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Pineal parenchymal tumors with intermediate differentiation: a long-term follow up study in Helsinki Neurosurgery

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Title Page**Title**

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Neurosurgery

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Title

Pineal parenchymal tumors with intermediate differentiation: a long-term follow up study in Helsinki
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Abstract:

Background: Pineal parenchymal tumors of intermediate differentiation (PPTIDs) are rare lesions with particular features compared to other pineal parenchymal tumors.

Methods: We present a retrospective review of the patients with histologically confirmed PPTIDs that were operated on in our department between 1997 and 2015. A demographic analysis, and an evaluation of preoperative status, surgical treatment, as well as immediate and long-term clinical and radiological outcomes were conducted.

Results: Fifteen patients with PPTIDs were operated on between 1997 and 2015. Gross total removal was achieved in 11 cases; two patients underwent near-total resection, one partial resection, and one received brachytherapy after an endoscopic biopsy. Other nine patients required external radiation therapy (4 due to a pleomorphic histology of their lesion including pineoblastoma features in 3 of them; 3 after a subtotal resection; two for tumor recurrence). No patient received chemotherapy. The survival rate of our patients was 57.1% at a mean follow-up of 137.2 ± 77.6 (39-248) months.

Conclusions: A proper multidisciplinary management of PPTIDs based on a gross total removal of the lesion, and an adjuvant radiotherapy in selected cases, may improve the overall survival of these aggressive tumors.

Key words:

Microneurosurgery, Pineal parenchymal tumors of intermediate differentiation, Pineal region lesions, Radiotherapy, Sitting position, Supracerebellar infratentorial approach

Abbreviations and Acronyms

FL-EBRT, fractionated linac-based external beam radiation therapy; GTR, gross total resection; PPT, pineal parenchymal tumor; PPTID, pineal parenchymal tumor of intermediate differentiation; SCIT, supracerebellar infratentorial; VPS, ventriculoperitoneal shunt; WHO, World Health Organization

Introduction

Pineal parenchymal tumors of intermediate differentiation (PPTIDs) are rare lesions with particular features compared to other pineal parenchymal tumors (PPTs) (Table 1) (Fig. 1).

Pineal region tumors represent less than 1% of all intracranial neoplasms, and PPTs comprise around 14-27% of all pineal region tumors.¹ The 2007 and the 2016 World Health Organization (WHO) Classification of Central Nervous System Tumors recognized three different PPTs: pineocytomas, pineoblastomas, and PPTIDs grade II-III. The WHO grade II-III PPTIDs represent between 20% and 62% of PPTs. This wide distribution reflects the rarity of the disease, and the variability of the grading and terminology used for these tumors.¹⁻³ Some PPTIDs, that are considered WHO grade II or III tumors, might contain mixed features with pineoblastomas.¹⁻³

In this paper we describe our multidisciplinary management of PPTIDs operated consecutively in Helsinki between 1997 and 2015. We aim to discover the key aspects in the management of these tumors that could determine a favorable long-term outcome.

Methods

We retrospectively reviewed the records of patients with histologically confirmed PPTIDs that were operated on in our department between 1997 and 2015. IMPAX version 6.5.5.1608 (Agfa, Mortsel, Belgium) was employed for the radiological analysis of the pre- and post-operative imaging. Finally, we revised the Finnish population register in July 2018 to determine the current status of the patients.

Microneurosurgery of PPTIDs

In most of the cases, we approach pineal tumors through a supracerebellar infratentorial (SCIT) route with the patient in the sitting praying position, as previously described.^{4,5}

The key aspects of the microsurgical management of PPTIDs are summarized in the Table 2.^{6,7}

Results

Twenty-three PPTs were operated in Helsinki Neurosurgery during the study period, and fifteen histologically confirmed PPTIDs were found. One foreign patient, who underwent partial resection, was lost at the follow up. Table 3 describes the characteristics of the 15 patients.

A patient, who is not included in our series, had a diagnosis of pineocytoma-pineoblastoma in 1987 and was operated to remove a ventriculoperitoneal shunt (VPS) in 2000. Unfortunately, the histopathology study of the patient was not available. This 14 year old male underwent a VPS and biopsy of a pineal tumor before radiation therapy delivered in Stockholm in November 1987. During the follow up the patient presented double vision and slight Parinaud's syndrome, which disappeared gradually. In May 1997, brain MRI demonstrated a stable controlled tumor. In August 2000, the VPS was removed, as the patient wanted to compete in karate. In 2015, an examination revealed slight visual problems, without hydrocephalus and with a smaller tumor at the radiologic imaging. In November 2010, the tumor was almost absent with only a small cystic component. The patient is still alive 368 months since surgery with a controlled disease.

