

# Clinical characteristics, late effects and outcomes in pineoblastomas in children: a single center experience

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## ABSTRACT

**Background.** Pineoblastomas (PB) are rare tumors of the central nervous system and are more common in children. There is no consensus about standard of care. The objective of this study is to analyze the outcome of children with PB.

**Methods.** Six patients with PB who were diagnosed between 1990-2012 were evaluated retrospectively. Demographics, age of diagnosis, first complaint, tumor region, diagnosis type, seeding metastasis to the spinal axis or cerebrospinal fluid (CSF), treatment and survival of these patients were recorded.

**Results.** Three patients had subtotal resection and all patients received chemotherapy and craniospinal irradiation (CSI) after diagnosis. Median follow-up after treatment was 5.5 (range:1-19) years. Two patients are alive with no evidence of disease for 7.5 and 10 years, one of whom was diagnosed with papillary thyroid carcinoma 9.5 years after treatment. One of the patients who died had lived for 19 years after diagnosis.

**Conclusions.** Pineoblastomas are rare but very aggressive tumors; more effective treatment strategies are needed. Survivors should be followed up for late effects such as second malignancies and endocrine deficiencies.

**Key words:** pineoblastoma, children, late effects.

Pineoblastoma (PB) is a rare embryonal tumor of the pineal gland.<sup>1</sup> Histologically, PB are classified as WHO grade IV tumors.<sup>2,3</sup> While they typically appear radiographically as focal enhancing mass, PB can also be locally invasive and spread outside the pineal region through the subarachnoid space.<sup>4</sup> In this study, we assessed the demographics, treatment, late effects and outcome of PB patients who were diagnosed and treated in the İstanbul University Oncology Institute (IUOI) during 1990-2012.

## Material and Methods

During 1990-2012, 516 children with brain tumors were diagnosed and treated in the IUOI. Among these patients six (1.16 %) were diagnosed with PB. Demographics, age of diagnosis, first complaint, tumor region, diagnosis type, seeding metastasis to the spinal axis or cerebrospinal fluid (CSF), treatment and survival of these patients were evaluated retrospectively from patient records. All patients had cranial and spinal axis MRI with contrast at diagnosis and during follow-up. Ethics Committee Approval: İstanbul University Cerrahpasa Medical Faculty Clinical Research Ethical Committee (12.02.2013/ 83045809-3507), İstanbul University Oncology Institute Academic Coordination Council (2013-206).

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## Results

There were six patients diagnosed with PB between 1990 and 2012. Three of them were female, the median age of diagnosis was 5.75 years (2-14). The demographics of the patients are shown in Table I and modality of treatment, and outcomes are shown in Table II.

All patients had cranial magnetic resonance imaging (MRI) with contrast at diagnosis. Staging included spinal axis MRI with contrast for all patients, and CSF cytology, for all but patient #2 (Table I) in whom lumbar puncture was contraindicated due to increased intracranial pressure. For pathologic diagnosis, three underwent only stereotactic biopsy because the tumor was considered unresectable by the neurosurgeons and three of them underwent subtotal resection of the tumor. In all patients, surgery was followed by craniospinal radiotherapy (CSRT) (except the 2-year-old patient) and chemotherapy.

All patients received CSRT after surgical biopsy or resection. One patient (Table I, pt #1)

received eight courses of chemotherapy before radiotherapy (RT) due to her young age (< 3 years old). The disease progressed and RT was initiated, however she died in the intensive care unit without completing RT. Two of our patients (#3 and #4) were re-irradiated after the first RT due to relapse.

As chemotherapy, the patients received the institutional protocols used for embryonal brain tumors in the respective years of diagnosis. The first four patients received 8 courses of vincristine (1.5 mg/m<sup>2</sup>, 1st day), etoposide (100 mg/m<sup>2</sup>/day x3 days) and cyclophosphamide (1gr/m<sup>2</sup>/day) (Table I, pt #1-3) or carboplatin (560 mg/m<sup>2</sup>/day) (Table I, pt #4).

