The Long-Term Postsurgical Prognosis of Patients With Pineoblastoma

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BACKGROUND: For this report, the authors comprehensively summarized the existing literature on patients with pineoblastoma and identified the variables and treatments that had an impact on outcomes. METHODS: A comprehensive search identified 109 studies that collectively described the outcomes of patients with pineoblastoma. Individual patient data were classified based on treatment and were subjected to univariate comparisons. Cox regression analysis included comparisons of survival outcomes controlling for age, extent of resection, and treatment group, and between-group survival comparisons were performed using the Kendall tau (rank correlation) statistic.

RESULTS: Two hundred ninety-nine patients met inclusion criteria. The overall survival rate was 54% (175 of 299 patients) at a mean follow-up of 31 ± 1.9 months (range, 1-159 months). The analyses demonstrated a markedly worse prognosis for children aged ≤5 years compared with older patients (5-year survival rate: 15% for children aged ≤5 years vs 57% for children aged >5 years; log-rank P < .00001). In addition, a graded increase in survival was observed with increasing degrees of resection (5-year survival rate: 84% for patients who underwent gross total resection vs 53% for patients who underwent subtotal resection vs 29% for patients who underwent debulking; log-rank P < .0001). Multivariate analysis indicated that not achieving gross total resection markedly worsened patient survival (subtotal resection: hazard ratio, 6.47; 95% confidence interval, 2.3-19; P = .001. debulking: hazard ratio, 9.27; 95% confidence interval, 3.2-27; P < .0001). CONCLUSIONS: The current findings emphasize the importance of aggressive surgical resection in the treatment of pineoblastoma. In addition, the authors conclude that clinical trials should not mix young patients with older patients or patients who undergo subtotal resection with patients who undergo gross total resection, because such heterogeneity may alter the variability of responses to treatment and reduce the likelihood of success.
Most of the available literature on overall survival (OS) in patients with pineoblastoma is in the form of case reports and single-institution studies with relatively small patient numbers. Although these data provide some useful information, the inherent biases and lack of statistical power of individual studies make it difficult to deduce expected outcomes for patients with pineoblastoma. Furthermore, clearly defined clinical factors in these patients that correlate with prognosis are difficult to identify uniformly. For these reasons, we undertook an extensive analysis of published survival among patients who were treated for pineoblastoma. Data was extracted from individual studies that provided explicit clinical and diagnostic features combined with survival data. Our objective was to summarize the existing literature and interrogate for factors associated with survival during the reported periods of follow-up.

MATERIALS AND METHODS

Article Selection

PubMed searches were performed with key words “pineoblastoma” alone and in combination with “treatment,” “morbidity,” and “mortality” using Boolean operators. Inclusion criteria were 1) patients who were treated for pineoblastoma and had follow-up data and 2) articles that contained appropriate information (age, sex, treatment modality, and follow-up survival data) for each patient to be disaggregated. After reviewing these articles, a thorough review of all referenced sources also was performed. Exclusion criteria for entire studies included 1) combined patient outcomes for all pineal tumors (ie, pineocytoma outcome combined with pineoblastoma outcome) or 2) lack of evidence of a diagnosis of pathology-proven pineoblastoma. Individual patients with the following criteria were excluded: 1) lack of confirmed histopathologic diagnosis of pineoblastoma; 2) mixed histology tumor (ie, pineocytoma-pineoblastoma variant); 3) nonpineal tumor; 4) treatment with an experimental chemotherapeutic agent, defined as any agent not among the standard chemotherapeutics used for pineoblastoma (vincristine, cisplatin/carboplatin, cyclophosphamide, etoposide, carbustine)15; or 5) incomplete data regarding adjuvant therapy.

Data Extraction and Statistical Analysis

Individual patient data were classified based on the treatment or combinations of treatment they received and were subjected to univariate comparisons. Continuous variables were compared using an independent samples t test or analysis of variance after statistical tests demonstrated a Gaussian distribution of the data. Continuous data were expressed as mean ± standard error. Comparisons of binary variables between groups were done the using Pearson chi-square test. Survival analysis was performed using Kaplan-Meier analysis with between-group differences analyzed using the log-rank test.

Cox regression analysis included comparisons of survival outcomes controlling for age, extent of resection, and treatment group, with comparisons of survival between groups using the Kendall tau statistic. We also tested interaction terms between each of the variables with age and Karnofsky performance status. The statistical significance of interactions was assessed with the use of backward, conditional, stepwise regression, in which statistical significance was estimated by means of the likelihood-ratio test to assess the effect of removing interaction terms for all strata of the given variable.16 After establishing that none of the interaction terms would significantly (unadjusted \( P > .2 \) for all terms) alter the log likelihood of the regression model if removed, we calculated the adjusted hazard ratios (HRs) without adjusting for interactions.