Symptoms

Twelve patients presented hydrocephalus as reason for evaluation and consequent diagnosis of the PPTIDs. Three other patients had incidental findings of the disease, as they performed radiologic studies for left side hemiparesis, persistent migraine, and an association of anosmia with memory problems in a third patient respectively. Acute hydrocephalus in 5 patients was associated with headache, nausea, vomit and unconsciousness, while slowly progressive hydrocephalus in the other 7 patients was related with ataxia, vertigo, incontinence, neurocognitive and memory deficits. Visual problems were identified in 6 patients with diplopia, Parinaud's syndrome, and unspecific visual disturbances. A history of stroke was present in 2 patients, one of them with motor deficit in the right leg.

Imaging

Brain MRI studies of two patients were not available, and other two patients had only contrast-enhanced T1-weighted MRI sequences with full enhancement of the tumors. In a patient with a low grade PPTID, MRI revealed a lesion that was hyperintense on T1- and hypointense on T2-weighted images, without contrast enhancement. In all the other ten tumors, MRI demonstrated lesions isointense on T1 and hypointense on T2-weighted images, with some cystic components, and a complete contrast enhancement except for one patient, who presented a ring enhancing lesion. The mean major diameter of the tumors was 2.6 ± 1.3 cm (1-5.5 cm).

Management

1. Microneurosurgery

Eleven patients underwent gross total resection (GTR). One foreign patient underwent partial resection, and returned to his country; another patient received brachytherapy after an endoscopic biopsy, two patients underwent near-total resections with small residual tumors. Eleven patients underwent a single stage tumor resection, all of them by a SCIT approach (6 midline, and 5 right paramedian approaches). Two patients underwent a two stage tumor resection (by re-opening the same SCIT approach in one case, and by a paramedian SCIT approach on the opposite side in the other one). Finally, one patient required 3 microneurosurgeries for the radical removal of a giant tumor: a right SCIT approach, a suboccipital midline approach to the fourth ventricle, and a posterior interhemispheric approach.

The sitting position was used in 13 cases, the prone position in one patient with a coronary heart disease, and the supine position in a patient following brachytherapy. Twelve cases presented hydrocephalus. Five patients with acute hydrocephalus required a VPS in one case, and an external ventriculostomy in 4 cases (followed by VPS in two of them) before tumor removal. However, only one patient had a VPS at the last follow up. Regarding to the seven patients with progressive hydrocephalus, a foreign patient received a VPS at his local hospital, and another patient underwent a definitive VPS after an insufficient endoscopic third ventriculostomy before brachytherapy. The other 5 patients underwent direct tumor removal as the first procedure, and only two patients required a VPS later on after surgery. At the last follow up, only 3 out of 15 patients needed a VPS.

2. Radiochemotherapy

Ten patients required radiation therapy. Details about the specific management are as follows.

A 68 year-old patient with a grade III pineocytoma-pineoblastoma underwent an endoscopic third ventriculostomy, followed by stereotactic biopsy, brachytherapy with iodine-125 seeds, and VPS. The last MRI studies, six years after surgery, showed a controlled disease with a very small remnant. However, the patient was in poor conditions with brain atrophy, progressive rigidity and aphasia. He died 101 months since surgery.

Fractionated linac-based external beam radiation therapy (FL-EBRT) was applied in 9 patients. The total dose in all cases was 54Gy divided in a daily dose of 1.8-2Gy.

2.a. Radiotherapy and histopathology

Three patients, who had a pleomorphic histology including pineoblastoma features, received FL-EBRT four to six weeks after GTR. Two patients are doing well up to now, 247 months and 238 months after surgery. The

third one, a 55 year-old patient, died 144 months after surgery in a province of Finland. Details about the reason of death were not available.

Other patient with a pleomorphic PPTID not including pineoblastoma features received adjuvant FL-EBR 4 weeks after GTR. This patient is currently alive 45 months after surgery. The tumor was characterized by a high proliferation index (MIB-1 20%), and a strong mitotic activity. It was composed by small rounded nucleus cells grouped as rosettes around the veins, and by some pineal cyst structures mixed with normal pineal tissue at the border of the sample, but without necrosis, nor mosaic type growing. Immunoreactivity was positive for synaptophysin and SMI 32.

2.b. Radiotherapy after partial resection of the tumor

Three patients required radiation therapy after an initial partial resection.

One of them, harbouring a low-grade PPTID with pineocytomatous-like rosettes, high reactivity to neurofilament and synaptophysin, and with a MIB-1 index of 4-5%, received radiotherapy for the residual tumor ten weeks after surgery. However, one year later, the tumor presented a slight growth. The Neurooncology team decided for a GTR. The new MIB-1 index was 2%. The patient is alive without recurrence of the tumor more than seven years after surgery.

