Survival and associated predictors for patients with pineoblastoma or pineal parenchymal tumors of intermediate differentiation older than 3 years: Insights from the National Cancer Database

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Abstract

Background. The management of pineal parenchymal tumors remains controversial.

Methods. The 2004-2017 National Cancer Database was queried for cases (age >3 years) with histologically confirmed pineal parenchymal tumors of intermediate differentiation (PPTID, n = 90) or pineoblastoma (n = 106).

Results. Within the PPTID group, median age was 41 years; 49% were males. Five- and 10-year survival were 83% and 78%, respectively. Adjuvant radiation and chemotherapy were administered in 64% and 17% patients, respectively. The effect of radiation with or without chemotherapy (HR 1.15, P = .81, and HR 1.31, P = .72, respectively), and extent of resection (HR = 1.07, P = .93) was not significant. Within the pineoblastoma group, median age was 25 years; 51% were males. Five- and 10-year survival were 66% and 42%, respectively. Adjuvant radiation and chemotherapy were administered in 72% and 51%, respectively. In multivariable analysis, patients with pineoblastoma who received both radiation and chemotherapy (n = 39) had significantly lower hazard of death (HR 0.35, 95% CI 0.14-0.85, P = .02) compared to those who received radiation alone (n = 20) or no adjuvant treatment (n = 19). Finally, females in the pineoblastoma group were found to have a lower hazard of death compared to males (HR 0.24, 95% CI 0.10-0.58, P = .001); this comparison trended toward statistical significance in the PPTID subgroup (HR 0.40, 95% CI 0.14-1.08, P = .07).

Conclusions. Survival rates were higher in patients with PPTID vs patients with pineoblastoma. Adjuvant chemoradiation was associated with improved survival in pineoblastoma and females had lower hazards of death. Further research should identify specific patient profiles and molecular subgroups more likely to benefit from multimodality therapy.

Key Points

• Adjuvant chemoradiation offers significant survival benefit in pineoblastoma.
• No survival benefit of adjuvant treatment was observed in the PPTID group.
• Females in the pineoblastoma group had significantly longer overall survival.
Pineal tumors are rare intracranial tumors that constitute 0.4% of all central nervous system neoplasms, with an estimated incidence rate of 0.11 per 100,000 population in the United States. These neoplasms are broadly categorized into germ cell tumors, pineal parenchymal tumors, and others. According to the WHO 2021 classification, pineal parenchymal tumors can be further subdivided into well-differentiated pineocytomas (~20%), pineal parenchymal tumors of intermediate differentiation (PPTID, ~45%), and poorly differentiated pineoblastomas (~35%), while very rarely papillary tumors and desmoplastic myxoid tumors may also be encountered.

Surgery, ranging from biopsy to gross total resection (GTR), plays a critical role in the treatment of pineal parenchymal tumors, and typically suffices for well-differentiated WHO 1 pineocytomas. However, due to low incidence and variations in histopathological behavior, different approaches exist for the management of PPTIDs and pineoblastomas. For example, reported rates of adjuvant radiation are highly variable and range from 35% to nearly 100% for PPTIDs and 27%-94% for pineoblastomas. In a multicenter retrospective study evaluating outcomes following treatment for 51 PPTIDs, 26 patients were treated with GTR, whereas 23 patients underwent stereotactic biopsy. Among those, only 34 were treated with radiotherapy. Chemotherapy has also been tested as an adjunct modality to surgery and radiation for PPTID, however, its role still has not yet been fully elucidated.

Most existing literature on pineal parenchymal tumors comprises institutional case series with a limited sample size. In light of the lack of consensus on the optimal strategy for higher-grade lesions, ie, pineal parenchymal tumors of intermediate differentiation (PPTID) and pineoblastomas. Herein, we did not observe an overall survival benefit of adjuvant radiation or adjuvant radiation with chemotherapy over no adjuvant treatment for PPTIDs. Within pineoblastomas, there was a longer survival in favor of adjuvant radiation and adjuvant radiation with chemotherapy. In addition, increasing age was significantly associated with higher hazard of death for PPTID and pineoblastomas, whereas female sex was associated with lower hazards of death in pineoblastomas, and trended toward statistical significance in PPTIDs. This analysis provides further insights into the therapeutic effect of adjuvant treatment for pineal parenchymal tumors and for the first time demonstrates survival disparities with regard to sex.

