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# SNO-EANO-EURACAN consensus on management of pineal parenchymal tumors

**Anthony P.Y. Liu, Bryan K. Li, Alexandre Vasiljevic, Michael C. Dewan, Benita Tamrazi, Birgit Ertl-Wagner, Jordan R. Hansford, Elke Pfaff, Martin Mynarek, Ho-Keung Ng, Derek S. Tsang, Nicholas G. Gottardo, Amar Gajjar, Eric Bouffet, Christelle Dufour, Barry Pizer, David Schiff, Michael D. Jenkinson, Giuseppe Lombardi, Patrick Y. Wen, Martin J. van den Bent, and Annie Huang**

All author affiliations are listed at the end of the article

**Corresponding Author**: Anthony P.Y. Liu, MBBS, MMedSc, Division of Hematology/Oncology, Department of Pediatrics, The Hospital for Sick Children, University of Toronto, 555 University Ave, Toronto, ON, M5G 1X8, Canada (anthony.liu@sickkids.ca).

**Abstract**

Pineal parenchymal tumors are rare neoplasms for which evidence-based treatment recommendations are lacking. These tumors vary in biology, clinical characteristics, and prognosis, requiring treatment that ranges from surgical resection alone to intensive multimodal antineoplastic therapy. Recently, international collaborative studies have shed light on the genomic landscape of these tumors, leading to refinement in molecular-based disease classification in the 5th edition of the World Health Organization (WHO) classification of tumors of the central nervous system. In this review, we summarize the literature on diagnostic and therapeutic approaches, and suggest pragmatic recommendations for the clinical management of patients presenting with intrinsic pineal region masses including parenchymal tumors (pineocytoma, pineal parenchymal tumor of intermediate differentiation, and pineoblastoma), pineal cyst, and papillary tumors of the pineal region.

**Key Points**

- Pineal region tumors are rare and biologically diverse entities for which best clinical practice remains to be established.
- This review aims to provide a consensus recommendation for clinical management of patients with intrinsic pineal region tumors and masses.

## Epidemiology, Differential Diagnosis, and Germline Predisposition

Tumors of the pineal region span rare and diverse entities which account for only 0.4% of central nervous system (CNS) neoplasms in children and adults.[1] They are more frequently diagnosed in males (M:F ratio 1.6:1) and exhibit age-dependent variation in incidence and type of lesion. Pineal region masses encompass cysts as well as intrinsic pineal parenchymal tumors (PPT), papillary tumors of pineal region (PTPRs), and other benign and malignant entities. Nonmalignant pineal cysts are amongst the most common pineal region masses, often incidentally diagnosed in about 1% of children, and up to 23% of adults.[2,3] PPTs span tumors with varying histology, grade, molecular, and clinical features including pineoblastoma (PB), pineal parenchymal tumor of intermediate differentiation (PPTID), and pineocytoma (PC). PBs typically affect children (mean age of diagnosis: 13 years) but with notable clinical heterogeneity: Cases in infants and young children tend to be far more aggressive and difficult to treat, while cases in older children and adolescents generally respond better to therapy and have superior survival outcomes.[4]

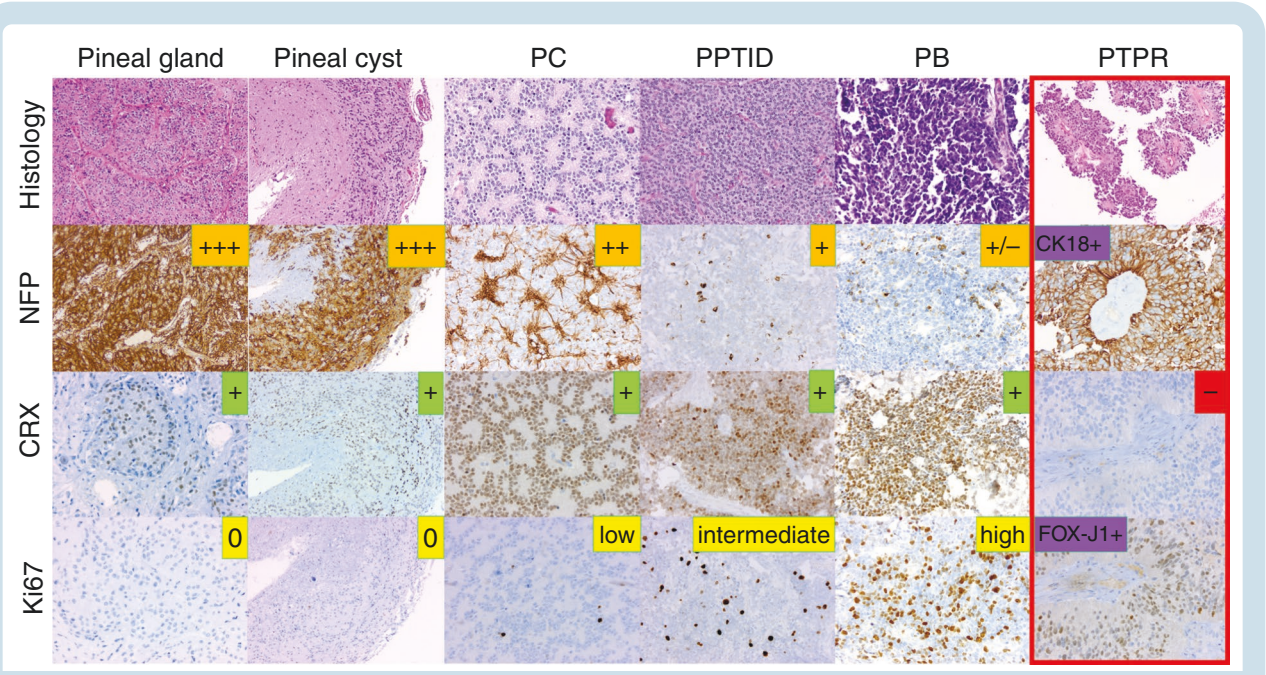


**Figure 1.** Histopathologic features of pineal parenchymal tumors and papillary tumors of the pineal region (PTPRs) in relation to the normal pineal gland. Characteristic lobular architecture of the normal pineal gland with strong expression of neurofilament proteins (NFP), pinealocytes with CRX transcription factor expression and negative Ki-67 stain are shown in relation to pineal cysts—with typical 3 layer walls of piloid astrogliosis, disrupted pineal parenchyma, and thickened leptomeninges, and pineocytoma (PC) - with strong typical NFP expression in large and irregular fibrillary pseudorosettes, CRX positivity and low Ki-67 index, and pineal parenchymal tumor of intermediate differentiation (PPTID) and pineoblastoma (PB)—higher grade lesions with diminished NFP expression and respective low-intermediate and high Ki-67 indices. PTPR are distinct tumors resembling ependymoma with expression of ciliogenesis transcription factor FOX-J1 and evidence of epithelial differentiation with cytokeratin 18 (CK18) immunopositivity and no CRX expression.

In contrast, PPTIDs, PCs, and PTPRs are predominantly seen in adults, with peaks around 20–40, 30–60, and 30 years of age, respectively.[5–7] The differential diagnosis for pineal region tumors also includes germ cell tumors (GCT), ependymoma, astrocytic tumors, and atypical teratoid/rhabdoid tumors (ATRT).[8] This review will focus on the clinical management of PPTs in children and adults.

While most PPTs are sporadic, some arise in the context of germline predisposition syndromes. These include PB developing in patients with retinoblastoma and germline *RB1* mutations—referred to as "trilateral retinoblastoma."[9] PBs in older children may be associated with germline microRNA (miRNA) biogenesis gene defects, such as *DGCR8* (DiGeorge syndrome) and *DICER1* (DICER1 cancer predisposition syndrome), as well as *APC* gene alterations (Turcot syndrome).[10–12] Thus, genetic counseling is recommended for patients with PB regardless of family history.

