The role of surgery in recurrent ependymomas

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OBJECTIVE The role of surgery in recurrent ependymomas and its contribution to the outcome are not well defined. While gross-total resection (GTR) has shown benefit in newly diagnosed patients with improvement in progression-free survival (PFS), its impact after recurrence is not known. Its role in distant relapses or multiple local recurrences is similarly less well understood. The objective of this study was to investigate whether GTR could prolong survival after recurrence.

METHODS In this paper, the authors identified patients with ependymomas who underwent surgery at Texas Children’s Hospital for recurrent ependymomas between December 2000 and December 2021. Surgical treatment was stratified as GTR, subtotal resection (STR), or a biopsy. Kaplan-Meier analysis was performed for PFS and overall survival (OS), and the log-rank test was used to assess statistical significance. The Cox regression model was used for multivariable analysis.

RESULTS Forty children were identified with a first ependymoma recurrence and follow-up data were collected. The median age was 5.46 years (95% CI 4.52–6.39 years) with a mean follow-up of 3.92 years (95% CI 2.42–5.42 years). In 26 patients (65%), the original tumor was located in the infratentorial space. Twenty-nine patients (72.5%) presented with local recurrence. Within this group, the 5-year PFS rates for the GTR and STR groups were 40.1% and 26.8%, respectively. The 5- and 10-year OS rates were 58.3% and 50% in the GTR group and 51% and 16.7% in the STR group, respectively. Fifteen patients presented with a second recurrence. The 5-year PFS and OS rates in patients who had GTR after a second recurrence were 33% and 50%, respectively.

CONCLUSIONS GTR of local recurrent ependymomas can result in long-term survival in first and second recurrences. Further and larger studies are necessary to elucidate the role of surgery in distal recurrences.

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KEYWORDS recurrent ependymoma; survival; outcomes; pediatrics; tumor

The role of surgery in a newly diagnosed ependymoma is well known,1–6 with gross-total resection (GTR) being an important prognostic factor that impacts progression-free survival (PFS), regardless of tumor location.7 Surgery for recurrent ependymomas with the aim of GTR followed by radiation therapy is a common salvage approach.5–10 However, the impact of GTR on survival for first recurrences is not well defined.4,11,12 One of the difficulties in elucidating the role of surgery in recurrent ependymomas is that most of these patients also receive radiation therapy to both local and distant recurrences, and many receive additional therapies. Does surgery with GTR of local recurrences or GTR of both local and distant recurrences contribute to a prolonged survival? This is the question that this retrospective study aimed to address within the context of a single-center experience.

Methods

This was a retrospective single-center study that included patients surgically treated for recurrent ependymomas at Texas Children’s Hospital from December 2000 to December 2021. This study was approved by the institutional review board of the Baylor College of Medicine.

Clinical data collected included age, sex, date of diagnosis, date of the recurrences, and last follow-up. Treatment information included surgery, which was defined...
that confirmed further progression. Overall survival (OS) was calculated from the day of the surgery of the first or second recurrence to the date of the last visit or the date of death if documented, in case the patient had died. All patients included had imaging studies available for at least 1 year after surgery.

Recurrences were categorized into three groups based on the MRI features: local, a recurrence that occurred within the field of the original tumor; distal, a solitary recurrence beyond the limits of the original tumor; and disseminated, either a combination of both recurrences or multiple synchronous distal recurrences.

IMRT was used for patients as a focal radiation treatment modality until PBT became available in 2006. The decision to transition from IMRT to PBT was largely made as an attempt to minimize the dose to the normal surrounding brain tissue and preserve cognitive function in young children. For both IMRT and PBT, prescription doses ranged from 50.4 to 54 Gy in 1.8-Gy fractions to the tumor with a 0.5- to 1-cm margin (clinical target volume).

**Statistical Analysis**

Data were descriptively reported as means or medians with 95% confidence intervals for continuous variables and counts and frequencies for categorical data. Kaplan-Meier analysis was performed for PFS and OS; the log-rank test was used to assess statistical significance. The Cox regression model was used for multivariable analysis with PFS and OS as dependent variables. Variables that were statistically significant on univariable analysis were included in the multivariable model. Variables of clinical significance, such as age, sex, pathological diagnosis, location of the original tumor, type of recurrence, and extent of resection, were also included in the multivariable model. A two-sided p value < 0.05 was considered as statistically significant. Statistical analysis was performed using SPSS version 28.0 (IBM Corp.).

