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Title

Gross total resection improves overall survival in children with choroid plexus carcinoma.

Permalink

<https://escholarship.org/uc/item/1934t59d>

Journal

Journal of neuro-oncology, 116(1)

ISSN

0167-594X

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Publication Date

2014

DOI

10.1007/s11060-013-1281-5

Peer reviewed

Gross total resection improves overall survival in children with choroid plexus carcinoma

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Received: 23 April 2013 / Accepted: 14 October 2013 / Published online: 29 October 2013
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Abstract Choroid plexus carcinoma (CPC) is a rare, malignant, primary brain tumor with a poor prognosis. While previous reports have shown benefits of aggressive surgery, very few large-scale studies have focused exclusively on the pediatric population, for whom the risks of aggressive surgery must be weighed carefully against the benefits. We performed a comprehensive systematic review of pediatric CPCs to test the effects of gross total resection (GTR) on overall survival (OS) and progression-free survival (PFS). A Pubmed search was performed to identify children with CPC who underwent surgical resection. Only disaggregated clinical cases in which extent of resection was confirmed by CT or MRI were included for analysis. Kaplan–Meier and multivariate Cox regression survival analyses were performed to determine the effects of extent of resection on OS and PFS. Disaggregated clinical data from a total of 102 pediatric CPC patients (age ≤ 18 years) with known extent of resection and overall survival were

analyzed. GTR was significantly associated with better OS by Kaplan–Meier analysis (logrank $p < 0.001$). Multivariate Cox regression analysis adjusting for age, gender, tumor location (supratentorial vs. infratentorial), and type of adjuvant therapy (chemotherapy, radiation, and combined therapy), showed that GTR independently increased OS ($p = 0.006$). While GTR also improved PFS on Kaplan–Meier analysis ($p = 0.027$), the effect did not meet our criteria for significance in our multivariate Cox model ($p = 0.120$). GTR improved OS of pediatric CPC and is recommended if it can be safely performed.

Keywords Choroid plexus carcinoma · Extent of resection · Gross total resection · Overall survival · Progression free survival · Pediatric

Abbreviations

GTR	Gross total resection
STR	Subtotal resection
OS	Overall survival
PFS	Progression free survival
EOR	Extent of resection
CI	Confidence interval

Electronic supplementary material The online version of this article (doi:10.1007/s11060-013-1281-5) contains supplementary material, which is available to authorized users.

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Introduction

Choroid plexus carcinoma (CPC) is a rare, malignant, primary brain tumor with a poor prognosis [1, 2]. It is classified by the World Health Organization as a grade III neoplasm. To date, there have been very few studies focused on a purely pediatric population [3], even though there is a higher incidence of CPC in children than in adults. The treatment for childhood tumors differs

substantially from adults due to considerations of ongoing development and long-term effects [4, 5].

While surgery is usually the first step in the management of patients with CPC, the decision to attempt a gross total resection (GTR) as the initial goal remains unclear [5–11]. Surgery for these tumors can be complicated by factors such as low blood volume in small children, increased tumor vascularity, and tumor dissemination, all of which can increase intraoperative bleeding and post-operative morbidity [12]. A recent large series from a Canadian databank of CNS tumors examining CPCs in children younger than 36 months failed to show a survival difference due to extent of resection (EOR) [13]. One published systematic review a decade ago showed the importance of gross-total resection on overall survival, but due to limited number of cases available at the time, its use of multivariate analysis was limited [3]. Moreover, most systematic reviews examining the extent of resection are based on binary data from aggregated datasets and are limited by the use of Chi square or logistic regression analyses at fixed time-points to compare survival at 2 or 5 years after resection [3]. These analyses introduce greater biases compared to a time-dependent survival analysis, such as a Cox regression analysis, when the clinical outcomes are time-dependent. In order to examine in greater detail whether GTR improves survival, we performed a comprehensive systematic review of literature to study whether EOR predicts overall survival (OS) and progression free survival (PFS) among pediatric CPC patients.