## Pathogenesis and Putative Cell-of-Origin

The pineal gland primarily functions to regulate the circadian rhythm through the secretion of melatonin. Its development starts between 2 and 4 weeks of gestation with an evagination from the diencephalon driven by homeobox genes.[13] The postnatal gland is comprised predominantly of pinealocytes, which are the neuro-secretory cells that produce melatonin, and associated interstitial cells including astrocytes and microglia. In keeping with the light-sensitive characteristics of both the pineal gland and the retina, both share common phototransduction signatures, specifically for transcription factor *CRX*.

PPTs and PTPRs are rare tumors with poorly understood biology. PTPRs are hypothesized to arise from ependymal cells of the circumventricular subcommissural organ.[14] In contrast, PPTs are thought to arise from pinealocytes, both high and lower-grade lesions frequently exhibiting histologic and molecular features, including expression of *CRX*, and enzymes for melatonin biosynthesis (*TPH1*, *HIOMT*) and phototransduction (*OPN4*).[15–18]

## Histopathologic and Molecular Features

In patients with pineal region tumors, histopathologic characterization is key to inform subsequent workup and approach for further management (Figure 1).

PCs are considered World Health Organization (WHO) Grade 1 neoplasms and comprise small, uniform, mature cells forming large pineocytomatous rosettes, with low mitotic activity and Ki-67 proliferative index. Immunohistochemical features include strong positivity for synaptophysin, NSE, and NFP, and variable expression of other neuronal markers. PCs are epigenetically distinct

from PPTIDs and PBs, and have no known recurrent genetic alterations.

PPTIDs are WHO grades 2–3 tumors characterized by diffuse sheets and/or large lobules of monomorphic round cells with moderate to high cellularity, round nuclei with mild to moderate atypia, salt-and-pepper chromatin, and more distinct cytoplasm than PBs. The criteria for PPTID grading remain poorly defined, although mitotic activity may help differentiate grade 2 (mean Ki-67 5.2 ± 0.4, range 2.3–7.2) and grade 3 (mean Ki-67 11.2 ± 2.0, range 3.0–20.0) tumors.[19] By immunohistochemistry, PPTIDs stain positive for synaptophysin, with variable labeling for NFP and chromogranin A. Interestingly, 75% of PPTIDs exhibit recurrent in-frame insertions of *KBTBD4*, encoding a Cul3 ubiquitin ligase adaptor, although its oncogenic role has yet to be determined.[20]

PBs are WHO grade 4, poorly differentiated, embryonal tumors that are composed of patternless sheets of densely packed "small round blue cells" with indistinct cell borders, high nuclear to cytoplasmic ratio, irregular hyperchromatic nuclei, occasional Homer Wright and Flexner-Wintersteiner rosettes, and frequent areas of necrosis. They have high Ki-67 proliferative indices (mean 36.4 ± 6.3, range of 20%–50%) and are characteristically immuno-positive for synaptophysin and NSE, while NFP and chromogranin A staining is inconsistent compared to PC and PPTID, with positivity more restricted to individual cells.[5,19] Importantly, retained BAF47/INI1 immuno-staining distinguishes them from ATRTs, which can also present as a small round blue cell tumor in the pineal region.

Recent multi-institutional studies have shown substantial epigenomic and genomic heterogeneity amongst PBs, and PBs are now classified into 4 molecular subgroups, namely miRNA processing-altered 1 (PB-miRNA1), miRNA processing-altered 2 (PB-miRNA2), RB1-altered (PB-RB1), and MYC/FOXR2-activated (PB-MYC/FOXR2).[4,12,21,22] PB-miRNA1 and PB-miRNA2 subgroups exhibit loss-of-function germline or somatic alterations of miRNA biogenesis genes *DICER1*, *DROSHA,* and *DGCR8*. Germline or somatic *RB1* alterations, as well as miR-17~92 oncogene alterations, are seen in PB-RB1. PB-MYC/FOXR2 tumors are enriched for FOXR2 proto-oncogene expression and can exhibit *MYC* copy number gains or amplification. A rare PB variant, termed pineal anlage tumors have prominent neuroectodermal and heterologous ectomesenchymal components and molecularly resemblance to PB-MYC/FOXR2 tumors.[4,21]

PTPRs are WHO grades 2–3 neuroepithelial tumors characterized by papillary and solid components, epithelial-like cells, and immunoreactivity for cytokeratins.[7,23] They are distinguished from PPTs by lack of CRX staining and positive expression of FOX-J1, a transcription factor which regulates motile ciliogenesis of the ependyma and choroid plexuses.[24,25] They have a wide range of proliferative activity (mean Ki-67 of 9%, range 0%–25%).[23] PTPRs have distinct methylation profiles with frequent chromosome 10 loss and *PTEN* loss in a subset of tumors.[7,26]

In summary, cumulative molecular studies have identified key diagnostic alterations that distinguish different pineal region tumors (ie, *DICER1*, *DROSHA*, *DGCR8*, *RB1*, *KBTBD4*, and *PTEN*). These somatic and germline molecular features should be leveraged together with histopathology and/or methylation profiling to establish a robust clinical diagnosis and inform any workup for inherited cancer predisposition syndromes.

## Clinical Presentation and Initial Medical Management

Due to the anatomy of the pineal region, patients often present with symptoms of obstructive hydrocephalus and increased intracranial pressure (ICP; headache, nausea, and vomiting), and gait disturbances.[27] Visual symptoms, including diplopia, altered acuity, and Parinaud's syndrome, may also occur. The patient must be presumptively stabilized with precautions for high ICP, while obtaining neuroimaging with avoidance of lumbar puncture, and managed in consultation with neurosurgery and critical care. When possible, patients should be transferred to a tertiary referral center for further workup and management.

## Diagnostic Imaging and Staging

Magnetic resonance imaging (MRI) remains the major imaging modality used for PPTs, but in an emergent or resource-limited setting, computed tomography (CT) can also provide critical information including tumor site, state (eg, hemorrhage), configuration, relation to vital structures, and extent of mass effect including hydrocephalus (Figure 2, Supplementary Figure 1). CT may also aid in distinguishing tumors with different patterns of calcification, such as GCTs (Supplementary Figure 1A) and PPTs (Figure 2C).[27,28] MRI (with and without contrast) most accurately delineates intrinsic pineal masses from tumors abutting the pineal gland, including astrocytic tumors originating from the thalami, brainstem, or corpus callosum.[27,28] Optimal MRI sequences are outlined in Supplementary Table 1. Where available, intraoperative MRI may facilitate surgical decision-making.[29] MRIs should be performed within 72 hours after surgery to avoid postoperative artifacts and accurately assess tumor residual.[30]

PBs can have heterogeneous imaging features with variable contrast enhancement, necrosis, hemorrhage, frequent evidence of local invasion, and leptomeningeal dissemination. Reflecting their high cellularity and malignant nature, PBs characteristically have restricted diffusion with low apparent diffusion coefficient values, as well as elevated choline, reduced N-acetylaspartate, and the presence of taurine on magnetic resonance spectroscopy. In contrast, PCs appear as well-circumscribed T1 hypo-/isointense and T2 iso-/hyperintense lesions, variably enhancing without diffusion restriction, and may be cystic with or without hemorrhage. Cystic PCs without hemorrhage may resemble pineal cysts. PPTIDs often demonstrate intermediate to high signals on T2-weighted images and may appear cystic with contrast enhancement. They may also exhibit diffusion restriction depending on tumor grade (grade 3 vs 2). No specific MRI findings reliably distinguish PPTIDs from PCs or PBs.