Inclusion and Exclusion Criteria

The NCDB registry was queried for all patients with a histologically confirmed pineal parenchymal tumor diagnosed between 2004 and 2017, inclusive. Cases were identified using the International Classification of Disease for Oncology, 3rd edition (ICD-O-3) topography code C75.3 (pineal gland), in combination with the corresponding pathology code (Supplementary Table 1). Only patients with “malignant/invasive behavior” were included. Following the initial identification of eligible patients, we evaluated the assigned “Tumor Grade” variable, which is defined in the data dictionary as “tumor resemblance to normal tissue,” and not based on the WHO grading system. Given the absence of an ICD-O-3 pathology code specific for PPTID, we categorized cases into the following groups, in accordance with the online SEER (Surveillance, Epidemiology, and End Results) guidelines (https://seer.cancer.gov/seer-inquiry/inquiry-detail/20140001/?q=pineal):

- PPTID: grade 2 pineoblastoma.
- “True” pineoblastoma: grade 3 or 4 pineoblastoma (which will simply be referred to as pineoblastoma thereafter).

Cases with missing grade or benign/borderline behavior were excluded. Furthermore, we excluded cases ≤3 years of age as this represents a distinct group of patients with a much worse overall prognosis and distinct treatment approach.
Primary Outcome

The primary endpoint was duration of survival at last follow-up, defined as the timeframe from time of diagnosis until death or censoring due to loss to follow-up or administrative limitations.

Covariates

We recorded data on the following covariates of interest: (i) patient demographics: age, sex, race, and Charlson Comorbidity Index (CC; 0, 1, 2, 3+); (ii) tumor characteristics: size in mm (defined as the largest tumor diameter); (iii) hospital characteristics: type of facility based on designation from the Commission on Cancer (community cancer programs, comprehensive community cancer programs, academic/research facilities, and integrative network cancer care programs [definitions provided in Supplementary Table 2]) and U.S. census region of reporting facility; (iv) treatment parameters: type of resection (biopsy alone, debulking/subtotal resection and GTR; based on SEER guidelines for site-specific surgery codes https://seer.cancer.gov/archive/manuals/2018/appendixc.html, accessed August 10, 2021) as well as administration of adjuvant treatment (radiation, chemotherapy, immunotherapy, hormone therapy, transplant therapy [autologous stem cell or bone marrow transplant]).

Statistical Analysis

Descriptive statistics (medians with interquartile ranges for continuous variables; frequencies with proportions for categorical variables) are presented. Outcome was examined in an as-treated fashion. Kaplan-Meier survival curves by sex, pathology, and different treatment groups were constructed and compared using the log-rank test. Univariate Cox proportional hazards regression models were built to evaluate the effect of age, sex, extent of resection, and adjuvant treatment on overall survival. Assumptions of proportional hazards were evaluated by examining the Schoenfeld residuals and log-log plots of survival against time. Multivariable analysis was performed adjusting for variables with P-values <0.05 in the univariate model. Statistical analysis was conducted using R Statistical Computing software version 3.1.2 (Vienna, Austria; https://www.R-project.org/). P-values equal to or less than 0.05 were considered statistically significant.

Results

Overall Cohort

A total of 1129 cases with pineal parenchymal tumors were identified in NCDB during the period 2004-2017. Among those, n = 342 cases were designated with borderline behavior and with pineocytoma histology (a clear distinction in survival between pineocytomas and “pineoblastomas” is presented in Supplementary Figure 1). In the remaining dataset, there were 577 cases with missing grade variable. This group was not systematically different from those with known grade (2/3/4), as demonstrated by the K-M survival curve in Supplementary Figure 2. Our final cohort consisted of 196 patients, of whom 106 were considered to have PPTIDs (no patients aged ≤ 3 years of age), and 90 to have pineoblastomas (after excluding 14 patients aged ≤3 years of age). The number of patients with PPTID and pineoblastoma who received chemotherapy alone after surgery was extremely small (n = 1 and n = 3, respectively) precluding meaningful comparisons and were therefore excluded from the final survival analysis.

Pineal Parenchymal Tumors of Intermediate Differentiation

Median age was 41 years (IQR: 28-56) and 49% were males. Most patients were white (81%) and had no Charlson comorbidities (87%). Median tumor size was 25 mm (IQR: 19-28 mm). Debulking/subtotal resection and biopsy were the most common forms of surgical treatment (45% and 44%, respectively), while GTR was achieved in 11%. Adjuvant radiation was administered in 64% of patients (available data for 102 patients) and the median radiation dosage was 5400 cGy. Chemotherapy was administered in 17% (single agent in 39% within this group), whereas hormone and immunotherapy were given in only one case each. This information is summarized in Supplementary Table 3.