**Results**

During the study period, 113 patients with a diagnosis of ependymoma were treated at our institution. Adequate information and follow-up were available for 85 patients, and they were the subject of this retrospective analysis. Among these 85 patients, 40 children were treated for a first ependymoma recurrence; 23 patients (57.5%) were male. The median age was 5.46 years (95% CI 4.52–6.39 years) with a mean follow-up of 3.92 years (95% CI 2.42–5.42 years). In 26 patients (65%), the original tumor was located in the supratentorial space; the remaining tumors were located in the infratentorial space; the remaining tumors were located in the supratentorial space; or spine (n = 2). Recurrence was local in 29 patients (72.5%). Distal recurrences occurred in 3 patients and disseminated (n = 2). Recurrence was local in 29 patients (72.5%). Distal recurrences occurred in 3 patients and disseminated disease in 8 patients. In 90% of the recurrences, the initial pathology was anaplastic ependymoma without significant histological change compared with the primary tumor. Demographic and baseline characteristics are described in Table 1.

The distribution of the type of recurrence and the type of surgery and subsequent adjuvant treatment with radiation therapy for first and second recurrences are summa-
All patients with recurrence had received focal radiation therapy as part of the treatment for the primary tumor: 30 patients (75%) received IMRT and 10 patients (25%) PBT.

Among the type of recurrences, only patients with local recurrences attained long-term OS. Patients with distal and disseminated first recurrences eventually died of disease progression. The 5-year OS rate for local recurrence was 52.9% \( (p = 0.004) \) (Fig. 3).

Regarding survival after recurrence by location of the original tumor, there were no significant differences among the three compartments (supratentorial, infratentorial, and spine) \( (p = 0.2) \) (Fig. 3).

**First Recurrence**

Among the 29 patients with a first local recurrence, 16 underwent GTR, 9 underwent STR, and 4 patients did not have surgery. In the 4 patients with no biopsy, the recurrence was determined on MRI studies. Seven patients with GTR and 5 patients with STR completed adjuvant treatment with focal radiation therapy. The exact radiation modality and distribution by extent of resection are shown in Fig. 1. The 5-year PFS rates for the GTR and STR groups were 40.1% and 26.8%, respectively. The 5- and 10-year OS rates were 58.3% and 50% in the GTR group and 51% and 16.7% in the STR group, respectively \( (p = 0.001) \) (Fig. 4).

Only patients with local recurrence who underwent GTR or STR attained long-term survival. The pattern of second recurrence, particularly in these two subgroups, is shown in Fig. 1, as well as the time to progression. There were no significant differences in the pattern or the time to progression among the subgroups (Fig. 1). Eleven patients also received adjuvant chemotherapy.

**Second Recurrence**

FIG. 1. Distribution of type of surgery and radiation therapy (RT) by pattern of recurrence, for the first recurrence. Radiosurg. = radiosurgery.

FIG. 2. Distribution of type of surgery and radiation therapy by pattern of recurrence, for the second recurrence. Bx = biopsy.
Multivariable Analysis

The variables of age, sex, original tumor location, pathology, radiation therapy, and type of recurrence did not influence PFS and OS in a multivariable analysis. Only the extent of resection (i.e., GTR vs no surgery) was found to have a statistically significant difference in OS in the Cox regression model (HR 7.2; p = 0.03).

Second Recurrence

Fifteen patients presented with a second recurrence that prompted additional treatment: 8 local, 4 distal, and 3 disseminated. Among these 15 patients, 12 had local recurrence first time. Seven of the 15 patients underwent GTR, 4 underwent STR, and 4 were not treated surgically (Fig. 2). Among the 4 patients who did not receive resection, 1 underwent biopsy to confirm the diagnosis of tumor recurrence as their prior recurrence occurred more than 5 years earlier. Only patients who underwent GTR experienced long-term survival. The 5-year PFS and OS rates for the GTR group were 33% and 50%, respectively (Fig. 4).

Discussion

While the treatment for newly diagnosed ependymomas is well established, the role of surgery in recurrent tumors remains controversial. Most studies show a benefit in PFS with GTR but that benefit does not necessarily correlate with a significant improvement in survival in some of those series. Ritzmann et al. published the largest series in recurrent ependymomas with 302 cases. They found a benefit of GTR over STR in PFS for first recurrences. However, while they performed multiple subgroup analysis based on primary tumor location and molecular subgroups, they did not assess the impact of extent of resection based on the pattern of recurrence (local vs distal) and on recurrences beyond the initial one.