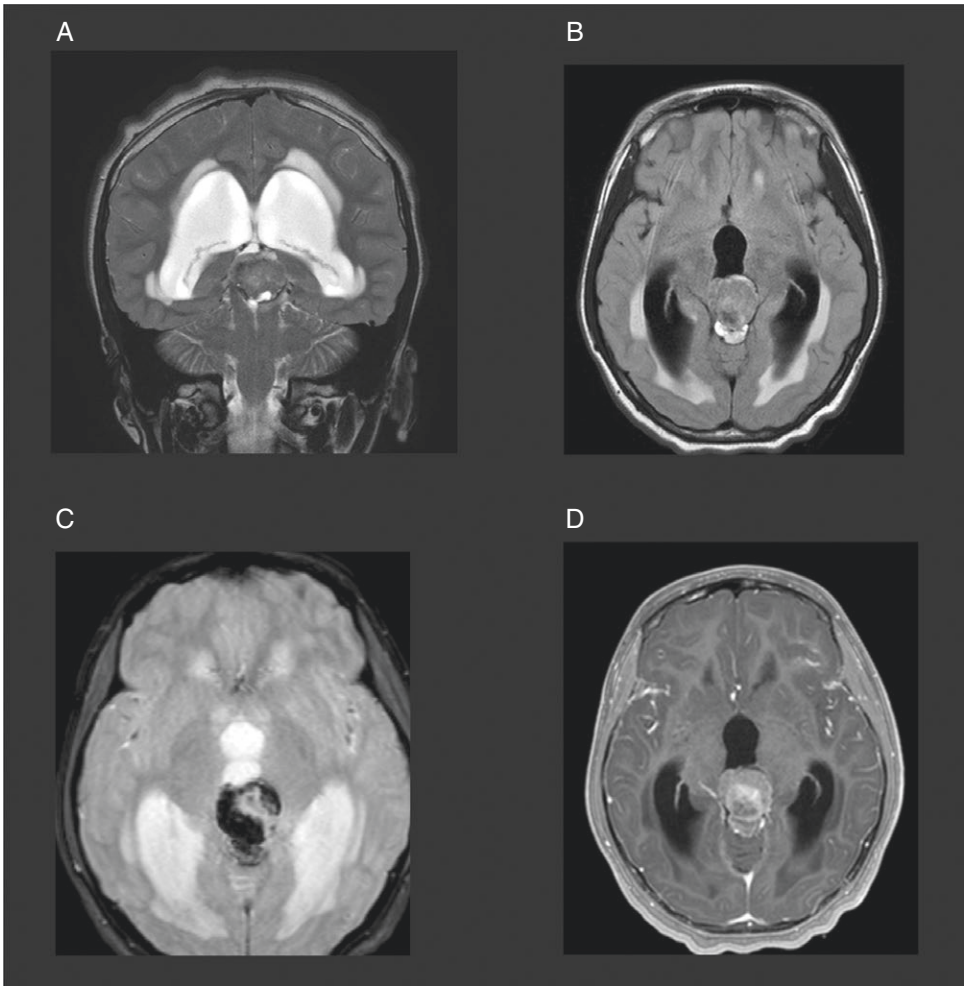


**Figure 2.** Magnetic resonance imaging (MRI) features of pineoblastoma. Coronal T2-weighted (A) and Axial FLAIR MRI showing pineal region tumor with marked hydrocephalus and transependymal CSF seepage. Axial gradient (C) and T1-MRI with contrast (D) showing scattered susceptibility of "exploded calcification" and avid contrast enhancement in the tumor.

Due to the propensity of malignant pineal lesions for craniospinal metastases, preoperative imaging of the complete neuroaxis, is a critical initial step for disease staging. CSF cytology obtained via LP preoperatively (if high ICP has been ruled out), or 10–14 days after surgery to minimize postsurgical debris, is critical for the evaluation of potential microscopic disease and to complete disease staging. As extra-CNS metastasis are rare events in PB and PPTID, routine extra-CNS staging is not needed but appropriate investigation should be undertaken if non-CNS metastases are suspected.[12]

GCT markers (alpha-fetoprotein, AFP, and human chorionic gonadotropin, HCG) should be obtained in both the serum and CSF (if can be safely collected) preoperatively. Detection of elevated levels of either or both markers in serum and/or CSF may be sufficient for the diagnosis of a GCT without the need for surgery and tissue sampling. Note however, GCT markers may be normal in patients with pure germinomas and mature teratomas, and nonsecretory nongerminomatous GCTs (NGGCTs), such as embryonal carcinomas.

## Perioperative Management, CSF Diversion, and Tumor-Directed Surgery

Neurosurgical management of pineal region tumors includes hydrocephalus treatment, diagnostic tissue acquisition (except for secreting GCTs), and safe feasible resection when indicated. Perioperative decisions are based on the patient clinical status and results of preoperative diagnostic studies. A tumor specimen may be obtained via open surgical, stereotactic, and endoscopic approaches. For patients with acute intracranial hypertension from obstructive hydrocephalus, an external ventricular drain may be inserted, most often via a frontal trajectory into the lateral ventricle to achieve ICP stabilization.[31]

Most patients with pineal region tumors present with insidious hydrocephalus which allows time for comprehensive preoperative diagnostics and multi-disciplinary consultation. CSF shunting is a reliable and durable hydrocephalus treatment and is invaluable in limited-resource

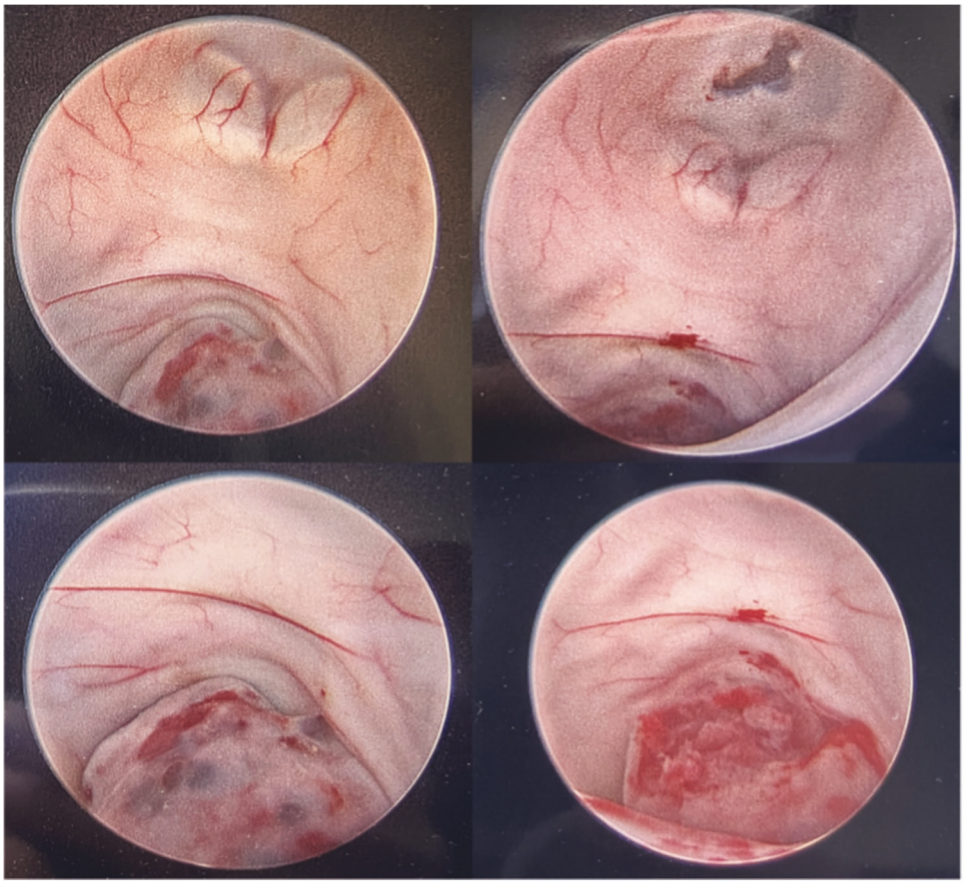

**Figure 3.** Cerebrospinal fluid diversion and biopsy in a pineoblastoma patient. Illustrative photos showing (A) visualization of the floor of the third ventricle and dorsally located PPTs with right frontal, endoscopic transforaminal approach, with (B) third ventriculostomy for hydrocephalus, followed by posteriorly directed scope toward PPT for (D) endoscopic diagnostic sampling of tumor tissue.