Pineoblastomas

Median age was 25 years (IQR: 13-47) and 51% were males. Most patients were also white (69%) and had no additional Charlson comorbidities (84%). Median tumor size was 29 mm (IQR: 22-39 mm). Debulking/subtotal resection was the most common form of surgical treatment (59%), followed by biopsy (32%), while GTR was achieved in 9%. Adjuvant radiation was administered in 72% of patients (available data for 89 patients) and the median radiation dosage was 5400 cGy. Chemotherapy was administered in 51% (single agent in 41% within this group), whereas hormone therapy and transplant therapy were given in three and four cases, respectively. This information is also presented in Supplementary Table 3. Compared with PPTID, patients with pineoblastoma were more likely to be younger (P < .001), harbor larger tumors (P = .016) and undergo chemotherapy (P < .001), as well as have worse overall survival (P < .001) (Supplementary Figure 3).

Comparison of Different Treatment Groups

Within the PPTID group, 50 patients (49%) underwent adjuvant radiation alone, 16 patients (16%) underwent radiation with chemotherapy, whereas the remaining (35%) had no adjuvant treatment (Table 1). No significant differences were observed between these groups with regard to baseline patient characteristics, with the exception of Charlson Comorbidity score, where patients with no comorbidities were more frequent in the no adjuvant treatment group (overall P = .04). There was no difference in terms of extent
of surgical resection (overall $P = .53$) or survival (log-rank $P = .94$) (Figure 1). The addition of radiation with or without chemotherapy did not confer overall survival benefit. Given more than 50% of patients were alive at the end of the study period, median survival times were not calculated (ie, exceeded 10 years). The 5-year survival was 83% for the no adjuvant treatment group, 83% for radiation alone group, and 80% for the chemoradiation group, while the 10-year survival rate was 75% for no adjuvant treatment group, 77% for radiation alone group, and 80% for the chemoradiation group.

Within the pineoblastoma group, 39 patients (48%) had radiation with chemotherapy, 20 patients (21%) had radiation alone, while the remaining (22%) had no adjuvant treatment (Table 2). No significant differences were observed between these groups, with the exception of age ($P = .024$) and sex ($P = .012$). Younger patients and males were more likely to undergo chemoradiation. Overall median survival was 8.1 years. Median survivals in those receiving no adjuvant treatment, radiation alone, and radiation with chemotherapy were 6.1, 6.9 and 11.8 years, respectively ($P = .068$) (Figure 2). The 5-year survival was 55% for no adjuvant treatment group, 62% for radiation alone group, and 78% for chemoradiation group, while the 10-year survival rate was 15% for the no adjuvant treatment group, 41% for radiation alone group, and 53% for the chemoradiation group.

Cox hazards Regression Analysis

In univariate Cox proportional hazards regression analysis, we noticed a significantly higher hazard of death increasing age, both for PPTIDs (HR 1.03, 95% CI 1.01-1.06, $P = .05$) and pineoblastomas (HR 1.03, 1.006-1.043, $P = .008$). In addition, females in the pineoblastoma group were also found to have a lower hazard of death compared to males (HR 0.37, 95% CI 0.17-0.77, $P = .008$ [see K-M curve in Supplementary Figure 4A]). This comparison trended toward statistical significance in the PPTID subgroup (HR 0.40, 95% CI 0.14-1.08, $P = .07$ [see K-M curve in Supplementary Figure 4B]). We did not observe a significant impact based on extent of resection. Finally, with regard to adjuvant treatment for PPTID, the effect of radiation with or without chemotherapy was not significantly associated with hazard of death compared to no adjuvant treatment. Within pineoblastomas, the point estimates of adjuvant radiation (HR 0.59, 95% CI 0.06-4.72, $P = .58$) and radiation with chemotherapy (HR 0.41, 95% CI 0.19-0.92, $P = .03$) were associated with lower hazards of death, however, it was not statistically significant in the overall survival (log-rank $P = .94$) (Figure 1). The addition of radiation with or without chemotherapy did not confer overall survival benefit.
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Cox hazards Regression Analysis

