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REVIEW

# Pineal parenchymal tumor of intermediate differentiation: a systematic review and contemporary management of 389 cases reported during the last two decades

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## Abstract

Pineal parenchymal tumor of intermediate differentiation (PPTID) is a WHO grade II and III tumor arising from pineal parenchymal cells. PPTID is a rare tumor accounting for less than 1% of all primary central nervous system neoplasms. Therefore, reports describing the clinical characteristics and biological features of PPTID are lacking. Moreover, the therapeutic strategy remains controversial. The current study aimed to evaluate treatment results and problems of contemporary therapeutic modalities of PPTID based on its features compared with other pineal parenchymal tumors. A comprehensive systematic literature review of 69 articles was performed, including articles on PPTID (389 patients) and similar tumors. Patient demographics, disease presentation, imaging characteristics, biological features, and current therapeutic options and their results were reviewed. We found that histopathological findings based on current WHO classification are well associated with survival; however, identifying and treating aggressive PPTID cases with uncommon features could be problematic. A molecular and genetic approach may help improve diagnostic accuracy. Therapeutic strategy, especially for grade III and aforementioned uncommon and aggressive tumors, remains controversial. A combination therapy involving maximum tumor resection, chemotherapy, and radiotherapy could be the first line of treatment. However, although challenging, a large prospective study would be required to identify ways to improve the clinical results of PPTID treatment.

**Keywords** Pineal parenchymal tumor of intermediate differentiation · Pineal parenchymal tumor · Pineal gland · Pathology · Radiotherapy · Chemotherapy

## Introduction

The pineal body, a small endocrine gland that modulates circadian and seasonal rhythms by melatonin secretion, is located in the epithalamus, ventral to the cerebral aqueduct. Pineal gland tumors are rare and account for less than 4% of all primary tumors in the central nervous system (CNS) [1, 24, 66]. Pineal parenchymal tumors (PPTs), including pineocytoma (PC), the pineal parenchymal tumor of intermediate differentiation (PPTID), and pineoblastoma (PB), are the second most common tumors of the pineal gland after germ cell tumors, comprising approximately 11–28% of all pineal region tumors [1, 5, 37, 88].

PC is a low-grade (WHO grade I) tumor, and total resection is an important prognostic factor. In contrast, PB is a high-grade (WHO grade IV) tumor, and due to a high risk of recurrence and cerebrospinal dissemination, a combination therapy involving direct surgery, radiotherapy, and chemotherapy is often recommended [50]. PPTID was

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first described by Schild et al. in 1993 and subsequently included in WHO classification 2000. It is now defined as a PPT with an intermediate malignancy between PC and PB and includes intermediate-grade (WHO grade II and III) tumors [61, 86]. Although some reports have recommended complete removal for low-grade (WHO grade II) and combination therapy for high-grade (WHO grade III) PPTID, in practice, it is not that straightforward [21, 79, 112]. Because of their rarity and heterogeneous biological aspects, there is no standard protocol for treating PPTID.

As large prospective PPTID case studies might not be feasible, personalized management of PPTID is needed for successful treatment. A better understanding of the tumor's pathological and clinical characteristics and the available therapeutic options may help accomplish this goal. Therefore, a systematic review was performed to characterize the clinical features of PPTID compared with from those of other PPTs. In addition, we evaluated the treatment outcomes and challenges associated with contemporary therapeutic modalities. Furthermore, a perspective is provided based on recent biological and technological advances to improve the clinical outcome of PPTID. Lastly, recommendations regarding future studies have been discussed.

## Methods

### Search strategy

The first study objective was to categorize the literature for data associated with clinical characteristics, biological features, and current therapeutic options of PPTID. Therefore, relevant literature describing the cases of PPTID with or without PC or PB cases was identified through a systematic search. A comprehensive review following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines of the bibliographic database PubMed, Embase, Web of Science, and Cochrane Library databases to December 2020 was performed [69]. The study protocol is available in PROSPERO (CRD42021259239). We also reviewed the related citation links suggested by the PubMed websites and reference lists of retrieved articles. The keywords used for the search were "pineal parenchymal tumor," "PPTID," and "intermediate differentiation," along with appropriate Boolean connectors.

### Selection criteria

Through careful review of the abstract, we included prospective or retrospective studies, case reports, and case series related to PPTID, published until December 2020. The literature search was restricted to articles written in English or Japanese. We excluded review or video articles, conference abstracts, book chapters, technical notes, or articles without clinically relevant PPTID data. When a patient's information overlapped in two different studies, information from only the primary study was included in our analysis.

### Search results

The initial search identified 327 records from the PubMed, Embase, Web of Science, and Cochrane Library databases. After removing 178 duplicate records, 82 of the remaining 149 articles were excluded as they were unrelated to the present analysis, and one article was excluded based on further eligibility assessment of the full text. A further three articles were included after reference crosscheck. As a result, 1039 cases of PPTs were reported (Table S1). Among them, 389 cases of PPTID from a total of 69 articles, including 24 case reports, 22 case series, or 23 cohort studies [2, 4, 7–13, 16, 18–21, 25–31, 35, 39, 40, 42–53, 55, 58, 59, 62, 63, 65, 67, 68, 73–76, 78–80, 83, 85, 87, 89, 90, 94, 99–102, 105–108, 110–112, 114], were identified and summarized for systematic review (Fig. 1, Table 1, Table S2, S3).

### Data extraction

The following information was extracted: age, sex, histopathological diagnosis of PPTs (PC, PPTID, PB, or mixed PC-PB), WHO grades of PPTID, reported number of each PPT subtype, treatments, clinical outcomes, and complications. Recent updates on the PPTID study were also extracted.

### Quality assessment criteria

The methodological quality of these studies was evaluated on four different domains, as previously described [41, 70], with slight modifications (Table 2). The domains were as follows: *patient selection* (Is the patient's case representative of the study, or is there some ambiguity in the selection criteria/methods which may result in patients with similar presentation not being reported?), *ascertainment* (Did the diagnosis of PPTID [and similar tumors] adequately meet WHO classification?), *causality* (Was a certain volume of the tumor resected (not including biopsy)? Was the follow-up long enough (a year or more) for outcomes to occur? Are any adverse events or complications reported?), and *reporting* (Is the case(s) described with sufficient detail to allow other researchers to replicate the study or to allow practitioners to make inferences related to their practice?). For each domain, the information quality of an article was rated as good, moderate, or insufficient (Table 3). Detailed information about the articles included in this review is provided as supplementary information (Table S2).

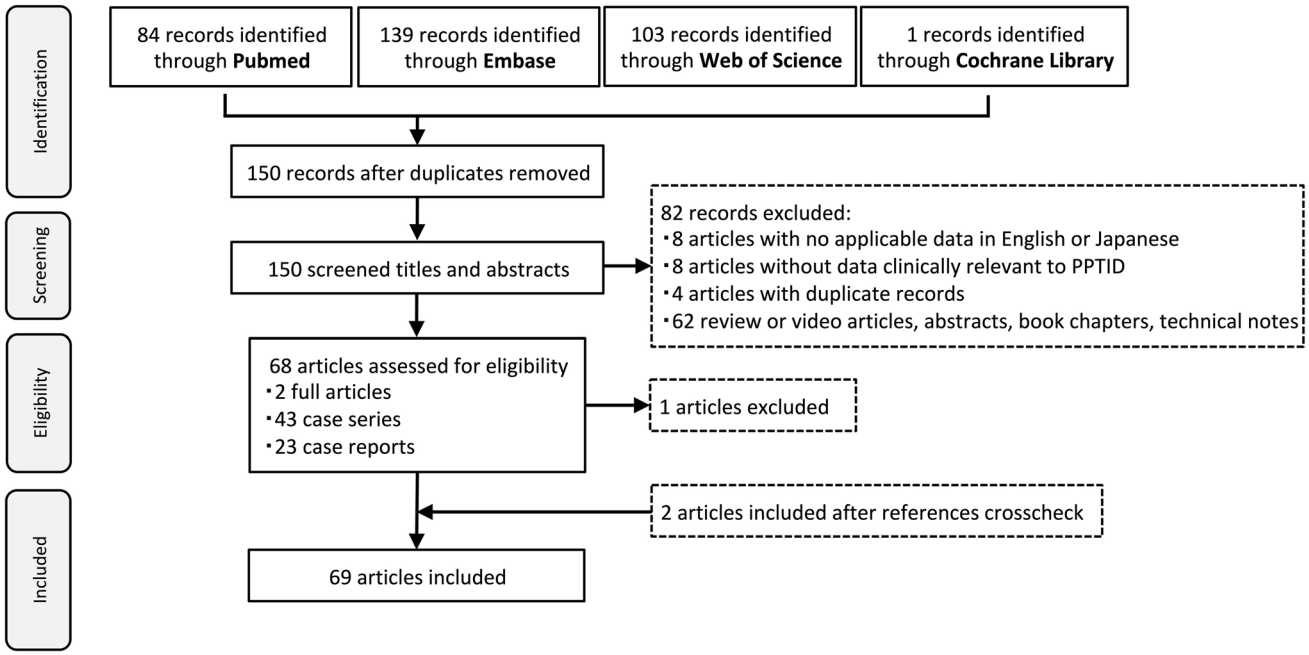



**Fig. 1** Study selection diagram and study design

## Statistical analysis

All statistical analyses were carried out using GraphPad Prism (Version 8.4.3, GraphPad Software LLC). In summary, chi-square tests were performed to compare two or more different groups of patients. Two-way ANOVA with Tukey post hoc test was performed to analyze age in the current WHO subtypes, such as PC, PPTID, and PB, and between sexes. Unpaired *t*-tests with Welch's correction were performed to compare ages between the male and female patients in cases of total reported PPTs, mixed PC-PB and PC with anaplasia, or mixed PC-PB/PPTID. Variables were described using means and standard deviations. Detailed information regarding the analysis is provided as supplementary information.