settings. In centers with neuro-endoscopic expertise, endoscopic third ventriculostomy is the preferred procedure, as tumor tissue sampling can be attempted during the same surgery (Figure 3),[32] and complication rate may be lower when compared to shunting based on systematic analysis of respective cohort studies.[33] If hydrocephalus needs to be treated, a third ventriculostomy should be performed first, followed by a tumor biopsy. Surgical trajectory can involve a single or 2 separate burr holes depending upon rostral extent of tumor and relative location to the foramen of Monro.

Factors influencing surgical resection include known/presumed histopathologic diagnosis, mass effect on neural structures, and a multimodal treatment that includes maximal safe resection. Due to the intimacy of pineal region tumors with crucial neurovascular structures, choice of surgical approach is most important and consequential. The pineal region can be accessed via numerous routes, each with advantages and limitations. Choice of optimal surgical corridor is critically informed by (1) the lesion's relationship with deep venous network, including the internal cerebral veins, basal veins of Rosenthal, and the vein of Galen; (2) angle of the straight sinus; (3) height of the tumor along the vertical axis created by the splenium and fourth ventricle floor; (4) relationship of the tumor with the tentorium; and (5) lateral extent of the tumor. For some tumors, a staged approach with multiple corridors may be needed for adequate resection. Anatomic and tumor-specific approaches most commonly used include:

1. Midline infratentorial supra-cerebellar approach for patients with a mildly sloped/straight sinus and a low-lying tumor.[34]
2. Lateral supra-cerebellar: A modified midline supra-cerebellar approach suitable for most pineal lesions,[35] particularly those extending laterally into the thalamus.
3. Occipital transtentorial: A versatile approach for large tumors that occupy supra- and infratentorial spaces[36] and require gentle occipital lobe manipulation to mitigate post-operative visual field deficits.
4. Interhemispheric transcallosal approach: Suited for tumors residing high along the splenial-fourth ventricle axis, and those extending anteriorly within the third ventricle.[37]

Gross tumor removal is usually the only treatment required in lower-grade pineal lesions such as PC, and is preferred for patients with PPTID. In the case of PB, pooled

cohort studies predating molecular classification suggest that surgical extent may not impact the survival of patients treated with intense multimodal therapy[38,39]; however, the prognostic impact of surgery relative to the recently described molecular subgroups of PB, and for younger patients treated with lower dose or no radiation remains unclear. For patients who underwent only minimal resection or biopsy of a bulky tumor at diagnosis, chemotherapy might facilitate second-look surgery by reducing tumor vascularity and volume.[40]

## Entity-Specific Management: Evidence and Recommendations

The role of adjuvant therapy for pineal region tumors varies according to tumor entity, histologic grade, and molecular class or subgroups. PCs can be managed by surgery alone, while multimodal therapy is essential for the cure of patients with PB (Table 1). However, the role and need for adjuvant therapy remains unresolved and controversial for patients with PTPR and PPTID. Hence, upfront enrollment in available clinical trials should be strongly encouraged for patients with pineal region tumors. Current evidence and best-practice recommendations for the treatment of PB patients off-trial are summarized below.

## Pineoblastoma

PB was first introduced as a distinct WHO diagnosis in 2000,[41] however it has long remained an orphan cancer often lumped with other histologically similar entities, and without dedicated clinical trials (Table 1). Cumulative data from 89 individually small trials or series published up to 2018, encompassed >500 PB patients with PB,[38,42] and reported vastly discrepant outcomes ranging from 0% to 92.9% overall survival (OS).[43,44] Pooled clinical cohort studies, prior to molecular classification of PB, indicate age and radiotherapy as important prognosticators. The pooled European-Head Start ($n = 135$)[39] and Australian-North American ($n = 178$) studies[38] showed superior survival for patients >3–4 years, but markedly worse outcomes in younger patients treated with radiation-sparing approaches. Non-metastatic disease was identified as a favorable prognostic factor for older children in both studies.[38,39] Interestingly, these studies indicate possible sex-specific survival factors, perhaps reflecting gender predilection reported in later defined molecular PB subgroups.[38]

There is now consensus for 4 DNA-methylation-based subgroups of PB (PB-miRNA1, PB-miRNA2, PB-RB1, and PB-MYC/FOXR2), along with a separate subgroup for PPTID (Figure 4).[4,21,22,45] PB-RB1 and PB-MYC/FOXR2 tumors are found almost exclusively in infants/young children (median age 2.1 and 1.4 years, respectively) and have dismal outcomes (5-year PFS/OS for PB-MYC/FOXR2: 17%/24%; PB-RB1: 19%/30%).[4] In contrast, PB-miRNA1 and PB-miRNA2 subgroup tumors arise in older children and adolescents (median age 8.5 and 11.8 years, respectively) and have good to excellent outcomes (PFS/OS of PB-miRNA1: 57%/70%; PB-miRNA2: 86%/100%). Notably, consensus analyses of PB-miRNA1 and PB-miRNA2 patients treated as per SJMB03 with risk-adapted 23.4 or 36 Gy CSI and high-dose chemotherapy with autologous stem-cell rescue (HDC-ASCR), or with 36 Gy CSI and standard-dose chemotherapy (SDC) on the COG high-risk embryonal brain tumor ACNS0332 trial, show comparable favorable outcomes. Both PB-miRNA1/2 patients with good risk clinical features (GTR, M0), had 5-year event-free survival (EFS) and OS of 100%, indicating less intensive therapy may be sufficient for this group of patients with lower-risk biological and clinical features.[4]

### Outcomes of Children and Adolescents With PB on Specific Trials

PB patients ≥3 years of age have been treated with higher doses of 36 Gy CSI and 54–58 Gy pineal region boost regardless of clinical risk features across multiple historical and recent studies. The early CCG-921 trial reported respective 3-year PFS/OS of 61%/73% for children >18 months old treated with high-risk radiation dose and volume followed by "eight-in-one-day" multi-agent chemotherapy regimen.[46] Similarly, the successor trial CCG-99701, with children ≥3 years received 36 Gy CSI with concomitant vincristine and carboplatin followed by SDC,[47] reported respective 5-year PFS/OS of 62%/81%.[48] In the more recent COG ACNS0332 study, where children >3 years received vincristine and randomized carboplatin therapy concomitant with 36 Gy CSI and 6 cycles of cisplatin, cyclophosphamide, vincristine, and randomized isotretinoin treatment, molecularly confirmed PB patients had respective 5-year EFS/OS of 62.8%/78.5%.[49] The role of carboplatin or isotretinoin remains inconclusive as ACNS0332 was underpowered for these evaluations. Irrespective of high CSI dose, and chemotherapy regimens, metastatic disease is an independent adverse prognosticator for inferior survival (5-year OS 50%–55%) and a 2–3-fold higher relapse risk.[38,39]