In univariate Cox proportional hazards regression analysis, we noticed a significantly higher hazard of death increasing age, both for PPTIDs (HR 1.03, 95% CI 1.036-1.06, $P = .05$) and pineoblastomas (HR 1.03, 1.006-1.043, $P = .008$). In addition, females in the pineoblastoma group were also found to have a lower hazard of death compared to males (HR 0.37, HR 0.17-0.77, $P = .008$ [see K-M curve in Supplementary Figure 4A]). This comparison trended toward statistical significance in the PPTID subgroup (HR 0.4, 95% CI 0.14-1.08, $P = .07$ [see K-M curve in Supplementary Figure 4B]). We did not observe a significant impact based on extent of resection. Finally, with regard to adjuvant treatment for PPTID, the effect of radiation with or without chemotherapy was not significantly associated with hazard of death compared to no adjuvant treatment. Within pineoblastomas, the point estimates of adjuvant radiation (HR 0.59, 95% CI 0.06-4.72, $P = .58$) and radiation with chemotherapy (HR 0.41, 95% CI 0.19-0.92, $P = .03$) were associated with lower hazards of death, however, it was not statistically significant in the former. The effect of age (HR 1.03, 95% CI 1.0008-1.05, $P = .04$), female sex (HR 0.24, 95% CI 0.10-0.58, $P = .001$) and adjuvant radiation with chemotherapy (HR 0.35, 95% CI 0.14-0.85, $P = .02$) on overall survival of patients with pineoblastoma remained significant in the multivariable analysis. These results are presented in Table 3.

Discussion

Herein, we queried the largest US cancer registry to investigate the survival patterns of patients aged >3 years diagnosed with PPTID or pineoblastoma. In summary, there was a longer survival in favor of adjuvant radiation with chemotherapy for pineoblastoma. However, we did not observe an overall survival benefit of adjuvant radiation (with or without chemotherapy) over no adjuvant treatment for PPTIDs. In addition, increasing age was significantly associated with higher hazard of death for PPTID and pineoblastomas, whereas female sex had a protective effect in the pineoblastoma group, which trended toward significance for PPTIDs.

While older large series of pineal parenchymal tumors (76 cases from 12 European centers, equally distributed PPTIDs, and pineoblastomas) indicated that neither extent of resection nor radiation improved survival, most experts would nowadays argue for aggressive adjuvant radiation (typically 54-56 Gy in the brain) and multimodal chemotherapy for pineoblastomas.5,7 According to our review of the relevant literature (Table 4), radiotherapy has been used in 19%-94% and chemotherapy in 29%-100%.29,10,16-26 These rates have been reported to be 64% and 48%, respectively, in a recent meta-analysis by Tate et al, numbers that are very commensurate to our analysis (ie, 72% and 51%). The effect of radiation on survival with regression analysis was
evaluated in 8 out of 14 studies and was found to be significant in four with a HR of 0.13-0.88. On the other hand, chemotherapy was found to be significant in one out of 3 studies (HR range 0.40-3.37). In summary, these highly variable rates reflect inherent differences in the center’s experience, chemotherapeutic regimen, and molecular tumor composition. The advent of genetic testing will allow for more optimal risk stratification and comparable analysis of outcomes across centers and epochs.

The role of adjuvant radiation in the postoperative management of patients with PPTID remains controversial, with highly variable rates of postoperative radiation reported in recent literature, ie, 55%-100%. In a recent patient-level meta-analysis of 127 PPTID cases, Mallick et al demonstrated that 36% received adjuvant radiation (out of 65 cases with available data). The median progression-free survival was 5.2 years and the overall survival was 14 years. Within the radiation group, 90% were treated with