# Results

## Clinical characteristics

### Demographics

PPTID occurs across all age groups (mean age, $37.9 \pm 17.3$ years; Table 4, S2) with two peaks, one in young adults and the other in aged individuals (Fig. 2A). As Fauchon et al. previously reported, higher grade tumors (according to WHO classification) occurred at a significantly younger age ($p < 0.001$, Table 4, Fig. 2A) [25]. Furthermore, grade II PPTID cases were significantly older than grade III cases ($p = 0.022$, Table 4, Fig. 2B) (demographics of the total PPT cohort is also shown in Supplemental Materials).

In presenting symptoms of PPTID, symptoms pertaining to increased intracranial pressure (ICP) mostly due to hydrocephalus (such as headaches, nausea, vomiting, or papilledema) were the most common, and similar to those observed with other pineal region tumors or PPTs (Table 5). Midbrain compression resulted in the second most common symptom: visual impairment, including Parinaud syndrome or other unspecified visual symptoms. Lower limb symptoms, such as gait disturbance (ataxia or spasticity), were also reported. Cognitive or memory disturbances and confusion were seen in six out of 85 patients.

### Imaging characteristics

On computed tomography, PPTID demonstrated vascular lobulated pineal masses, extending into adjacent structures such as ventricles or thalami, that are usually hyperdense due to high cellularity, with peripheral exploded calcifications [111]. Magnetic resonance imaging (MRI) showed several patterns, usually a heterogeneous hypointensity on T1-weighted images, heterogeneous hyperintensity on T2-weighted images, and heterogeneous cystic enhancement with less progressive local invasion, and a lower possibility of intracranial dissemination and CSF-spread to the spine than PB [40, 49, 100, 111]. Komakula et al. showed the results of contrast scans demonstrating marked heterogeneous (10/11) and uniform (1/11) enhancement in PPTID [49].

**Table.1** Characteristics of included studies

| Author (year) | Study design | Main data | Years of enrollment | Number of PPT cases | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Total | PC | Mixed PC-PB, PC with anaplasia | PPTID | | PB | (% of PPTID) |
| | | | | | | | WHO grade 2 | WHO grade 3 | | |
| Jouvet et al. (1994) [X] | Case series | HP | 1975–1992 | 20 | 5 | 1 | 8 | | 6 | 40 |
| Min et al. (1994) [X] | Case series | HP | N/A | 17 | 7 | | 7 | | 3 | 41 |
| Numoto (1994) [X] | Case series | SS, HP | N/A | 11 | 5 | 2 | | | 4 | 0 |
| Mena et al. (1995) [X] | Cohort study | Im, HP, OS | 1970–1990 | 35 | 21 | 3 | | | 11 | 0 |
| Schild et al. (1996) [X] | Cohort study | RT, CT, OS | 1935–1995 | 30 | 9 | 2 | 4 | | 15 | 13 |
| Jouvet et al. (2000) [X]* | Cohort study | HP, EFS, OS | 1972–1995 | 66 | 11 | 39 | | | 16 | N/A |
| *Cases not duplicate of Jouvet et al. (1994) | | | | 54 | 9 | 33 | | | 12 | N/A |
| Kurisaka et al. (1998) [X] | Case series | PS, RT, CT, OS | 1984–1990 | 67 | 47 | | | | 20 | 0 |
| | | | | 4 | 1 | 2 | | | 1 | 0 |
| Tsumanuma et al. (1999) [X] | Cohort study | SS, HP (MIB-1 LI), RT, CT | 1958–1998 | 13 | 4 | 4 | | | 5 | 0 |
| Fauchon et al. (2000) [X]** | Cohort study | Im, SS, HP, RT, CT, DFS, OS | 1972–1997 | 76 | 19 | 28 | | | 29 | N/A |
| **Data extracted from Lutterbach et al. (2002) | | | | 28 | | | 12 | 11 | 5 | 82 |
| Rickert et al. (2001) [X] | Case series | HP (MIB-1 LI), GA | 1982–1999 | 9 | 3 | | 3 | | 3 | 33 |
| Lutterbach et al. (2002) [X]*** | Cohort study | SS, RT, CT, PFS, OS | N/A | 64 (101)# | | | | | | 41 (37)# |
| ***Cases not duplicate of Fauchon et al. (2000) | | | | 11 | | | N/A | | N/A | N/A |
| Yamane et al. (2002) [X] | Cohort study | HP | N/A | 23 | 4 | | 5 | | 14 | 22 |
| Anan et al. (2006) [X] | Case report | PS, Im, SS, RT, CT | N/A | 1 | | | | 1 | | 100 |
| Fevre-Montange et al. (2006) [X] | Case series | GA | N/A | 13 | 3 | | 6 | | 4 | 46 |
| Kumar et al. (2006) [X] | Case series | HP | 1991–2003 | 21 | 4 | | 7 | | 10 | 33 |
| Pusztaszeri et al. (2006) [X] | Case report | PS, HP | N/A | 1 | | | | 1 | | 100 |
| Sasaki et al. (2006) [X] | Case report | PS, HP | N/A | 1 | | | 1 | | | 100 |
| Arivazhagan et al. (2008) [X] | Cohort study | HP | 1990–2004 | 33 | 6 | 3 | 7 | | 17 | 21 |
| Fevre-Montange et al. (2008) [X]**** | Case series | HP, GA | 1979–2006 | 14 | 7 | | 7 | | | 50 |
| ****Cases not duplicate of Fevre-Montange et al. (2006) | | | | 9 | 2 | | 7 | | | 78 |
| Senft et al. (2008) [X] | Case report | PS, Im, HP, RT | N/A | 1 | | | | 1 | | 100 |
| Shimada et al. (2008) [X] | Case report | PS, Im, HP (MIB-1 LI) | N/A | 1 | | | 1 | | | 100 |
| Kim et al. (2009) [X] | Case report | PS, Im, HP | 2004 | 1 | | | | 1 | | 100 |
| Maeng (2009) [X] | Case report | PS, Im, HP | N/A | 1 | | | 1 | | | 100 |
| Yalcin et al. (2009) [X] | Case series | HP (MIB-1 LI) | 1990–2001 | 10 | 2 | | 5 | | 3 | 50 |

**Table.1** (continued)

| Author (year) | Study design | Main data | Years of enrollment | Number of PPT cases | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Total | PC | Mixed PC-PB, PC with anaplasia | PPTID | | PB | (% of PPTID) |
| | | | | | | | WHO grade 2 | WHO grade 3 | | |
| Fukuda et al. (2010) [X] | Cohort study | HP (MIB-1 LI) | N/A | 46 | 8 | | 9 | 16 | 13 | 54 |
| Li et al. (2010) [X] | Case report | PS, Im, HP (MIB1-LI), WB/FC | N/A | 1 | | | 1 | | | 100 |
| Stoiber et al. (2010) [X] | Case series | PS, DS, RT, CT | 1982–2003 | 14 | 4 | | 1 | | 9 | 7 |
| Cohan et al. (2011) [X] | Case report | PS, Im, HP, DS | N/A | 1 | | | 1 | | | 100 |
| Harris et al. (2011) [X] | Cohort study | Im (MRS) | 2003–2007 | 7 | 1 | | 1 | | 5 | 14 |
| Komakula et al. (2011) [X] | Case series | PS, Im, SS, RT, CT | 1985–1995 | 11 | | | 11 | | | 100 |
| Zhu et al. (2011) [X] | Cohort study | Im (ADC), HP (MIB-1 LI) | 2005–2010 | 26 | 10 | | 7 | | 9 | 27 |
| Ohtake et al. (2011) [X] | Case report | PS, CC | 2009 | 2 | | | | 2 | | 100 |
| Fevre-Montange et al. (2012) [X] | Cohort study | HP (MIB-1 LI), DS, RT, CT, DFS | N/A | 33 | 2 | | 19 | 8 | 4 | 82 |
| Fukuoka et al. (2012) [X] | Case report | PS, Im, RT, CT, HP (MIB-1 LI) | N/A | 1 | | | 1 | | | 100 |
| Kanno et al. (2012) [X] | Case series | HP (MIB-1 LI) | 1992–2011 | 12 | 3 | | 5 | 1 | 3 | 50 |
| Kathpal et al. (2013) [X] | Case report | PS, Im, SS, HP, RT | N/A | 1 | | | | 1 | | 100 |
| Wang et al. (2013) [X] | Case report | PS, Im (apoplexy) | N/A | 1 | | | 1 | | | 100 |
| Yi et al. (2013) [X] | Case report | PS, Im, RT, CT | 2010 | 1 | | | | 1 | | 100 |
| Bielle et al. (2014) [X] | Case report | PS, CC, Im, HP | 1998 | 1 | | | | 1 | | 100 |
| Ito et al. (2014) [X]***** | Case series | Im, SS, HP (MIB-1 LI),DS, RT, CT, PFS, OS | 1992–2011 | 15 | 6 | | 5 | 1 | 3 | 40 |
| ****Cases not duplicate of Kanno et al. (2012) | | | | 4 | 4 | | | | | 0 |
| Kakigi et al. (2014) [X] | Cohort study | Im (FDG-PET) | 1993–2012 | 12 | 5 | | 4 | | 3 | 33 |
| Watanabe et al. (2014) [X] | Case series | Im, SS, HP (MIB-1 LI), DS, RT, CT, PFS, OS | 2000–2013 | 5 | | | 5 | | | 100 |
| Awa et al. (2014) [X] | Cohort study | HP, Im | 1995–2013 | 20 | 6 | | 8 | | 6 | 40 |
| Rachana et al. (2014) [X] | Case series | Im, HP | 1989–2010 | 19 | 5 | | 3 | | 11 | 16 |
| Park et al. (2015) [X] | Case series | Im, SS, HP, DS, RT, CT | 1997–2014 | 8 | 3 | | 5 | | | 63 |
| Patil et al. (2015) [X] | Case report | PS, Im, SS, HP | N/A | 1 | | | 1 | | | 100 |
| Das et al. (2016) [X] | Case series | HP, Im (MRS), HP (MIB-1 LI), DS, RT | 2010–2013 | 5 | | | 3 | 2 | | 100 |
| Kang et al. (2016) [X] | Case report | PS, Im, HP, GA, DS | N/A | 1 | | | | 1 | | 100 |
| Singla et al. (2016) [X] | Case report | PS, Im, SS, HP | N/A | 1 | | | | 1 | | 100 |
| Yoon et al. (2016) [X] | Case report | PS, Im, HP | N/A | 1 | | | 1 | | | 100 |
| Yu et al. (2016) [X] | Cohort study | PS, HP, DS, RT, CT, PFS, OS | 2005–2012 | 27 | | | 18 | 9 | | 100 |
| Coy et al. (2017) [X] | Cohort study | HP | N/A | 56 | 17 | | 28 | | 11 | 50 |