In Europe, the multi-center SKK-HIT 91 and HIT 2000 trials respectively evaluated the impact of pre-RT chemotherapy (SDC with high-dose methotrexate, HDMTX), and intensification of induction chemotherapy with intraventricular MTX on survival of patients ≥4 years with metastatic PB. While the HIT-91 study suggested pre-chemotherapy radiation increases metastatic progression,[47] this was not observed in the pooled European-Head Start cohort study, thus the role of pre-RT chemotherapy and intraventricular MTX remains unclear.[38] Therefore, pre-irradiation chemotherapy akin to the SIOPE approach for high-risk medulloblastoma is a strategy that requires further evaluation. Similar to risk-adapted radiation used in medulloblastoma trials, earlier studies aimed to reduce CSI dose for PB patients with average risk (AR) clinical features (non-metastatic and ≤1.5 $cm^2$ post-resection residual).[21,50] The SJMB03 risk-adapted trial which combined 23.4 or 36 Gy CSI with standard dose or HDC-ACSR chemotherapy reported respective 5 years PFS/OS of 100/100% and 56.5%/60.3% for patients with AR and HR PB.[21] Notably, several studies have reported metastatic relapse

**Table 1.** Outcome of Pineoblastoma Patients Treated on Prospective Trials

| Non-infant protocols | | | | | | Infant protocols | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | CCG-921 (≥18 m) | CCG-99701 | ACNS0332 | SJMB03 | PNET HR + 5 | Baby POG (POG 8633) | CCG-921 (<18m) | HIT2000 | SJYC07 | HS-I/II/III |
| | Cohen BH et al., 1995 | Jakacki RI et al., 2015 | Hwang EI et al., 2018 | Liu APY et al., 2020 | Dufour C et al., 2021 | Duffner et al., 1995 | Jakacki RI et al., 1995 | Friedrich C et al., 2013 | Liu APY et al., 2020 | Abdelbaki MS et al., 2020 |
| Duration | 1986–1992 | 1998–2004 | 2017–2013 | 2003–2013 | 2009–2012 | 1986–1990 | 1986–1992 | 2001–2005 | 2007–2017 | 1991–2009 |
| *N* | 17 | 23 | 27 | 42 (12 treated per protocol) | 9 | 11 | 8 | 8 | 12 | 23 |
| Age median (range) | N/A | 10.7y (3.5–17.9) | 8.7y (3–18.1) | 8.4y (2.9–20.4) | 13y (6–19) | 0.7y (0.13–2.9) | N/A | 1.9y (0.01–3.6) | 1.2y (0.4–2.6) | 3.1y (0.4–5.7) |
| $M^+$ | N/A | 6 | 11 | 18 | 3 | 7 | N/A | 3 | 5 | 11 |
| Treatment approach after initial surgery | CSI Randomized maintenance SDC | CSI + Carbo + VCR Maintenance SDC × 6 | CSI + VCR +/– Carbo Maintenance SDC x 6 +/– isotretinoin | CSI with risk-stratified dosage (AR = 23.4Gy; HR = 36Gy) Maintenance HDC-ASCR x 4 | Pre-RT chemotherapy RT (CSI / focal RT) Maintenance SDC | SDC with CSI deferral to 3 years of age | SDC, RT sparing | M0: HIT-SKK × 5 + CSI<br>M+: ivc MTX; Carbo/VP16 + tandem HDC-ASCR; CSI for poor responders to induction/residual after HDC | Induction SDC × 4<br>Consolidation:<br>$M^0$ (IR): focal RT<br>$M^+$ (HR): CYM/Topo x 2<br>Maintenance metronomic therapy | Induction SDC × 5<br>HDC × 1<br>CSI for > 6y/residual after induction |
| CTX regimen | VCR, CCNU vs 8-in-1: MP, VCR; CCNU or carmustine; procarbazine, HU, CDDP, Ara-C, cyclophosphamide | VCR, CYM, (CDDP) | VCR, CYM, CDDP +/– isotretinoin | VCR, CYM, CDDP | Pre-RT:<br>• Carbo, VP16 × 2<br>• HDC (TT)-ASCR × 2<br>Maintenance:TMZ | CYM, VCR × 2 CDDP, VP16 × 1 | 8-in-1 regimen | HIT-SKK induction:<br>• Cy1: CYM, VCR<br>• Cy2–3: HDMTX, VCR<br>• Cy4: Carbo, VP16<br>HDC:<br>• Cy1: Carbo/VP16<br>• Cy2: CYM/TT | Induction regimen: HDMTX, CDDP, CYM, VCR; VBL for $M^+$ (HR) patients | Induction regimens:<br>• A: VCR, CDDP, CYM, VP16<br>• A2: A + HDMTX for $M^+$<br>• D: A2 for Cy 1,3,5; VCR, CYM, oral VP16, TMZ for Cy2,4<br>• D2: D with reduced CYM and HDMTX doses<br>HDC: Carbo/TT/VP16 |
| **RT given** | N/A | CSI in all | CSI in all | CSI (risk-stratified) in all | Focal RT for $M^0$<br>CSI for $M^+$ | CSI: 6 at progression | N/A | CSI: 4 (3 at progression) | Focal RT in 6<br>CSI at progression in 2 | CSI: 7 (4 at progression) |
| **PFS/EFS** | 3yPFS and OS of 61% ± 13% and | 5yPFS 62% | 5yEFS 65.7% | 5yPFS AR: 100%<br>5yPFS HR: 56.5% | 5yPFS 67% | All progressed<br>Median PFS=: 3m (2–11m) | All progressed within 4 months | 5yEFS 24% (sPNET + PB, no difference between the 2 groups) | 2yPFS $M^0$: 14%<br>2yPFS $M^+$: 0% | 5yPFS 9.7% |
| **OS** | 3yOS 73% ± 12% | 5yOS 81% | 5yOS 75.7% | 5yOS AR: 100%<br>5yOS HR: 60.3% | 5yOS 89% | All died of disease<br>Median OS: 11m (3–34m) | N/A | 5yOS 40% (sPNET + PB, no difference between the 2 groups) | 2yOS $M^0$: 14%<br>2yOS $M^+$: 0% | 5yOS 13% |

AR, average-risk; Ara-C, cytarabine; carbo, carboplatin; CCNU, lomustine; CDDP, cisplatin; CPM, cyclophosphamide; CSI, craniospinal irradiation; CTX, chemotherapy; Cy, cycle; EFS, event-free survival; HDC-ASCR, high-dose chemotherapy with autologous stem-cell rescue; HDMTX, high-dose methotrexate; HS-I/II/III, Head Start I/II/III; HR, high-risk; HU, hydroxyurea; ivc, intraventricular; IR, intermediate-risk; m, month(s); $M^+$, metastatic disease; $M^0$, localized disease; MP, methylprednisolone; *N*, number; N/A, not available; OS, overall survival; PB, pineoblastoma; PFS, progression-free survival; POG, Pediatric Oncology Group; RT, radiotherapy; SDC, standard-dose chemotherapy; sPNET, supratentorial primitive neuroectodermal tumor; TT, thiotepa; TMZ, temozolomide; topo, topotecan; VBL, vinblastine; VCR, vincristine; VP16, etoposide; y, year(s).

