series, the reported frequency of metastases ranged between 15 - 45 %[26,46,47].

The presence of metastases at presentation has been identified as a negative prognostic factor in different series, while the statistical strength was borderline in some[7,8,26,27,30,31,47]. Of note, there were also series which did not show a different outcome in metastatic versus non-metastatic disease[48,49]. This observation might be explained by the small numbers in the respective series, or possibly by an overlying effect of the different behaviour of the molecular subtypes.

- **Postoperative residual tumour:**

The presence of postoperative residual disease has been identified in several series as an independent negative prognostic factor[8,26,45,48,49], although this effect has not been constant over all series[7,27,29,31,47,50]. One explanation for the difference in the observed impact of postoperative residual tumour on prognosis may be the different definitions used in the series, which limits the comparability. In some series only postoperative tumour size > 1.5 cm^2 was regarded as relevant residual disease[26,49], whereas in other series any residual tumour on postoperative MRI[29,47], or the relative estimate of less than near total resection[30] has been considered for risk group allocation. Also, treatment factors may have accounted for compensation of a higher risk.

In the series with available molecular subtyping, no obvious difference was observed in the frequency of incomplete resection between the different pineoblastoma molecular subtypes[7,8].

- **Postoperative treatment:**

The postoperative treatment of children with pineoblastoma has generally been based on a treatment regimen established for patients with high-risk medulloblastoma or "CNS-primitive neuroectodermal tumour (CNS-PNET)", the latter diagnosis being used before the 2016 update of the 4th edition of the WHO classification of CNS tumours.[51] In historic series, a terminology differing from the WHO classifications of CNS tumours was used[52-54]. The term 'pineal PNET' was used in some older series instead of pineoblastoma[46,47,55,56]. While there might not have been a full overlap, most of the tumours previously described as 'pineal PNET' do represent pineoblastoma according to retrospective re-evaluation[13].

The majority of protocols that have been used to treat patients older than 3 to 5 years at diagnosis included treatment with irradiation to the craniospinal axis with boost to the tumour region and metastases, combined with chemotherapy using different drug combinations and intensities[26,29,46-50,56-58].

- **Irradiation:**

Based on the previously assumed high risk disease profile of pineoblastoma and on the observation of metastatic relapses, CSI has been used as the mainstay of most treatment regimens for older children amenable for the use of CSI.

The age cut-off for most protocols for the use of CSI was children aged 3 years and over at diagnosis[26,47-49]; this was 4 years of age for the HIT-2000 trial[29], and 5 years in the PNET HR+5 trial[59].

Conventional fractionation with a CSI dose of 36 Gy was used in most trials, with a boost to the primary tumour to 54–56 Gy, and a boost to metastases.[46-49,58,59] Other evaluated irradiation schemes included hyperfractionated radiotherapy and hyperfractionated accelerated radiotherapy (HART) with CSI doses of up to 39 Gy[29,50,60].

Some series included children as young as 18 months at diagnosis in the treatment schedules with CSI[48,50,61]. CSI dose in these trials was 23.4 Gy (conventional fractionation)[46] and 31.2 Gy (hyperfractionated, accelerated fractionation)[50].

Efforts have been made to reduce CSI for disease considered average-risk (AR) i.e., non-metastatic and ≤1.5 cm^2 post-resection residual. A lower CSI dose of 23.4 Gy was used for average risk patients treated within or according to the SJMB03 and SJMB12 regimens[26].

There were two series which evaluated the safety of focal irradiation and the omission of CSI for selected patients with localized disease[50]. In these series high dose chemotherapy was part of the treatment. While the concept may deserve further evaluation for selected patients, the small number of evaluated patients precludes a recommendation to use this outside of a trial for older patients that are eligible for CSI[50,59].

- **Chemotherapy:**

Chemotherapy strategies employed have included upfront post-operative chemotherapy either as conventional chemotherapy or post-operative induction followed by high-dose chemotherapy. Continuous complete remission or objective response on post-operative chemotherapy have been observed in up to 78% of patients[27,50,59]. The use of etoposide and carboplatin induction, followed by tandem-high dose chemotherapy with thiotepa has been reported as being well tolerated in the PNET HR+5 trial[59].

Post-irradiation chemotherapy regimens include conventional maintenance chemotherapy as well as high-dose chemotherapy with autologous stem cell rescue[26,29,48,49]. Tolerable toxicity rates have been reported for the post-irradiation chemotherapy regimen used in HIT-2000 and SJMB03[29,62]. On the other hand, the CCG-99702 trial that evaluated the use of high-dose myeloablative chemotherapy following CSI was closed early due to toxicity, with more than

20% of patients developing veno-occlusive disease on consolidation[58]. Severe toxicity was also observed in another protocol that had used high-dose thiotepa after irradiation[50].

Concomitant chemotherapy (vincristine and/or carboplatin) during irradiation was used in some of the trials[29,46,48,49].

- **Outcome:**

The outcome rates for all of the above-mentioned series were comparable and ranged between 60-70% for 5-year PFS in the overall treated cohorts that included patients with different clinical risk factors and molecular subtypes. In the series that had used combined treatment with HART and high-dose chemotherapy, a 5-year PFS of 83% was reached, while the toxicity was significant and the number of treated pineoblastoma patients was too small (n=9) to draw comparative conclusions[50].

Direct comparisons of outcome were possible for pineoblastoma patients treated on the different COG trials,[31] as well as for patients treated within SJMB03 and ACNS 0332.[8] In the latter two trials, the outcome was excellent for average-risk patients. No difference in outcome was observed in direct comparison of the SJMB03 cohort, where a CSI dose of 23.4 Gy was used for average risk patients to the ACNS 0332 cohort, where a CSI dose of 36 Gy was used. In a sub-cohort analysis, patients with clinical average risk disease (completely resected, non-metastasised) and molecular evidence of PB-miRNA group1/2 had an excellent 100% 5-year PFS and OS in both trials.[8,26,49] This suggests that the use of 23.4 Gy may be sufficient for the treatment of average risk PB-miRNA group1/2 patients. However, the small numbers of treated patients indicate caution with regard to clinical conclusions and verification of this finding in a larger cohort of prospectively treated patients would be desirable.

There are no comparative data that show the superiority of specific post-operative chemotherapy regimens. A weak and statistically inconclusive positive prognostic effect has been observed for the use of intensified chemotherapy regimens for treatment of clinically high-risk M+ patients in a pooled cohort[27]. It remains to be clarified if high-risk patients benefit from post-operative high-dose chemotherapy with autologous stem cell support and if it might have a role in avoiding CSI in selected vulnerable patients as suggested in two series[50,59]. Of note, the rate of combined and distant relapses was 77–100% of observed relapses after treatment[27,29]. Omission of CSI may therefore be associated with an increased risk for distant relapses and should not be used outside of a clinical trial in patients old enough to tolerate CSI.