**Table.1** (continued)

| Author (year) | Study design | Main data | Years of enrollment | Number of PPT cases | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Total | PC | Mixed PC-PB, PC with anaplasia | PPTID | | | |
| | | | | | | | WHO grade 2 | WHO grade 3 | PB | (% of PPTID) |
| Iorio-Morin et al. (2017) [X] | Cohort study | RT, PFS, OS | –2014 | 46 | 26 | | 7 | | 13 | 15 |
| Raleigh et al. (2017) [X] | Cohort study | SS, HP, DS, RT, CT, PFS, OS | 1992–2015 | 38 | 13 | | 10 | 8 | 7 | 47 |
| Bando et al. (2018) [X] | Case report | PS, Im, SS, HP, DS, RT, CT | 2009 | 1 | 1 | | | | | 0 |
| Kumar et al. (2018) [X] | Cohort study | Im, SS, DS, RT, PFS, OS | 2006–2016 | 14 | 8 | | 4 | | 2 | 29 |
| Yamasaki et al. (2018) [X] | Cohort study | Im (ADC, MRS) | 2003–2016 | 9 | 3 | | 4 | | 2 | 44 |
| Abbassy et al. (2018) [X] | Case series | PS, DS, PFS | 2013–2016 | 4 | 1 | | 1 | | 2 | 25 |
| Chatterjee et al. (2019) [X] | Case series | PS, SS, HP (MIB-1 LI), RT, PFS | 2006–2016 | 16 | | | 6 | 10 | | 100 |
| Choque-Velasquez et al. (2019) [X] | Cohort study | DS, RT | 1997–2015 | 23 | 4 | | 16 | | 3 | 70 |
| Lee et al. (2019) [X] | Case series | HP, GA | N/A | 8 | 1 | | 3 | | 4 | 38 |
| Martinez et al. (2019) [X] | Case report | PS, Im, HP, GA | N/A | 2 | | | | 2 | | 100 |
| Verma et al. (2019) [X] | Case series | HP, Im, SS, HP (MIB-1 LI), RT, CT | 2007–2016 | 74 | 5 | | 31 | 8 | 30 | 53 |
| Ahn et al. (2020) [X] | Case series | PS, Im, HP (MIB-1 LI), DS, RT | 2009–2016 | 6 | 2 | | 4 | | | 67 |
| Beduk et al. (2020) [X] | Case report | PS, Im, SS, RT | N/A | 1 | | | 1 | | | 100 |
| Fomchenko et al. (2020) [X] | Case report | PS, Im, SS, HP (MIB-1 LI), GA, DS, RT | N/A | 1 | | | 1 | | | 100 |
| Li et al. (2020) [X] | Cohort study | GA, DS, RT, CT, EFS, OS | N/A | 51 | | | 1 | | 50 | 2 |
| Wu et al. (2020) [X] | Cohort study | HP, HP (MIB-1 LI), RT, OS | 2008–2017 | 41 | 3 | | 18 | 11 | 9 | 71 |
| Kumar et al. (2020) [X] | Case report | PS, CC, HP, DS | N/A | 1 | | | | 1 | | 100 |

*PC* patient characteristics, *PS* presenting symptoms, *Im* imaging study, *SS* spinal seeding or other dissemination, *HP* histopathology, *WB/FC* western blot/flow cytometry, *GA* genomic analysis, *DS* extent of direct surgery, *RT* radiotherapy, *CT* chemotherapy, *DFS* disease-free survival, *EFS* event-free survival, *PFS* progression-free survival, *OS* overall survival.

**Table.2** Tool for evaluating the methodological quality of case reports and case series

| Domains | Leading explanatory questions |
|---|---|
| Selection | 1. Does the patient(s) represent(s) the whole and consecutive experience of the investigator (center) or is the selection method unclear to the extent that other patients with similar presentation may not have been reported? |
| Ascertainment | 2. Did the diagnosis pf PPTID (and similar tumors) adequately meet WHO classification? |
| Causality | 3. Was a certain volume of the tumor resected (not including biopsy)? |
| | 4. Was the follow-up long enough (at least more than a year) for outcomes to occur? |
| | 5. Are any adverse events or complications reported? |
| Reporting | 6. Is the case(s) described with sufficient details to allow other researchers to replicate the study or to allow practitioners make inferences related to their practice? |

## Biological features

### Histopathological and molecular features

Histopathological studies to characterize and distinguish PPTs from other pineal tumors have been performed for many years. Moreover, immunostaining techniques are now widely used for classifying PPT grades.

Neurofilament (NF), a neuronal marker expressing in soma, axon, or dendrite, is one of the most important benign markers of PPT, with intensive immunopositivity of NF suggesting PC [28, 107]. In an international multicenter retrospective study with 66 PPT cases from 12 institutions, in addition to grades I (PC) and IV (PB), the authors divided the "mixed/intermediate" types of PPT into two grades (II and III) based on NF staining and mitosis index [43]. Grade II included PPT with fewer than six mitoses and positive immunostaining of NF, and grade III included PPT with either six or more mitoses or fewer than six mitoses but negative immunohistochemistry of NF. This histopathological feature–based grading successfully demonstrated clinical prognosis and event-free 5-year survival (grades I through IV with 100%, 87.5%, 65%, and 20% survival, respectively) [43]. Furthermore, Fauchon et al. reported that PPTID grades II and III differed based on 5-year survival (74% and 39%) and recurrence rates (26% and 56%) [25].

Other neuronal markers that vary depending on the subtype, and thus could be useful to distinguish PPTID from other PPTs, are also available. Immunostaining of synaptophysin, which normally participates in synaptic transmission, showed diffuse, cytoplasmic, and variable intensity, especially in PC or PPTID [42, 76]. Chromogranin A, which has multiple functions, such as forming complexes with ATP and catecholamines, can also be expressed in PC or PPTID, with a pseudostratified architecture [42, 43, 84]. Neuron-specific enolase (NSE) demonstrated immunopositivity in a wide spectrum of PPTs but was strongly expressed in PC or PPTID [43]. Glial markers, such as glial fibrillary acid protein (GFAP) or S-100 protein, are rarely positive in PPTs with glial differentiation [107]. Although there is no evidence of correlation with survival, NeuN, a biomarker for neurons, was also expressed in PPTID with a higher rate in low-grade tumors [16, 46].

The MIB-1 index via immunostaining with a monoclonal antibody, detecting cell proliferation-associated antigen Ki-67, is also used to categorize PPTs. The MIB-1 index was reported as a malignancy factor associated with PPT grades (I: 0%; II: 5.2%; III: 11.2%; IV: 36.4%) [28] and is an important marker for distinguishing PPTID from PB or even between grades II and III. More specifically, Verma et al. reported that clinical progression occurred in both grades II and III of PPTID but was more common in the cases with an MIB-1 index of > 10% in their large single-institutional series [100]. In a recent study of grade II ($n = 18$) and III ($n = 11$) cases, the group with MIB-1 index ≤ 5% and mitotic count ≤ 3/ 10 HPFs had a significantly longer overall survival than the group with MIB-1 index > 5% and mitotic count > 3/ 10 HPFs, respectively, suggesting that, like other neoplasms in the CNS, cell proliferation and mitosis are critical factors related to clinical prognosis of PPTID [105]. Furthermore, this study demonstrated that CD24 and preferentially expressed antigens in melanoma (PRAME) expression are markers that, along with the WHO criteria, may help evaluate PPTID grading and prognosis, and aid in making therapeutic decisions. Classification of PPTID into small-cell or large-cell morphologic subtypes also showed distinct clinical outcomes [79].