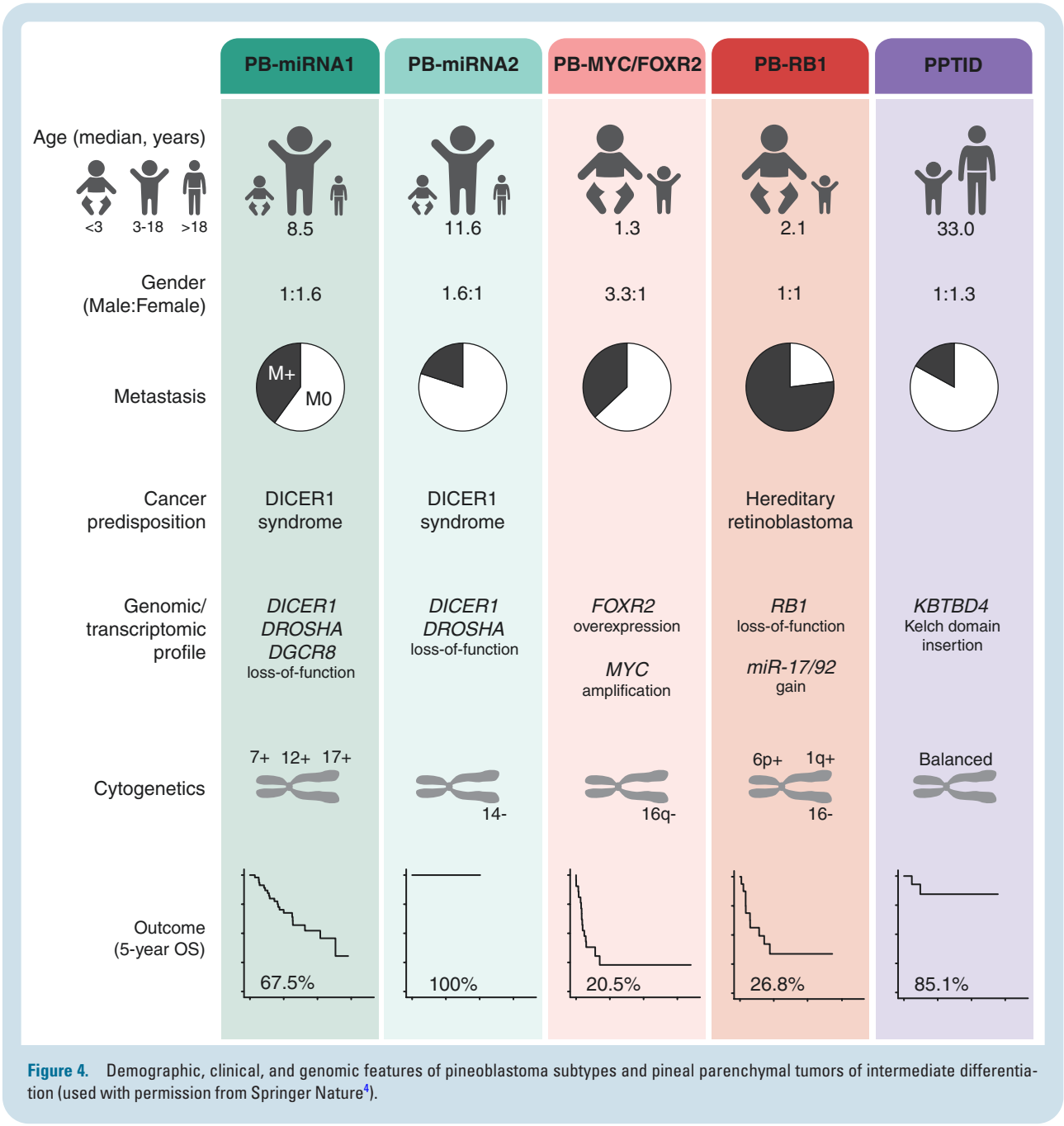


**Figure 4.** Demographic, clinical, and genomic features of pineoblastoma subtypes and pineal parenchymal tumors of intermediate differentiation (used with permission from Springer Nature[4]).

in patients with localized PB treated with reduced dose CSI or focal RT. The SJMB96 trial reported metastatic relapse in 2 patients with partially resected, localized PB treated with risk-adapted CSI.[51] Similarly, in the PNET HR + 5 trial, which reported respective 5-year EFS/OS of 67%/89% for 9 PB patients, 3/6 patients with localized, histologically diagnosed PB treated with HDC-ASCR and focal RT had metastatic relapse 1.4, 2.7, and 4.6 years after diagnosis (all with residual disease), while 3 others were in long-term remission (1 had GTR, 2 with residual disease).[50] These findings suggest treatment outcomes of PB patients may be determined by clinical risk features as well as tumor-specific biology (Table 1).

## Infants/Young Children

In contrast to older children, survival of infants and young children with PB treated with SDC and radiation-sparing HDC chemotherapy-based trials have been disappointing.[21,39,52,53] The historic SDC-only Baby POG trial reported 11 enrolled patients <3 years old, who uniformly progressed and ultimately succumbed within 13 months, despite salvage RT.[27,44,54] Similarly, PB patients <18 months treated with only SDC on CCG-921, progressed at a median of 4 months with a 100% death rate by 15 months.[42] The recent SDC-based SJYC07 trial with risk-adapted SDC and RT for children <3 years old also reported only a 14% 2-year

**Table 2.** Recommendations for Therapeutic Approach to Patients With Pineal Parenchymal Tumors

| Diagnosis | Patient/disease characteristics | Recommendations for therapy |
|---|---|---|
| PB | ≥3 years, localized | • PB-miRNA1/2 patients, GTR/NTR: Standard dose embryonal type chemotherapy combined with CSI 23.4Gy + tumor bed boost (up to 54Gy)<br>• Other molecular subtypes/non-classifiable PB, non-resectable (STR or less): Standard or high-dose embryonal type chemotherapy combined with tumor bed boost (up to 54Gy) with consideration of 36 or 23.4 Gy CSI depending on patient age and clinical status. |
| | ≥3 years, metastatic | • CSI 36 Gy + tumor bed boost (up to 54Gy) → embryonal type maintenance chemotherapy (high-risk protocols), OR<br>• Pre-RT chemotherapy → CSI 36 Gy + tumor bed boost (up to 54Gy) → embryonal type maintenance chemotherapy |
| | <3 years | • No standard regimen—High-dose chemotherapy-containing regimens → Consider focal RT in localized disease, although evidence is very limited |
| PPTID | Localized, GTR | Consider observing grade 2 tumors; and upfront focal RT (54–59.4Gy) in grade 3 tumors, recognizing that controversy in RT field (focal vs. CSI) remains. |
| | Localized, STR | Upfront focal RT (54-59.4 Gy), recognizing that controversy in RT field (focal vs. CSI) remains. |
| | Metastatic | Surgery + up to 36 Gy CSI and focal tumor boost +/- adjuvant chemotherapy (consider embryonal type regimen, limited evidence) |
| Pineocytoma | | Surgery, focal RT or SRS is to be considered if total removal is not possible |
| PTPR | | Surgery<br>Consider focal RT in cases of STR, high proliferative index, or relapse |
| Pineal cyst | | Observation, surgical intervention if symptomatic |

CSI, craniospinal irradiation; GTR, gross-total resection; PB, pineoblastoma; PPTID, pineal parenchymal tumor of intermediate differentiation; PTPR, papillary tumor of pineal region; RT, radiotherapy; SRS, stereotactic radiosurgery; STR, subtotal resection.

