Pineocytomas: A Long-Term Follow up Study of Four Cases in Helsinki Neurosurgery

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Abstract

Background: Pineocytomas are rare benign lesions with a relatively good prognosis if gross total resection can be achieved.

Report of cases: We present a retrospective review of four patients with histologically confirmed pineocytomas consecutively operated on after 1997. All of our patients were alive at a mean follow-up of 224.5 months (range 204-246). A gross total resection was accomplished in all cases. The cornerstones for the surgical resection of pineocytomas are reported.

Conclusions: A proper management of pineocytomas, based on the gross total microsurgical resection of the lesion, results in an excellent long term outcome of these pineal lesions.

Abbreviations and Acronyms

GTR: Gross Total Resection; PPT: Pineal Parenchymal Tumor; WHO: World Health Organization

Introduction

Pineal region tumors represent less than 1% of all intracranial neoplasms. Pineal parenchymal tumors (PPTs), a group of relatively heterogeneous pineal lesions, comprise around 14-27% of all pineal region tumors. According to the 2007 World Health Organization (WHO) Classification of Central Nervous System Tumors the WHO grade I pineocytomas account between 14% and 30% of the PPTs. The 2016 World Health Organization (WHO) Classification of Central Nervous System Tumors did not add new feature to the classification system for primary CNS soft tissue tumors [1-3].

Pineocytomas have distinct features when compared to other pineal parenchymal tumors (Figure 1) (Table 1). Their prognosis is usually very good, and microsurgical management is still considered the gold standard [4].

<table>
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<th>Grading</th>
<th>WHO grade I</th>
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<tr>
<td>Incidence, age and sex distribu-</td>
<td>14-60% of PPTs, at all ages (mean: 38 years old), without sex predilection.</td>
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<td>tion</td>
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<td>Localization</td>
<td>Pineal region; however, extensions into the posterior third ventricle are often seen.</td>
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Grading WHO grade I

- Symptoms and signs: Hydrocephalus, neuro-ophtalmologic dysfunction, changes in mental status, brainstem or cerebellum dysfunction, hypothalamic-based endocrine abnormalities, and rarely, pineal apoplexy.

- Neuroimaging: Brain MRI: low or isointense on T1 and hyperintense on T2-weighted images with strong, homogeneous contrast enhancement. Usually less than 3 cm in diameter.

- Macroscopy: Well-circumscribed lesions with a grey-tan, homogeneous or granular surface. Cystic formation may be present.

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**Histopathology (Figure 2)**
Well-differentiated tumor composed of relatively small, uniform, mature cells resembling pineocytes. Pineocytomatous rosettes composed of abundant and delicate tumor cell processes with irregular hyperchromatic nuclei and prominent processes with bulbous extensions. Mitotic figures are absent or less than 1/10 HPF.

**Immunohistochemistry**
Usually strong reactivity for synaptophysin, NSE and NFP. Variable staining for class III $\beta$-tubulin, tau protein, PGP 9.5, chromogranin and the neuropeptide serotonin. Immunoreactivity for retinal S-antigen and rhodopsin. In tissue culture pineocytoma cells can synthesize serotonin and melatonin.

**Genetics**
Monosomy or loss of chromosome 22, deletions in the distal 12q region, and partial deletion or loss of chromosome 11 may be related to tumor progression. There is also high-level expression of genes coding for enzymes related to melatonin synthesis (TPH1, HIOMT), and genes involved in retinal phototransduction (OPN4, RGS16, CRB3)

**Histogenesis**
Pineal parenchymal tumors mimic the developmental stages of the human pineal gland and arise from pineocytes or their precursor cells.

**Prognostic and predictive factors**
Large interval between the onset of symptoms and surgery, no metastasis, the 5-year survival rate ranges from 86% to 100%, no relapses following gross total resection. Pineocytomas with glial, neuronal and retinoblastic elements appear to have a prognosis similar to conventional pineocytomas.

**Table 1:** Features of pineocytomas according to the 2007 World Health Organization (WHO) Classification of Central Nervous System Tumors [1-3]

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**Figure 1:** Microphotographs of a surgically treated pineocytoma. (A) Hematoxylin and eosin stain with small, uniform, mature cells resembling pineocytes and pineocytomatous rosettes. (B) Positive monoclonal antibody to non-phosphorylated neurofilament (SMI 32 stain), and (C) Ki67 index with very low proliferation activity

In this paper we report on the microsurgical management of four pineocytomas operated consecutively in Helsinki Neurosurgery between 1997 and 2015.

**Report of cases**
Four patients with histologically confirmed WHO grade I pineocytomas were operated during the study period. We reviewed the Finnish population register in July 2018 to assess the current status of our patients.