Summary of published series:

Publication	Therapy	Nr. of pts.	Outcome	Risk factors/conclusions
Jakacki, JCO 1995[46]	CCG 921: A: VCR, CCNU, Prednisone or B: “8 in 1” and CSI + boost for patients > 18 mth (CSI 23,4 Gy for <3y; 36 Gy for ≥3y)	N=17 patients (≥ 18 month of age at diagnosis)	3-y PFS: 61±13% 3-y OS: 73±12%	Superior outcome of patients with “pineal PNET” compared to non-pineal “supratentorial PNET”. Extent of resection did not impact on survival.
Pizer, EJC 2006[47]	PNET3: CSI (35 Gy) and boost (56Gy) Either alone or after postoperative chemotherapy:	N=14 pineal “PNET” (≥ 3 years at diagnosis)	5-y EFS: 71% 3-y OS: 71% 7/8 patients with M0 were NED at last follow-up vs. 2/6 with initial M+	Confirmation of relatively good survival for ‘pineal PNET’ (compared to other ‘stPNET’)

	VCR, VP-16, CBDCA/Cyclo			Worse prognosis for patients with metastases.
Massimino, PBC 2013[50]	HD-MTX, VP-16, Cyclo, CBDCA, followed by CSI-HART (2x1.3 Gy/day; to 31.2 Gy for children < 10 years, 39 Gy for older children) and/or boost tumour site 59.7 Gy followed by high-dose Thiotepa and ASCR	N=9 with pineal "PNET" (≥ 18 month at diagnosis.)	5-y PFS 83±15% 3/9 patients with "pineal PNET" did receive focal radiotherapy only	Confirmation of relatively good survival for "pineal PNET". In selected patients, omission of CSI was possible (criteria: M0, no progression on induction)
Gerber, IJROBP 2014[29]	HIT2000 HFRT (2x1 Gy) CSI (36 Gy) + boost (68Gy tumour region/ 72Gy residual tumour) followed by CCNU, CDDP, VCR	N=11 with pineoblastoma (≥ 4 and < 21 years at diagnosis) only M0	5-y PFS/OS: 64±15% All observed relapses (4 of 11 M0 patients) were distant.	Feasibility of HFRT + chemotherapy; high rate of distant relapses
Jakacki, PBC 2015[48]	COG 99701: CSI (36 Gy) + boost (55.8 Gy) + VCR + CBDCA followed by Cyclo, VCR ± CDDP	N=23 with pineoblastoma (≥ 3 and < 22 years at diagnosis)	5-y PFS: 62±11% 5-y OS: 81±9% 5-y PFS (M0/GTR): 88±12% (n=8) vs. 5-y PFS (M0/less than GTR): 42±18% (n=9)	Extent of surgical resection was relevant for M0 pts.
Nazemi, PBC 2016[58]	CCG 99702: Induction: Cyclo, VCR CSI (36 Gy) + boost (55.8 Gy) + VCR Consolidation: CBDCA, VCR, Thiotepa and CBDCA, VCR, Cyclo with ASCR	N=2 with pineoblastoma	Both pineoblastoma patients were alive at last FU	Trial closed early due to toxicity (VOD)
Parikh, Neurosurg Online 2017[30]	Institutional series St. Jude:	N=24 ≥ 5 years at diagnosis.	9 of 10 M0/GTR (or NTR) were alive at last follow-up	Negative impact of less than GTR, and of M+ stage
Hwang, JCO 2018[49]	ACNS 0332: CSI (36 Gy) + boost (55.8 Gy) + VCR ± CBDCA followed by: CDDP, VCR, Cyclo ± Isotretinoin	N=27 with pineoblastoma (≥ 3 and < 22 years at diagnosis.)	Pooled outcome for 36 patients with CNS embryonal tumours / pineoblastoma: 5-y EFS: 63% 5-y OS: 79%	Moderately good survival for molecularly confirmed PB/CNS-ET

Liu, Acta Neuropath 2020[26]	SJMB03: Risk-adapted RT: CSI 23.4 or 36 Gy + boost, followed by chemotherapy: CDDP, Cyclo, VCR, (+ ASCR)	N=30 within protocol + 12 off protocol (≥ 3 and < 22 years at diagnosis.)	Average risk (n=18): 5-y PFS/OS: 100% High risk (M+, or residual disease > 1.5 cm2) (n=24): 5-y PFS: 57±10% 3-y OS: 60±10%	Very good outcome for M0 patients with GTR/NTR despite CSI dose of 23.4Gy Negative prognostic impact of M+ and incomplete resection
Dufour, NeuroOnc 2021[59]	PNET-HR+5: Carboplatin/etoposide, followed by HD-Thiotepa +ASCR, risk-adpated RT: CSI for M+ (36 Gy) + boost (54 Gy), TMZ maintenance	N=9 (M0 = 6) with pineoblastoma, (see supplementary data) (≥ 5 and < 21 diagn.)	Survival for pineoblastoma pts. (see supplementary data) 5-y PFS: 67% 5-y OS: 89%	Moderately good survival for pineoblastoma with use of induction / HDCT and risk-adapted RTI.

Table 3. Summary of the published literature on treatment series for patients with pineoblastoma, older than 3-5 years of age at diagnosis. Abbreviations: ASCR, autologous stem cell rescue; CBDCA, Carboplatin; CDDP, Cisplatin; CSI, craniospinal irradiation; Cyclo, cyclophosphamide; ET Embryonal tumour; FU, follow-up; GTR, gross total resection; HD, high dose; HDCT, high-dose chemotherapy; MTX, methotrexate; NED, no evidence of disease; NTR, near total resection; OS, Overall survival; PFS, Progression free survival; RT, radiotherapy; TMZ, temozolomide; VCR, vincristine; VOD, veno-occlusive disease; VP-16, etoposide; vs. versus.

Publication	**Therapy**	**Nr. of pts.**	**Outcome**	**Risk factors /conclusions**
Fauchon, IJROBP 2000[63]	Collected data from 12 European neurosurgical centres	Of 76 pineal parenchymal tumours n=29 pineoblastoma	Outcome not differentially reported for older patients with pineoblastoma	Poor outcome for grade 4 pineal parenchymal tumours.
Tate, Cancer 2012[45]	Meta-analysis on 109 publications	N=299 pineoblastoma patients	5-y OS: 57% for children ≥ 5 years at diagnosis	Age and extent of resection strongest prognostic factors.
Mynarek, NeuroOnco 2016[27]	Pooled SIOP-E and HeadStart series:	N=78 patients ≥4 years at diagnosis	5-y PFS 63±6% 5-y OS: 66±6% Impact of use of HDCT in M+ patients: HR (PFS): 0.372 (0.06–2.17), p=0.27	Limited negative impact of M+ stage, No impact of residue Strong positive prognostic effect of radiotherapy, no difference between RT strategies Observed impact for use of HDCT statistically inconclusive.

Pfaff, Acta Neuropath 2019[13]	DKFZ series:	N=107 cases with confirmed PB (all ages)	No detailed clinical/treatment analyses	Subtypes miRNA altered 1A/B and 2 arose in older children.
Li, Acta Neuropath 2020[7]	RBTC registry data:	N=91 overall; N=35 with clinical data and age ≥ 3y at diagn.)	For patients ≥3yr : 5-y PFS: 58% 5-y OS: 77%	Subgroups 1-3 with miRNA altered processing arose in older children. High survival rates for group2/3. Metastatic disease neg. prognostic.
Liu, Acta Neuropath 2021[26]	Meta-analysis on DKFZ, ACNS0332, RBTC, SJ Series	N=178 cases with pineoblastoma, 101 ≥3 and <18 years at diagnosis	Most ≥3 and <18 years of age were: PB-miRNA1 (n=71): 5-y PFS: 57% 5-y OS: 70% PB-miRNA2 (n=19): 5-y PFS: 86% 5-y OS: 100%	Excellent outcome (100% PFS/OS) for average risk patients with PB-miRNA group1 or 2 with no difference between SJMB03 (CSI dose 23,4 Gy, see above) and ACNS 0332.
Hansford, NeuroOnc Adv 2022[31]	Pooled cohort COG and institutional series	N=122 patients ≥ 3 years at diagnosis	5-y PFS: 61±6% 5-y OS: 67±5% For patients with localized disease: 5-y PFS: 72±6% 5-y OS: 83±5%	Good survival for patients with localized disease. No clear impact of GTR, Neg. prognostic impact for metastatic disease. No prognostic impact of HDCT. No survival difference between COG trials.