In a unique case report with multiple RNA and protein analyses of PPTID, a mutation of the epidermal growth factor receptor variant III (EGFRvIII) was reported. Since EGFRvIII, the most common variant of the EGF receptor has been detected in a large percentage of patients with glioblastoma multiforme but not in normal brain tissue, the author indicated the possible future use of molecular-targeted agents against EGFRvIII probably being beneficial to PPTID patients [59, 60].

### Genetic features

Little is known about underlying genetic alterations or molecular subgroups of the aggressive variants of PPTs,

**Table.3** Included articles were assessed on the domains of patient selection, ascertainment, causality, and reporting. With respect to each domain, the available information in the studies was evaluated as good (green), moderate (orange), and poor (red)

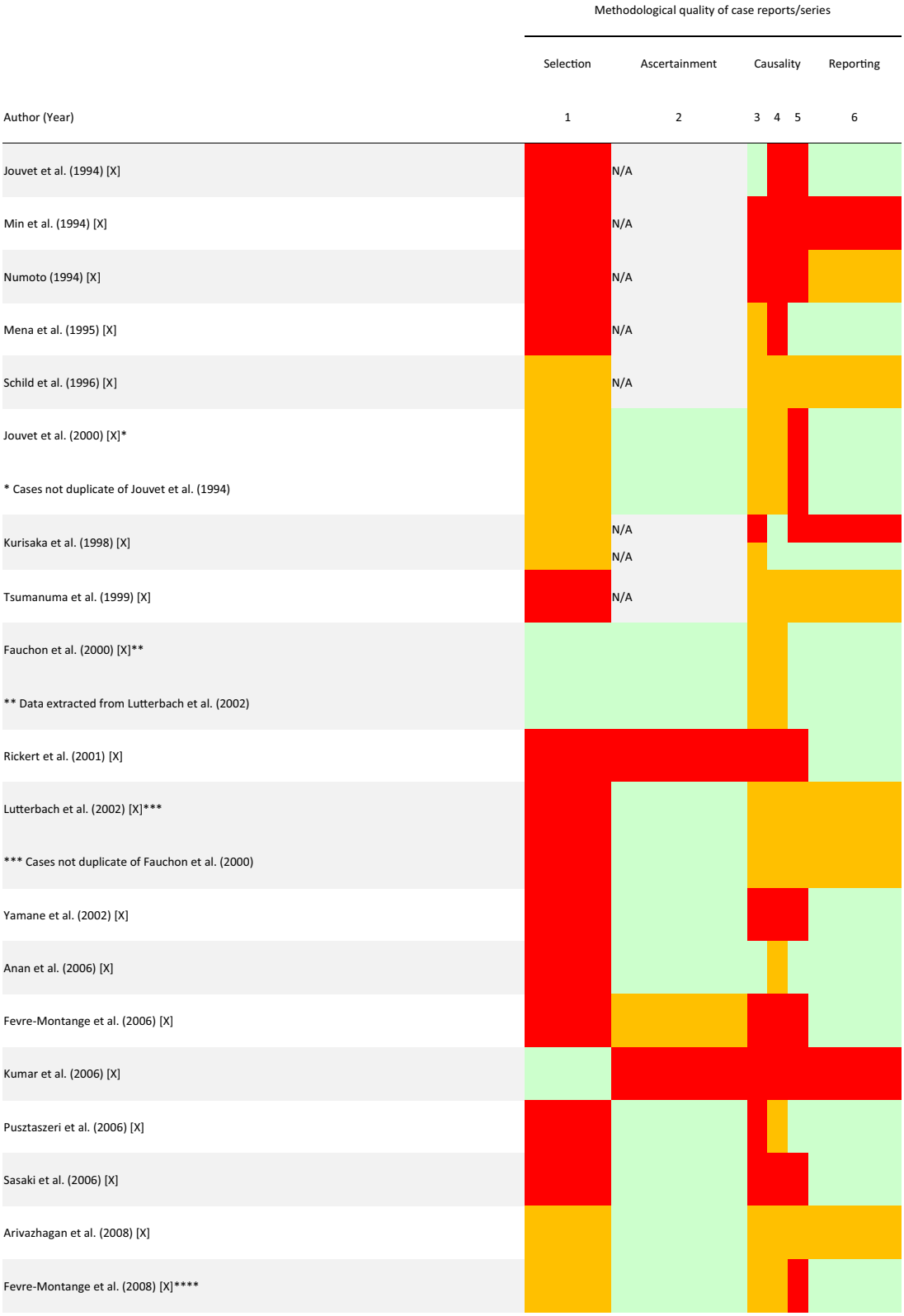
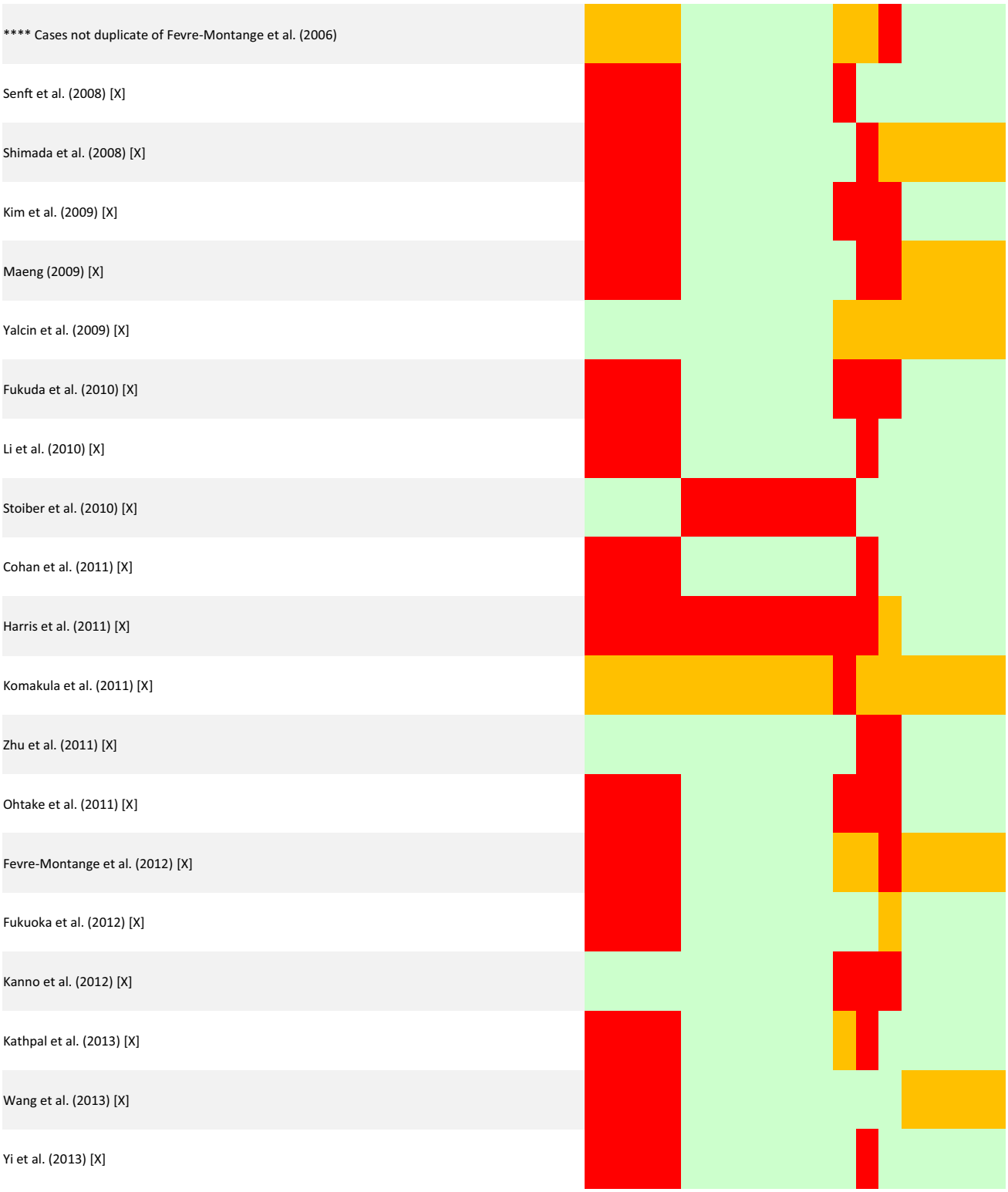
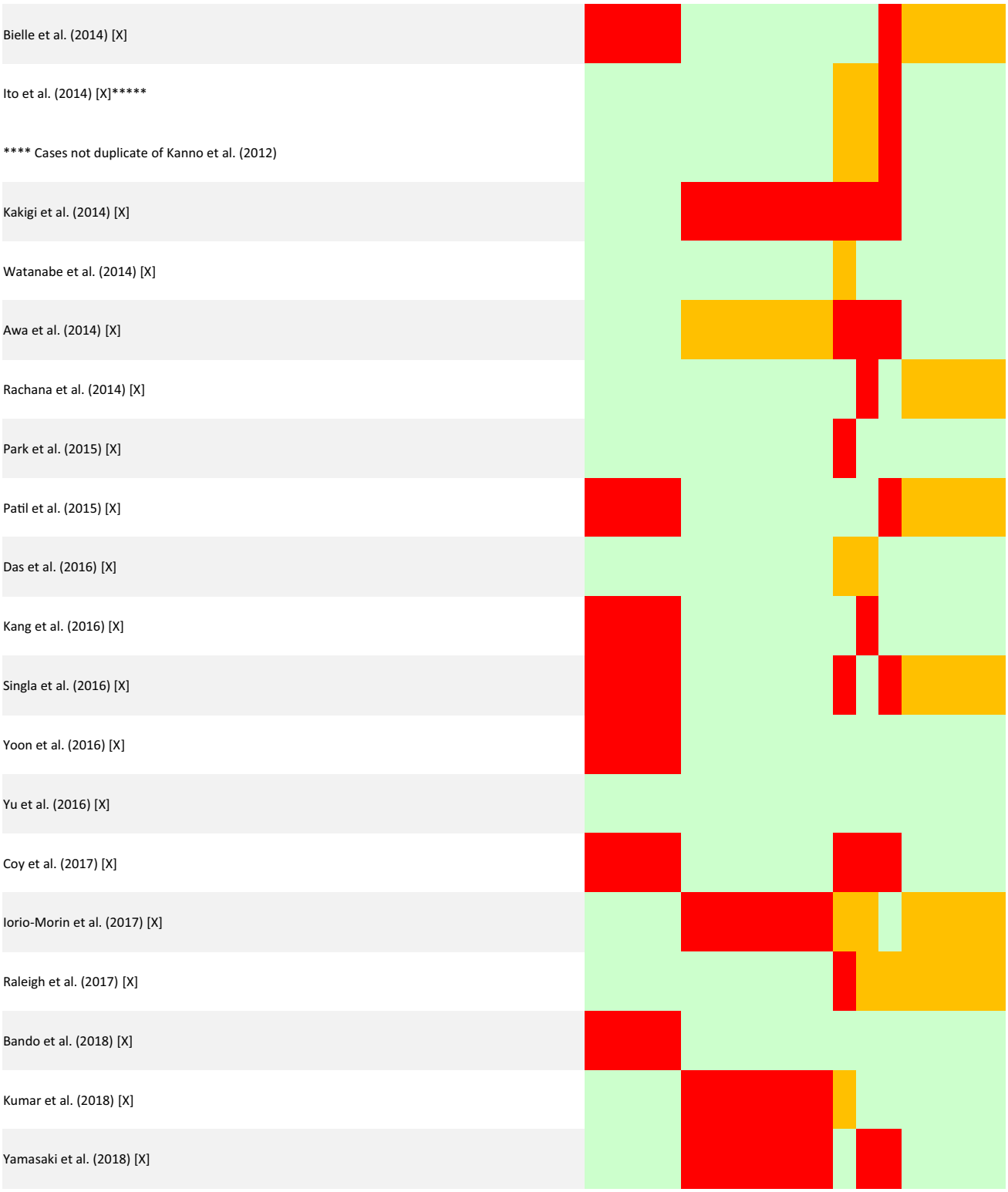