Methods

Article selection

A comprehensive systematic review of the English-language literature was performed. Articles published after 1975 were identified via PubMed search using the key word “choroid plexus carcinoma”, and included in the database, to reflect the era of modern microscopic neurosurgery and standard use of CT and MRI to confirm extent of resection. All manuscripts were individually reviewed to identify choroid plexus carcinoma patients with confirmed diagnosis and individual clinical information available. Only pediatric patients 18 years of age and under, with clearly defined extent of resection confirmed by CT or MRI as well as progression-free and overall survival were included. Articles published with aggregated data sets, where individual patient data were grouped, were excluded in this analysis. For the final analysis, we identified 42 articles with a total of 102 patients who met the criteria (Supplemental Table 1). Individual patient data from selected studies were pooled and analyzed.

Data extraction

Data from case reports and institutional series were extracted with the following information: age, gender, extent of resection (GTR vs. STR), adjuvant radiotherapy, adjuvant chemotherapy, recurrence or progression of disease, metastasis, time to recurrence or progression of disease, mortality, cause of death, time to mortality, tumor location (supratentorial including: lateral ventricle, third ventricle, supratentorial cerebral; infratentorial including: fourth ventricle, cerebellopontine angle, infratentorial cerebral), tumor control at 1 and 5 years and duration of follow-up. Cause of death was categorized as either due to disease (as a direct result from CPC), due to surgery (as a result from CPC resection, and would not have perished otherwise in that perioperative period. Iatrogenic causes include examples such as intraoperative hemorrhage), or due to unrelated cause (unrelated to having a diagnosis of CPC). All mean values are presented with standard error of mean (SEM).

Statistical analysis

PFS and OS were analyzed by building Kaplan–Meier curves and differences assessed by logrank test. Cox proportional hazards model was fitted by backward stepwise model selection while accounting for confounding variables, including: age, extent of resection, tumor location, adjuvant therapy (radiation, chemotherapy or both). Means of continuous variable were analyzed using ANOVA, and categorical values were analyzed using the Pearson’s Chi square test. Fisher’s exact test was used if the expected cell count in a contingency table was less than 5. *P* values less than 0.05 were considered statistically significant. Analyses were performed using the statistical software package SPSS 20 (IBM Inc.).

Results

Patient demographics

Disaggregated clinical information obtained from 101 articles resulted in an overall cohort of 322 patients less than or equal to 18 years of age with a diagnosis of CPC. The age distribution showed that that vast majority of CPCs occur in very young children. When this population was divided into quartiles by age, 25 % of patients were 9 months or younger, 50 % of patients were 20 months or younger, and 75 % of patients were 4 years or younger. In 102 patients, both the precise extent of resection verified by either CT or MRI and the length of overall survival were known. All subsequent statistical analyses were performed

Fig. 1 Distribution of CPC patients by age. The 102 pediatric CPC patients in our database was plotted in this histogram. An inverse relationship exists between age and incidence of CPC. The mean age of diagnosis was 3.02 years, and median age was 1.67 years

Table 1 Demographics of Pediatric CPCs by Extent of Resection

	GTR (n)	STR (n)	<i>p</i> value
Mean age			
Years	3.24 (48)	2.81 (54)	0.564
Gender			
Male	53 % (23)	54 % (27)	1.000
Female	47 % (20)	46 % (23)	
Tumor location			
Supratentorial	85 % (33)	83 % (38)	1.000
Infratentorial	15 % (6)	17 % (8)	
Adjuvant therapy			
No adjuvant	11 % (5)	20 % (10)	0.556
Chemotherapy	55 % (24)	42 % (21)	
Radiation	9 % (4)	8 % (4)	
Combined therapy	25 % (11)	30 % (15)	
Cause of death			
Due to disease	75 % (9)	94 % (33)	0.052
Due to surgery	0 % (0)	3 % (1)	
Unrelated cause	25 % (3)	3 % (1)	
Metastasis			
Metastasis	13 % (4)	19 % (4)	0.700
No metastasis	87 % (27)	81 % (17)	

on only this group of 102 patients. For these patients, the mean age was 3.02 years, and the median age was 1.67 years. Both statistics were not statistically significantly different from those of the total 322 pediatric CPC