Table 4: Summary of the published literature on registry or pooled series for patients with pineoblastoma, older than 3-5 years of age at diagnosis. Abbreviations: CSI, craniospinal irradiation; HDCT, high-dose chemotherapy; OS, Overall survival; PFS, Progression free survival; RT, radiotherapy;

3.1.4 Current treatment protocols applied in Europe

The table below shows a summary of current treatment approaches for pineoblastoma according to national group. This has been compiled using information provided by SIOPE REST group members and may not be completely representative of protocols used by all institutions within a country.

It demonstrates the current heterogeneity in protocols used.

Pineoblastoma treatment > 3-5 years					
	Disease status	Induction chemotherapy	Radiotherapy	Maintenance	Notes
UK CCLG **As per SJMB03**	M0 and GTR	-	23.4 Gy CSI + boost to 55.8Gy	SJMB 96/03 4x CDDP/ VCR/ Cyclo 4g/m2 with ASCR	Plan to move to SJMB12 maintenance chemo with 3g/m2 Cyclo/cycle and no ASCR
	M+ and incomplete surgical resection	-	36 Gy CSI + boost to 55.8Gy		

Germany HIT (followed also by Hungary. Switzerland, Netherlands)	M0	-	35.2 CSI + boost	Maintenance CDDP/ lomustine/ VCR	Recent decision to use 23.4 Gy + SJMB12 chemo for M0 + MiRNA altered
	M+	2x SKK chemo: Cyclo/VCR 2x HD MTX/ VCR CBDCA/ VP-16 intraventricular MTX	HFRT 40Gy CSI +boost	Maintenance CDDP / lomustine/ VCR	
France PNET HR+	M0	2x CBDCA/ VP-16 Followed 2x HD thiotepa + ASCR	54 Gy to tumour bed + 9 Gy boost to any residual tumour	6x TMZ	
	M+		36 Gy CSI + boost to 54Gy		
Spain As per COG 99703			36 Gy CSI + boost to 55.8Gy concurrent CBDCA (35mg/m2)	Maintenance 6x VCR/ Cyclo (2g/m2)	consider radiation de-escalation in methylation subgroup miRNA 2
Italy	M0	Intensive Induction chemo (MTX, VP-16, Cyclo and CBDCA ± VCR) 2x HD thiotepa 600mg/m2 with ASCR	Focal RT 54Gy		
	M+		CSI + tumour boost		

Pineoblastoma < 3-5 years at diagnosis				
	Induction	Consolidation	Radiotherapy	Maintenance
UK CCLG	Headstart 2 5x induction chemo (CDDP/VCR/Cyclo/ VP-16/ MTX)	HDCT: CBDCA/ VP-16/ thiotepa		
Germany HIT	CBDCA/ VP-16 96-hours induction Followed by re-surgery if applicable	For patients with response/CR: HDCT 1: CBDCA/ VP-16 +ASCR HDCT 2: Thiotepa/ Cyclo +ASCR	Incomplete response after induction: CSI 24 Gy May be preceded in younger children by bridging chemo (TMZ, VBL,	6x cisplatin/ CCNU/ VCR

			metronomic, early phase)	
France	2x CBDCA /etoposide	2x HD thiotepa + ASCR	Risk-adapted RT M0: focal RT 54 Gy M+: CSI 18 Gy for age < 3 years and 23.4 Gy for 3 < age < 5 years	6x TMZ
Spain COG 99703 – 3 tandem transplants Alternative: Headstart 2 with only 1x HD	3x CDDP/ VCR/ Cyclo/ VP-16 Or 5x induction chemo (CDDP/ VCR/ Cyclo/ VP-16/ MTX)	3x HDCT CBDCA/ thiotepa +ASCR Or 1 x HDCT CBDCA/ VP-16/ thiotepa +ASCR	Focal RT for non-metastatic disease	
Italy **Same approach as > 3 yrs**	Intensive Induction chemo (MTX, VP-16, Cyclo, and CBDCA ± VCR)	2x HD thiotepa 600mg/m2 + ASCR	Focal RT 54Gy	

Table 5: Summary of treatment protocols used at the draft of the ESCP guideline. This may be subject to adaptions. Abbreviations: ASCR, autologous stem cell rescue; CBDCA, Carboplatin; CDDP, Cisplatin, CSI, Craniospinal Irradiation; CT, chemotherapy; Cyclo, cyclophosphamide; GTR, Gross Total resection; HD, High Dose; HDCT, High Dose Chemotherapy, MTX, methotrexate; RT, radiotherapy; STR,Subtotal resection; TMZ, temozolomide; VP-16, etoposide.

3.1.5 Recommendations for treatment of patients with pineoblastoma

I) Recommendations for treatment of patients younger than 3-5 years at diagnosis, or ineligible for upfront CSI

General considerations:

- According to published data, the risk of relapse is high in young patients with pineoblastoma treated with radiation-sparing regimens
- By intensive combination chemotherapy a very small subset of patients with pineoblastoma can be cured.
- Young patients with pineoblastoma may have developed the tumour based on a predisposing germline alteration, mostly *RB1*. For *RB1*-altered pineoblastoma or where molecular profiling is not available, genetic counselling and germline testing should be performed. The diagnostic evaluation should include a fundoscopy if possible, during a general anaesthesia procedure (e.g. central line placement) and attention should be paid to evaluate the MRI for the presence of an evolving retinoblastoma.

Therapy selection in patients with pineoblastoma ineligible for upfront CSI is difficult given the multitude of therapy protocols published without clear benefit of one over the other and the high risk of relapse when treated without radiotherapy.

The group **suggests expert consultation** in these children to discuss individual therapy options and is open to receiving requests on therapeutic options.*

* A request for a consultation may be sent by direct email to one of the members of the Pineal Tumour ESCP writing group (see first page), or an ERN-Rare Embryonal and Sarcomatous Tumour Board discussion may be requested as outlined on the ERN PaedCan webpage: https://paedcan.ern-net.eu/e-health/

Resection

Please find detailed considerations on the neurosurgical approach in chapter 2.3

- The importance of the degree of resection is poorly established in this age group. Resection in the pineal cavity in young children can be challenging. Although a maximal safe resection is considered a standard of care, the safety of the intervention is important.
- Resection should only be performed in experienced centres. If the patient is being treated in a centre without adequate expertise, they should be referred to a centre that does.
- In the case of postoperative bulky, residual tumour, re-resection should be considered. However, second-look surgery should not delay the start of further therapy.
- As a significant proportion of pineoblastoma are reported to be chemotherapy-sensitive, in the case of postoperative residual tumour, chemotherapy can be started and an early MRI assessment undertaken. Second surgery should then be considered for any remaining residual before proceeding to consolidation treatment (see below).

Chemotherapy and high-dose chemotherapy

- There is no information on the best chemotherapy approach. No published chemotherapy protocol was demonstrated to be able to spare radiotherapy.
- Given the high risk of recurrence and the young age, intensive chemotherapy regimens with high-dose chemotherapy (like HIT[42] or Head-Start[41]) may be considered, respecting the clinical status of the patient and local experience.
- The role of intraventricular chemotherapy is poorly established. There is no published evidence that suggests a clinical benefit and the only data on intraventricular chemotherapy come from the HIT series with intraventricular MTX[42]. For intraventricular. MTX, there are concerns on toxicity when given together with craniospinal radiotherapy. Given the high rate of treatment failures in young children treated with radiation-sparing approaches, the use of intraventricular MTX is not encouraged, because some of them may go on to have CSI. If used, intraventricular MTX should be reserved to very-high-risk situations such as metastatic pineoblastoma in a very young patient.
- Primary palliative care may be considered in special situations. However, the authors are of the opinion that this should be reserved to exceptional cases with severe disease-associated morbidity and after careful discussion with the family.

