

Factors influencing overall survival rates for patients with pineocytoma

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Abstract Given its rarity, appropriate treatment for pineocytoma remains variable. As the literature primarily contains case reports or studies involving a small series of patients, prognostic factors following treatment of pineocytoma remain unclear. We therefore compiled a systematic review of the literature concerning post-treatment outcomes for pineocytoma to better determine factors associated with overall survival among patients with pineocytoma. We performed a comprehensive search of the published English language literature to identify studies containing outcome data for patients undergoing treatment for pineocytoma. Kaplan–Meier analysis was utilized to determine overall survival rates. Our systematic review identified 168 total patients reported in 64 articles. Among these patients, 21% underwent biopsy, 38% underwent subtotal resection, 42% underwent gross total resection, and 29% underwent radiation therapy, either as mono- or adjuvant therapy. The 1 and 5 year overall survival rates for patients receiving gross total resection versus subtotal resection plus radiotherapy were 91 versus 88%, and 84 versus 17%, respectively. When compared to subtotal resection alone, subtotal resection plus radiation therapy did not offer a significant improvement in overall survival. Gross total resection is the most appropriate treatment for pineocytoma. The potential benefit of conventional

radiotherapy for the treatment of these lesions is unproven, and little evidence supports its use at present.

Keywords Pineocytoma · Surgery · Gross Total Resection · Radiotherapy · Survival

Introduction

Pineocytomas account for 0.4–1.0% of all intracranial tumors [1]. The published literature on the appropriate management of this tumor is sparse due to the relative rarity of this lesion, and thus management of pineocytoma varies between centers based on clinician preference. Studies often combine pineocytomas with other pineal region tumors of different histologies [2, 3]. This is a significant limitation of such analyses, as different tumor histology portends markedly different prognoses, and requires different treatment paradigms.

Because of these limitations, the expected prognosis for patients with these tumors after surgery is not well known [3, 4]. Further, the relative benefit of post-operative adjuvant radiotherapy for patients with this tumor is not known, and thus the importance of obtaining gross total resection is unclear. Due to the difficult location of these tumors and the high risk of serious neurological complications, this is an important question that demands a more definitive answer [5].

To attempt to address these concerns, we systematically reviewed the published literature with the aim of determining if surgical resection of any kind is superior to biopsy alone, if subtotal resection with adjuvant post-operative radiotherapy can replace gross total resection, as it has in other tumors, and to determine the role of radiotherapy in patients with subtotal resection.

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Materials and methods

Article selection

A systematic search of the existing English language literature was conducted to assemble a comprehensive review of overall survival after treatment of pineocytoma. Articles were identified via PubMed search using Boolean searches with key words “pineocytoma” alone and in combination with “treatment,” “mortality,” and “morbidity.” After reviewing these articles, a thorough review of all references was additionally performed.

All references that contained disaggregated data specifically addressing post-treatment survival with adequate follow-up in patients who had undergone surgery (biopsy or resection) of histologically confirmed pineocytoma were included in our analysis. Any paper that did not provide at least some follow-up survival data for pineocytoma patients was excluded.

Data extraction

Tumor characteristics including median largest dimension and volume were not consistently reported in our included studies, preventing analysis. Treatment modality was stratified into three groups based on reported extent of resection. These included gross total resection (GTR), subtotal resection (STR), and simply biopsy. Further substratification of data was performed based on treatment with or without post-operative adjuvant fractionated radiotherapy (XRT).

Useable data regarding stereotactic radiosurgery as sole or post-operative adjuvant therapy for this lesion was too sparse (2 patients) to draw any meaningful statistical comparisons, and thus these patients were excluded from our analysis. Overall survival (PFS) was calculated at the 1-year and 5-year time points. If study data were presented such that these variables could not be reliably ascertained, these studies were excluded from further analysis.

Statistical analysis

Pearson's χ^2 test was used to analyze for differences in pre-operative categorical factors including gender and presence of hydrocephalus. Fisher's exact test was used if there were less than five values per cell. Analysis of variance (ANOVA) was used to evaluate for statistical differences in pre-operative continuous factors, including age. Kaplan–Meier analysis was used to generate overall survival curves. Differences in time to mortality were analyzed by the log-rank test. Cox proportional hazard modeling was used to assess for differences in overall survival adjusting for differences in pre-operative variables. Analyses were carried out using SPSS version 16.0 (SPSS, Inc.).