One patient (Table I, pt #5) received 8 courses of chemotherapy consisting of vincristine (1.5 mg/m<sup>2</sup>), cyclophosphamide (1gr/m<sup>2</sup>/day), procarbazine (50mg/m<sup>2</sup>) and CCNU (100mg/m<sup>2</sup>), all given in one day. She was given growth hormone 3 years after the end of chemotherapy for one year. While the PB remained controlled ever since, her medical history was not unremarkable: She developed papillary thyroid

**Table I.** Characteristics of patients.

Patient No (#)	Gender	Age (years)	Complaint	Primary Tumor Region	Spinal axis	CSF
1	Female	2	Ataxia	Pineal region	Negative	Negative
2	Female	3.5	Ataxia, tremor	Pineal region	Negative	Not analyzed
3	Male	3.5	Parinaud syndrome vomiting	Pineal region	Positive	Positive
4	Male	8	Parinaud syndrome headache	Pineal region	Negative	Negative
5	Female	10	Headache, vomiting	Pineal region	Negative	Negative
6	Male	14	Headache	Pineal region	Negative	Negative

**Table II.** Modality of treatment and outcome of patients.

Patient No (#)	Biopsy	Resection	Chemotherapy	Radiotherapy	Survival from diagnosis (months)	Results
1	Yes	No	Yes	Yes*	12	Exitus
2	Yes	No	Yes	Yes	42	Exitus
3	Yes	No	Yes	Yes	24	Exitus
4	No	Subtotal resection	Yes	Yes	228	Exitus
5	No	Subtotal resection	Yes	Yes	126	Alive
6	No	Subtotal resection	Yes	Yes	90	Alive

\*: received radiotherapy due to progressive disease, died without completing radiotherapy.

cancer 9.5 years after treatment for PB. She underwent total thyroidectomy and received radioactive iodine ablation therapy. The patient developed seizures 11 years after treatment. Repeated MRI showed there were hyperintense lesions on the subcortical white matter of the left temporal lobe without contrast enhancement. Later, she developed premature ovarian failure. At the time of this report, the patient is 24 years old and continues receiving anticonvulsants, and hormone replacement for thyroid hormone and ovarian hormones. She has good cognitive function and graduated from university.

A fourteen year old male (Table I, pt #6), received postoperative CSRT followed by intensive chemotherapy consisting of ifosfamide (1.8 g/m<sup>2</sup>/d x 5 days, etoposide 100 mg/m<sup>2</sup>/d x 5 days, and carboplatin 560 mg/m<sup>2</sup>/day) for eight courses. The tumor responded, but a contrast enhancing residual remained visible by MRI. It could not be resected and did not progress later. The patient is alive, with good cognitive function. Remaining health concerns for him are low testosterone and obesity. He graduated from university and lives independently.

In the first two patients (Table I, pt #1-#2) the tumor progressed under treatment, both of their family declined further treatment and the patients passed away.

The tumor of the third patient (Table I, pt #3) progressed one month after the end of the first line treatment. He received further treatment with a second series of radiotherapy (RT) to the temporal lobe and 12 courses of temozolomide (150mg/m<sup>2</sup>/day X 5 days, every 28 days) chemotherapy. The tumor progressed again and treatment was switched to CCNU (100mg/m<sup>2</sup>/day, every six weeks), nimotuzumab (150 mg/m<sup>2</sup> /dose once a week for 12 weeks and then every other week thereafter), vinorelbine (25mg/m<sup>2</sup>/day on the same day) and intrathecal methotrexate (12 mg once every week for 3 times). The MRI revealed no response to these protocols, and the treatment was switched again to irinotecan (50mg/m<sup>2</sup>/day X 5 days) and temozolamid (100mg/m<sup>2</sup>/day X 5 days)

every 3 weeks. The patient died two years after diagnosis due to progressive disease.

A later recurrence was observed in a patient who had subtotal resection at the age of 8 years (Table I, pt #4). In this patient the residual tumor appeared stable at first, but then progressed after five years. At this time, he was treated with RT to pineal region and 8 courses of vincristine (1.5 mg/m<sup>2</sup>), cyclophosphamide (1gr/m<sup>2</sup>/day), procarbazine (50mg/m<sup>2</sup>) and CCNU (100mg/m<sup>2</sup>). After 1 year, new tumor appeared as an intradural mass in the sacral region (S2). The family refused a biopsy. He was treated again with only local RT to sacral region. The patient lived for 19 years after the first diagnosis of the PB. He had cognitive and endocrinological problems. He died due to a traumatic fall in his house.

None of the patients had a family history of malignancy, none had ophtalmologic evidence of retinoblastoma.

In our study, the median survival time was 5.5 (range:1-19) years. Only 2 patients are alive and are long term survivors.