Irradiation

- This section refers to patients ineligible for CSI at diagnosis. Because strategies including upfront CSI are much more likely to be curative, the choice of a radiation-sparing regimen with a high risk of relapse should be carefully weighed against the probably more efficient CSI-containing regimens that are associated with long-term neurotoxicity.
- The role of focal radiotherapy is not established in pineoblastoma. Scarce data suggests that focal irradiation of the tumour bed might be effective in controlling disease in non-metastatic pineoblastoma after intensive chemotherapy including high-dose chemotherapy and autologous stem cell rescue[27,50], but this is based on very small case numbers and on patients without available molecular classification.
- The dose to the tumour bed is usually 54Gy.
- Data on the efficacy of "bridge-to-CSI" chemotherapy is scarce. Single survivors received CSI due to incomplete response to chemotherapy. Depending on the age at diagnosis, the use of CSI after bridging chemotherapy may be considered individually[27].
- For patients treated without radiotherapy in frontline therapy, irradiation may be used at relapse. However, data on effectiveness are lacking.
- Based on the existing evidence we would not recommend CSI doses lower than 23.4Gy in pineoblastoma.

Surveillance

- In children treated with CSI-sparing chemotherapy, close surveillance of potential relapses during and after chemotherapy is recommended given the potentially effective option of radiotherapy at relapse, if the child is considered old enough to receive CSI at this timepoint.

Tumour predisposition

- Genetic counselling and germline diagnostics may be initiated before the information on the molecular subtype is available, or otherwise after diagnosis of a pineoblastoma of the PB-*RB1* subtype[64].
- Patients with *RB1*-altered pineoblastoma should be screened for retinoblastoma.
- The presence of a DICER1 predisposition syndrome is rare in this age group and limited to PB-miRNA1/2.
- Staging and follow-up should consider tumour predisposition and affected patients and family members should be included into a cancer predisposition surveillance program for early detection of associated other malignancies[65].

II) Recommendation for treatment of older patients, eligible for CSI

General considerations:

- According to current available data, prognosis of pineoblastoma in older patients is dependent on the molecular subtype and clinical risk factors.
- Patients with PB-miRNA-altered, localized disease, and complete or near complete resection are considered to have a good prognosis with combined "standard" treatment with irradiation to the craniospinal axis and the tumour bed, and chemotherapy (see above).

- Patients with metastatic disease or molecular groups PB-*MYC/FOXR2*-altered are considered to have an increased risk for progression/relapse and intensified treatment may be used. It is less certain as to the negative prognostic impact of residual tumour >1.5 cm^2.
- Treatment should be primarily based on national therapy guidelines. Members of the clinical advisory group or the national representatives would be happy to provide advice (see title page).

Resection:

Please find detailed considerations on neurosurgical approach within the chapter 2.3 on neurosurgical management.

- Once the diagnosis of pineoblastoma is confirmed, maximal *safe* resection is recommended.
- Resection should only be performed in experienced centres. If the patient is being treated in a centre without adequate expertise, they should be referred to a centre that does.
- In the case of postoperative bulky, residual tumour, re-resection should be considered. Second surgery should, however, not delay the start of further therapy
- As a large proportion of pineoblastoma are reported to be chemotherapy-responsive, upfront chemotherapy treatment may be used in case of postoperative residual tumour and an early MRI assessment undertaken. Second surgery should then be considered for any remaining residual before proceeding to radiotherapy (see below).

In cases of metastatic disease, the surgical strategy should be considered on an individual basis.

Radiotherapy:

The mainstay of the treatment is the use of irradiation to the craniospinal axis with a boost to the tumour bed and any metastatic deposits.

*For patients with localized disease and molecularly proven PB-miRNA-altered (group 1 or group2) – **standard risk**:*

- Limited evidence suggests that CSI dose of 23.4 Gy and tumour bed dose of 54 Gy is probably sufficient for treatment, when combined with CNS embryonal-tumour type chemotherapy.

*For patients with clinical or molecular risk factors as metastatic disease, and /or PB-MYC/FOXR2 – **high risk**:*

- According to current available data, there is an increased risk for progression/relapse for patients with one or more of these risk factors present.
- Whilst further specific evidence is lacking, a CSI dose of 36.0 Gy and tumour bed dose of 54 Gy may be used for patients with these risk factors present.
- Although residual tumour > 1.5 cm^2 has been historically included in high-risk grouping, it is unclear whether it is a true high-risk feature that per se predicts metastatic relapse. Therefore, the presence of residual disease alone may not require treatment with higher dose of CSI i.e. 36 Gy especially as the tumour bed/residual will receive a radiotherapy boost. A better approach to bulky residual disease may be chemotherapy-reductive treatment before radiotherapy (see below).

Please note, that current available data do not suggest routine use of focal irradiation. This may be confined to the treatment of young patients who are not eligible for treatment with CSI

and it may be combined with high-dose chemotherapy treatment (see section for young children).

- Please note that PB-*RB1* have so far only be described in patients younger than 4 years at diagnosis. In the unexpected case that PB-*RB1* is diagnosed in a child older than 4 years at diagnosis, an individual treatment recommendation may be sought with the members of the clinical advisory group or the national representatives.

Chemotherapy:

Combined treatment should routinely include post-irradiation maintenance chemotherapy according to a CNS embryonal-tumour treatment protocol.

- Possible chemotherapy regimens used in the treatment of pineoblastoma include: SJMB03[26] / SJMB12; ACNS 0332[49]; POG 9970148; HIT-2000[29]; PNET-5 MB[66]

Post-operative treatment for patients with postoperative residual tumour:

- A reasonable option for upfront treatment would be 2 courses of carboplatin / etoposide (as used in the SIOP HR-MB protocol) although other embryonal CNS tumour protocols may be used.

Patients with standard-risk pineoblastoma:

- Please note that the evidence for sufficient treatment of patients with standard-risk pineoblastoma with a CSI dose of 23.4 Gy is limited to the data of the SJMB03 / SJMB12 protocol (or protocol-like treatment)[26]. For treatment of standard-risk patients with 23.4 Gy CSI, the use of maintenance chemotherapy treatment according to SJMB03/ SJMB12 may therefore be preferred. Please note, that after the closure of SJMB03 the dose of cyclophosphamide was 4 cycles of 2 x 1.5 g/m^2 (3g /cycle) instead of 2 x 2 g/m^2 (4g /cycle) and the autologous stem cell support was abandoned. The patients published in the cited paper as having received SJMB03-like treatment were treated with this reduced dose of cyclophosphamide and no stem cell support with acceptable toxicity (personal communication).
- While it may be speculated that equivalent results may be achieved with another comparable maintenance chemotherapy regimen, comparative data have so far only shown equivalence of SJMB03 with ACNS0332 and 36 Gy CSI have been used in other protocols for all patients irrespective of risk status[8].

Patients with high-risk pineoblastoma:

- A high-risk protocol may be chosen for treatment of high-risk patients (i.e. SJMB03[26] / SJMB12, ACNS 0332[49], or POG 9970148)
- Comparative data are available that show equivalence of COG-99701, and ACNS0332 (while data on SJMB03 have not been included in the latter comparison)[31].

High-dose chemotherapy (HDCT):

- Current available data does not support the routine use of (myeloablative) high-dose chemotherapy with autologous stem cell support in combination with CSI outside of a trial.
- The combination of high-dose chemotherapy with autologous stem cell support and CSI has been used for the treatment of metastatic patients in limited series[50,59]. No superiority can be assumed based on the available data.
- Based on the good outcome of combined CSI and maintenance chemotherapy treatment for standard-risk patients, the use of combined high-dose chemotherapy with autologous

stem cell support with focal irradiation should be confined to young children not eligible for treatment with CSI in the context of a clinical trial or national recommendations.