PFS/OS for intermediate-risk patients >12 months of age with completely resected, localized disease treated with delayed focal RT, while high-risk patients had dismal 0% PFS and OS.[21]

CCG-99703, which evaluated 3 rounds of tandem HDC-ASCR for young children with malignant brain tumors, reported 5-year PFS of 29% for 8 patients with histologically diagnosed PB.[55] Similarly the Head Start I-III trials which used a single cycle of HDC-ASCR consolidation post-SDC induction, with risk-stratified CSI, also reported poor 5-year PFS/OS of 9.7%/13% for 23 patients ≤6 years at diagnosis.[56,57] Although the use of HDC-ASCR correlated with improved PFS and OS, 35% (8/23) of patients did not receive full consolidation therapy due to early progression during and after induction therapy, indicating possible roles for a shorter induction phase, increased HDC-ASCR cycles and maintenance therapy in future trials. Of note, in HIT 2000, among 3 metastatic cases in young (<4 years old) patients, who received CSI for incomplete response to an extended intensified induction regimen with HDC-ASCR consolidation, 2/3 survived suggesting CSI may benefit a proportion of very high-risk PB patients.[58]

## Adults

Data on adults with PB are sparse hence treatment approaches have largely been extrapolated from the management of PB in children and adolescents.[59]

## Recommendation for Therapeutic Approach in the Context of PB Molecular Subgroups

Current evidence suggests a combination of surgery, multi-agent chemotherapy, and radiation represent important treatment modalities, and may be tailored to molecular features of PB arising in children and adults.

Given the excellent outcomes of PB-miRNA1/2 patients with AR clinical features (near-total or complete resection, non-metastatic) regardless of SDC or HDC and risk-adapted 23.4 or 36 Gy CSI treatment, de-escalation with abbreviated SDC and/or reduced dose 23.4 Gy CSI can be undertaken for these lower-risk patients. Of note, only local failures were reported in a pooled cohort of PB-miRNA2 patients, strengthening the proposition for reduction in adjuvant intensity for AR PB-miRNA2 patients. For miRNA1 patients with partial resection and/or metastatic disease, outcomes were comparable regardless of intensified HDC or a higher dose of 36 Gy CSI. Thus, currently, maximum safe surgery followed by (1) high-dose CSI and embryonal tumor-type chemotherapy (CCNU/cyclophosphamide, cisplatin, and vincristine), or (2) pre-irradiation chemotherapy followed by high-dose CSI and abbreviated chemotherapy courses (Table 2), remains the best available therapeutic option for these high-risk patients, inclusive of the rare patients with high-risk PB-miRNA2 tumors.[6] Notably, nearly 70% of failures in PB- miRNA1 patients were distant and often late, suggesting a need for therapy extension with or without novel agents, and improved targeting of microscopic or overt metastatic disease.

There is currently no treatment regimen that offers significant survival benefits for infants and young children with PB, a majority of which have highly metastatic *FOXR2/MYC* and *RB1*-altered subgroups. The benefit of SDC regimens with intraventricular MTX or early focal radiation has not been consistently shown to significantly improve PB outcomes. Currently, used treatment options include intensive chemotherapy regimens incorporating HDC-ASCR, which has been employed to postpone radiation in these young children, but the actual benefit to long-term survival remains unproven.[4] Importantly, early, upfront enrollment in novel clinical trials should be offered, when available, to these very high-risk patients.

## Pineal Parenchymal Tumor of Intermediate Differentiation

PPTIDs are rare and heterogeneous lesions, which can be difficult to distinguish histologically from PB. Histology-based studies report 5-year PFS and OS of 42%–82% and 39%–84%, respectively,[60–65] with conflicting observations regarding PFS/OS of WHO Grade 2 vs 3 PPTID.[61,63,66] Patients with molecularly classified PPTID in the PPT consensus had a fair prognosis with 5-year PFS/OS of 81%/86%,[4] with further epigenomic heterogeneity aligning with *KBTBD4* status being suggested.[67] There is a paucity of data on clinical and treatment-related prognostic factors for PPTID and existing histology-based data is often contradictory, potentially confounded by the inclusion of PB.[60,62–64,66] Surgery is often performed with complete resection achieved in a substantial proportion of patients[60–66,68–70] and GTR is recommended in most studies,[71] however the impact of surgical resection has been variably reported.[60–63,66,72] Similarly, the role of adjuvant RT and chemotherapy has also been variably linked to PPTID patient survival.[61,62,73] Varying modality, dose, and field of RT including focal to whole brain or CSI ± local boost and gamma knife have also been frequently used to treat PPTID[60–62,64–66,68–70,73–76]; however, whether adjuvant RT benefits patients with Grade 3, metastatic or sub-totally resected tumors.[60,62,63,66,76] or all PPTID, remains unclear.[65] There are no standardized chemotherapy regimens,[60,61,64–66,73–75] platinum-based antineoplastic agents frequently combined with alkylating agents, vinca alkaloids, and topoisomerase inhibitors have been used for PPTID patients.[62]

### Recommendation for Therapy

Robust prospective studies/data are lacking and much needed to inform best practices for PPTID patients. Based on current existing data, a 3-step treatment algorithm for PPTID is proposed (Table 2).[60]

## PC, PTPR, and Pineal Cyst

### Pineocytoma

PCs are low-grade pineal parenchyma tumors with infrequent metastasis for which surgical resection is the primary treatment modality. There is no prospective randomized data on PC. A systematic review of 166 patients treated with surgery with/without focal RT reported 5-year PFS of 90% versus 75% in patients with resected versus biopsy-only tumors respectively.[77] Patients with tumor GTR had 5-year PFS of 100%, while RT did not correlate with improved survival for patients with tumor residual. Surgical resection alone is recommended as the first-line standard of care in patients with histologically confirmed PCs (Table 2). In the setting where total tumor removal is not possible, and for patients with recurrent tumors, focal RT or stereotactic radiosurgery may be considered as an alternative treatment.

### Papillary Tumors of Pineal Region

PTPR recurs locally in up to 3-quarter of cases and rarely with leptomeningeal dissemination.[78,79] The role of adjuvant therapy including focal RT with/without chemotherapy for PTPR remains unclear. Complete tumor resection and younger patient age have been linked to better OS,[78,80,81] while higher tumor mitotic activity and proliferative index (≥10%) have been correlated with inferior patient PFS.[23]

Maximal safe resection remains the mainstay for the management of PTPR patients; however, focal RT should be considered for non-resectable, highly proliferative, or recurrent tumors (Table 2). Case reports also suggest a potential role for bevacizumab, or mTOR inhibition for *PTEN*-altered PTPR.[82–84]

### Pineal cyst

Most pineal cysts are asymptomatic and discovered incidentally. Simple pineal cysts not causing CSF obstruction or visual problems should be managed conservatively.[85] Most pineal cysts (> 80%) do not change in size over time, while a minority decreases in size, and an even smaller proportion grows modestly.[85] Even the value of serial imaging is uncertain, as most have stable size or imaging characteristics.[3] Patients with nonspecific symptoms such as headache or fatigue, 2 sequential scans separated in time (eg 1 year apart) to demonstrate stability is reasonable[86]; unless there are concerning imaging, symptoms, or elevation in GCT tumor markers, long-term imaging follow-up is not necessary.[87,88]

Pineal cysts should be managed conservatively with patient counseling and reassurance (Table 2). Rarely, larger pineal cysts causing compression of the tectum and cerebral aqueduct and resulting in visual disturbance or hydrocephalus warrant surgical treatment via open or endoscopic cyst fenestration and/or cyst wall resection. Similar surgical considerations discussed above for PPT apply to pineal cysts. Though there remains some management controversy for larger cysts, nonspecific symptoms and headaches unrelated to hydrocephalus in patients with simple cysts are not well-accepted indications for surgical intervention.[87,89]

## Future Directions

Future efforts to refine the management of patients with PPTs require harmonized molecular-based diagnostic

practices and treatment strategies to produce high-quality clinical evidence across different jurisdictions, ideally in the context of prospective trials. With the rarity of individual diagnoses, including new entities such as *SMARCB1*-mutant desmoplastic myxoid tumor,[90] international collaboration is critical to power analyses for meaningful clinical impact.