**Table.3** (continued)



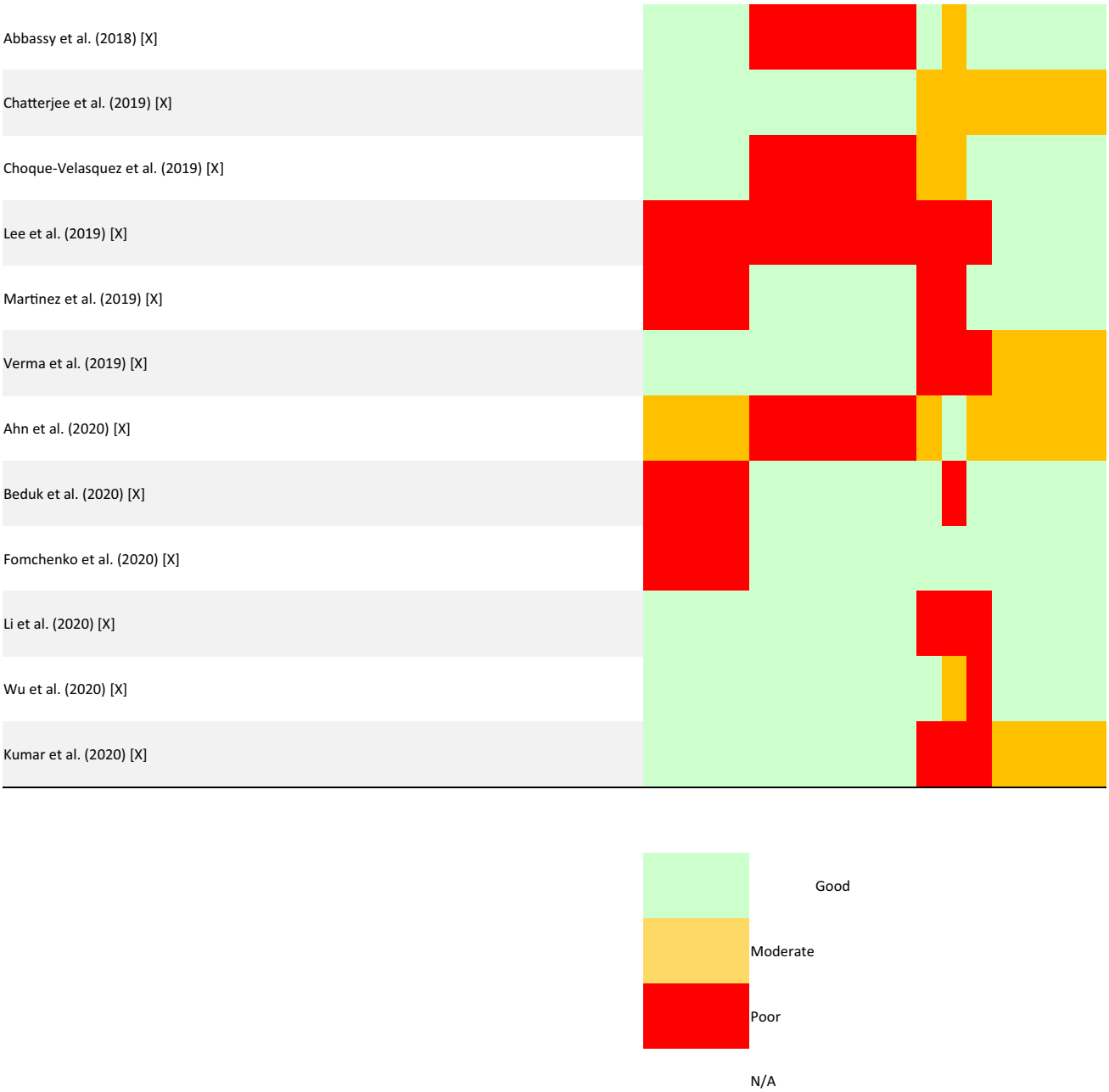

including PPTID [77]. Recently, unsupervised clustering based on DNA methylation patterns was performed in an international collaborative study investigating 195 pineal region tumors and 20 normal pineal gland controls. This revealed different entities and subtypes using primary histopathological diagnoses of pineal region tumors, including PPTID [77]. Methylation-based findings proposing a PPTID marker may not apply to all cases [58];

**Table.3** (continued)




nevertheless, genetic approaches for PPT recharacterization would help define a more rational patient stratification in clinical trials and optimize the treatments with more targeted therapeutic approaches [77].

**Table.3** (continued)




## Current therapeutic approaches

### Direct surgery

Definitive management of PPTID is still unclear. Previous studies have recommended various treatment approaches ranging from microsurgery or radiotherapy alone to combined treatment with direct surgery, external irradiation, and chemotherapy [53]. Among them, microsurgery reportedly plays a vital role in decreasing the local mass effect and providing a maximal tumor sample. Therefore, gross total resection (GTR) has been considered the treatment strategy of choice for PPTs, especially for cases demonstrating less aggressive clinicopathological features, such as PC or grade II PPTID [50, 85, 90]. Moreover, long-term follow-up indicated that achievement of GTR is associated with improved disease control and overall survival, regardless of tumor grade of PPTID [112] and even PPTs [79, 112]. Indeed, in some cases, GTR can be achieved by greater progress in microsurgery and perioperative care or even by staged surgery; however, aggressive resection could result in debilitating neurological deficits because of proximity to