Fig. 2 GTR was associated with improved overall and progression-free survival. **a** Kaplan–Meier analysis shows a statistically significant difference in overall survival between the gross-total and subtotal resection groups ($p < 0.001$). **b** Kaplan–Meier analysis shows a statistically significant difference in progression-free survival between the gross-total and subtotal resection groups ($p = 0.027$)

patients, and the overall age distribution of this smaller cohort (Fig. 1) was similar to that of the total 322 patients identified. The follow-up time ranged from 1 to 235 months with a mean of 29 months, and both statistics were also not significantly different from those of the 322 patients. When the 102 patients were stratified by EOR,

Table 2 Gross total resection improves overall survival

Population	Kaplan–Meier <i>p</i> value	Cox regression	
		<i>p</i> value	Hazard ratio (95 % CI)
Total pediatric	<0.001	0.006	0.291 (0.121–0.699)
Younger than median	<0.001	NA	NA
Younger than mean	0.001	NA	NA
Older than median	0.111	NA	NA
Older than mean	0.179	NA	NA

Kaplan–Meier with logrank comparison and multivariate Cox regression analyses were performed for the total pediatric population and the four subgroups to test the effect of extent of resection on overall survival. Multivariate analyses adjusted for age, gender, tumor location, and adjuvant therapy use. Hazard ratios represented the hazard of death for GTR over STR, and 95 % confidence intervals (CI) for each were included. Mean Age = 3.02 years; median age = 1.67 years

there were 48 patients (47 %) with confirmed GTR, and 54 patients (53 %) with confirmed STR (Table 1). There were no significant differences between the GTR and STR groups in terms of mean age ($p = 0.564$), male to female ratio ($p = 1.000$), supratentorial or infratentorial tumor location ($p = 1.000$), use of adjuvant therapy ($p = 0.556$), cause of death ($p = 0.052$), or metastasis ($p = 0.700$). Age, gender, tumor location, and the use of adjuvant therapy were incorporated into the multivariate Cox regression analyses.

Gross total resection improves overall survival

We first performed a Kaplan–Meier analysis to determine the effect of EOR on OS (Fig. 2a). GTR was associated with longer OS compared to STR, and a logrank test confirmed that this difference was significant ($p < 0.001$) (Table 2). The estimated median OS based on Kaplan–Meier analysis for STR was 16 months, whereas for GTR it was not possible to be estimated because more than half of the patients were still alive at the time of their last follow-up.

We also performed multivariate Cox regression analysis to test whether GTR improved OS while controlling for patient age, gender, tumor location, and adjuvant therapy use. Tumor location was classified as either supratentorial or infratentorial. We classified the use of adjuvant therapy into four groups: no adjuvant therapy, chemotherapy only, radiotherapy only, or combined chemotherapy and radiotherapy groups. In the multivariate Cox regression model, GTR independently and significantly ($p < 0.001$) improved OS with a hazard ratio of 0.291 (95 % CI 0.121–0.699).

Because age is an important factor when considering treatment choice in children, we further analyzed subgroups

Table 3 Gross total resection not associated with improved progression free survival

Population	Kaplan–Meier <i>p</i> value	Cox regression	
		<i>p</i> value	Hazard ratio (95 % CI)
Total pediatric	0.027	0.120	0.505 (0.371–3.369)
Younger than median	0.040	NA	NA
Younger than mean	0.043	NA	NA
Older than median	0.422	NA	NA
Older than mean	0.892	NA	NA

Kaplan–Meier with logrank comparison and multivariate Cox regression analyses were performed for the total pediatric population and the four subgroups to test the effect of extent of resection on progression free survival. Multivariate analyses adjusted for age, gender, tumor location n, and adjuvant therapy use. Hazard ratios represented the hazard of death for GTR over STR, and 95 % CI for each were included. Mean Age = 3.02 years; median age = 1.67 years

of the pediatric population divided by the mean (3.02 years) and median (1.67 years) ages (Table 2). Four separate groups were analyzed: two groups for those younger than either the mean or median age, and two groups for those older than either the mean or median age. We found through Kaplan–Meier analysis that GTR was associated with improved OS among those younger than the median age ($p < 0.001$) as well as among those younger than the mean age ($p = 0.001$) (Table 2). In contrast, GTR was not associated with significantly improved OS among those in either the older than median age group ($p = 0.111$), or older than mean age group ($p = 0.179$). The multivariate Cox regression model was not able to be fitted for those subgroups due to insufficient sample size (Table 2).