In most of the cases, we approached pineal parenchymal tumors through a supracerebellar infratentorial route with the patient in the sitting position, which has been reported previously by our group [5-8].

The microsurgical management of pineocytomas is summarized in the Table 2 [9-12].

1. An adequate preoperative evaluation of the craniospinal magnetic resonance imaging, proper cytologic studies and tumor markers in blood and cerebrospinal liquid is essential for the correct management of pineal region tumors.
2. A careful evaluation of the relation between the deep venous system and the tumor in the MRI is the more critical aspect for the surgical planning.
3. Long microsurgical instruments are required to approach the pineal region.
4. We prefer to place the patient in a sitting praying position whether the supracerebellar infratentorial or occipital interhemispheric approaches are suitable surgical routes.
5. Concomitant hydrocephalus may be treated opening the posterior wall of the third ventricle at the same microsurgical stage in case of slowly progressive hydrocephalus. However, in acute events, shunt or endoscopic procedures might represent the first option.
6. Small occipital craniotomies (3-4cm) are performed to approach the pineal region. The supracerebellar infratentorial route is preferred when the lesion expands under the level of the tentorium and posterior to the deep venous system. The occipital interhemispheric approach is preferred for tumors with more supratentorial component between the deep venous system and the splenium. In our experience, pineocytomas are usually small tumors with short supratentorial extension.
7. After a paramedian suboccipital craniotomy, the dura is opened under the microscope based on the ipsilateral transverse sinus. Strong retraction with dural stitches provides an adequate surgical view of the supracerebellar cistern.
8. Under high magnification, we access the quadrigeminal cistern over the superior surface of the cerebellar hemisphere, while cerebrospinal fluid is released.
9. A dark tight membrane covering the quadrigeminal cistern is sharply opened, and once the tumor is recognized, we coagulate and cut its posterior wall.
Microsurgical ring forceps are used to obtain a tumor sample for the immediate and definitive histological study. An internal decompression of the tumor is performed with a thumb regulated suction and bipolar forceps or ring microforceps. Continuous irrigation maintains a clean surgical field. A microsurgical dissection is performed aiming to reach the posterior wall of the third ventricle to release more cerebrospinal fluid. The tumor is dissected from the surrounding neurovascular structures by water dissection technique, cotton dissection, and using micro-scissors and bipolar microforceps. Once the tumor is 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. Extreme caution should be taken along the dissection of the inferior border of the lesion as small bleedings may occlude the cerebral aqueduct. In case of large tumors, a microsurgical mirror or an endoscope may be helpful to recognize some residual tumor at this inferior hidden area. Accurate hemostasis is carried out with bipolar coagulation, and small pieces of Surgicel® (Ethicon Inc, Johnsons & Johnson: Switzerland) and Tachosil®. (Takeda Austria GmbH: Linz, Austria)

Table 2: Microneurosurgical management of pineocytomas

Case 1
A twenty-year-old female was referred from the neurological department. She presented with right hand tremor and anisocoria with the left pupil enlarged. Brain MRI revealed a pineal cystic lesion compressing the tectal plate. The patient underwent a supracerebellar infratentorial approach in sitting position with gross total tumor resection in January 1998. During the postoperative course, the patient developed Parinaud’s syndrome, which improved gradually in the following months. The histologic diagnosis was grade I pineocytoma. In June 1998, at medical evaluation the patient presented slight double vision, with almost complete resolution of the gaze paresis. The patient continues to do well with no evidence of recurrence more than 246 months following surgery.

Case 2
A twenty-year-old female was evaluated in our department after a head trauma few days before. Cranial CT and the following brain MRI revealed an incidental 1.8x1.5x1.5 cm pineal cystic lesion with ring enhancement after contrast medium administration (Figure 2).

Figure 2: MRI spectrum of case 2 WHO grade I pineocytoma
The patient underwent a supracerebellar infratentorial approach in sitting position with gross total resection in July 1999. The postoperative course was uneventful.

Case 3
A six-year-old female was evaluated in our department after six months of continuous headache and nausea without any neurological deficit. Cranial CT and brain MRI revealed an incidental 1x1x1 cm pineal lesion with mixed solid and cystic components. There was no evidence of hydrocephalus (Figure 3).

Figure 3: MRI spectrum of case 3 WHO grade I pineocytoma
The patient underwent a supracerebellar infratentorial approach in sitting position with gross total resection in March 2000. The postoperative course was uneventful. The histologic diagnosis was grade I pineocytoma. In September 1999, the patient was normal at medical evaluation. She continues to do well with no evidence of recurrence more than 228 months following surgery.