**Table.4** Age and sex of 551 PPTs cases

| $N=551$ | Total | Male ($N=261$) | Female ($N=290$) | $p$-value | Statistic |
|---|---|---|---|---|---|
| Age (years, mean ± SD) | 31.8 ± 20.0 | 29.7 ± 19.5 | 33.8 ± 20.3 | 0.016 | Welch |
| PC | 41.2 ± 17.2$^{‡‡‡}$ ($N=112$) | 37.7 ± 16.2$^{♯}$ ($N=52$) | 44.7 ± 17.0$^{♯♯}$ ($N=60$) | ‡‡‡; < 0.001 | 2way ANOVA |
| **PPTID** | **37.9 ± 17.3$^{‡‡‡}$ ($N=226$)** | **35.2 ± 16.5$^{♯}$ ($N=107$)** | **40.3 ± 17.6$^{♯♯}$ ($N=119$)** | (< 0.001; PC vs PPTID) | (Tukey post hoc) |
| **Grade unknown** | **36.1 ± 18.4 ($N=64$)** | **30.7 ± 18.3 ($N=26$)** | **39.4 ± 17.6 ($N=38$)** | (< 0.001; PPTID vs PB) | (Tukey post hoc) |
| **WHO grade 2** | **41.4 ± 16.1* ($N=89$)** | **38.5 ± 14.4$^{§}$ ($N=40$)** | **43.9 ± 17.1$^{§§}$ ($N=49$)** | ♯ vs ♯♯; 0.004 | 2way ANOVA |
| **WHO grade 3** | **35.0 ± 16.8* ($N=73$)** | **34.9 ± 16.6$^{§}$ ($N=41$)** | **35.2 ± 17.2$^{§§}$ ($N=32$)** | ***; 0.022** | **2way ANOVA** |
| PB | 16.3 ± 16.3$^{‡‡‡}$ ($N=168$) | 15.6 ± 17.2$^{♯}$ ($N=82$) | 17.0 ± 15.4$^{♯♯}$ ($N=86$) | **§ vs §§; 0.28** | **2way ANOVA** |
| **Mixed PC-PB, PC with anaplasia** | **37.5 ± 23.9 ($N=12$)** | **39.6 ± 25.5 ($N=7$)** | **34.0 ± 20.9 ($N=5$)** | **0.028 Welch** | |
| **Mixed PC-PB/PPTID** | **37.0 ± 17.0 ($N=33$)** | **35.8 ± 15.3 ($N=13$)** | **37.8 ± 18.0 ($N=20$)** | **0.72 Welch** | |
| | | | | **0.74 Welch** | |

critical structures [45, 89]. In a surgical series with 38 PPTs, including ten grade II and eight grade III PPTID cases, GTR was achieved in four cases (40% grade II and 50% grade III cases) and was associated with improvement of disease control and overall survival regardless of tumor grade [79]. In another series of eighteen grade II and nine grade III PPTID cases, with sixteen cases of GTR, both PFS and OS were significantly longer in the GTR cases than in the non-GTR cases (5-year PFS; 80% in GTR and 45.5% in non-GTR, 5-year OS; 100% in GTR and 53% in non-GTR) [112]. Following chemotherapy and radiation, comparatively low rates of disease recurrence (grade II; 10%, grade III; 25%) and mortality (grade II; 10%, grade III; 37.5%) were demonstrated with long overall follow-up (median 4.1 years) [79].

As for the selection of surgery for PPTID, due to tumor location and invasion toward the surrounding prominent areas, less resection or even biopsy may be feasible [21]. Depending on tumor extension, supracerebellar infratentorial or occipital interhemispheric approaches have commonly been used, with or without modifications, for approaching

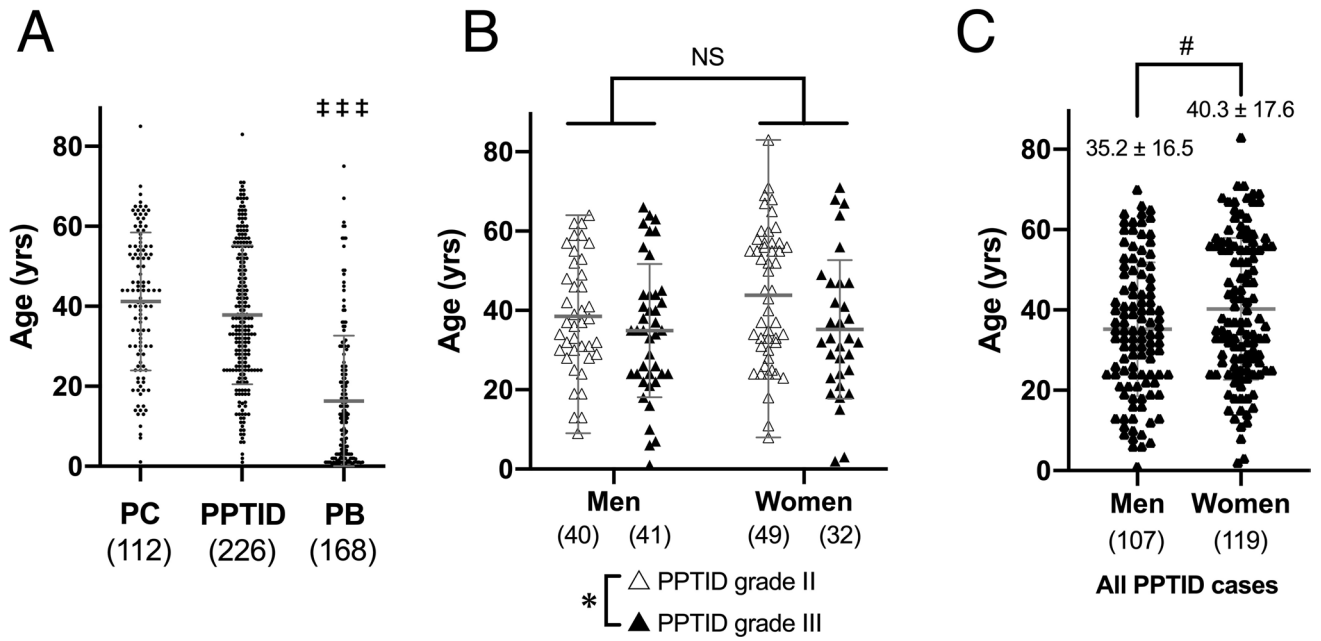



**Fig. 2** **A** In all PPT cases diagnosed according to WHO guideline, higher grade PPT is significantly younger than lower grades ($p<0.001$; 1-way ANOVA, $^{‡‡‡}p<0.001$ vs PC or PPTID; 1-way ANOVA with Tukey post hoc test). **B** In PPTID cases, grade II is significantly younger than grade III (*$p=0.022$; 2-way ANOVA). **C** In the total cohort of PPTID regardless the grade, PPTID occur significantly earlier in men than women ($^{♯}p=0.028$; unpaired $t$-test with Welch's correction)

**Table.5** Presenting symptoms of 85 PPTID cases

| Presenting symptoms | $N=85$ |
|---|---|
| ICP increased symptoms | |
| Headache | 63 |
| Nausea | 5 |
| Vomiting | 6 |
| Nausea and/or vomiting | 26 |
| Papillo edema | 3 |
| Hydrocephalus | 4 |
| Limb symptoms | |
| Gait disturbance | 16 |
| Weakness | 4 |
| Spasticity/tremor | 4 |
| Cognitive/memory disturbance | 6 |
| Confusion | 1 |
| Visual impairments | 36 |
| Photophobia | |
| Parinaud | |
| Anisocoria | |
| Double vision | |
| Other unspecified visual impairments | |
| Hemifacial hypoesthesia | 1 |
| Hearing impairment | 1 |
| Tinnitus | 1 |
| Giddiness | 1 |
| Urinary incontinence | 2 |
| Seizures | 2 |
| Hyponatremia | 1 |
| Hemorrhage (radiographical) | 1 |
| No symptoms (incidental) | 2 |

the pineal region [18]. Especially, in the supracerebellar infratentorial approach, Choque-Velasquez et al. reported that approach-related postoperative complications were significantly lower in paramedian approaches than in midline approaches (9% and 29%, respectively) [18]. Cerebrospinal dissemination at diagnosis, an important factor determining the outcome in PPTs, is less common in PPTID, and only a biopsy might be feasible in such cases [79, 90, 102]. Since possibilities of tumoral recurrence and spread certainly exist, adjuvant therapies, such as chemotherapy or (stereotactic) radiation, may be required, especially in aggressive high-grade PPTID [16, 52].

### Radiotherapy

Because of the complexity of PPT surgery, especially considering the proximity of an irregularly shaped tumor to the critical surrounding nervous system, nonsurgical management options, such as radiotherapy, have emerged as important alternative treatments for PPTID, mainly after surgical intervention. However, optimal management is yet to be determined.