The discovery of molecular PPT subgroups represents a critical step towards biology-informed risk stratification to guide the optimal use of conventional modalities, as well as to develop and test new therapeutic approaches and agents. For the lower-risk PB-miRNA1 and PB-miRNA2 patients (ie, localized resectable disease), strategies to safely reduce intensity or eliminate CSI and/or chemotherapy will be a critical next step, and may be expedited by the development and adoption of novel biomarkers for minimal residual disease. For the higher-risk PB-miRNA1 patients, innovative strategies to treat or mitigate metastatic disease are needed. Studies of predictive markers, including germline genetic alterations, as well in-depth studies of targetable biological mechanisms to overcome radiation- and chemoresistance and novel drug delivery methods will be important.

For infants and young children with PBs (PB-MYC/FOXR2 and PB-RB1) which have the highest incidence of metastases, control of disease remains very challenging as the benefit of limited field or CSI remains unclear. Nonetheless, CSI should be avoided for these very young, particularly neuro-cognitively vulnerable patients. Greater efforts to incorporate IT therapy for the treatment or prophylaxis of metastatic disease, as well as upfront experimental therapeutic trials are urgently needed. Development of high-fidelity models and studies of targetable mechanisms and novel agents for these ultra-high-risk patients should be a priority. Recently studies of a *Rb1* deficient murine PB model have identified clinically validated drugs targeting lysosomal biogenesis as potential new therapies.[91] Although a MYC/FOXR2 PB model remains to be established, such models will be very valuable to test agents targeting MYC and/or FOXR2 signaling in PB.[92–94] Emerging novel strategies which leverage cellular or immune-based therapies also represent important novel therapeutics for embryonal brain tumors including PB. Notably, checkpoint protein B7H3, which is frequently upregulated in embryonal tumors, may be targeted using radiolabeled monoclonal antibody (Omburtamab) or CAR-T cells (NCT04185038).[95–99] In the case of PPTID, adapting the proposed 3-step algorithm will allow patient outcomes to be interrogated in conjunction with biomarkers such as histologic variants and methylation subtypes. For patients with *PTEN*-altered PTPRs, the use of mTOR inhibitors or PI3K inhibitors as salvage would facilitate the evaluation of their efficacy in this relapse-prone entity.

Given the central location of pineal masses, ideally proton beam treatment where available should be considered, and an equity-driven practice be followed to build and share such resources.[100,101] In addition, the use of liquid biopsy techniques such as circulating-tumor DNA analysis from CSF samples should be integrated into upcoming prospective trials as a molecular marker of residual disease to establish personalized care.[102,103]

## Summary

The recent progress made in our biological and clinical understanding of PPTs is an illustration of the importance of international collaboration and the support of high-quality tumor banking and patient registries for uncommon CNS tumors. The definition of entities through integrated histopathologic and molecular approaches helped to advance risk prognostication and will inform the next generation of prospective clinical trials. For high-risk PB, there is an urgent need for robust translational research and subsequent evaluation of rational novel therapeutics. Due to its rarity, these will have to be conducted in large international trial consortiums. Similarly, for favorable-risk disease, de-escalation of therapy needs to be evaluated. Likewise, a unified treatment strategy for patients with PPTIDs and PTPRs will provide further evidence of the optimal approach for their management as significant ambiguities remain.

## Supplementary material

Supplementary material is available online at *Neuro-Oncology* (https://academic.oup.com/neuro-oncology).

## Keywords

clinical treatment guidelines | pineal parenchymal tumors | papillary tumor of pineal region | pineal cyst | risk-stratification

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## Authorship statement

Study conception and design: A.P.Y.L., P.Y.W., M.J.vdB., and A.H.; literature review: all authors; draft manuscript preparation: A.P.Y.L., B.K.L., A.V., M.C.D., B.T., B.E.-W., J.R.H., E.P., M.M., H.-K.N., D.S.T., N.G.G., D.S., and M.D.J.; revised the manuscript critically and approved the final version of the manuscript: all authors.

## Data availability

No new data were generated or analyzed in support of this research.

## Affiliations

Division of Haematology/Oncology, The Hospital for Sick Children, Toronto, Ontario, Canada (A.P.Y.L., E.B., A.H.); Department of Paediatrics and Adolescent Medicine, School of Clinical Medicine, The University of Hong Kong, Hong Kong, China (A.P.Y.L.); Department of Pediatrics, Icahn School of Medicine at Mount Sinai, New York, New York, USA (B.K.L.); Laboratory Medicine and Pathobiology, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada (B.K.L., A.H.); Faculté de Médecine Lyon Est, Université Claude Bernard, Lyon, France (A.V.); Service D'Anatomie Et Cytologie Pathologiques, CHU de Lyon, Lyon, France (A.V.); Division of Pediatric Neurological Surgery, Vanderbilt University Medical Center, Tennessee, USA (M.C.D.); Department of Radiology, Children's Hospital Los Angeles, Los Angeles, California, USA (B.T.); Division of Neuroradiology, Department of Diagnostic & Interventional Neuroradiology, The Hospital for Sick Children, Toronto, Ontario, Canada (B.E.-W.); Neurosciences and Mental Health Program, Research Institute, The Hospital for Sick Children, Toronto, Ontario, Canada (B.E.-W.); Department of Medical Imaging, University of Toronto, Toronto, Ontario, Canada (B.E.-W.); Michael Rice Centre for Hematology and Oncology, Women's and Children's Hospital; South Australia Health and Medical Research Institute; South Australia Immunogenomics Cancer Institute, University of Adelaide, Adelaide, South Australia, Australia (J.R.H.); Division of Pediatric Glioma Research, Hopp Children's Cancer Center Heidelberg (KiTZ), Heidelberg, Germany (E.P.); Pediatric Glioma Research Group (B360), German Cancer Research Center (DKFZ), Heidelberg, Germany (E.P.); Department of Pediatric Oncology, Hematology and Immunology, Heidelberg University Hospital, Heidelberg, Germany (E.P.); Department for Pediatric Hematology and Oncology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany (M.M.); Mildred Scheel Cancer Career Center HaTriCS4, University Medical Center Hamburg-Eppendorf, Hamburg, Germany (M.M.); Department of Anatomical and Cellular Pathology, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong, China (H.-K.N.); Radiation Medicine Program, Princess Margaret Cancer Centre, Toronto, Ontario, Canada (D.S.T.); Department of Pediatric & Adolescent Oncology and Haematology, Perth Children's Hospital and Brain Tumor Research Program, Telethon Kids Cancer Centre, Telethon Kids Institute, University of Western Australia, Perth, Western Australia, Australia (N.G.G.); Department of Oncology, St. Jude Children's Research Hospital, Memphis, Tennessee, USA (A.G.); Department of Pediatric and Adolescent Oncology, Gustave Roussy, France (C.D.); INSERM, Molecular Predictors and New Targets in Oncology, Paris-Saclay University, Villejuif, France (C.D.); School of Life Sciences, University of Liverpool, Liverpool, UK (B.P.); Division of Neuro-Oncology, Department of Neurology, University of Virginia, University of Virginia School of Medicine, Charlottesville, Virginia, USA (D.S.); Department of Neurosurgery, The Walton Centre NHS Foundation Trust, Liverpool, UK (M.D.J.); Institute of Systems, Molecular and Integrative Biology, University of Liverpool, Liverpool, UK (M.D.J.); Department of Medical Oncology, Oncology 1, Veneto Institute of Oncology IOV-IRCCS, Padova, Italy (G.L.); Center for Neuro-Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts, USA (P.Y.W.); The Brain Tumor Center at Erasmus MC Cancer Institute, University Medical Center Rotterdam, Dr molewaterplein 40, Rotterdam, The Netherlands (M.J.v.d.B.); Arthur and Sonia Labatt Brain Tumour Research Centre, Hospital for Sick Children, Toronto, Ontario, Canada (A.H.); Department of Medical Biophysics, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada (A.H.)

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