A twenty eight year-old girl, who had a giant tumor with high immunoreactivity to neurofilament and a MIB-1 index of 20%, underwent three surgeries along four months for a subtotal resection of the tumor with an intercurrent fungal infection. The radiotherapy was delayed 5 months since the initial surgery. The residual tumor after the last surgery was well controlled by radiotherapy, and at the last clinical evaluation the patient was able to use a rollator with moderate left side hemiparesis, presented slight diplopia, and needed assistance for her activities. Brain MRI did not show recurrence of the pineal lesion. However, spinal MRI demonstrated multiple cervical, dorsal and lumbar metastases (Fig. 2). The patient died 39 months after surgery.

The last one, a foreign patient with a PPTID highly reactive to neurofilament and synaptophysin, and with a MIB-1 index of 4-5%, was recommended to receive radiation therapy after a partial resection. This patient was lost at the follow-up.

2.c. Radiotherapy for tumor recurrence

Two patients required radiation therapy for tumor recurrence.

A patient with a very small residual PPTID after surgery was initially followed strictly every six months. The histopathology revealed a high proliferation index (10-15%) and some mitotic activity. In March 2016, after 6 years, the patient received FL-EBR for a slow growth of the tumor. In September 2017, the last brain MRI showed a controlled lesion. The patient died from pneumonia in December 2017 (Fig. 3).

The second patient, a 67 year-old male underwent GTR of a PPTID. The histological examination revealed a MIB-1 index up to 20% with pineoblastoma features, MAP-2 (+), SYP (+), Cg (+), GFAP (-). Five years after surgery, a small recurrence appeared in MRI studies. The patient with long lasting diabetes, depression, memory problems and anemia was recommended to have follow-up MRI studies. After one year the recurrence was bigger and evident. The patient underwent stereotactic radiosurgery with a single dose of 14 Gy. One year follow-up MRI, as well as subsequent follow-up radiologic studies, did not show any recurrence. The 79 year-old patient died 12 years after surgery with severe vascular dementia.

It is worth noting that another patient, harbouring a pineal lesion and a large cerebellar venous angioma draining big segments of the cerebellum and midbrain, underwent GTR as unique treatment. The histologic examination revealed a moderate to high proliferation (MIB-1 10%). The immunohistochemistry was positive for synaptophysin, chromogranin, and MAP-2+. The Neurooncology team determined strict follow up. Fifteen years after surgery, a very small recurrence appeared at the brain MRI in May 2018. The Neurooncology team decided to re-evaluate the patient after six months before to deliver radiation therapy (Fig 4).

No patient received chemotherapy.

Outcome

1. Tumor control

At the last radiologic evaluation, 10 patients were free of the disease, 3 patients (Fig. 2-4) presented small controlled tumors; however, as described, one of them had spinal metastasis. One patient had a very small remnant after brachytherapy, and one patient with partial resection was lost at the follow up.

2. Morbidity

Six patients did not present any new symptom in the postsurgical evaluation. Nine patients had some postoperative complication: 4 patients presented meningitis that solved with medical treatment. In 3 of them, a VPS had to be removed. Other 5 patients developed immediate postoperative complications, such as Parinaud's syndrome (1 case), lower cranial nerves paresis requiring tracheostomy (2 cases), an occipital epidural

hematoma with left side hemiparesis that required reoperation (1 case), double vision due to sixth cranial nerve paresis (1 case), and slight double vision without nerve paresis (1 case).

Overall, at the last clinical evaluation, two patients presented a bad outcome after multiple surgeries and brachytherapy, and one patient had mild neuropsychological deficits. Another patient presented depression and some double vision, thus needing assistance for walking few months after surgery. Later, the patient was only evaluated in the Cancer center, and we just know that she is alive more than 20 years after surgery.

3. Mortality

The survival rate of our patients was 57.1% at a mean follow-up of 137.2 ± 77.6 (39-248) months without considering the patient lost at the follow up. The 5-year survival rate was 92% (11/12 patients) and the 10-year survival rate was 71% (5/7 patients).

As mentioned, six patients died. Three patients, who underwent GTR with good postoperative outcome and without tumor recurrence, died due to reasons unrelated to the disease (respectively chronic cardiac disease, pneumonia, and severe progressive vascular dementia). Two patients with a controlled disease, but poor progressive clinical outcome, died after some period of treatment. One of them died eight years after brachytherapy; the other, three years after multiple surgeries. The last patient died in another province of Finland 12 years after surgery (the reason was unavailable).