Gross total resection may not independently improve progression-free survival

Previous studies have implicated that CPC recurrence may be associated with worse OS [14–16]. Because GTR was associated with increased OS, we tested whether it also improved PFS. The median PFS by Kaplan–Meier analysis was 13 months for STR, but unable to be calculated for GTR since more than half of the patients did not have progression or recurrence (Fig. 2b). Logrank test showed that GTR significantly improved PFS ($p = 0.027$) (Fig. 2b; Table 3). However, the multivariate Cox regression analysis on PFS adjusting for age, tumor location, and adjuvant therapy found that GTR did not independently improve PFS ($p = 0.120$).

To assess whether GTR could have improved PFS in children stratified by age, we tested the statistical

significance of this association in the same four subgroups used in the analysis for OS: those who were diagnosed when younger or older than either the median or mean age of the pediatric population. Univariate logrank test of Kaplan–Meier analysis showed that GTR was associated with improved PFS among those younger than the median age ($p = 0.040$) as well as among those younger than the mean age ($p = 0.043$) (Table 3). In contrast, GTR was not associated with improved PFS for those older than either median age ($p = 0.422$) or mean age ($p = 0.892$) groups.

Discussion

Although surgery is accepted as the standard initial treatment for CPCs, the benefits of aggressive surgery must be carefully weighed against the risk of causing new neurological deficits and other serious complications. This consideration is particularly important in children for two reasons: (1) CPCs are usually large and very vascular, with GTR a challenging goal; (2) debilitating neurological deficits in young children often have a profound impact on normal development. Therefore, the goal of this study was to identify how survival was affected by extent of resection, thereby facilitating surgical decision-making.

Our primary observation was that GTR significantly improved OS for the general pediatric CPC population, independently of age, use of adjuvant therapy and tumor location. We found no significant difference in the cause of death between the GTR and STR groups that could have confounded this result. Thus, based on our data we can recommend that for the general pediatric CPC population, aggressive resection may be pursued if it can be safely performed.

We separately investigated younger and older children to address the following two issues: (1) clinically these two groups of patients may be very different and require different approaches to surgical considerations, and (2) the precise benefits of GTR for these specific age subgroups may vary. It has been suggested that the risks associated with surgery may be much higher among younger pediatric patients, and the neurological sequelae may have a larger impact on the cognitive development of these patients as they have not yet reached many of the crucial milestones in childhood development [13]. Coincidentally, the median and mean ages of the CPC population fell close to what most clinicians consider as infants/toddlers and older children. Therefore, for the sub-group analysis, it seemed appropriate to analyze the younger and older sub-populations based on which side of the median or mean age a patient falls rather than creating an artificial age cut-off to differentiate the two age groups. Moreover, our method for division allowed for the most balanced division of the two

groups such that each group could have the greatest chance of having sufficient number of patients for statistical analysis.

When analyzed separately, the younger and older pediatric CPC populations seemed to respond to GTR differently: both OS and PFS were significantly improved in younger groups but not in older groups. Although our data may suggest that survival benefit from GTR is mainly found among the infants and toddlers of the pediatric population, we were not able to fit proper multivariate Cox regression models (due to insufficient sample size) controlling for gender, tumor location, and adjuvant therapy to definitely verify this effect. However, our univariate survival analysis does reveal an interesting finding that emphasizes the need for future research to more specifically identify for which age group GTR provides the most survival benefit and if different adjuvant treatment paradigms have different outcomes for patients of different ages. Additionally, our result will hopefully prompt future research into whether there might be some intrinsic biological difference between tumors that clinically present in younger versus older patients. For now, our analysis suggests that it has an overall survival benefit for the general pediatric population.

