Clinical Outcomes and Patterns of Failure in Pineoblastoma: A 30-Year, Single-Institution Retrospective Review

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Key words
- Combined modality
- MIB-1
- Neurosurgery
- Pineal-parenchymal tumors
- Pineoblastoma
- PNET
- Radiation
- Radiosurgery
- Retinoblastoma
- Supratentorial

Abbreviations and Acronyms
CSI: Craniospinal irradiation
DFS: Disease-free survival
GTR: Gross total resection
LFFS: Local failure-free survival
LMD: Leptomeningeal disease
MFFS: Metastatic failure-free survival
OS: Overall survival
PPT: Pineal parenchymal tumor
SRS: Stereotactic radiosurgery
STR: Subtotal resection
WHO: World Health Organization

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OBJECTIVE: **To update outcomes and assess prognostic factors in the modern, multimodality treatment of patients with pineoblastoma.**

METHODS: **The medical records of patients with pineoblastoma evaluated at the M.D. Anderson Cancer Center between 1982 and 2012 were reviewed retrospectively.**

RESULTS: **Thirty-one patients with medical records suitable for review were identified. The majority of patients were female (67.7%) with a median age at diagnosis of 18.2 years (range, 0.3–52.8 years). Twenty-one patients underwent surgical resection, recorded as gross total (n = 9) or subtotal (n = 12) resections. Thirty patients received radiation with photon-based therapy (n = 16), proton-based therapy (n = 13), or radiosurgery (n = 1) to a median craniospinal irradiation dose of 36 Gy (range, 23.4–40 Gy) and a median focal dose of 54 Gy (range, 40–58.4 Gy). Twenty-eight patients received chemotherapy before (n = 10), during (n = 10), and after (n = 22) radiation. Median overall survival was 8.7 years for the entire cohort, with 2-, 5-, and 10- year actuarial rates of 89.5%, 69.4%, and 48.6%, respectively. Median disease-free survival was 10 years with 2-, 5-, and 10- year actuarial rates of 84.3%, 62.6%, and 55.7%, respectively. Univariate analysis failed to correlate age, sex, or extent of surgical resection with disease-free or overall survival.**

CONCLUSIONS: **Modern, multimodality treatment of pineoblastoma yields a high rate of overall survival, with acceptable short- and long-term toxicity. A greater M-stage at presentation and development of disease recurrence correlate with worse overall survival. Patients who received focal radiation initially experienced a greater rate of disease recurrence compared with those treated to the craniospinal axis.**

INTRODUCTION

Tumors in the pineal region are extremely rare, representing 0.4%–1.0% of all intracranial neoplasms in adults and 3.0%–8.0% in children (15). Comprising 15%–30% of pineal tumors, pineal-parenchymal tumors (PPTs) are the second largest subgroup after germ cell tumors (37). The World Health Organization (WHO) recognizes 4 major subgroups of PPTs: pineocytoma (WHO grade I), PPT of intermediate differentiation (WHO grade II/III), pineoblastoma (WHO grade IV), and the recently established pineal papillary tumor (WHO grade undefined) (27). Pineoblastoma, accounting for 25%–50% of PPTs, is most commonly seen in children and adolescents and historically carries a poor prognosis because of its high rate of relapse and propensity for seeding throughout the craniospinal axis, present in 15% of patients at diagnosis (15, 37, 39, 41).

Defined as a primitive embryonal tumor of the pineal gland, pineoblastoma is treated in a similar manner to high-risk medulloblastoma and supratentorial primitive neuroectodermal tumors, despite recent evidence of biological differences (26, 27). Treatment most commonly begins with maximal safe surgical resection. Complete resection can be difficult to achieve because of its deep location and proximity to surrounding neurovascular structures. Adjuvant radiotherapy consisting of craniospinal irradiation (CSI) with a local boost usually is recommended, with or without concurrent, systemic chemotherapy. Given the paucity of patients diagnosed with pineoblastoma, adjuvant treatment recommendations are not well established. Despite advancements in management, overall survival (OS) remains poor, with the authors of one study reporting 5-year survival rates of 10% among pediatric patients (11). To update outcomes and assess potential prognostic

factors in the context of patients treated with a modern, multimodality approach, including surgical resection, radiation, and chemotherapy, we conducted a retrospective review of our single-institution experience with this patient population.