Significance was defined as a \( P \) value < .05. All descriptive and statistical analysis was performed using SPSS statistical software (version 1.50; SPSS, Inc., Chicago, Ill).

RESULTS

Overall Results

Our search resulted in 109 publications,1,3,4,7,10,17-61 amounting to 299 nonduplicated, disaggregated patients who were treated for pineoblastoma (see Fig. 1). The sample size distribution among the 109 studies was as follows: <5 patient (80% of studies), 5 to 10 patients (12% of
studies), and >10 patients (8%) of studies. The OS rate was 54% (175 of 299 patients) at a mean follow-up of 31.9 months (range, 1-159 months). In addition, the median survival improved significantly for patients who were treated after 2000 relative to patients who were treated before 2000 (P < .01).

Table 1 summarizes the characteristics of the patients reported in the literature who received various combinations of conventional therapies. Notably, patients who underwent surgery and also received chemotherapy were markedly younger than other cohorts, likely because of the large number of very young children treated with this combination in the literature. In addition, a greater percentage of patients who underwent subtotal resection (STR) received postoperative adjuvant therapy compared with patients who underwent GTR. Not surprisingly, rates of tumor dissemination throughout the central nervous system differed between patient cohorts treated with different strategies, because patients with disseminated disease at diagnosis more often received adjuvant chemotherapy or radiation. This is most likely selection bias, and these differences between groups form the basis of our Cox regression analysis to control for the complexity of these patient cohorts.

**Young Patient Age Significantly Predicts Worse Survival**

Univariate analysis demonstrated a markedly worse prognosis for children aged ≤5 years compared with older children, adolescents, and adults (5-year survival rate 15% for children aged ≤5 years vs 57% for children aged ≥5 years; log-rank P < .00001) (Fig. 2).

Multivariate Cox regression analyses (Table 2) were performed with age classified as a continuous variable and as a binary variable using age 5 years as the cutoff point. In both models, reduced age predicted a worse outcome; however, although the proportional hazard of death declined with each year of age (HR, 0.98; 95% confidence
interval [CI], 0.97-0.99; \( P < .01 \), the regression model using age as a binary variable better explained the data, because an age \( \leq 5 \) years portended an increase in the proportional hazard of death (HR, 3.88; 95% CI, 1.1-13.4; \( P = .032 \)) after correcting for the effects of extent of resection, treatment combinations, rates of intracranial dissemination, and preoperative hydrocephalus (Table 2).

**Aggressive Surgical Resection Improves Survival**

We observed a graded increase in survival with increasing degrees of resection (5-year survival rate: 84% for GTR vs 53% for STR vs 29% for debulking; log-rank \( P < .0001 \)) (Fig. 3). Multivariate analysis indicated that, even when controlling for the effects of very young age, intracranial dissemination, and other combinations of adjuvant therapies, not achieving GTR markedly worsened patient survival (STR: HR, 6.47; 95% CI, 2.3-19; \( P = .001 \); debulking: HR, 9.27; 95% CI, 3.2-27; \( P < .0001 \)) (Table 2).

**The Role of Adjuvant Therapy in Pineoblastoma**

Figure 4 depicts univariate comparisons for patients who received various combinations of therapies and suggests that patients in the surgery plus conventional chemotherapy group had worse survival outcomes than other groups (2-year survival rate: 35% for surgery + external-beam radiotherapy [XRT] vs 31% for surgery + chemotherapy vs 60% for surgery + XRT + chemotherapy; log-rank \( P < .05 \)). Given the potential for bias with the larger number of very young patients in this group, we used Cox regression analysis to correct for age, extent of resection, and rates of central nervous system dissemination at diagnosis. This multivariate analysis demonstrated that the surgery + chemotherapy group fared marginally worse in the proportional hazard of death compared with the surgery alone group, even after correcting for age, extent of resection, and rates of central nervous system dissemination at diagnosis (HR, 3.37; 95% CI, 0.95-12; \( P = .061 \)) (Table 2).
Given these results, we used univariate comparisons within subgroups to determine whether there was a cohort in which postoperative adjuvant radiotherapy was indicated in particular. The addition of XRT to GTR did not improve survival in our univariate analysis (log-rank \( P \) value, non-significant); however, the addition of XRT to STR did yield a survival benefit (Fig. 4, bottom) (2-year survival rate: 53% for STR vs 64% for STR + XRT; log-rank \( P < .05 \)).