## Discussion

The pineal region is compromised of the pineal gland, posterior third ventricle, tela choroidea and velum interpositum. The primary pineal tumors are pineoblastoma (PB) and pineocytoma.<sup>5</sup> Pineoblastomas are rare supratentorial tumors, comprising less than 1% of childhood brain tumors. Pineoblastomas commonly affect children and young adults, and in our study the median age at presentation was 5.75 years (range: 2-14).<sup>6</sup> They mainly occur with a short history of clinical symptoms.<sup>7,8</sup> Signs and symptoms may be nonspecific. Pineoblastomas usually cause third ventricle compression and hydrocephalus leading to vomiting, headaches and somnolence.<sup>7-10</sup> In our center 6 patients with PB were diagnosed among 516 pediatric brain tumors (1.16 %) between 1990-2012 and the most common symptoms were headache, Parinaud's syndrome and ataxia.

Pineoblastomas are embryonal brain tumors similar to medulloblastomas at the histological level, however, at the molecular level there is little similarity. Histologically, these tumors exhibit a classic small round blue cell tumor appearance and Homer Wright and Flexner-Wintersteiner rosettes may also be seen occasionally like medulloblastomas. Positivity for the master regulator of retinal photoreceptor differentiation, CRX, is positive in 100% of pineal parenchymal tumors but it is noticed rarely in medulloblastomas.<sup>1</sup> Similar treatment strategies with high risk medulloblastomas have been suggested for PB.<sup>11</sup> Additionally, PBs -like medulloblastomas- have a tendency to metastasize to the subarachnoid space. All patients should have an additional metastatic evaluation with MRI of spinal axis and CSF cytology. In our study, 1 of 6 patients had spinal axis seeding metastasis with imaging and CSF positivity.

Germ-line RB-1 mutations predispose to pineoblastoma, in addition de Kock et al.<sup>12</sup> have reported that DICER1 is an important susceptibility gene for PB and demonstrated PB to be a manifestation of a germ-line DICER1 mutation. Additionally, mutually exclusive alterations in other microRNA-processing pathway genes as DROSHA, and DGCR8 were common in PB.<sup>13</sup> Liu et al.<sup>14</sup> designed a study of molecular characteristics of PB and made five groups as PB-miRNA1, PB-miRNA2, PB-MYC/FOXR2, PB-RB1, PPTID. Specification of pineal tumor molecular grouping in CNS tumor classification is suggested to be correlated with clinical characteristics and outcome. None of our patients had an ophthalmic manifestation of retinoblastoma and any of the mutations were not investigated in our cases.

Surgery, radiotherapy and chemotherapy are essential for treatment. Surgery as a cornerstone of the treatment offers rapid symptom relief and is reported to be important for long-term survival.<sup>15</sup> Although gross total resection (GTR) is generally recommended, this is not possible in most cases.<sup>16-20</sup> In a recent retrospective analysis of pediatric and adult PB study,

totally 64 patients were included and 42 were children. Twenty-six (61.9%) of the pediatric patients had GTR, and 16 (38.1%) had subtotal resection, however, there was no significant association between the extent of resection and overall survival.<sup>21</sup> In our series, the patients who are still alive had subtotal resection, and all of those that had no resection at all died. Radiation therapy and systemic chemotherapy are also as essential as surgery in this rare aggressive tumor.<sup>19</sup> All of our patients received CSRT, followed by systemic chemotherapy. Craniospinal irradiation followed by local boost to the tumor bed should be standard.<sup>22</sup> On the other hand, maximal surgical resection followed by five cycles of intensive chemotherapy and consolidation with myeloablative chemotherapy and autologous hematopoietic cell rescue (HDCx/AuHCR) and/or CSRT was evaluated in the Head Start I, II, and III study.<sup>23</sup> They found that CSRT and HDCx/AuHCR were statistically associated with improved survival.

Biswas et al.<sup>24</sup> reported a case series where comprehensive CSRT was used in 15 of 17 patients (88%), one patient who received whole brain and ventricular radiation had local and leptomeningeal relapse and died of progressive disease. In a series of 25 patients, progression free survival rates were reported as 47.1 %, 12,5 % and 0 % for those who received CSRT, whole brain RT and focal RT, respectively.<sup>23</sup> In our series, all patients had CSRT except the one, who was less than 3 years old. A recent study from Germany evaluated the treatment of infants with tumors of the central nervous system (1 patient with PB) with Proton Beam Therapy (PBT) and concluded that PBT is feasible for very young children with central nervous system tumors in the short term.<sup>25</sup> None of our patients received PBT, it is not available in our country yet.