METHODS

Patient Selection and Clinical Data

The medical records of all patients with a pathologic diagnosis of pineoblastoma who presented to The University of Texas M.D. Anderson Cancer Center between 1982 and 2012 were reviewed retrospectively. All pathologic specimens underwent institutional review to confirm diagnosis. Permission to perform this retrospective review was obtained from The M.D. Anderson Cancer Center Institutional Review Board.

Clinical data collected included demographic information, date and method of initial diagnosis, presenting signs and symptoms, initial treatment plan, date and extent of surgical resection(s), timing and duration of chemotherapeutic agent(s), timing and parameters (including dose, modality, volume, and field) of radiation, date and location of recurrence, toxicity, and last documented status. Pathologic data also were reviewed, including immunohistochemistry staining, MIB-1 labeling, rosette formation, and presence of necrosis. On the basis of the extent of disease at presentation, patients were classified according to standard Chang classification (5). The extent of resection was obtained from operative and postoperative notes as well as imaging studies. Gross total resection (GTR) was defined as no evidence of remaining tumor, and subtotal resection (STR) was defined as any amount of residual tumor. Recurrence was defined as progression based on imaging findings or pathologic confirmation, whichever occurred first. Leptomeningeal disease (LMD) was defined as either positive cerebrospinal fluid sampling or commensurate imaging findings as reported by a neuroradiologist. Grade 3 and 4 acute and late toxicities were assessed using the Common Terminology Criteria for Adverse Effects, Version 4.0. Follow-up information was gathered from the M.D. Anderson Cancer Center Tumor Registry. Study endpoints included response to treatment, duration of response, OS, and toxicity.

Statistical Analysis

Local failure-free survival (LFFS), metastatic failure-free survival (MFFS), OS, and disease-free survival (DFS) were calculated with the Kaplan-Meier method and defined as the time interval from date of diagnosis to date of local disease recurrence, metastatic recurrence, death of any cause, or recurrence of any kind, respectively (23). If no death occurred, date of last follow-up was used. Univariate Cox regression analysis, carried out using the exact partial-likelihood method to handle tied failures, was used to examine correlations between patient and treatment characteristics and outcomes. The Fisher exact test was used to determine the statistical significance of radiation field size on disease recurrence and disease recurrence on death. Statistical significance was defined as a probability value ≤ 0.05.

RESULTS

Patient Characteristics

A total of 33 patients were identified, but 2 were excluded from further analysis because of incomplete medical records. Demographic characteristics for the 31 patients included in final analysis are shown in **Table 1**, with detailed patient-specific characteristics provided in **Table 2**. There were 21 female and 10 male patients, with a median age of 18.2 years (range, 0.3–52.8 years) at diagnosis. Although patients were identified between 1982 and 2012, the majority of patients (n = 22, 71%) were treated either in the year 2000 or after. Initial symptomatology related to increased intracranial pressure with headache being the most commonly reported symptom (n = 23, 74.2%), followed by vision changes (n = 19, 61.3%), and vomiting (n = 18, 58.1%). Of those with vision changes, 6 patients (31.6%) had symptoms consistent with Parinaud's syndrome, with the remainder reporting blurry or double vision.

Table 1. Demographic Characteristics for 31 Patients with Pineoblastoma Evaluated at M.D. Anderson

Treatment years	1982–2012
Median age, years; range	18.2; 0.3–52.8
Sex	
Female	21 (67.7%)
Male	10 (35.5%)
Ethnicity	
Caucasian	21 (67.7%)
Black	5 (16.1%)
Hispanic	4 (12.9%)
Unknown	1 (3.2%)
Presenting symptoms	
Headache	23 (74.2%)
Vision changes	19 (61.3%)
Vomiting	18 (58.1%)
Nausea	7 (22.6%)
Gait instability	5 (16.1%)
Pathologic characteristics	
Necrosis	9 (29%)
Homer-Wright rosettes	4 (12.9%)
Flexner-Wintersteiner rosettes	2 (6.4%)
Initial treatment intervention	
Biopsy	18 (58.1%)
Surgery	11 (35.5%)
Radiation	1 (3.2%)
Unknown	1 (3.2%)
M stage	
MX	4 (12.9%)
M0	20 (64.5%)
M1-M2	2 (9.5%)
M3-M4	5 (16.1%)
Initial surgical resection (n = 30)	
Subtotal resection	12 (40%)
Gross total resection	9 (30%)
No surgical resection	9 (30%)
Initial radiation (n = 30)	
Modality	

MX = distant metastasis cannot be evaluated.

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