### Table 2. Comparison of Different Treatment Modalities Within Malignant Pineoblastomas

| Variable                                | No RT or Chemo | RT Alone | RT + Chemo | P-value |
|------------------------------------------|----------------|----------|------------|---------|
| **Age, median [IQR]**                   |                |          |            |         |
| N = 19                                   | 26.0 [19.5;52.0] | 39.0 [22.0;58.0] | 19.0 [10.0;36.5] | .024    |
| **Age group, n (%)**                    |                |          |            |         |
| 18+                                      | 15 (78.9%)     | 15 (75.0%) | 22 (56.4%) | .15     |
| 3-17                                     | 4 (21.1%)      | 5 (25.0%) | 17 (43.6%) |         |
| **Male sex, n (%)**                     |                |          |            | .012    |
| N = 19                                   | 11 (57.9%)     | 4 (20.0%) | 23 (59.0%) |         |
| **Race, n (%)**                         |                |          |            | .65     |
| White                                    | 12 (63.2%)     | 14 (70.0%) | 28 (71.8%) |         |
| Black                                    | 5 (26.3%)      | 6 (30.0%) | 8 (20.5%)  |         |
| Other                                    | 2 (10.5%)      | 0 (0.00%) | 3 (7.69%)  |         |
| **Hispanic ethnicity, n (%)**           |                |          |            |         |
| N = 19                                   | 2 (10.5%)      | 1 (5.00%) | 3 (7.69%)  |         |
| **Facility type, n (%)**                |                |          |            | .17     |
| Community                                | 0 (0.00%)      | 0 (0.00%) | 2 (22.2%)  |         |
| Comprehensive Community                 | 2 (25.0%)      | 1 (10.0%) | 0 (0.00%)  |         |
| Academic                                 | 3 (37.5%)      | 8 (80.0%) | 6 (66.7%)  |         |
| Integrated                               | 3 (37.5%)      | 1 (10.0%) | 1 (11.1%)  |         |
| **Hospital region, n (%)**              |                |          |            | .008    |
| Midwest                                  | 0 (0.00%)      | 2 (10.0%) | 4 (10.3%)  |         |
| Northeast                                | 2 (10.5%)      | 5 (25.0%) | 1 (2.56%)  |         |
| South                                    | 6 (31.6%)      | 1 (5.00%) | 3 (7.69%)  |         |
| West                                     | 0 (0.00%)      | 2 (10.0%) | 1 (2.56%)  |         |
| **Charlson Comorbidity Scale score, n (%)** |            |          |            | .11     |
| 0                                       | 14 (73.7%)     | 16 (80.0%) | 36 (92.3%) |         |
| 1                                       | 4 (21.1%)      | 4 (20.0%) | 2 (5.13%)  |         |
| 2                                       | 1 (5.26%)      | 0 (0.00%) | 0 (0.00%)  |         |
| 3+                                      | 0 (0.00%)      | 0 (0.00%) | 1 (2.56%)  |         |
| **Tumor size (largest diameter) in mm, median [IQR]** | 29.5 [20.8;40.2] | 24.0 [22.0;40.0] | 30.0 [23.8;37.0] | .94 |
| **Brain radiation dosage in cGY, median [IQR]** |            |          |            |         |
| Peds (n = 19)                            | NA             | 5592 [5580; 9540] | 5580 [5445; 5580] | .21 |
| Adults (n = 34)                          | NA             | 5400 [5220; 5400] | 5400 [4770; 5670] | .69 |
| **Type of resection, n (%)**            |                |          |            | .25     |
| Biopsy alone                             | 3 (23.1%)      | 3 (27.3%) | 10 (43.5%) |         |
| Debulking/subtotal resection             | 9 (69.2%)      | 8 (72.7%) | 9 (39.1%)  |         |
| Gross total                              | 1 (7.69%)      | 0 (0.00%) | 4 (17.4%)  |         |

**Abbreviations:** IQR, interquartile range; NA, not applicable; RT, radiotherapy. Bold denotes statistical significance.

*For patients with available data.
fractionated radiation and only 10% underwent Gamma Knife. In contrast to our findings, the authors found that adjuvant radiation was significantly associated with better overall survival (21 vs 14 years). This could be explained by reporting bias in the included studies, i.e., cases that respond to radiation are more likely to be published. It should be noted that this association has not been analyzed in individual reports given their small sample size. Given the lack of evidence of overall survival benefit with adjuvant chemoradiation, patients can possibly be observed after GTR in the absence of disseminated disease. However, this analysis did not assess whether the observation is associated with early recurrence. Spinal/distant failure represents the most common pattern of recurrence (63%) and necessitates spinal radiation and more extensive radiation fields. Thus, future studies should investigate the impact of observation on patterns of recurrence, especially in the context of associated toxicity and quality of life.

The role of adjuvant chemotherapy is even more controversial for PPTIDs, ranging from 4% to 60% across studies. The number of patients in most reports is rather small thereby precluding more meaningful analysis. In the meta-analysis by Mallick et al, chemotherapy was administered in only 23% of PPTID cases (out of 43 patients with available data) and was not significantly associated with improved survival. However, this study did not differentiate between patients who received chemotherapy alone vs those who also received radiation as part of their adjuvant therapy. Some authors have recommended chemotherapy for pediatric patients to minimize the amount of craniospinal radiation, especially in cases of neuro-axial dissemination. In our series, only one pediatric patient underwent chemotherapy alone and was thus excluded from the analysis. Therefore, all patients who received chemotherapy also received radiation; however, the combination treatment still did not confer a survival benefit over no adjuvant therapy.