Discussion

In this paper we describe our multidisciplinary management of PPTIDs treated consecutively in Helsinki Neurosurgery between 1997 and 2015. Based on our retrospective analysis, the GTR was the most important factor to obtain a good long term survival rate and tumor control in our series. GTR might be achieved thanks to the combination of these variables: an essential proper team work (neurosurgeon, anesthesiologist, scrub nurse and all involved personnel), adequate principles of positioning and approach, skillful microneurosurgery based on the principle “simple, clean and safe”, and not less importantly, the surgical experience of the neurosurgeon.^{4,7-10}

PPTIDs are divided morphologically into three subtypes, a) lobulated pattern, an endocrine-like and high vascular lesion, b) diffuse growth pattern, similar to oligodendroglioma-neurocytoma, and c) transitional type with areas of lobulated and diffuse growth patterns, associated with areas of pineocytomatous rosettes.¹¹ Even though the grading criteria to differentiate PPTIDs grade II and III are not well established, the 2007 WHO

Classification of Central Nervous System Tumors considers two variables such as the proliferative activity and the immunoreactivity for neurofilament protein as outcome predictors.^{1,12} Thus, WHO grade II PPTIDs may consist of lobulated, transitional or diffuse subtype patterns, which have a higher expression of neurofilament, 0–5 mitoses per 10 high-power field, and moderate MIB-1 (Ki-67 equivalent antibody) labeling indices. High-grade PPTIDs do not contain pineocytomatous rosettes. They have higher MIB-1 indices, more than 6 mitoses per 10 high-power field, or less than six mitoses per 10 high-power field, but negative for neurofilament. MIB labeling indices are higher in PPTIDs (8–11.8%) compared to pineocytomas (1.6%), but lower than in pineoblastomas (24–27%).¹³ Endothelial proliferation and necrosis are more common in higher grade PPTIDs. PPTIDs have to be considered as potentially aggressive neoplasms.^{1,11}

Nevertheless, subsequent studies did not confirm any correlation between the immunoreactivity and the mitotic index, the Ki-67 proliferation index, and the survival rate in PPTID patients.^{14–16} Moreover, some authors found cut-offs of 3–4 mitosis/high-power field to determine high mitotic activity.^{15,16}

Small biopsy samples sometimes might offer difficulties to assess accurately mitotic counts. In this regard, the Ki-67 proliferation index would be a useful marker of proliferation. Yu et al. determined the Ki-67 proliferation index ranging from 1% to 15% in grade II PPTIDs and from 3% to 40% in grade III PPTIDs.¹⁶ Fevre-Montange et al. found a Ki-67 proliferation index of 0%, $5.2 \pm 0.4\%$, $11.2 \pm 2\%$, and $36.4 \pm 6.2\%$, respectively in pineocytomas, PPTIDs grade II, PPTIDs grade III, and pineoblastomas.¹⁷ In other series, the Ki-67 proliferation index was 1.7% and 12.6%, respectively in low-grade and high-grade tumors.¹⁵

These results indicate the heterogeneity of PPTIDs' proliferation activity, and the lack of correlation with the neurofilament immunoreactivity. In conclusion, other proposals to classify PPTIDs include mitosis $<4/10$ high-power field and Ki-67 $<5\%$ for grade II, and mitosis $\geq 4/10$ high-power field and/or Ki-67 $\geq 5\%$ for grade III PPTIDs.¹⁵

The 5 year survival rate for WHO grade II PPTIDs is 74%, and 34% for WHO grade III.^{1,18,19} Factors affecting the survival of PPTs are morphological subtype, as well as histologic grading according to the presence or the absence of necrosis, mitotic index and NFP immunostaining.¹ The relapse rate for WHO grade II PPTIDs was 26%, with recurrence generally restricted to the location of the primary tumor. In WHO grade III lesions, recurrence occurred in 56% of the cases, mainly occurring outside the pineal region, despite adjuvant radiotherapy.¹⁸

Based on the described variability of definitions and aiming to discover prognostic factors, we did not classify PPTIDs in low or high grade, but all cases were included in a single group. Thus, our five-year and ten-year

survival rates for PPTIDs were 92% and 71% respectively. Even though we have PPTID patients with more than 20 years of survival, our follow up period would be insufficient to properly determine the 15-20 years survival rate. Variables related with a good outcomes in our series were: a) the GTR, which we consider the most important variable in spite of a patient with a 5x5cm tumor, who required multiples surgeries with a bad clinical status after all of them; b) a continuous and accurate follow up to discover incipient recurrences, initially every six months, and later every year in those with a high risk of recurrence such as partially resected or high grades tumors; and c) radiotherapy for patients with partial resections, small recurrences at the follow up, and pleomorphic variants with pineoblastoma features, or very high proliferation index and high mitotic activity as well. We had a good tumor control but bad long-term clinical outcome after treatment with brachytherapy. However, our experience is restricted to only one patient.

We are unable to consider the histologic grading as a variable related with the survival and the tumor control rate. Firstly, our sample is small with a big variety of immunohistologic features; secondly, the two patients with a tumor-related death underwent GTR and brachytherapy respectively, with absence of tumor recurrence at the last follow up.