Case 4
A sixty-five year-old female was evaluated in our department for uncontrollable vertigo and right hand tremor. Brain MRI revealed a 1.5 cm solid pineal lesion with homogeneous enhancement after contrast medium administration (Figure 4).

Figure 4: MRI spectrum of case 4 WHO grade I pineocytoma
The patient underwent a supracerebellar infratentorial approach in sitting position with gross total resection in March 2000. The postoperative course was uneventful. The histologic diagnosis was grade I pineocytoma. In June 2000, at medical evaluation the patient presented a small wound laceration that was treated with antibiotics. The patient continues to do well with no evidence of recurrence more than 220 months following surgery.
The patient underwent a supracerebellar infratentorial approach in sitting position with gross total resection in July 2000. During the postoperative course, the patient presented Parinaud’s syndrome and some balance disturbances that improved gradually.

The histologic diagnosis was a grade I pineocytoma. About one year postop, the patient did not show any residual visual problems. However, slight balance disturbances were still present. The patient continues to do well with no evidence of recurrence more than 204 months following surgery.

**Discussion**

In this paper we report about the microsurgical management of four patients who harbored benign pineocytomas and who were operated consecutively in Helsinki Neurosurgery between 1997 and 2015. All our patients are alive at a mean follow-up of 224.5 months (204-246).

A gross total resection was accomplished in all the cases.

A systematic review of pineocytomas in 166 patients by Clark, et al. concluded that gross-total resection is the optimal treatment for pineocytoma and offers a potential cure for these lesions. However, in patients with subtotal resection, adjuvant radiation therapy might be of benefit, which remains debated. The study demonstrated that 21%, 38%, and 42% of patients had undergone a biopsy, subtotal resection, and gross-total resection respectively. Radiation therapy was applied in 28% of afflicted patients. The 1- and 5-year progression-free survival rates between the gross-total resection group and the subtotal resection plus radiation therapy group were significantly different with superior outcome in the GTR cohort (100% vs. 94% at 1 year, and 100% vs. 84% at 5 years, respectively). Importantly, no statistically significant difference existed in the progression free survival rate between the “subtotal resection” patients and “subtotal resection plus radiation therapy” patients. Thus, in this large compilation, Gross total resection was superior to radiation therapy and partial resection [4].

Another study on stereotactic Gamma Knife radiosurgery (SRS) for histologically confirmed tumors reported 20-year local control rate of 81% and a survival rate of 76%. The actuarial median time to recurrence was not reached after 20 years and there were no recurrences observed after 45 months following stereotactic radiosurgery. These results are similar to survival and local control rates (of 80%) reported post SRS at 20 years follow-up for germinomas, the most radiosensitive pineal tumors [13].

According to the literature and as confirmed in our small cohort, pineocytomas have very good prognosis. Even though radiosurgery might achieve a good outcome in the treatment of these lesions, the microsurgical management is still considered the gold standard [4,14]. When gross total resection can be achieved, the patient may be considered cured since a recurrence is extremely rare. However, skillful and diligent microneurosurgery is required when dealing with these seated lesions in order to avoid severe complications.

Variables such as proper team work (Neurosurgeon, anesthesiologist, scrub nurse and all involved personnel), suitable principles of positioning and approach, skillfully conducted microneurosurgery based on the principle “simple, clean and safe”, and not less important, the surgical experience of the Neurosurgeon are essential in achieving GTR [7-9,15].

It is well known that pineal parenchymal tumors may mimic pineal cysts in the pattern of their post-contrast enhancement of their cystic components. MRI studies from three of our four patients revealed some cystic components, and one of the cases was initially considered as pineal cyst (Figure 2). Only after a careful analysis of the surgical specimen, a pineocytoma was confirmed. In this regard, a careful case-by-case evaluation and cooperation between the neuroradiologists and the neurosurgeons is advised [16,17]. However, it is worth to mention that currently, no MRI method is able to specifically differentiate benign cysts from malignant tumors with cystic components such as pineoblastomas, germinomas, or mature teratomas.

Thus, atypical cystic lesions should be more frequently followed, and neurosurgical diagnostic/therapeutic interventions would be correctly indicated [18-23].

The small number of patients represents a significant limitation of our study. However, as these tumors are extremely rare, we consider it especially important to report our long term observations in this selected series of PPT patients.

**Conclusion**

The gross total microsurgical resection currently represents the standard management for pineocytomas, and may be curative.

**Conflict of Interest**

The senior author, Prof. Juha Hernesniemi, is an Aesculap counselor. The C. Ehrnrooth Foundation partially supports the present project. The authors have no personal financial or institutional interest in any of the drugs, materials, and devices described in this article.

**References**