The Impact of Disseminated Disease at Diagnosis

Univariate analysis using the Kaplan-Meier method indicated a worse outcome for patients who had disseminated disease at initial diagnosis (2 year survival rate: 56% for no dissemination vs 37% for disseminated disease; log-rank \( P < .0001 \)) (Fig. 5). Given the likely selection bias noted above, we used Cox regression analysis to attempt to determine whether disseminated disease independently predicted worse survival given the different treatments these patients typically receive, and we observed that disseminated disease remained an independent predictor of mortality after correcting for confounding variables (HR, 2.99; 95% CI, 1.7–5.3; \( P = .0002 \)) (Table 2).

DISCUSSION

The principle findings of our current analysis are that surgical resection improves the survival of patients with pineoblastoma and that aggressive surgery improves survival in a dose-dependent fashion. Residual disease confers a greater than 5-fold increase in the independent proportional hazard of death when the analysis is controlled for patient age, disease stage, and differences in management strategies. This is a critical point given the technical difficulty and risk associated with aggressive surgery in this area. Despite these challenges, our results strongly support the idea that it is not wise to leave tumor behind unless absolutely demanded by the tumor’s pathoanatomy and quality-of-life concerns. Simply put, the published literature suggests that no current adjuvant therapy or combination of therapies can replace GTR.

Our analysis demonstrated that children aged <5 years at the time of pineoblastoma diagnosis have decreased survival compared with individuals aged >5 years. This is consistent with the idea that pineoblastoma has a predilection to be very aggressive in young children, as discussed by Cuccia and colleagues. Also consistent with this idea of a more aggressive phenotype in infant pineoblastoma, Hinkes and colleagues suggested that childhood pineoblastomas demonstrated a 0% 1-year survival rate among children aged <3 years. This suggests that clinical trials of future therapies should not mix very young patients with older patients but, rather, should focus on younger patients almost as though they have a different disease.

The role of adjuvant postoperative therapy remains undefined, and our analysis does not support the universal use of chemotherapy in these patients, because, at best, this provides marginal benefit above radiotherapy and surgery. We observed that patients who underwent STR benefited from adjuvant treatment with XRT. Our analysis does not suggest that STR + radiotherapy can reasonably substitute for GTR. Our data suggest that XRT is indicated in patients for whom GTR is unsafe, such as those who have tumors with significant involvement of critical structures, such as the brainstem or veins of the Galenic system. More recent modalities, such as gamma-knife radiotherapy, have been suggested as an adjunct to conventional radiotherapy or as a substitute for surgical resection, but convincing data are lacking. Finally, several promising experimental therapies are being evaluated for the treatment of pineoblastoma, including vorinostat (a histone deacetylase inhibitor), retinoic acid, and high-dose chemotherapy with autologous stem-cell rescue.

There were some limitations to this study. Our objective in writing the current report was to summarize the published literature regarding pineoblastoma. However, it should be acknowledged that this review is not class 1 or 2 data and ideally should be supplanted with more definitive, prospective data. Our analysis is limited by the quality and accuracy of composite studies and may reflect source study biases. It is impossible for us to control for the quality...
of the data reported in the literature. We cannot confirm the histologic grade, extent of resection, or adequacy of radiation therapy, which likely vary between studies, thus rendering it impossible to validate these common definitions across all publications in which they are reported.

Although the possibility of between-center heterogeneity is an issue with any systematic literature review, our use of individual patient data allows for the correction of many confounding covariates using regression analysis, and individual patient data represent the gold standard for analysis of multistudy survival data. This likely reduces the effect of management heterogeneity among centers but cannot completely eliminate it. However, our use of individual patient data does prevent these data from completely complying with consensus guidelines for meta-analyses (ie, the Meta-Analysis of Observational Studies in Epidemiology [MOOSE] criteria).

In conclusion, the results from the current, disaggregated, comprehensive analysis of published patients who were treated for pineoblastomas emphasize the importance of aggressive surgical resection in the treatment of these tumors. Furthermore, these results suggest the basis for future prospective work with these tumors. More specifically, the findings suggest that clinical trials should not mix young patients and older patients or patients with subtotally resected tumors and patients who underwent GTR, because this heterogeneity probably will alter the variability of responses to treatment, and reduce the likelihood of demonstrating benefit.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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