Whether the extent of resection influences prognosis in PPTID also remains to be determined. Extent of resection was not significantly associated with overall survival in our analysis, and there was no difference in the distribution of adjuvant treatment groups over different types of resection. This is in contrast with WHO grade 2 diffuse gliomas, where literature has consistently shown survival benefit with more extensive resections. It should be noted though that only 11% of patients achieved a GTR (n = 9), thus precluding any meaningful analyses to be performed on this subset (especially in the context of relatively short follow-up of 10 years). Given the intricate location of these lesions and anatomical proximity to critical structures, complete resection can be difficult to achieve and largely dependent on the surgeon’s experience. Across all literature, a gross or near total resection was achieved in 25%-73% (25% in a recent systematic review). Similarly, Nam et al and Mallick et al did not demonstrate a survival benefit in favor of more aggressive resections.4,30 As always clinical judgment is paramount in weighing the risks and benefits of surgical resection. When pursued, as is common in our practice, a goal of maximal safe surgical resection should be balanced against the current paucity of evidence supporting benefit from more complete removal.

Finally, another important finding of our study pertains to the positive effect of female sex on overall survival. This effect was statistically significant for pineoblastomas and trended toward significance for PPTIDs. In order to determine the strength of this relationship, we assessed the influence of patient sex on survival using the combined PPTID and pineoblastoma group (n = 210) as well as the entire dataset of “malignant” pineal parenchymal tumors (n = 765). In each of these larger datasets, females continued to demonstrate a significantly higher survival (P = .003 and P = .02, respectively [see Supplementary Figure 4C and D]). To the best of our knowledge, this association is reported for the first time in an original research.
study. Interestingly, in their meta-analysis, Mallick et al also found females to have better overall survival (21 vs 72 years) compared to males.\(^{30}\) The pathophysiology underlying this correlation requires further investigation. Given the strength of the association, this finding is unlikely to be spurious and may reflect disparities in the molecular underpinnings of these tumors in males vs females. For example, according to the consensus study by Liu et al, there is a strong male preponderance for PB-MYC/FOXR2 tumors, which represent the pineoblastoma subgroup with the worst prognosis (5-year survival of 24%).\(^{9}\) Alternatively, to the extent that many patients undergo chemoradiation, emerging evidence suggests higher susceptibility of female cells to the senescence-inducing impacts of cytotoxic therapy.\(^{34}\)

### Strengths and Limitations

The present analysis represents one of the largest studies to date investigating the overall survival and associated predictors in patients with PPTID and pineoblastomas using a rigorous methodology to reduce sampling bias. National databases allow the pooling of a large number of cases which may not be otherwise feasible in single-institutional studies. However, there are several limitations. First, the NCDB aggregates data from CoC-accredited hospitals only, therefore results are not population-based. Second, there may be residual confounding as the data lack granularity on clinical information, such as overall tumor volume, the presence of hydrocephalus, performance status (eg, Karnofsky or ECOG), neuro-axial dissemination (which can be underestimated at the time of surgery), specific radiation or chemotherapeutic regimens used.\(^{10,18,22,36,38}\) Third, information on recurrence is not available in the database, thereby precluding analysis of progression-free survival. Interestingly, our literature review showed that progression-free and overall survival were very similar (ie, within 10%) in most articles (Table 4), thereby denoting that each outcome can be a surrogate for the other. Fourth, we did not have access to the type of modality used for administration of radiation, ie, fractionated vs Gamma Knife vs intensity-modulated, etc. Fifth, no data were available regarding neurocognitive outcomes nor quality of life. Finally, there was no information on histopathological and molecular markers. Whether there is a modifying effect of these markers on response to treatment has only been recently explored. For example, Chatterjee et al studied pathologic prognostic factors of PPTIDs and found mitotic index (greater than 4/10 hpf) and Ki-67 (greater than 5%) to be associated with worse prognosis.\(^{29}\) Likewise, Raleigh et al (75 patients with mean follow-up of 4.1 years) categorized PPTIDs into small-cell and large-cell neoplasms. Histopathologic classification along with extent of resection and neuro-axial spread were the most important prognostic factors for overall survival. Finally, Liu et al presented a novel classification scheme based on molecular data from 221 patients.\(^{9}\) Four molecular subdivisions were described: PB-miRNA1, PB-miRNA2, PB-FOXR2, and PB-RB1. As aforementioned, survival was best for PB-miRNA2 tumors and worst for PB-FOXR2 and PB-RB1. We encourage future work to investigate the role of these markers on survival of patients with pineal parenchymal tumors and their differential effects on treatment response.