Regarding the radiosurgical treatment of PPTIDs, a study based on the use of stereotactic Gamma Knife radiosurgery for histologically defined tumors determined a poor local control with poor survival rate for PPTIDs. Stereotactic radiosurgery was used as the primary treatment modality in 4 cases, and as a treatment for recurrence in 3 cases. They reported an actuarial local control and a survival rate of 50% and 56% at 5 years follow up, respectively. However, five patients had less than 2 years of follow-up. The median time to recurrence was 34 months. These results contrast with the 80% survival rate and 80% actuarial local control reported at a 20 years follow up for germinomas, which are the most radiosensitive tumors of the pineal region.²⁰ Lutterbach et al. reviewed prognostic factors in higher grade PPTs in patients over 18 years of age who had received radiotherapy. They included patients with post-operative adjuvant radiotherapy and those treated only with radiotherapy. They found better spinal control in patients with PPTIDs versus pineoblastomas.²¹ Radiotherapy does appear to have a positive influence on survival for higher grade PPTs.¹⁸ It is not known if radiotherapy for grade II PPTIDs at the time of diagnosis may delay tumor recurrence, or if there is a benefit in those patients who have had GTR.¹⁸ There is no established dose-effect efficacy for craniospinal radiotherapy for PPTID grades.^{18,21}

Debajyoti Chatterjee et al. described the outcome of 16 PPTIDs. GTR was performed in 4 cases, subtotal excision in 5 cases, and the other 7 cases underwent endoscopic biopsy. All of them underwent radiotherapy, and

only one case chemotherapy. Only three patients had long term follow up (10, 10 and 5 years), 6 patients were lost at the follow-up, and the rest had less than 35 months of follow-up. Three patients died at 3, 4, and 4 months after surgery.¹⁵

Even though we do not have a protocol for the management of those rare tumors in our department, our retrospective analysis showed us that the administration of radiation therapy allowed to control recurrent and/or small residual PPTIDs. However, in a histologic low grade tumor that underwent partial resection followed by radiation therapy, the tumor grew after a year of follow up and required GTR. Patients with pineoblastoma features, or very high proliferation index and high mitotic activity, had a good long term outcome after GTR and radiation therapy.

In 2016, a review performed by Kang et al. described the multidisciplinary management (surgical resection and radiochemotherapy) of PPTIDs.²² 160 patients were re-evaluated and only 30 of them received some kind of chemotherapy. Chemotherapy schemes included a wide variation of agents such as: vincristine, lomustine, prednisone, cisplatin, vinblastine, bleomycin, etoposide, carboplatin, dibromodulcitol, 5-fluorouracil, methotrexate, ifosfamide, etoposide, carboplatin, cyclophosphamide, nimustine, vindesine, and interferon. Very few cases had a long follow up more than 5 years, and the role of chemotherapy as an adjuvant therapy has still to be confirmed.²²

Although PPTIDs might rarely occur in the pediatric population, the treatment plan usually follows similar schemes as for the pineoblastoma treatment. Thus, chemotherapy is used in children with recognized response. Moreover, chemotherapy might be an important adjuvant treatment when radiotherapy is not recommended.¹¹ Previous reports determined that chemotherapy was insufficient to prevent leptomeningeal relapse.^{11,18}

In our series, chemotherapy was unnecessary after GTR and adjuvant radiotherapy. On the other hand, we did not have any pediatric patient with a PPTID. However, when indicated, we agree to use chemotherapy in children with PPTIDs.

Conclusion

A proper multidisciplinary management of PPTIDs based on a GTR of the lesion, and an accurate cranial adjuvant radiotherapy in selected cases, may improve the overall survival of these tumors. A strict follow up is imperative for these aggressive lesions due to their frequent recurrences.

Disclosure

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Figure Legends

Fig. 1 Microphotographs of a surgically treated pineal parenchymal tumor of intermediate differentiation. **A** and **C**, Hematoxylin and eosin stain with moderately high cellularity and mild to moderate nuclear atypia. **B**, Positive monoclonal antibody to non-phosphorylated neurofilament (SMI 32 stain). **D**, Ki67 index with high proliferation activity

Fig. 2 MRI spectrum of case 10 PPTID. **A** and **B**, Preoperative cerebral MRI studies. **C**, Last cerebral MRI with a very small pineal remnant after radical resection and radiation therapy. **D**, Last spinal MRI with multiple metastases in cervical, thoracic, and lumbar levels

Fig. 3 MRI spectrum of case 9 PPTID. **A**, Preoperative cerebral MRI study. **B**, Immediate postoperative cerebral MRI study with a very small residual pineal lesion. **C**, Cerebral MRI study before radiation therapy delivery. **D**, Last cerebral MRI study with a small controlled remnant after radiation therapy