PC is treated with surgical resection, sometimes followed by conventional local radiotherapy or stereotactic radiosurgery, depending on tumor behavior and recurrence [27, 50]. PPTID, especially WHO grade III, or PB, usually requires alternative treatments. Chatterjee et al. reported on 16 PPTID cases (median age, 29 years; range, 2–50 years), including six grade II and ten grade III cases, treated mainly by microsurgery and conventional radiotherapy, except for a case which required additional chemotherapy due to local recurrence [16]. Three out of six patients with low-grade (grade II PPTID) tumors were followed up and all patients were alive without recurrence. In high-grade (grade III) cases, among seven out of ten patients, four were alive (57%; 2 had local recurrences, 1 showed spinal metastasis) with over 15-month progression-free survival, and three patients died. Among the three unfavorable outcomes, two showed higher MIB-1 index values of 12 and 30 [16]. Das et al. reported five PPTID cases, including three grade II, and two grade III cases, treated using radiotherapy alone. Four patients underwent R2 resection (macroscopic residual tumor at primary tumor site), and the other only had a biopsy. Nevertheless, a dose of 54 Gy in 30 fractions to the primary lesion resulted in a good partial response in four cases and one stable case, with neither recurrence nor neurocognitive disorders [21]. However, their cohort was adult (median age, 44 years; range, 24–62 years) and the follow-up period was short (median, 21.4 months). Ahn et al. treated four cases of grade unspecified PPTID (median age, 44.5 years; range, 8–58 years) using cyberknife radiosurgery (CKRS) alone (marginal dose, 18 Gy; isodose curve, 80–85%; 3 fractions), with a longer follow-up (median, 42 months; range, 22–140 months) period. Two tumors disappeared completely, and one tumor partially regressed after CKRS with no acute or late CKRS-related complications; however, a case with high MIB-1 index (30%) showed local progression 14 months after CKRS and died 21 months after CKRS. One of the biggest PPTID cohort studies, including 18 grade II and 11 grade III cases, combining direct surgery with radiation, demonstrated that the median overall survival of grade II and III was significantly different (77 months and 22 months) [105]. This report also showed the difference in median overall survival rate between recurrent and non-recurrent cases (46 months and 77 months respectively).

### Chemotherapy

Currently, microsurgery and radiotherapy are regarded as the preferred treatments for high-grade PPTs, including PPTID. In fact, among 69 included papers on PPTID, 49 (71.0%) and 39 (56.5%) described direct surgery and radiotherapy,

respectively. In turn, only 27 (39.1%) of them addressed chemotherapy (Table S3).

To date, platinum-based antineoplastics are commonly used for PPTID, but the indications and protocols for chemotherapy are yet to be standardized [10], and various combinations of systemic chemotherapy for PPTID have been reported. Before the WHO classification 2000, Kurisaka et al. reported two cases of mixed PC-PB, which is considered a similar entity to PPTID, treated with combined adjuvant treatment, including chemotherapy. After initial mass reduction, chemotherapy via carboplatin/ifosfamide or cisplatin/vinblastine/bleomycin was administered, followed by radiation. The result of Karnofsky's performance scale after over 2 years of follow-up indicated that chemotherapy should be administered before radiotherapy; otherwise, a lower concentration of drugs in the tumor tissue resulting from a reduced blood supply causes damage to the blood vessels after irradiation [53].

Other combination regimens, such as carboplatin/etoposide, cisplatin/carboplatin/etoposide, vincristine/lomustine/cisplatin, cisplatin/etoposide/cyclophosphamide/vincristine, vincristine/nimustine/carboplatin/interferon β, and ifosfamide/cisplatin/etoposide (ICE), were used for some grade II and III PPTID cases [7, 10, 31, 48, 78, 102]; a previous article has described the details of each of these drugs [102]. Yi et al. reported the case of a 37-year-old patient with PPTID grade III who was successfully treated with a procarbazine/lomustine/vincristine (PCV) regimen combined with partial surgical removal and irradiation (54 Gy; 27 fractions) 1 month after surgery [110]. Despite the shorter follow-up period in this study (only 6 months), no signs of recurrence or neurological deficits were reported. The authors suggested that combining microsurgery and radiotherapy with chemotherapy may be a feasible and efficient therapeutic approach for treating PPTID.

## Discussion

The current systematic review evaluated the patients' clinical characteristics, biological features, and the current therapeutic options for treating PPTID. The review aimed to gain insights for individualized PPTID management in the future.

The principal cell of the pineal gland is the pineal parenchymal cell or pinealocyte, which is surrounded by a stroma of fibrillary astrocytes and sympathetic neurons [57, 76]. Most tumors are a result of displaced embryonic tissue (germ cell tumors), malignant transformation of pineal parenchymal cells (PPTs), or transformation of surrounding astroglia (gliomas) [5, 91]. Pineal region tumors constitute 3–8% of pediatric brain tumors [1, 50, 66, 81] and 0.4–4.0% of all intracranial tumors in adults [51, 66, 81]. Among them, PPTs account for 1.2–42% [51]. Kumar reported that PPTs have a higher incidence in the Western population than in the Far East. Before PPTID was classified as a PPT with an intermediate prognosis between PC and PB by WHO in 2000, the subtype showing intermediate histological characteristics was not clearly defined, and was thus described as mixed PC-PB or PC with anaplasia [42, 43, 53, 67, 73, 99]. Despite the 10% incidence of PPTID previously reported in systematic reviews [6, 14], the current review reports an incidence of 15–82% in the literature, with 20 or more PPTID cases [9, 20, 28, 30, 39, 43, 46, 51, 62, 79, 105, 107, 114]. Furthermore, studies with a relatively large number (> 50) of PPT cases reported the PPTID incidence to be 40–60% of all PPTs (Table 1 and S2).

Although previous reports suggested that PPTs (including PPTID) occur predominantly in women [14, 64], our comprehensive analysis did not show any significant sex-related differences in PPTID ($n = 332$; 161 men and 171 women, Table S4), the same as in the total PPT cohort ($n = 727$; 359 men and 368 women, Table S4). Regarding the age, our findings demonstrated that higher grade PPTs were significantly more common in younger individuals (Table 4, Fig. 2, and S1), and importantly that the cohort of higher grade (grade III) PPTID was significantly younger than that of the lower grade PPTID cohort (grade II) (Fig. 2B). Moreover, the present study indicates that PPTs (Figure S1) and even PPTID (men; $35.2 \pm 16.5$ years old, women; $40.3 \pm 17.6$ years old, Fig. 2C) occur significantly earlier in men than in women. These findings suggest that sex-specific factors might not affect neoplasmic transformation but could be associated with tumor progression of PPTs, including PPTID [36, 93, 96, 103, 109]. Previous research on malignant tumors has reported sex-related differences in the frequency of DNA methylation. Furthermore, studies have shown a possible relationship between the methylation rate and the malignancy risk and even a possible difference in therapeutic reactiveness [54, 82, 104]. DNA methylation was also studied in PPTID, as mentioned above [77]. Still, little is known about sex-specific impact. Therefore, further studies in cases of PPT, including PPTID, focusing on sex-specific factors, may have significant implications and could lead to novel therapeutic approaches.

As expected, in disease presentations of 85 PPTID cases, the increased ICP-related symptoms due to obstructive hydrocephalus were the most common in PPTID, followed by visual impairments, including Parinaud's syndrome (Table 5) [16, 49, 112]. In addition to other symptoms, such as gross motor symptoms and cognitive or memory disturbance, several other minor symptoms were reported. Among them, seizures are usually a late sign associated with increasing ICP due to obstructive hydrocephalus [49].

Importantly, our study revealed that intratumoral hemorrhage is less common in PPTID than in PB or some germ cell tumors that often demonstrate hemorrhage or necrosis in the pineal region [17, 66, 86]. A study in 23 PPTs, including 16 PPTID, stated apoplectic hemorrhage as a rare presentation, which is consistent with our study as we observed only one PPTID case with a hemorrhagic presentation [18, 49]. This observation may help in the preoperative prediction of the tumor subtype. Urinary incontinence was observed in only two (one grade II and one grade III case) out of 85 cases. Although uncommon in PPTID [63, 65], it could be a hazardous feature in pineal region tumors once the tumor invades the periaqueductal gray of the midbrain, which forms part of the neural circuit of the micturition reflex [3, 34, 63, 65, 97].

Various imaging patterns of PPTID have been reported in 38 papers (Table S3). These reports summarized that it is challenging to distinguish PPTID from other PPTs or pineal region tumors based on imaging, even with positron emission tomography [44]. Compared with the pineocytoma and PPTID on computed tomography, PB and germinoma frequently presented with hyperattenuating masses, reflecting highly cellular histological features [44]. In their preoperative MRI study of 25 PPTID, Yu et al. reported that irregular marginal and aggressive masses with local brain invasion were seen in 60% of cases, and nodular and clear marginal masses in the remaining 40%. Similarly, Komakula et al. showed a broad spectrum of PPTID imaging in 11 cases, demonstrating bulky, aggressive masses with local brain invasion in nine cases and circumscribed masses in two cases [49]. MR spectroscopy (MRS) is sometimes used to detect metabolites or molecules in a CNS tumor. Harris et al. used MRS for evaluating nine germ cell tumors and seven PPTs, including one PC, one PPTID, and five PB, and suggested the usefulness of MRS in PPT characterization [35]. On the other hand, MRS in one out of five patients in Das et al. showed non-specific results for PPTID [21]. Yamasaki et al. conducted the most recent MRS study, including PPTID. They showed a lower lipid peak non-specifically in PPT subtypes compared to germinomas. Therefore, MRS may be a valuable option to detect the specificity of PPTID; however, it has not yet been studied extensively. In summary, none of the current imaging modalities can differentiate PPTID from other PPTs or germ cell tumors. Imaging studies have been primarily used for deciding the treatment strategy (direct or radiosurgery) rather than a preoperative diagnosis of PPTID.

Dissemination or spinal seeding is usually one of the poor prognostic factors of CNS tumors. Twenty previous articles on PPTs, including PPTID, examined disseminated cases and suggested that dissemination is a crucial radiological finding that could affect the treatment strategy [40, 49].