### Conclusions

In summary, our analyses found that adjuvant radiation with or without chemotherapy did not confer overall survival benefit in patients >3 years with PPTID, whereas the opposite held true for pineoblastomas. Increasing age was associated with higher hazard of mortality, whereas extent of resection and tumor size did not correlate with survival. Female sex was associated with lower hazards of death in pineoblastomas and trended toward statistical significance in PPTIDs. Given the need to balance the risks and benefits of adjuvant therapies—especially in patients with expected long-term survival, clinical and molecular predictors of
Table 4. Summary of Basic Demographics, Treatment Characteristics, and Associated Outcomes in Main Studies on Pineal Parenchymal Tumors of Intermediate Differentiation (PPTIDs) and Pineoblastomas

| Author, Year | Study Design | No. of Patients | Age, Median | Female Sex, n (%) | GTR, n (%) | Radiation, n (%) | CHT, n (%) | 5-year PFS | 5-year OS | Rad HR for OS (95% CI) | CHT HR for OS (95% CI) | Other Observations |
|--------------|--------------|-----------------|-------------|-------------------|-----------|-----------------|-----------|-----------|----------|------------------------|----------------------|-------------------|
| Liu, 2021    | COG ACNS0332, RBTC/HSC, SJCRH | 96 (PB-miRNA1) | 8.5         | 59 (62%)          | 27 (43%)  | 57 (92%)        | 64 (100%) | 56.70%    | 70%      | NR                     | NR                   | Intermediate outcome |
|              |              | 23 (PB-miRNA2)  | 11.8        | 9 (39%)           | 9 (50%)   | 15 (94%)        | 15 (83%)  | 86%       | 100%     | NR                     | NR                   | Best outcome       |
|              |              | 34 (PB-MYC/FOXR2) | 1.4        | 8 (25%)           | 11 (55%)  | 8 (44%)         | 16 (89%)  | 16.70%    | 24%      | NR                     | NR                   | Worst outcome       |
|              |              | 25 (PB-RB1)     | 2.1         | 12 (52%)          | 6 (37.5%) | 6 (55%)         | 9 (60%)   | 19%       | 30%      | NR                     | NR                   | Worst outcome       |
| Liu, 2020    | SJMB03, SJYC07 | 58              | 6.2         | 113 (51%)         | 22 (38%)  | 52 (90%)        | 58 (100%) | 60%       | 61%      | NR                     | NR                   | None               |
| Abdelbaki, 2020 | Head Start I, II, III trials | 23            | 3.1         | 11 (48%)          | 8 (35%)   | 7 (30%)         | 23 (100%) | 9.70%     | 13%      | 0.30 (0.11-0.86)        | 0.40 (0.16-0.99)      | None               |
| Jin, 2020    | NCDB registry | 211             | 8           | 95 (45%)          | 19 (9%)   | 136 (65%)       | 167 (79%) | NR        | NR       | 0.38 (0.21-0.67)        | 0.74 (0.38-1.46)      | Age <4 years, mets at Dx are worse |
| Deng, 2018   | SEER registry | 123             | 6           | 64 (52%)          | 20 (16%)  | 36 (29%)        | NR        | NR        | 60.50%   | NR                     | NR                   | Age <5 years, tumor size >3cm are worse |
| Tian, 2018   | Retrospective | 18              | 4.3         | 10 (56%)          | 13 (72%)  | 5 (28%)         | 13 (72%)  | NR        | 28%      | NR                     | NR                   | None               |
| Myranek, 2017 | Pooled European SIOP-E and US Head Start | 132 (all) | 4.2         | 71 (54%)          | NR        | 36 (27%)        | 105 (80%) | 41%       | 43%      | 0.42 (0.22-0.78)        | NR                   | M1 disease, age <4 years are worse |