If the impact of resection on survival after the first recurrence is questionable, then the role of surgery in subsequent recurrences is even less clear and not well assessed. Resection of locally recurrent ependymomas is considered as a treatment option, but without clear evidence of the impact on the survival for these patients. Thus, in this study we wanted to investigate whether GTR could prolong PFS and OS after recurrence.

Furthermore, the risks of surgery for multiple recurrent ependymomas increase with subsequent operations. Knowing the impact of these surgeries on survival is important, especially when complications such as gastrostomy, tracheostomy, or cranial nerve deficits can significantly disrupt the quality of life of the children and their families.

To the best of our knowledge, this is the first study to analyze the role of surgery in recurrent ependymomas on multiple recurrences. Our findings suggest that GTR can result in long-term survival not only for first local relapse, but also for second recurrences. Thus, in our series up to 50% of the children with second recurrences survived more than 10 years after a complete resection. None of the patients with STR on second recurrence reached the 5-year survival time point. This benefit seems to be present only for local multiple recurrences. In our series, distal recurrences and disseminated tumors did not benefit from GTR.

Tsang et al. showed that distal first recurrences followed by radiation therapy can also have a prolonged PFS. In our series, none of the patients with distal or disseminated first recurrences survived, but the very small number of patients in these groups precludes us from making a significant conclusion.

Adjuvant radiation therapy is well accepted as a therapeutic option at the time of first recurrence. There is no consensus about the volume of the radiation field. In our series, the distribution of patients who received adjuvant treatment after surgery for local recurrences was reasonably even between the groups: 43% of the GTR group and 50% of the STR group. Thus, radiation therapy should not play a significant role as a confounding factor between these two groups. The fact that adjuvant radiation therapy after the first recurrence had not been used as consistently as it was for the primary tumor (100% of patients)}
received field radiation therapy after the initial surgery) certainly reflects a change in practice over time. As previously mentioned, adjuvant radiation therapy after first recurrence was not consistently used prior to 2015. Our institution incorporated consistent use of adjuvant radiation therapy as a treatment modality for first recurrences in 2015. The volume of the radiation therapy field and the radiation modality for recurrences, which depended on the site, size, and pattern of recurrence (local vs disseminated), as well as the time from initial treatment, could also explain the lack of consistency in delivering radiation therapy at the time of first recurrence. Overall, CSI was used only for disseminated recurrences. The decision to use stereotactic radiosurgery versus fractioned radiation therapy was assessed on a case-by-case basis after a detailed discussion with the family. Questions regarding the volume and modality of radiation therapy for recurrences could not be addressed in this retrospective study.

Limitations

There are several limitations in this retrospective study. The most important limitation is that we did not assess patients based on molecular classification and 1q and 6p status. It is well known that distal and disseminated recurrences occur early in patients with 1q gain and 6p loss. So, their presence may not have had an effect on local recurrences. Furthermore, the small number of patients could have prevented us from finding significant differences in variables with a known impact on survival, such as age, sex, and radiation treatment, or from pursuing further subgroup analysis.

We have not included an assessment of the neurological morbidity associated with the extent of resection. The
small number of patients; the retrospective nature of the analysis, which precluded good neurological assessment before and after the procedure; and other confounding factors such as tumor location or prior surgeries prevented us from being able to reliably analyze this morbidity.

Finally, the nonstandard definition of progression used in this study could represent an additional limitation. Because of the subjective nature of the latter, this limitation could have been highlighted by a long study period with different observers. However, we believe that the multidisciplinary approach and discussion of every case provided a reliable definition of the endpoint.

Conclusions

In our series, GTR of local recurrent ependymomas can result in long-term survival for first and second recurrences. Larger prospective studies with a uniform approach to local recurrences may better delineate the role of surgery in local and distal recurrences.

References


Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Aldave, Okcu, Whitehead, Chintagumpala. Acquisition of data: Aldave, Ruggieri, Paulino. Analysis and interpretation of data: Aldave, Okcu, Paulino, Whitehead, Weiner, Chintagumpala. Drafting the article: Aldave. Critically revising the article: Aldave, Okcu, Whitehead, Chintagumpala. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Aldave. Statistical analysis: Aldave. Administrative/technical/material support: Aldave, Okcu, Paulino. Study supervision: Aldave.

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