Fig. 4 MRI spectrum of case 8 PPTID. **A**, Preoperative cerebral MRI study. **B**, Immediate postoperative cerebral MRI study with gross total resection of the pineal tumor. **C**, Cerebral MRI study 13 years after surgery with an incipient recurrence. **D**, Cerebral MRI study 15 years after surgery with a very small recurrence

Table 1. Features of Pineal Parenchymal Tumors of Intermediate differentiation pineoblastomas according to the 2007 World Health Organization (WHO) Classification of Central Nervous System Tumors.^{1,11}

Grading	WHO grade II or III (grading criteria not well established)
Incidence, age and sex distribution	> 20% of PPTs (0-60%), at all ages with slightly female preponderance
Symptoms and signs	Similar to other tumors of the pineal region. Hydrocephalus, neuro-ophthalmologic dysfunction (Parinaud's syndrome), changes in mental status, brainstem or cerebellum dysfunction, and hypothalamic-based endocrine abnormalities. Cerebrospinal metastases occur in a minority.
Neuroimaging	There are no pathognomonic features on neuroimaging for PPTIDs. It can be difficult to distinguish PPTIDs from pineocytomas or pineoblastomas. Heterogeneously hypointense and heterogeneously hyperintense on T1 and T2- weighted images respectively, with uniform contrast enhancement.
Macroscopy	Similar to that of pineocytoma, a circumscribed soft tumor lacking gross evidence of necrosis.
Histopathology	Neurocytoma-like tumor with moderately high cellularity, mild to moderate nuclear atypia, and low to moderate mitotic activity. The PPTID includes transitional cases in which typical pineocytomatous areas are associated with a diffuse pattern. Occasional giant cells, Homer Wright rosettes or ganglion cells may infrequently be seen.
Immunohistochemistry	Synaptophysin and neuron-specific enolase positivity. Variable reactivity to neurofilament protein, chromogranin A, retinal S-antigen and S-100 protein. PPTID Grades II and III can be distinguished on the basis of mitotic activity (higher in high grade PPTID) and neurofilament protein

	immunoreactivity (higher in low grade PPTID).
Genetics	The most common chromosomal imbalances are +4q, +12q, and -22. In a real-time PCR analysis, the expression of 4 genes (PRAME, CD24, POU4F2 and HOXD13) is distinctly high, almost the same level as in pineoblastomas, and in contrast to the low expression of these genes in pineocytoma.
Histogenesis	The occurrence of mixed tumors (pineocytoma-pineoblastoma) confirms the existence of a spectrum from pineocytoma through PPTID to pineoblastoma.
Prognostic and predictive factors	The five-year survival rate of patients with PPTIDs is 39% to 74%. PPTIDs rarely produce extraneural metastases. Factors affecting the survival of PPTs are the morphological subtype, as well as the histologic grading according to the presence or the absence of necrosis, mitotic index and NFP immunostaining. Focal relapse around 20%.

PPT, pineal parenchymal tumor; PPTID, pineal parenchymal tumor of intermediate differentiation; WHO, World Health Organization.

Table 2. Microsurgical key points for the management of PPTIDs.

1. Under high magnification (approx. 15x), the superior cerebellar cistern and the quadrigeminal cistern are opened by a supracerebellar route with release of cerebrospinal fluid.
2. When a high vascularized area is suspected, intraoperative indocyanine green angiography is used to define vascular structures.
3. The posterior surface of the tumor is separated from the venous structures using a thumb regulated suction and bipolar forceps. The water dissection technique may be used and a continuous irrigation maintains a clean surgical field.
4. Microsurgical ring forceps are used to obtain a tumor sample for immediate histological study.
5. An internal decompression with a thumb regulated suction tube and bipolar or ring microforceps is performed aiming to find and open the posterior wall of the third ventricle.
6. The tumor is dissected from the surrounding neurovascular structures by water dissection technique, cotton dissection, and using microscissors and bipolar microforceps.
7. Once medial, lateral, and superior surfaces of the tumor are separated from the adjacent tissue, under soft but continuous traction –using bipolar microforceps or ring microforceps- the tumor is separated from its inferior border by using a thumb regulated aspiration.
8. A microsurgical mirror or an endoscope may be helpful to recognize some residual tumor, particularly at

the inferior border of the field.

9. A careful hemostasis with bipolar coagulation, Surgicel® (Ethicon Inc, Johnsons & Johnson, Switzerland) and Tachosil® (Takeda Austria GmbH, Linz, Austria) is carried out, and the closure is accomplished under the microscope.

Table 3. Characteristics of 15 PPTID cases operated in Helsinki Neurosurgery between 1997 and 2015.