According to the data from the Surveillance, Epidemiology and End Results (SEER) between 1973-2007<sup>26</sup>, the most important factors were age and degree of spread of tumor in 95 adult patients with PB; younger patients with local disease had the best prognosis. Parikh et al.<sup>20</sup>, in 41 pediatric pineoblastoma cases, have reported



that, similar to other primitive neuroectodermal tumors, the most significant predictors of survival are age and metastatic disease status on presentation. In the SIOP/UKCCSG PNET 3 study, relatively good survival for non-metastatic pineal PNETs was reported, and there was no evidence that pre-radiation chemotherapy improved outlook.<sup>27</sup> Although pineoblastomas were classified as primitive neuroectodermal tumors in previous studies, it is classified under embryonal malignancy group in the recent WHO CNS classification.<sup>28</sup>

The analysis of 135 children with pinealoblastoma in the European Society for Paediatric Oncology (SIOP-E) and US Head Start pooled data showed that in children younger than 4 years of age at diagnosis, conventional chemotherapy without RT was not sufficient to induce sustained remissions in PB.<sup>29</sup> Friedrich et al.<sup>30</sup> reported a prospective study about CNS-PNET/PB. In this study, from January 2001 to January 2005, 17 eligible children aged <4 years diagnosed as CNS-PNET/PB were prospectively treated in the trial HIT-2000. In nonmetastatic disease (n= 11) HIT-SKK systemic multiagent chemotherapy followed by CSRT were given. Patients with metastatic disease (M1-M3, n=6) received shorter induction chemotherapy with carboplatin and etoposide, followed by tandem high-dose chemotherapy (HDCT) for those, who had good response to induction therapy. During induction and HDCT, patients received intraventricular methotrexate. Craniospinal RT was given to all patients with poor response to induction or with residual disease. The authors found that short and more intensive induction chemotherapy followed by HDCT was more effective than prolonged moderate induction chemotherapy.<sup>30</sup> In another prospective metacentric trial, including 11 children and adolescents with PB, all patients had surgery followed by hyperfractionated RT accompanied by weekly intravenous vincristine and then 8 cycles of maintenance chemotherapy (lomustine, cisplatin, and vincristine).<sup>31</sup> The authors concluded that this treatment strategy

was feasible without major acute toxicity and survival rates were comparable to those of a few other recent studies but superior to those of most other series, including the previous trial, HIT 1991.<sup>31</sup> Gorski et al.<sup>32</sup> used nivolumab in pediatric patients with recurrent brain tumors with some transient partial responses. Although in this series, there was only one patient with PB who had received only one dose of nivolumab, it was suggested to be a promising option in recurrent brain tumors. Additionally, in a retrospective study with limited small sample size with embryonal tumors, HDMTX combined with dose-intensified multiagent chemotherapy was used; it was suggested that in children with high-risk brain tumors who have a poor outcome, High-dose chemotherapy (HDC) and autologous stem-cell transplantation (auto-SCT) could be an option in treatment and promising to improve survival rates.<sup>33</sup>

A retrospective study from China indicated that aggressive surgery as first-line therapy in PB and younger age was associated with poorer prognosis.<sup>34</sup>

In our series, the patients who lived longer were older than the others. However, they also had resection even it was subtotal, while the others had no resection.

In conclusion, PB are aggressive tumors necessitating intensive treatment including surgery, CSRT and chemotherapy. High dose chemotherapy is promising in some studies, especially in young patients. Metastasis is a poor prognostic factor. Patients should be treated in institutions with dedicated neurooncology experience and they should be followed up for long term side-effects such as second malignancies, and endocrine deficiencies.

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### Author contribution

The authors confirm contribution to the paper as follows: study conception and design: RK, data collection: BK, OG; analysis and interpretation of results: RK, BK, OG. Author; draft manuscript preparation: RK, BK, OG. All authors reviewed the results and approved the final version of the manuscript.

### Ethical approval

Istanbul University Cerrahpasa Medical Faculty Clinical Research Ethical Committee (12.02.2013/ 83045809-3507), İstanbul University Oncology Institute Academic Coordination Council (2013-206).

For this type of study formal consent is not required.

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### Conflict of interests

Johannes Wolff is employee of AbbVie Pharmaceuticals. The other authors declare that they have no conflicts of interest with regard to this research.

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