|              |              | 57 <=4 years of age | NR        | NR        | 11 (19%) | 53 (93%) | 11%      | 12%      | 0.61 (0.28-1.29) | NR                   | M1 disease       |
|              |              | 78 >4 years of age | NR        | NR        | 25 (32%) | 52 (67%) | 63%      | 66%      | 0.13 (0.03-0.48) | NR                   | None               |
| Farnia, 2014 | Retrospective | 31              | 18.2        | 21 (67%)         | 9 (30%)   | 26 (87%)        | 28 (90%)  | 62.60%    | 69.40%   | 0.55 (0.06-5.06)        | NR                   | None               |
| Tate, 2011   | Systematic review | 299           | 3.4 (Sx + CHT)-28 (Sx + RT) | NR | 150 (50%) | 191 (64%) | 145 (48%) | NR | 15% for age <=5 years, 57% for age >5 years | 0.88 (0.43-1.78) | 3.37 (0.95-11.98) | STR, age <5 years, dissemination are worse |
| Gilheeney, 2008 | Retrospective | 11             | 8.7         | 5 (45%)          | 3 (27%)   | 8 (73%)         | 11 (100%) | NR        | 7 (64%)  | NR                     | NR                   | None               |
| Author/Year | Study Design | No. of Patients | Age, Median (yr) | Female Sex, n (%) | GTR, n (%) | Radiation, n (%) | CHT, n (%) | 5-year OS | 5-year PFS | Rad HR for OS (95% CI) | CHT HR for OS (95% CI) | Other Observations |
|-------------|--------------|----------------|------------------|-------------------|-----------|-----------------|-----------|-----------|-----------|----------------------|----------------------|-------------------|
| Hinkes, 2007 | HIT -SKK87, HIT -SKK92, HIT91 trials | 11 | 3.6 | 4 (36%) | 2 (18%) | 7 (64%) | 10 (91%) | NR | NR | None |
| Lee, 2005 | Registry | 34 | 35 | 12 (36%) | 10 (30%) | 11 (32%) | 10 (29%) | NR | NR | None |
| Guruvajaran, 2000 | Retrospective | 12 | 15.5 | 4 (33%) | 5 (42%) | 23 (61%) | 25 (63%) | 14 (35%) | NR | None |
| Fauchon, 2000 | Multicenter | 38 | NR | 27 (71%) | 23 (61%) | 22 (58%) | 8 (21%) | NR | NR | None |
| Liu, 2021 | Retrospective | 43 | 33 | 24 (56%) | 10 (30%) | 10 (29%) | 9 (21%) | NR | NR | None |
| Nam, 2020 | Retrospective | 37 | 37 | 8 (47%) | 16 (84%) | 16 (84%) | 12 (40%) | NR | NR | None |
| Chatterjee, 2019 | Retrospective | 16 | Mean 28.3 | 6 (38%) | 4 (25%) | 16 (100%) | 16 (100%) | NR | NR | None |
| Compagnon, 2019 | Retrospective | 15 | 55 | 11 (73%) | 10 (67%) | 11 (73%) | 10 (67%) | NR | NR | None |
| Mallick, 2016 | Retrospective | 8 (Grade II) | 41 | 6 (15%) | 4 (10%) | 6 (15%) | 4 (10%) | NR | NR | None |
| Raleigh, 2016 | Retrospective | 8 (Grade III) | 31.7 | 2 (25%) | 4 (50%) | 2 (25%) | 6 (75%) | NR | NR | None |
| Komay, 2001 | Retrospective | 11 | Mean 23 | 4 (36%) | 3 (27%) | 6 (55%) | 3 (27%) | NR | NR | None |
| Fauchon, 2000 | Multicenter | 37 (intermediate grade) | Mean 40.3 | 15 (46%) | 15 (46%) | 15 (46%) | 15 (46%) | NR | NR | None |

**Abbreviations:** CHT, chemotherapy; CTR, extent of resection; GTR, gross total resection; HR, hazard ratio; NCDB, National Cancer Database; NR, not reported; OS, overall survival; PFS, progression-free survival; PPTID, pineal parenchymal tumor of intermediate differentiation; Rad, radiation; RT, radiotherapy; SEER, Surveillance, Epidemiology, and End Results; STR, subtotal resection.

- M1 disease means the presence of CNS metastases at diagnosis.
- In this study, HR > 1 was associated with better survival.

Only studies with at least 10 patients, published after 2000 were included.
therapeutic benefit may help ensure optimal patient selection for multimodality therapy.

Supplementary Material

Supplementary material is available at Neuro-Oncology Advances online.

Keywords

chemotherapy | National Cancer Database | pineal parenchymal tumor | radiation | survival

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