Case	Patient	Symptoms	MRI Imaging	Tumor size LxWxH (cm)	Surgical treatment	Date of surgical removal	Histopathology	Immediate postoperative imaging	Immediate postoperative clinical status	RT (WAS)	Reason for RT	Last clinical FU in HUH	Date last FU in HUH	Pineal tumor at last FU	Alive May 2018	Survival months	Reason of death
1	30 F	Left hemiparesis, incidental finding	NAI	1x1x1	GTR (Right SCIT)	Dec.97	MIB-1: 1-2%, P53(-), GFAP(-), Cg (+), SYP(+), MAP-2(+)	Uneventful	Uneventful	No	No	Normal	Mar.00, FU in original center	No	Yes	248	
2	47 F	Progressive hydrocephalus	NAI	NAI	GTR (midline SCIT)+EVT +VPS	Jan.98	1 Mit./10HPF, MIB-1: 9%, pleomorphic variant with pineoblastoma features), NF (+) and SYP (+), Cg (+/-)	Occipital epidural hematoma	Epidural hematoma and left hemiparesis	Yes, 54Gy (6 WAS)	Pineoblastoma features.	Depression, help for walking, double vision	Sep.15	No	Yes	247	
3	70 M	Progressive hydrocephalus in patient with history of stroke and C7 cervical fracture	T1: ISO T2: HYPO T1 Contrast: full (+)	2x1.4x1.6	EndTV+STx Biopsy+VPS +Brachytherapy	Jul.98	5 Mit./10HPF, Ki-67: 20%	Uneventful	Uneventful	Yes, Brachytherapy	BT	Assistance for walking, memory problems	Apr.04	Small	Died: 26.12.2006	101	Poor clinical status
4	33	Acute	T1 Contrast: full	1.3x1x1.	VPS+STxBio	Sep.98,	7-13 Mit./10HPF, Ki-		Uneventful	Yes, 54Gy (4	Pineoblast	Normal	Feb.17	No	Yes	238	

	F	hydrocephalus, double vision	(+)	5	psy+PR (midline SCIT)+ GTR (SCIT - redo)	Oct.98	67: 10-25% pleomorphic variant with pineoblastoma features more than pineocytoma			WAS)	oma features						
5	55 F	Acute hydrocephalus, right leg paresis due to history of stroke	T1 Contrast: full (+)	1.5x1.5x 1.5	EVT+ VPS + GTR (midline SCIT) + removal of VPS due meningitis	Jan.99	MIB-1: 1-2% some pineoblastoma features, few mitotic features, no necrosis, pineocytoma, SYP (++)	Uneventful	Meningitis, ataxia	Yes, unknown dose	Pineoblast oma features	Follow up in center of origin	Jan.99, FU in original center	No	Died: 31.01.20 11	144	Unknown
6	70 M	Acute hydrocephalus, unconsciousness, left side hemiparesis,	T1: ISO T2: HYPO T1 Contrast: Ring (+)	1.7x1.5x 1.5	EVT+GTR (midline SCIT)	Feb.99	MIB-1: 5%, SYP (+), GFAP (+) in the periphery	Small cerebellar hematoma	Some double vision and left side hemiparesis	No	No	As preoperati vely	May.99, FU in original center	No	Died: 12.12.20 03	46	Coronary disease
7	70 F	Acute hydrocephalus	T1: ISO T2: HYPO T1 Contrast: full (+) Microcystic component	1.9x1.8x 1.7	EVT+VPS+ GTR (midline SCIT)	Jan.00	MIB-1: 5%, GFAP (-), SMI 32 (-), SYP (++), Cg (+), P53-, MAP2 +, Pineocytomatous rosettes but atypia.	Uneventful	Parinaud's S.	No	No	Normal	Aug.15	No	Yes	223	
8	39 F	Migraine and incidental finding	T1: ISO T2: HYPO	1.8x1.5x 1.7	GTR (midline	Oct.03	MIB-1: 10%, SYP (+), Cg (+), MAP-2+;	Uneventful	Double vision	No	No	Only slight headache	Apr.18	Small	Yes	178	