## Current and future diagnostic approaches

Histopathological study is an accessible and widely used method to predict the biological aggressiveness and clinical prognosis of PPTID. Indeed, the WHO classification, mainly based on histopathological assessment such as MIB-1 index, is generally consistent with patient survival. Therefore, it is the gold standard for PPTID diagnosis and plays an essential role in the clinic [16, 20, 25, 27, 30, 39, 42, 43, 67, 68, 73, 79, 99, 106, 107]. However, histopathological study for PPTID grading and therapeutic decision-making has some critical limitations and caveats. Most importantly, histopathological assessment can be subjective and may vary depending on the size of the resected tumor and intratumoral heterogeneity of the molecular and morphological aspects [12, 29]. Some unusual and aggressive cases of PPTID have been reported [45, 47, 100]; therefore, creating a therapeutic strategy based on histological diagnosis alone may not be the best approach, especially in biopsy cases.

In recent studies, genetic analysis led to a change in the primary diagnosis of some cases [77]. Pfaff et al. subgrouped 27 cases of PPTID based on DNA methylation patterns. These subgroups correlated with distinct clinical features and genetic alterations; however, only 15 cases (56%) were primarily diagnosed as PPTID based on histopathological assessment [77]. Another study by Fomchenko et al. presented an unusual case that was most consistent with PPTID, but resulted in extensive metastasis despite aggressive surgical interventions, radiotherapy (proton beam), and chemotherapy (temozolomide), and required subsequent resection of metastatic lesions and craniospinal radiation [29]. Exon sequencing of the case demonstrated an *H3K27M* mutation, which is usually seen in pediatric glioma, and suggested that genomic analysis may be needed to develop a further understanding of the biological features of PPTID. Since PPTID exhibits substantial heterogeneity and sometimes includes aggressive variants, comprehensive molecular and genetic characterization might reduce the intensity of the treatment and improve the clinical prognosis [65].

## Therapeutic options and strategy

According to previous reports, grade II PPTID without metastasis or the presence of neurofilament were adequately managed by microsurgery with or without radiotherapy [28, 87]. However, the treatment approach of grade III PPTID, or cases with spinal seeding or histological evidence of necrosis or mitosis, is not consistent across studies. It is clear that GTR seems the most appropriate treatment for all these neoplasms and that complete resection should also be recommended even in aggressive variants [28].

Due to concerns regarding operative complications in microsurgery, radiotherapy is helpful as a non-invasive

treatment, especially in developing brain tissue [113]. Some studies have demonstrated favorable radiotherapy results and suggested it as the primary therapeutic option for PPTID [4, 21]. However, these studies had some significant limitations. Das et al. (median age, 44 years; range, 24–62 years) and Ahn et al. (median age, 44.5 years; range, 8–58 years) primarily consisted of adult patients, and their cohorts were older than the overall average age in our study. Furthermore, these studies had a shorter follow-up period (median, 21.4 months) than similar studies [4, 49, 113]. Moreover, the latter study did not specify the WHO grading of the included PPTID cases; therefore, the effectiveness of CKRT against aggressive cases cannot be evaluated. These studies suggest that (stereotactic) radiosurgery could be a useful therapeutic option for PPTID. Even though PPTID is a rare disease, further study with aggressive cases with a higher recurrence risk is needed to evaluate the role of radiotherapy in PPTID treatment [4].

Even though some reports showed the effectiveness of (stereotactic) radiotherapy for PPTID, a critical dilemma is that the majority of the higher grades of PPTID cases are pediatric or belong to the younger age group. Thus, the toxic effect of radiotherapy on the developing CNS, including cognitive or endocrine functions, is of great concern, and its use should be reduced if possible. Combination treatment with chemotherapy may play a crucial role in some cases. However, chemotherapy has its independent adverse effects. Few articles have discussed the evidence of chemotherapy-specific side effects on PPTID. An in vitro study using normal human neural stem and precursor cells (NSPCs) suggested that certain types of chemotherapy could result in neurocognitive toxicity because of the sensitivity of NSPCs to the adverse effects [32, 33]. Furthermore, molecularly targeted agents were reported as potentially neurotoxic compared to ordinary chemotherapeutic agents [33]. Since larger molecules, such as chemotherapeutic agents, cannot pass the blood–brain barrier, the effect of chemotherapy could be enhanced with radiotherapy. Further research of the adverse events related to combining chemotherapy and radiotherapy is required.

These studies provide valuable insights into the contemporary management of PPTID in daily practice. Based on the current evidence, primary surgical debulking is advised for both grades of PPTID. For cases with additional risk factors, additional chemotherapy, radiotherapy, or their combination should be planned while carefully considering their long-term adverse effects [18].

## Future perspective for improving clinical outcomes

Endovascular embolization currently plays a supporting and vital role in CNS tumors, especially in benign cases, and may be considered a therapeutic option for PPTID. However, possibly due to the vascular, anatomical, and functional location, limited experience has been reported for pineal lesion and nothing has been demonstrated for the tumors arising from the pineal region [92]. Besides, no study has evaluated endovascular embolization as a therapeutic choice for PPTID microsurgery, possibly because of the blood supply complexity and vascular fragility based on malignant features. However, recent technological developments in endovascular treatment may enable the local delivery of chemotherapeutic agents into the arterial territory of malignant intracranial neoplasms [15, 22, 95, 98]. Intra-arterial administration of chemotherapeutic agents has long been a therapeutic modality for brain tumors owing to the increased association of systemic drug toxicity and poor concentration within the tumor with intravenous administration [53]. Poor rationalization of drug injection protocol due to an intact blood–brain barrier has limited the translation for clinical cases [22]. A recent challenging in vivo animal study using radiolabeled bevacizumab conjugated with deferoxamine model of glioblastoma in mice has demonstrated the effectiveness of intra-arterial administration of the chemotherapeutic agent into the brain, and also osmotic opening of the blood–brain barrier, in contrast to the intravenous route [56]. Therefore, further development of endovascular drug delivery combined with an accurate choice of chemotherapeutic agents may provide novel therapeutic alternatives in previously hard-to-tread malignant tumors of the CNS.

Robot-assisted surgery has evolved since the early 1980s and expanded to several specific fields. In the neurosurgical field, robot-assisted procedure has been used to improve the feasibility and effectiveness of several procedures requiring high-level accuracy and safety, such as surgery of deep-seated brain tumors [23]. The pineal region is one of the deepest and smallest and is located close to a highly vascular area. Therefore, stereotactic robot-assisted biopsy seems to have several advantages in avoiding complications or improving diagnostic accuracy, especially for malignant tumors such as higher grades of PPTID. Further development of robot-assisted neurosurgery may contribute to better clinical outcomes and therapeutic indications of PPTID.

The main reasons why the therapeutic strategy of PPTID has not yet been clearly defined include a low number of patients in research studies, a broad spectrum of underlying molecular and genetic mechanisms, and varying therapeutic timings and options, including the dose of radiotherapy or the variety of chemotherapy. To overcome these limitations and standardize the therapeutic strategy of PPTID, an international bidirectional study, including both retrospective and prospective clinical trials, will be helpful. Moreover, further assessment of clinical and biological features and correlational studies with gene expression and regulation would lead to a novel classification of PPTID or other subtypes

of PPTs. It might not seem currently feasible; however, the recent success in the genomic study of medulloblastoma is encouraging for conducting time-consuming studies in rarer CNS tumors [38, 71, 72].

### Potential biases and limitations

Our study had limitations. Firstly, we did not search for literature describing tumors similar to PPTID other than mixed PC-PB or PC with anaplasia because the PPTID defined by WHO classification 2007 was the focus of our study. Secondly, we only included observational studies, and they had a small sample size, possibly resulting in a lack of high-quality evidence in our study. Thirdly, none of the included studies had performed statistical analyses for the treatment of PPTID; thus, the golden therapeutic standard is still lacking. Lastly, adverse effects of included treatments for PPTs, such as radiotherapy and chemotherapy, have not been fully assessed yet.

## Conclusions

In PPTID, higher grade tumors arise in younger population than lower grade tumors, and female patients are older than male patients. PPTID includes a broad spectrum of characteristics, including both benign and malignant forms. Better local control can be achieved through the contemporary management of benign cases, such as grade II tumors. However, a standard approach to treat malignant tumors, including grade III tumors or cases with aggressive features, is lacking. Other therapeutic strategies need to be evaluated through international multicenter studies. Novel technology–assisted surgery would help maximize the initial debulking. Genetic and molecular targeting strategies might improve the effect of adjuvant therapy and the clinical outcomes of PPTID.

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**Author contribution** Conception and design: H. T., T. Y.
Literature search and data analysis: H. T.
Summarized the included studies: H. T., R. T.
PROSPERO registration: Y. N.
Drafted and/or critically revised the work: H. T., N. S.
Revised the manuscript: All authors.
Funding acquisition: H. T.
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**Data availability** Derived data supporting the findings of this study are available from the corresponding author upon request.

Study protocol is available in PROSPERO (CRD42021259239) and follows the checklist of Preferred Reporting Items for Systematic review and Meta-Analyses (PRISMA).

## Declarations

**Ethics approval** For this type of study, formal consent is not required.

**Consent to participate** As this was a retrospective analysis of the studies that had been published in the past, no consent to participate was necessary.

**Consent for publication** The authors of this study grant the Publisher the sole and exclusive license of the full copyright.

**Competing interests** The authors declare no competing interests.

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