Tumour predisposition

- Upon detection of somatic *DICER1* pathogenic variants in the tumour, genetic counselling and germline investigation should be offered to the family to determine if DICER1 syndrome is present.
- Staging and follow-up should consider tumour predisposition and affected patients and family members should be included into a cancer predisposition surveillance program for early detection of associated other malignancies[43].
- With current knowledge, there is no evidence to generally recommend deviation from the above-described treatment for patients with DICER1 syndrome specifically in reference to radiotherapy dosing.

3.2 Pineal parenchymal tumour of intermediate differentiation (PPTID)

3.2.1 Introduction

Pineal parenchymal tumours of intermediate differentiation (PPTID) account for 20-50% of tumours of pineal parenchymal origin [28,63,67,68] and mainly affect young adults with a median age at diagnosis of 30-44 years[36,68-74]. However, a certain proportion of cases occur in paediatric/adolescent patients[8]. Historic series of PPTID describe morphological heterogeneity, ranging from well-differentiated tumours to poorly differentiated neoplasms[28,54,75,76]. Metastatic disease at diagnosis is described in 10-20% of cases[8,63,70,72,73,77]. Reports on the prognosis of PPTID patients differ with 5-year overall survival rates ranging from 54-86%[8,69,72,78].

Molecularly, PPTID exhibit relatively flat copy-number profiles[8]. Recent insights into the molecular pathology of PPTIDs have revealed in-frame small insertions in the *KBTBD4* gene (Kelch repeat and BTB domain-containing protein 4) to be characteristic for this tumour type[8,13,21,79]. Of note, *KBTBD4* alterations are not specific to PPTID, as they are also seen in some group 3 and group 4 medulloblastomas with the same insertion of 6–9 nucleotides found in a subset of group 3 MB, while a different insertion type is seen in group 4 MB[80].

Nonetheless, in combination with clinical/radiological and histopathological information, *KBTBD4* alterations are discriminatory enough to have been included in the WHO desirable diagnostic criteria for PPTID[81], and *KBTBD4*-status is extremely helpful in distinguishing PPTID from pineoblastoma[79]. Absence of this alteration should result in careful consideration of an alternate diagnosis. The DNA methylation profiling has identified two distinct molecular entities PPTID-A and PPTID-B[13]. In contrast to pineoblastoma, neither *DROSHA* nor *DICER1* alterations have been detected in molecularly confirmed PPTIDs[8]. Two recent case reports describe *DICER1* somatic and constitutional mutations in patients with PPTID, however, these cases were not molecularly confirmed and so are likely to have been pineoblastoma[16,17].

Although the histological diagnosis correlates with the molecular classification in the majority of cases, DNA methylation studies of pineal tumours have highlighted a potential discrepancy between the pathological and molecular classification of the tumour. In a cohort of 58 pineal tumours, the clustering of histologic pineoblastoma with methylation class PPTID ($n = 2$) and histological PPTID with the molecular PB-miRNA1 class ($n = 1$) has been reported[26]. Similar findings have also been reported in a large international consensus study showing 14% discrepancy between the histological and molecular characterization of PPTIDs[8].

3.2.2 Neuropathological diagnosis

Definition

Histologically, PPTID are characterized by diffuse sheets of monomorphous round cells resembling central neurocytoma or more rarely oligodendroglioma[36,37]. Small fibrillary pseudorosettes may occasionally be seen. Neoplastic cells harbour rounded nuclei with finely granular chromatin. They are smaller compared with cells in pineocytoma. Necrosis is uncommon. In the 2021 WHO classification, PPTID grading is not settled and these tumours may be grade 2 or grade 3[1]. No consensual criteria have been established to grade PPTID.

Diagnostic criteria according to the 2021 WHO classification

Essential

Demonstration of pineal parenchymal differentiation by histopathological and immunophenotypic features (e.g. positivity for synaptophysin) + increased proliferative/mitotic activity + absence of criteria qualifying for the diagnosis of pineoblastoma + pineal region location

For unresolved lesions, a DNA methylation profile aligned with PPTID confirms the diagnosis.

Desirable

Molecular demonstration of *KBTBD4* in-frame insertions

Recommended diagnostic work-up

The diagnosis of PPTID is based on standard histology, which is usually supplemented by immunohistochemical and molecular analyses. PPTID should be differentiated from pineocytoma and pineoblastoma. In contrast to pineocytomas, PPTID do not show pleomorphic cells or large fibrillary pseudorosettes.

Proliferative activity should be assessed by mitotic count and Ki67/MIB1 proliferation index. In PPTID, mitotic activity is moderate and the mean proliferation index is around 10%[36]. A higher Ki67 index should always raise the possibility of a pineoblastoma.

Immunohistochemically, PPTID shows diffuse expression of synaptophysin. Cytoplasmic neurofilament-protein (NFP) immunopositivity is typically seen in a few neoplastic cells[36]. In contrast to neurocytoma, NeuN is not expressed. Glial markers (GFAP, OLIG2) are negative.

Molecular analysis of *KBTBD4* gene (Kelch repeat and BTB domain- containing protein 4) is highly recommended for the diagnostic work-up of PPTID[8,13,21]. The presence of the *KBTBD4* alteration confirms the diagnosis of PPTID and rules out the possibility of pineoblastoma or pineocytoma. As some medulloblastomas may show the same *KBTBD4* alteration, the pineal location of the tumour should be ascertained[80].

Neoplasms with PPTID characteristics but *without KBTBD4 alteration* should be submitted to DNA methylation profiling to check their alignment into the PPTID methylation class (using for example the Heidelberg brain tumour classifier (www.molecularneuropathology.org).

3.2.3 Clinical features and summary of available evidence for treatment

Clinical behaviour:

Historical retrospective and institutional data on the clinical behaviour and response to therapy for PPTID is difficult to interpret, as molecular classification according to the current standard is lacking for most. It is therefore possible that some of the reported PPTID, in particular the reported grade 3 tumours, may actually have been pineoblastoma. The current WHO

classification does not include consensus grading criteria, and a CNS WHO grade 2 or 3 may be assigned[1].

The only study reporting the outcome of a molecularly clear cohort according to current criteria is the series by Liu et al that reported a 5-year PFS and OS of 80.8% (95%CI: 63,4-100%) and 86.2% (95%CI: 70.00-100%) respectively. Among 43 molecularly classified PPTID, 14 belonged to the paediatric age group[8]. More heterogenous outcome has been described in morphologically defined retrospective series, that mostly refer to adult patient cohorts and report 5-year OS rates between 54-84%[69,70,74,78,82-85].

Factors influencing prognosis:

Metastatic Disease: The majority of patients with PPTID present with localized disease, while leptomeningeal and CSF spread has been reported in up to 20% of cases[8]. In the Liu et al study, 3 of the 15 PPTID patients presented with spinal metastatic disease. Two of these belonged to the paediatric age group and both died of progressive disease[8]. Watanabe et al reported the outcome of 5 adult patients, 2 of whom had spinal metastatic disease. One of these patients subsequently died of disease progression[77].

Pathology: The proliferation index and histological grade have historically been used as markers for tumour aggressiveness. In a study by Yamashita et al, that included molecular evaluation of *KBTBD4* status, the histological grade had no impact on survival duration[78]. In other studies, an increased proliferation index[74,85,86], or other morphological high-risk features[72] were associated with a higher risk for progression and death. However, as described above, these series may include tumours that on molecular evaluation do not represent PPTID tumours, such as pineoblastoma. For molecularly confirmed PPTID, no consensus criteria for grading have been defined as yet.

Extent of surgical resection: Due to the deep location of the pineal gland and surrounding neurovascular structures a gross total resection is often not possible. Rates for gross total or near total resection range between 11-60%. In most series on PPTID, gross total or near total resection is associated with superior outcomes[8,30], but this effect is not uniformly shown[69,82].