		in MRI	T1 Contrast: full (+) Microcystic component		SCIT)		CD45 (-), Ck (-). P53 (+/-).										
9	55 F	Progressive hydrocephalus, unspecific visual problems	T1: ISO T2: HYPO T1 Contrast: full (+) Microcystic component	3.4x2.3x2.6	STR (Right SCIT)	Jan.10	MIB-1 10-15% . Proliferation with some mitosis but still no pineoblastoma criteria	Uneventful	Uneventful	Yes, 54Gy (6 years after surgery).	For recurrence.	Depression , suicide attempt	Sep.17	Small	Died: 1.12.2017	95	Pneumonia
10	28 F	Progressive hydrocephalus, diplopia	T1: ISO T2: HYPO T1 Contrast: full (+) Cystic component	5.4x5.5x4.8	RR (Right SCIT+IVVA +POIH) + RT	Dec.10-Mar.11	MIB-1: 20%, NF (++)	Uneventful	Tracheostomy, no paresis	Yes. 54Gy (20 WAS)	Partial Resection, high proliferation index	Left-side hemiparesis, dependent for daily activities	Aug.13	Small	Died: 15.03.2014	39	Poor clinical status, spinal methastasis
11	57 F	Acute hydrocephalus	T1: ISO T2: HYPO T1 Contrast: full (+) Cystic component	2.8x2.4x2.7	EVT+PR (Right SCIT) + RT + GTR (Left SCIT)	Dec.10, Mar.12	MIB-1: 2% to 4-5%, some pineocytes, NF (+), SYP (+), P53 (-) GFAP (-), Cg (-)	Uneventful	Uneventful	Yes, 54Gy, (10 WAS)	Partial resection.	Normal	Mar.17	No	Yes	91	
12	58 F	Progressive hydrocephalus, visual	T1: ISO T2: HYPO T1 Contrast: full	2.1x1.7x2.4	GTR (Right SCIT)	Sep.11	MIB-1: 7-8% SYP (+++) NF (+), P53 (-) , GFAP (-), more	Uneventful	Uneventful	No	No	Normal, no new deficits	Dec.16	No	Yes	82	

		disturbances	(+) Cystic component				pineocytoma appearance.										
13	24 F	Progressive hydrocephalus, diplopia	T1: ISO T2: HYPO T1 Contrast: full (+) Cystic component	2.5x3.4x 3	GTR (Right SCIT)	Oct.14	MIB-1 20%, SYP (+), SMI 32 (+), Cg (-), BRAF (-), PCK (-), no necrosis, pleomorphic aspect without pineoblastoma features	Uneventful	Disorientated , still bed ridden, no new deficits	Yes, 54Gy (4 WAS)	High proliferatio n and high mitotic activity	Normal, mild neuropsych ological deficit	Oct.16	No	Yes	45	
14	46 M	Progressive hydrocephalus, Parinaud's syndrome	T1: HYPER T2: HYPO T1 Contrast: very small internal enhancement Cystic component	3.4x4.5x 3.4	VPS+PR (Right SCIT)	Mar.15	MIB-1: 4-5%, NF (++), SYP (++) P53>5%, pineocytoma appearance with some atypia	Hematoma in operative bed	Paresis of the pharynx, bed-ridden, left hemiparesis, obeys commands, totally dependent	Recommended	Recommen ded	Left side hemiparesi s, pharynx paresis, obey commands	Apr.15	Lost	Foreign	Lost	
15	67 M	Incidental finding, anosmia, memory problems.	T1: ISO T2: HYPO T1 Contrast: full (+)	1.5x1.5x 1.5	GTR (midline SCIT)	Apr.02	MIB-1 up to 20% with pineoblastoma components, MAP-2 (+), SYP (+), Cg (+), GFAP (-),	Uneventful	Slight double vision	14Gy SRS (6 years after surgery)	Recurrence	Dementia for cortical and subcortical hemorrhag es	Feb.14	No	Died: 04.2014	144	Severe vascular dementia

L, length; W, width; H, height; NAI, not available information; T1, T1 weighted images; T2, T2 weighted images; T1 Contrast, T1 after contrast administration; ISO, Isointense image; HYPO, hypointense image; HYPER, hyperintense image; BT, brachytherapy;

GTR, gross total resection; PR, partial resection (<90%); STR, subtotal resection (>90%); VPS, ventriculoperitoneal shunt; EndTV, endoscopic third ventriculostomy; EVT, external ventriculostomy; STx Biopsy, stereotactic biopsy; SCIT, supracerebellar infratentorial approach, IVVA, suboccipital approach to the fourth ventricle; POIH, posterior occipital interhemispheric approach; WAS, weeks after surgery; SRS, stereotactic radiosurgery; FU, follow up; HUH, Helsinki University Hospital;

Syp, synaptophysin, NF neurofilament, Ck cytokeratin, PCk, pancytokeratin, Cg, chromogranin, Mit./10HPF, mitosis per ten high power fields

Title

Pineal parenchymal tumors with intermediate differentiation: a long-term follow up study in Helsinki Neurosurgery

Abbreviations and Acronyms

FL-EBRT, fractionated linac-based external beam radiation therapy; GTR, gross total resection; PPT, pineal parenchymal tumor; PPTID, pineal parenchymal tumor of intermediate differentiation; SCIT, supracerebellar infratentorial; VPS, ventriculoperitoneal shunt; WHO, World Health Organization

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Disclosure

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