Because GTR had such a significant impact on OS and that there is some evidence linking CPC recurrence to OS, we had originally hypothesized that GTR would also have a significant impact on PFS. Indeed, we found that GTR significantly improved PFS in our Kaplan–Meier analysis. However, this effect was not significant in the multivariate Cox regression, suggesting that GTR may not independently improve PFS when controlling for other potentially confounding factors. It was not immediately clear why GTR did not independently improve PFS. Perhaps, if our sample size were larger, an association would have been reached. Additionally, it may be possible that CPC is overall biologically aggressive that it microscopically infiltrates the brain through the choroid plexus that GTR does not significantly prevent or delay recurrence. In our analysis, we found no difference in the reported rate of metastasis between GTR and STR, and that may be a contributing mechanism to tumor recurrence. Also, we found no significant difference in the cause of death between GTR and STR groups, suggesting that STR patients were not dying of other causes at a different rate. Overall, our result is not entirely surprising given that few studies have demonstrated a direct beneficial effect of either GTR or adjuvant therapy on PFS. Thus far, only limited evidence suggests that tumors that do recur were associated with worse OS. Therefore, the role of GTR in preventing recurrence or improving PFS remains a topic of debate in the CPC literature [14].

Moreover, without reviewing more details of each case, including radiographic imaging and understanding tumor

volume and location of each tumor progression, a better understanding of the potential link between EOR and PFS would be difficult. Ultimately, to critically address this concern and definitively investigate the effects of adjuvant on PFS, we will need to prospectively collect PFS data on CPC patients to be able to make this direct comparison.

One significant finding of our multivariate analysis was that the use of adjuvant therapy significantly improved OS (data not shown). Over the last few decades, both techniques in radiation and the use of chemotherapy have changed dramatically and evolved to become much more targeted. As more data emerge, the role of specific radiation and chemotherapy regimens will become prominent. Indeed, an ongoing clinical trial in Europe specifically examines the role of targeted chemotherapy on choroid plexus tumors [17].

Even though our database might be limited to cases with only disaggregated clinical information, we believe that there is strong external validity. For example, estimated 5-year survivals based on our Kaplan–Meier analysis (data not shown) were similar to previously reported rates at 58.1 ± 6.1 % (one standard deviation) and 20.9 ± 5.1 % for GTR and STR, respectively [18].

We recognize that a systematic review of literature cannot produce the quality of evidence of a prospective randomized study. However, given the lack available data from prospective studies contributable to the rarity of this disease, our systematic analysis of the literature provides the best current evidence. While an obvious inherent bias resulting from publication of only patients with favorable outcome cannot be ruled out, the low incidence of CPC dramatically lowers this potential bias because almost every case is worth publishing or included in large institutional series. We also limited our analysis to only disaggregated clinical data because it allowed us to incorporate time as a continuous variable in survival analyses such as Kaplan–Meier and Cox regression to further reduce statistical bias. Thus, even though we lost some CPC cases that were published as aggregated data, we were able to perform better statistical analysis as a result.

Conclusion

Our study presents one of the largest systematic reviews of the survival benefit of gross total resection specifically for the pediatric CPC population. We found that GTR improved OS independently of age, gender, use of adjuvant therapy and tumor location. Our results not only corroborate previous data supporting maximum surgical resection of CPCs, but also show that GTR may provide survival benefit even for very young patients if it can be safely

performed. While GTR was associated with better PFS, it did not independently prolong PFS. Further research, especially prospective studies, are needed to better understand not only the clinical response of CPCs to different treatment modalities, but also potential intrinsic biological differences between different CPCs.

Acknowledgments None.

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

Funding M. Z. Sun is a Howard Hughes Medical Institute Medical Research Fellow. M. Safaee was supported by a grant from the Doris Duke Charitable Foundation. Dr. Oh received a National Research Service Award from the National Institutes of Health (F32NS073326-01). Dr. Ivan is funded by the National Research Education Foundation through the American Association of Neurological Surgeons. Dr. Parsa was partially funded by the Reza and Georgianna Khatib Endowed Chair in Skull Base Tumor Surgery and currently by the Michael J. Marchese Professor Chair.

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