Surgery Alone vs. Adjuvant Therapy: As mentioned above, inference on treatment effects based on molecularly unconfirmed historic series is limited, especially, as most series that evaluated treatment effects refer to adult cohorts. In the Yu et al study, adjuvant therapy resulted in significantly improved OS (p=0.05), but not PFS (0.06)[74]. Malick et al reported a statistically better survival for the patients who received adjuvant radiation, compared to those who did not. However, no impact of adjuvant chemotherapy was seen in their cohort.[69] In other series, adjuvant therapy (chemotherapy and/or radiotherapy) did not result in improvement in PFS or OS[72,82].

Radiotherapy: In the literature, various radiation volumes and techniques have been employed for the treatment of PPTID including focal radiotherapy to the pineal region and the craniospinal axis, as well as stereotactic radiosurgery[8,74,77,84,87]. Malick et al reported improvement in disease control and overall survival with the use of radiotherapy, while no association was seen in the Yamashita et al study[69,83]. The data is too sparse for any meaningful conclusion regarding the use of CSI versus focal radiotherapy. In practice, focal radiotherapy is generally utilized for localized PPTID with doses between 50.4-54.0 Gy, especially if the surgical excision was less than gross total resection[74,77,84].

Chemotherapy: Regimens based on cisplatin, etoposide and cyclophosphamide have been employed in different institutions and clinical trials that included pineoblastoma. The role of chemotherapy is not established for PPTID based on the available literature[8,69,72].

Patterns of Failure: Both local and distant site recurrences have been reported. In several series, distant, leptomeningeal relapses were the most prominent pattern of recurrence[8,72,83,84,88].

Publication *Author/ Date/Type*	Cohort description *nr. of patients /paediatric patients; median age; if reported*	Therapy	Reported Outcomes	Risk factors/conclusions
Yu, 2015[74] Pathology review of PPTID (single institutional study) No molecular classification	PPTID=27 Median age: 29.7 (2-62) years <18 years of age: Not reported	Surgery: GTR 59% STR 22% PR 19% Adjuvant therapy: Radiosurgery: 2 RT (field not specified):17 RT+Chemo =2 None: 8	5-year PFS: 74% 5-year OS: 81%	High mitotic count was associated with impaired outcome. GTR significantly better than Non-GTR (p=0.002) 15/16 patients with GTR free of relapse at last follow-up; of these 5 had no adjuvant treatment
Mallick, 2016[69] Meta-analysis of PPTID: 29 studies	PPTID=127 Median age: 33 (4.5-75) years <18 years of age= Not reported	Surgery(n=122): GTR/NTR:25% STR: 39% Biopsy only: 31% RT (n=65): CSI: 22% local: 23% WVRT: 3% Whole Brain: 2% Gamma Knife: 6% no RT details: 15% No RT: 29% Chemotherapy (n=43): Given: 70.5% Not Given: 30.5%	5-year PFS: 52% 5-year OS: 84% Failure: 24/127: leptomeningeal/ spinal 63% local 37%	Outcome for females better than males Adjuvant RT associated with better overall survival (p = 0.009). No impact of age or extent of surgery.
Raleigh, 2016[72] Histo-pathological review and molecular analysis of PPT (single institutional study)	Entire cohort of PPT= 38 PPTID =18 Median Age: 32.4 (3.3 – 65) years <18 years of age= Not reported	Surgery: GTR: 8/18 Radiotherapy: CSI: 12 Local: 2 Chemotherapy: 11	5-year PFS:82% 5-year OS: 76%	Neuraxis spread and morphological “large-cell” subtype were associated with impaired survival
Chatterjee, 2019[84] Pathology review of PPTID (single institutional study) No molecular classification	PPTID= 16 Median age: 28.2 (2-55) years <18 year of age=Not reported	Surgery: GTR: 4 STR 5 Endoscopic biopsy: 7 RT: (n=16) Local, 50-54 Gy: 16 CSI: 1	Grade II: (n=3) all patients alive without recurrence. Grade III: (n=7) 3 died 4 alive: relapse-free: 2 local relapse:1	High tumour grade, high MIB-1 Index and STR associated with poor prognosis.

		Chemotherapy: 1 (Cisplatin/Etoposide)	metastatic relapse: 1 In 2 of 3 tumours of patients who died, MIB-1 index was high.	
Wu, 2020[85] Retrospective histopathology and clinical Review of PPTID (multi-institutional study) No molecular classification	N=29 Median age: 30 (8-62) years <18 years of age=4	Surgery: 29 Surgery+RT: 16	Median Overall survival: Grade II: 77 months Grade III: 22 months	High expression of preferentially expressed antigen on melanoma (PRAME) and CD24 associated with shorter survival
Liu, 2021[8] Molecular classification of international cohort of PPT	Entire cohort of PPT=221 PPTID=43 <18 years of age=14	Surgery (n=17) GTR/NTR: 10 STR/Biopsy: 7 RT (n=13) CSI: 7 Focal RT: 3 No RT: 3 Chemo (n=15) High Dose: 5 Standard Dose: 4 No chemo: 6	5-year PFS: 81% 5-year OS 86%	Patients with metastatic disease (n=2) died of PD All patients who received focal RT (n=3) were alive STR/Biopsy associated with significantly lower PFS
Kerezoudis, 2022[82] National cancer data base query	Entire cohort of PPT= 1129 PPTID =103 <18 years of age=9	Surgery (n= 82). GTR: 11% STR: 45% Biopsy 44%. RT (n=104): 64% Chemotherapy (n=103): 17% paediatric patients: surgery alone: 4 RT alone: 2 RT and chemotherapy: 3	5-year OS: Surgery only: 83% RT alone: 83% RT and chemo:80%. 10-year OS: Surgery only: 75% RT alone: 77% RT and chemotherapy: 80%	Extent of resection or adjuvant treatment were not found to be associated with improved survival
Szathamari et al 2022[88] Review of data on all pineal tumours in children	Entire cohort of pineal tumours = 151 PPTID=5 Median age not reported	RT: 5 Chemotherapy: 1(salvage)	Alive: 4 (1 after salvage chemo), all after GTR Dead: 1 (metastatic recurrence)	Small series GTR+RT curative in 3/5.

Table 6: Summary of published retrospective series on PPTID that included children. Abbreviations: CSI, craniospinal irradiation; CT, chemotherapy; GTR, gross total resection; HDCT, high dose chemotherapy; N, number; NTR, near total resection; OS, overall survival; PPT, pineal parenchymal tumours; PR, partial resection; PFS; progression free survival; RT, radiotherapy; STR, subtotal resection.

3.2.4 Recommendations for treatment

- Optimal treatment strategies for paediatric patients with PPTID remain unknown, owing to their rarity and limited data.
- The available literature suggests that complete removal of the tumour (gross total/near total resection) offers the best chance of cure and long-term survival. However, there is recognition that surgery in the pineal region is challenging, and a maximal safe resection is therefore recommended. The detailed considerations on the neurosurgical approach outlined in chapter 2.3 on neurosurgical management do also apply for PPTID. Resection should only be performed in experienced centres. If the patient is being treated in a centre without adequate expertise, they should be referred to a centre that does.
- A review of literature based largely on adult patient outcomes suggests that completely resected, non-metastatic, PPTID can be observed with close clinical and MRI surveillance. Extending this recommendation to the paediatric age group requires careful individualised consideration.
- Children with molecularly classified PPTID, with localized but incompletely resected tumours should be treated with focal adjuvant radiotherapy (50.4-54Gy has been used effectively in many studies). Note that we strongly recommend the evaluation of the *KBTBD4* status and/or DNA methylation before proceeding to a focal irradiation.
- The reported cases of disseminated leptomeningeal relapses with subsequent disease-associated death are of concern, and the risk for metastatic relapses should be considered. Based on the current available data, this does not vindicate a general recommendation for the use of CSI. In individual cases this may nevertheless be evaluated. Contact to the advisory group is welcomed in these cases.
- It is unclear whether PPTID occurs in very young children (under the age of 3). Such cases should be discussed with the advisory group for individualized recommendations.