Results

Clinical characteristics of included patients

Our search identified a total of 64 references [1–64] which met our inclusion criteria, providing disaggregated data on 168 patients with pineocytoma (Table 1). Males made up 52% of the population, and females 48%. The median age among patients was 30 years. Presenting symptoms most commonly encountered included headaches (75%), nausea (23%), and visual changes (17%). The presenting sign most commonly encountered included hydrocephalus (65%). Most tumors were of conventional histology (72%).

146 patients included data describing extent of tumor resection. Of these, 61 (42%) underwent GTR, 55 (38%) underwent STR, and 30 patients (21%) underwent biopsy. Post-operative XRT or radiosurgery (RS) was utilized on 29% of patients. Patients were followed from 3 to 165 months. Shorter follow-up times were reported in case reports or among patients who expired.

The effect of surgical resection of any kind compared to biopsy alone

When comparing rates of overall survival in patients who underwent biopsy, with or without radiation therapy, and those who underwent any surgical resection, with or without radiation therapy, there were no significant differences between the two groups in gender or age ($\chi^2 P = 0.8$, ANOVA $P = 0.06$, respectively). Notably, patients treated with surgical resection suffered pre-operative hydrocephalus

Table 1 Clinical characteristics

	Number of patients (%)
Gender	
M/F	86/80 (52)
Median age (range)	30 (2–74)
Hydrocephalus	
Present at diagnosis	97/149 (65)
Absent at diagnosis	52/149 (35)
Histology	
Conventional	121/168 (72)
Neuronal	24/168 (14)
Other	23/168 (14)
Treatment	
Biopsy	30/146 (21)
STR	55/146 (38)
GTR	61/146 (42)
Post-operative adjuvant radiation	
Yes	66/168 (39)
No	102/168 (61)

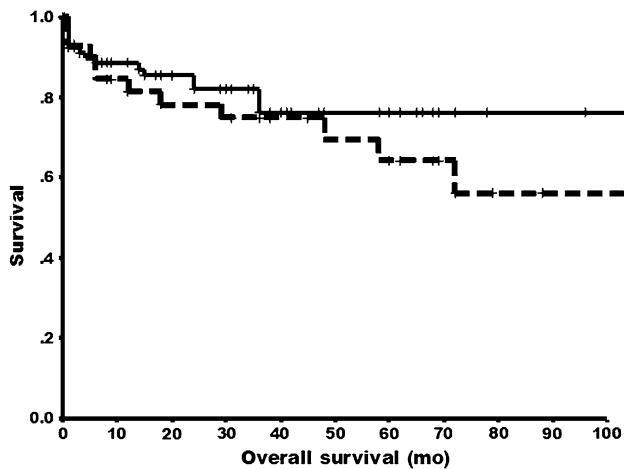


Fig. 1 Comparison of overall survival between patients treated with surgical resection (*solid line*) versus biopsy and radiation (*dashed line*)

more often than patients undergoing biopsy alone (71 vs. 50%, $\chi^2 P < 0.05$). When comparing surgical resection versus biopsy, the 1 and 5 year overall survival rates were 89 versus 82%, and 76 versus 64%, respectively. Although the trend was toward improved survival with surgical resection, this difference did not reach statistical significance (log-rank, $P = 0.19$) (Fig. 1). Thus, despite a suggestion of benefit we have insufficient data to definitive conclude that surgical resection provides a survival benefit compared to a biopsy with or without XRT.

Subtotal resection with adjuvant radiation cannot replace gross total resection

Overall survival rates between patients undergoing GTR without radiation therapy versus patients undergoing subtotal resection STR plus adjuvant XRT were compared to analyze potential prognostic factors. When comparing patient characteristics between the two groups, there were no significant differences in gender ($\chi^2 P = 0.4$), age (ANOVA $P = 0.9$), or presence of hydrocephalus (Fisher's exact test $P = 0.08$). The one and five-year overall survival rates for the GTR group versus the STR plus XRT group was 91% versus 88%, and 84 versus 17%, respectively. On Kaplan–Meier analysis, these differences represented a statistically significant improvement (log-rank, $P < 0.05$) (Fig. 2).