3.3 Pineocytoma

Pineocytoma is a rare pineal parenchymal tumour that typically occurs in adults between the 4th and 6th decade of life[36]. It is exceedingly rare in the paediatric age group, with only single cases or small series reported[36,72]. Therefore, the diagnosis of pineocytoma in a child should only be made after careful review of clinical, neuroradiological, histopathological and possibly molecular data.

3.3.1 Neuropathological diagnosis

Definition

On H&E sections, pineocytomas are typically composed of sheets of cells with a variable number of large and irregular fibrillary pseudorosettes ('pineocytomatous' pseudorosettes). Neoplastic cells are medium-sized and larger than in PPTID. In some cases of pineocytoma, a few cells may show a ganglioid appearance with a large amount of cytoplasm, bizarre atypical nuclei, and prominent eosinophilic nucleolus ('pleomorphic' variant of pineocytoma)[33]. Pineocytomas are positive for synaptophysin. NFP immunoexpression is usually higher than in PPTID and pineoblastoma, and especially highlights pseudorosettes.

Diagnostic criteria according to the 2021 WHO classification [1]

Essential diagnostic criteria:

Pineal region location + demonstration of pineal parenchymal differentiation by histopathological and immunophenotypic features (e.g. positivity for synaptophysin) + absence of criteria qualifying for the diagnosis of PPTID or pineoblastoma + low proliferative/mitotic activity

Recommended diagnostic work-up:

The *diagnosis* of pineocytoma is based on standard histology, which is usually supplemented by immunohistochemistry. There are 2 main differential diagnoses for pineocytoma in the paediatric population: 1) pineal glial pseudocyst, and 2) PPTID. The distorted pineal parenchyma in the pineal cyst may closely resemble pineocytoma. In this situation, the examination of neuroradiological data (presence of a cystic lesion?) and the demonstration of a three-layered architecture (outer sclerotic leptomeninges, NFP-positive middle pineal parenchyma, and inner GFAP-positive piloid gliosis) are critical to rule out this differential diagnosis. In contrast to pineocytoma, 'pineocytomatous' pseudorosettes and pleomorphic cells are not seen in pineal cysts and PPTID. Compared with PPTID, NFP immunoexpression in pineocytoma is higher.

Proliferative and mitotic activity should be assessed by mitotic count and KI67/MIB1 proliferation index, respectively. In PC, the median Ki67/MIB1 proliferation index is typically lower than in PPTID[36]. However, Ki67/MIB1 proliferation index in PC has not been thoroughly evaluated in children and young adults and it may be higher than in older adults.

Molecular testing of PC is recommended when no definite diagnosis has been reached with histology and immunohistochemistry. No specific molecular alterations have been described for pineocytoma to date. However, pineocytomas do not show *KBTBD4* alterations nor *DICER1* mutations or *DROSHA* deletions[19,37]. In difficult cases, the analysis of the methylation profile of the tumour may be needed (for example, EPIC array and classification by the Heidelberg brain tumour classifier (www.molecularneuropathology.org)). However, it should be noted that pineocytoma share the same methylation class as pineal cyst and normal pineal gland. In this situation, the demonstration of chromosomal imbalances in the CNV profile favours the neoplastic nature of the tumour.

3.3.2 Clinical behaviour and evidence for treatment

The clinical behaviour of pineocytoma is that of slowly growing tumours over several years. Surgery is the mainstay of treatment, and is curative for most patients[89]. For the few reported paediatric patients, no tumour-related death has been observed[63,72]. In adult patients, an inferior outcome after less than gross total resection has been shown, while the addition of adjuvant radiotherapy did not improve survival[89].

3.3.3 Recommendations for treatment

As pineocytoma is very rare in the paediatric age group, molecularly confirmed exclusion of other diagnoses is essential (see above). Referral for expert diagnostic review by a national or international reference is recommended in case of doubt.

- Maximal safe resection with the aim of gross total resection should be the initial treatment approach, with a subsequent watch and wait strategy.
- A surveillance strategy is also recommended for patients with less than total resection and a molecularly confirmed diagnosis of pineocytoma. Adjuvant radiotherapy was not

associated with a survival benefit for adult patients with less than gross total resection and is not recommended within routine clinical practice.

- Chemotherapy has no defined role in pineocytoma.
- For individual constellations that require non-surgical treatment, discussion with the advisory group is recommended.

Other pineal region tumours

3.4 Papillary tumour of the pineal region (PTPR)

3.4.1 Introduction

Papillary tumour of the pineal region (PTPR) is a rare tumour entity initially reported by Jouvet et al in 2003 and established as a disease entity in the 2007 WHO Classification[28,90]. PTPR most commonly occur in the third decade but has been rarely described in the paediatric population with around 30 cases in children reported in the literature[91].

PTPR is a neuroepithelial tumour thought to arise from the specialized ependymocytes of the subcommissural organ (SCO), a circumventricular organ presumably involved in CSF regulation and located at the entrance of the aqueduct of Sylvius, anterior to the pineal gland and below the posterior commissure involved in CSF regulation[90]. PTPRs are not derived from pineal parenchyma. They share morphological features with papillary ependymoma and choroid plexus tumours which all commonly express FOXJ1, a transcription factor involved in the regulation of ciliogenesis as opposed to CRX, a transcription factor involved in the differentiation of the pineal and retinal cell lineages[38,92]. Although precise histological grading can be challenging, their biological behaviour may correspond to CNS WHO grade 2 or 3, generally grade 2[93]. No consensual criteria have been established for PTPR grading[81]. One study showed that increased proliferation (Ki67/ proliferation index $\geq$ 10%) and/or mitotic activity (≥3 mitoses per 10 high-power fields) are associated with worse outcomes[94].

PTPR has a distinct molecular profile showing typical chromosomal alterations as well as specific DNA methylation and mRNA expression profiles allowing distinction from histopathological mimics such as PPTID and ependymomas. PTPR shows characteristic loss of chromosome 10 which has been linked to *PTEN* mutations and activation of the PIK3/AKT/mTOR signalling pathway[92,95]. PTPR can be divided into two subgroups based on methylation profile with an observation that hypermethylated PTPR group 2 tumours may have a shorter progression-free survival[92].

PTPRs generally present as an isolated pineal mass but leptomeningeal dissemination at presentation has been described[96]. Gross total resection is the first line treatment for PTPR and non-recurrence and overall survival is associated with the extent of surgical resection. However, there is a high rate of local recurrence after surgery in a similar fashion to ependymomas and so various combinations of chemo- and radiotherapy have been used in an attempt to reduce this risk[97].

3.4.2 Neuropathological diagnosis

Essential diagnostic criteria according to the 2021 WHO classification

Papillary growth pattern with epithelial-like cells + characteristic immunohistochemical staining pattern (*e.g.,* positivity for cytokeratins, SPDEF, CD56/NCAM) + pineal region location.

For unresolved lesions, a DNA methylation profile aligned with PTPR confirms the diagnosis.

Recommended diagnostic work-up

The diagnosis of PTPR relies on the examination of H&E sections and immunohistochemical analysis. Molecular biology is usually not needed to reach an accurate diagnosis but may be required in challenging cases.

On H&E sections, PTPR is typically characterized by epithelioid cells arranged in papillary structures and solid areas[106,111].