The role of adjuvant radiation in cases of subtotal resection

We performed a subgroup analysis to determine whether post-operative adjuvant XRT combined with STR offered a survival advantage compared to patients receiving STR alone. There were no significant differences in gender

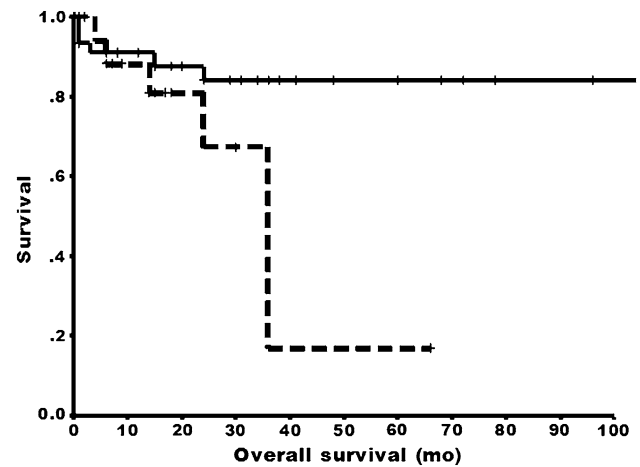


Fig. 2 Comparison of overall survival between patients treated with gross total resection (*solid line*) compared to subtotal resection and postoperative radiotherapy (*dashed line*)

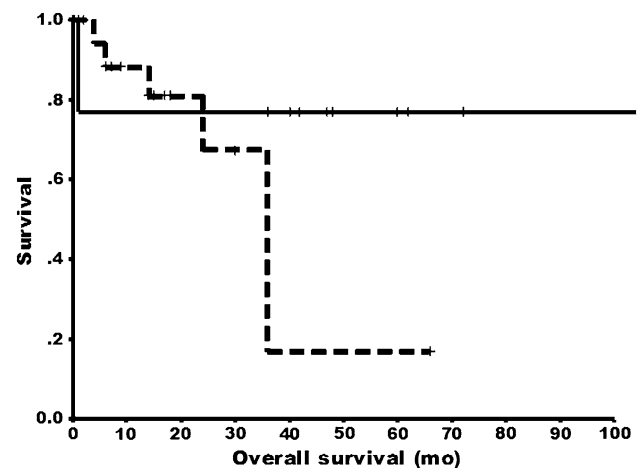


Fig. 3 Comparison of overall survival between patients treated with subtotal resection alone (*solid line*), compared to subtotal resection and postoperative radiotherapy (*dashed line*)

(Fisher's exact $P = 0.2$), age (ANOVA $P = 0.8$), or pre-operative rates of hydrocephalus between the groups (Fisher's exact $P = 0.6$). The 1 and 5 year overall survival rates for the STR group versus the STR plus XRT group was 77 versus 88%, and 77 versus 17%, respectively. Although there is a trend toward decreased survival in patients treated with subtotal resection plus radiation therapy, this difference was not statistically significant (log-rank, $P = 0.14$) (Fig. 3).

Discussion

At present, the post-treatment prognosis of patients with pineocytoma remains unclear. Furthermore, there is no

clear agreement on what treatment course to utilize in order to best minimize patient mortality rates [65, 66]. The rarity of these tumors has made it difficult to define the behavior of this lesion and its response to therapy.

In lieu of class 1 data, we have systematically reviewed the published English language literature on pineocytoma in an attempt to provide better information and guidance in the management of these tumors. Our analysis suggests that aggressive surgical resection provides a survival benefit over subtotal resection. When compared to GTR, the addition of adjuvant XRT to STR does not appear to provide an equivalent survival outcome.

On further analysis of patients receiving STR versus those undergoing STR plus XRT, the addition of adjuvant radiation does not yield a survival benefit when compared to STR alone. Considered in light of the superiority of GTR to STR, it would appear that pineocytoma is relatively resistant to radiation and is optimally treated with aggressive surgery rather than XRT.

Study limitations

Our goal in authoring the current study was to summarize the published literature regarding pineocytoma. However, it should be acknowledged that this review is not class 1 or 2 data, and should ideally be supplanted with more definitive data if and when this becomes available. Our analysis is limited by the quality and accuracy 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, and adequacy of radiation therapy, which likely vary between studies, therefore rendering it impossible to validate these common definitions across all publications in which they are reported. Furthermore, our use of Kaplan–Meier analysis largely precludes the use of formal meta-analysis methods, including the calculation of a Q-statistic which allows for a determination of survival data heterogeneity. This consequently prevents us from addressing the potential for systematic flaws or differences among studies in a statistically meaningful way. Finally, due to the diverse range of data presentation, we are limited in our ability to study and control for certain variables. Potential confounders inconsistently presented across studies cannot be reviewed.

Conclusion

In conclusion, we have assembled a systematic review of the published pineocytoma literature and offer data on survival rates following different treatment strategies. These data appear to indicate optimal survival rates

following GTR. Given the relatively rarity of this tumor, this study aims to improve upon the small sample sizes offered by individual institutions by providing a more comprehensive review of outcome characteristics for patients with pineocytoma.

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