Mitotic count and Ki67 proliferation index should be assessed.

Differential diagnoses include pineal parenchymal tumours (especially PPTID) in the case of prominent solid areas, conventional ependymomas, choroid plexus tumours and metastases of adenocarcinoma.

PTPR is typically GFAP- and synaptophysin-negative and CK18/CAM5.2-positive. In contrast to most ependymomas, PTPR does not show significant GFAP immunopositivity and expresses cytokeratin 18/CAM5.2. In contrast to choroid plexus tumours, PTPR expresses CD56/NCAM but not E-cadherin. EMA expression may be seen in both ependymoma and PTPR. Immunoexpression of SPDEF is mostly seen in PTPR. PPTID differ from PTPR by a strong and diffuse expression of synaptophysin and CK18/CAM5.2 negativity. In contrast to pineal parenchymal tumours, they show FOXJ1 nuclear immunopositivity and lack of CRX immunoexpression.

In difficult cases, DNA methylation profiling may be performed in order to confirm the diagnosis (for example, by using the Heidelberg brain tumour classifier (www.molecularneuropathology.org)). Besides a matching methylation profile, the CNV plots may also show a loss of chromosome 10 which is a frequent feature of these tumours[92].

Analysis of *PTEN* gene may be performed, notably in cases where a therapy targeting the PI3K/AKT/mTOR pathway is being considered.

3.4.3 Summary of available evidence for treatment

In a French retrospective series of 31 predominantly adult cases (5 children), 21 (68%) had gross total resection. Fifteen patients received radiotherapy after complete (n=9) or incomplete (n=6) resection of the tumour. Of 29 evaluable patients, 21 (72%) experienced recurrence (19 local, 1 local and spinal, 1 spinal) with 8 deaths (1 not related to disease) in the mean follow-up period of 4.2 years giving an estimated 5-year OS and PFS of 73% and 27%. On univariate analysis, gross total resection was the only clinical factor associated with overall survival and recurrence but did not reach statistical significance[98].

In a further retrospective series of 44 patients, 32 were still alive after a median follow-up of 63.1 months. Twelve patients (27%) experienced progressive disease, with 7 undergoing two relapses and 5 more than two. Median PFS was 58.1 months. Only gross total resection and younger age were associated with a longer OS, radiotherapy and chemotherapy having no significant impact. The study did not provide clear evidence for a role for adjuvant radiotherapy or chemotherapy in the treatment of PTPR[99].

A systematic review of 71 case reports and case series identified 177 patients with PTPR with a mean age of 33 years, 53% male. Surgery was performed on 82% and gross total resection was achieved in 71.4% of cases. 56.8% recurred after a median of 29 months. Three-year overall survival was 83.5%. Multivariable analysis was performed in 133 patients with relevant dataset – tumour size and surgical treatment were associated with survival at 36 months. There was no observed benefit to gross total resection or adjuvant treatments i.e. radiotherapy (44%), chemotherapy (10.3%) and radiosurgery (10.8%)[91].

In a review of 31 reported cases of PTPR in paediatric patients, 50% of 22 patients with follow-up data had a recurrence; this included 40% of 15 patients with gross total resection. All patients who received chemotherapy alone either upfront (n=2) or as adjuvant treatment to surgery (n= 3) had tumour recurrence. 2 of 6 (33.3%) patients who received combined chemotherapy and radiotherapy had a recurrence and 2 of 4 (50%) who received radiotherapy

alone had recurrence. Salvage therapy for recurrence was usually a combination of complete resection, radiotherapy and chemotherapy. Only one (3.2%) patient in the analysis died.[97]

The presence of *PTEN* mutations raises the possibility of treatment with mTOR inhibition. There is a single case report of a 28-year-old male with PTPR subtype 2, loss of chromosome 10 on DNA methylation and loss of expression of PTEN in tumours cells and strong staining for phosphorylated Akt. His tumour was incompletely resected and had recurrent relapses following radiosurgery and radio-chemotherapy. Everolimus was started following further disease progression and 19 months after the start of treatment, contrast enhanced tumour volume had decreased by 75% and there was significant improvement in neurological symptoms, performance status and quality of life[100].

3.4.4 Recommendations for treatment

- The data suggests that gross total resection is the only factor associated with improved recurrence and survival rates although it should be noted that a significant risk of recurrence remains even following gross total resection.
- Therefore, maximal safe resection with the aim of gross total resection should be the initial treatment approach.
- Completely resected PTPR should have close clinical and MR surveillance. Upfront adjuvant treatment would not be recommended due to limited evidence of benefit.
- Radiotherapy could be considered for older patients with growing or recurrent PTPR.
- Young patients need careful discussion.
- The limited data suggests that these tumours are not chemosensitive and so it is difficult to recommend chemotherapy as part of the treatment for PTPR.
- Due to the rarity of these tumours, consideration of adjuvant treatment should be discussed with the advisory group.

3.5 Desmoplastic myxoid tumour of the pineal region, SMARCB1-mutant

Desmoplastic myxoid tumour, SMARCB1-mutant is a new addition to the 2021 WHO Classification of CNS Tumours.[81] It is a rare tumour that occurs in the pineal gland and is a SMARCB1-mutant tumour lacking histopathological signs of malignancy. Histological grading for this tumour as for PPTID and PTPR is yet to be defined.

Thomas et al described seven SMARCB1-deficient intracranial tumours, all located in the pineal region in 4 females and 3 males with a median age of 40 years (range 15-61 years).[101] The histology was of spindled and epithelioid cells embedded in a desmoplastic stroma alternating with a variable extent of a loose myxoid matrix with all cases showing loss of nuclear SMARCB1/INI1 protein expression. There was also frequent expression of EMA and CD34. Ki67/MIB1 proliferation index was low in the majority of cases with a median of 3%. This was in contrast to adult ATRT which display frank signs of malignancy and predominantly arises in the sellar region or in the cerebral hemispheres.

DNA methylation profiles were obtained from six tumour samples with sufficient DNA quality. Five tumours were not classifiable (calibrated scores for methylation class < 0.9) and only one showed marked similarity with ATRT-MYC (calibrated score: 0.91). However, by unsupervised t-SNE analysis and hierarchical clustering analysis, all tumours were located closely together in the vicinity of the ATRT-MYC subgroup and poorly differentiated chordomas but formed a separate cluster.

None of the patients had evidence of metastatic disease and gross total resection was achieved in 4 patients. Three patients, 2 with residual disease, received focal radiotherapy and one patient received additional multimodal chemotherapy. After a median observation period of 48 months, three patients were alive with stable disease, all had gross total resection,

one received radiotherapy. One patient with residual tumour treated with radiotherapy experienced tumour progression. Three patients, 2 with residual disease succumbed to disease – one with residual disease had no adjuvant treatment, the other with residual disease received chemotherapy and radiotherapy and the third with gross total resection did not have further details on adjuvant therapy.

Due to the rarity of these tumours, they should be discussed with the advisory group.

3.6 Pineal cysts

Differentiation of pineal lesions that require further diagnostic and intervention from incidental pineal cysts is relevant. Simple pineal cysts are a frequent finding on MRI and typically present with a well circumscribed and homogenous appearance of < 20 mm diameter and a thin, uniform capsule that may show a rim enhancement.[102,103] Atypical findings are a larger size, a multicystic or septated appearance, a variable wall thickness that exceeds 2 mm, or contrast enhancement within the lesion.[103,104] Growth of a simple pineal cyst is very rare and one single follow-up imaging after 1 year is deemed sufficient if there are no atypical radiological features or growth observed.[102] Age-adapted normal values for size and morphology of the cystic pineal gland for children 0–5 years of age have been evaluated by the European Retinoblastoma Imaging Consortium[6].

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