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Second Surgery and the Prognosis of Choroid Plexus Carcinoma – Results of a Meta-analysis of Individual Cases

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Abstract. *Tumors of the choroid plexus (CPT) are rare. While choroid plexus papillomas (CPP) are regarded as benign, choroid plexus carcinomas (CPC) have a dismal prognosis, and there is limited information available regarding the best treatment. Maximal possible surgery is generally believed to be the major prognostic factor, but data to answer the question, of whether second surgery improves the prognosis of CPC have been missing. A database of all cases of CPT reported in the literature until 2004 was created to determine prognostic factors and analyze therapeutic modalities. Eight hundred and fifty-seven cases of CPT were identified. Three hundred and forty-seven patients had CPC, 15 atypical choroid plexus papillomas (APP) and 495 CPP. Besides histology, complete resection was confirmed to be the most important prognostic factor in each of the subgroups defined by the three histological diagnoses. In CPP, complete resection was more frequently achieved (80.4%) than in APP (61.5%) or CPC (39.6%). Among the subgroup of incompletely resected CPC, 22.6% of the patients had second surgery. The prognosis of these patients appeared better when compared to incompletely resected CPC without second surgery (2-year overall survival 69% versus 30%). There was no such difference within the subgroup of CPP. This study suggests, if complete resection is not possible in the first surgery of a choroid plexus carcinoma, a second resection should be considered.*

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Choroid plexus tumors (CPT) are rare tumors of neuroectodermal origin that comprise 0.4-0.6% of all brain tumors (1, 2). Most cases occur in children less than 2 years of age (4, 7, 8, 10), but the number of adults with these tumors might be underestimated (11).

On histology, tumors of the choroid plexus are categorized in carcinoma (CPC), atypical papilloma (APP) and papilloma (CPP), the latter accounting for 65-75% of the CPT (6, 15). The distinction can be difficult, and their histological appearance may not correlate with the biological behavior (3, 5). Because of this biological diversity and the rarity of the CPT, optimal treatment had been difficult to find, and the current treatment recommendations are based on little more evidence than expert opinions. It has been widely accepted that gross total resection of the tumor improves the overall prognosis of patients with CPT (1, 12-14, 16, 17). This is supported by some case reports and small series with long-term survivors after complete resection (14, 5). The largest of those came from the French pediatric oncology group with 22 patients: overall survival of CPC patients with complete resection was 86%, whereas all but one patient with incomplete resection had tumor recurrence within 2 to 23 months (1). Literature reviews (14) and meta-analyses (17, 18) confirmed complete resection as the major prognostic factor. Some authors emphasized the importance of adjuvant treatment, at least for CPC (3, 16, 18).

A high risk of intraoperative hemorrhage is known as one of the challenges when operating a CPT and it sometimes results in tumor left behind in the first surgery. Preoperative embolisation, second surgery from a different approach, chemotherapy, or – in the case of CPP – wait and let the infant grow older, have been recommended (1, 17). However, this discussion is based on even less data then the similar discussion about the more frequent ependymoma,

Table I. *Characteristics of the study cohort.*

	CPP	APP	CPC	Total
Number	495 (57.8%)	15 (1.8%)	347 (40.4%)	857 (100%)
Age (years)				
Median	6	2	2	3
Range	0.00-73	0.17-53	0.00-69	0.00-73
Gender				
Male	248 (50.1%)	7 (46.7%)	185 (53.3%)	440 (51.3%)
Female	208 (42.00%)	8 (53.3%)	143 (41.2%)	359 (41.9%)
Unknown	39 (7.9%)	0	19 (5.5%)	58 (6.8%)
Tumor site				
Supratentorial	254 (51.3%)	10 (66.7%)	250 (72.0%)	514 (60.0%)
Infratentorial	192 (38.8%)	3 (20.0%)	69 (19.9%)	264 (30.8%)
Other sites	10 (2.0%)	0	5 (1.4%)	15 (1.7%)
Unknown	39 (7.9%)	2 (13.3%)	23 (6.6%)	64 (7.5%)
Extent of resection				
Biopsy	21 (4.2%)	0	24 (6.9%)	45 (5.3%)
Subtotal/partial resection	53 (10.7%)	5 (33.3%)	124 (35.7%)	182 (21.2%)
Gross total resection	303 (61.3%)	8 (53.4%)	97 (28.0%)	408 (47.6%)
Unknown	118 (23.8%)	2 (13.3%)	102 (29.4%)	222 (25.9%)

which is also still unresolved (19, 20). To address this question, a systematic literature review of studies with CPT was performed, and the impact of second surgery on survival of CPP and CPC was elucidated.

Materials and Methods

A database was created following the same procedure as previously described (17, 18). Briefly, all reports of CPT cases ever published and recorded in the National Library of Medicine ('Medline-Database') in the English, French or German languages until September 2004 were evaluated. In addition, patient data were also extracted from older publications and book chapters cited in these articles. The included variables of the database were: first author, publication year, age at diagnosis, gender, duration of symptoms until diagnosis, tumor location, histology, presence of metastases, metastases location, extent of first surgery, extent of second surgery (biopsy/ subtotal + partial/gross total resection), radiotherapy and chemotherapy, event-free time, type of event, observation time, vital status, cause of death. Events were defined as relapse, progression or death. When patients died during the first surgery or the tumors were diagnosed at autopsy, observation time was set to zero and the vital status became "death". Patients published without observation time and vital status were encoded as observation time=0, vital status=survival. Publications with extractable information for only two variables or less were excluded from the analysis. In case of several publications of the same group, only the most recent publication was used for data-entry. Finally, the generated database was validated by comparing the number of cases, age, distribution of histology and tumor location with an existing database of all CPT which had recorded data until 1997 (17, 18).

Statistical analysis was performed using the statistical package for social studies (SPSS® Inc., Version 12.0.1., Chicago, Illinois, USA). We used the methods of Kaplan and Meier (21) to estimate the median overall survival (OS). For the analysis of OS, death was the only event. Patients were censored at their date of last follow-up.

The hypothesis was addressed in two ways. First, the differences in the frequency of age, gender, histology, tumor location, metastases, chemotherapy and radiation were examined by an analysis of variance (ANOVA) and χ^2-tests. Differences in OS were compared with log-rank tests. This analysis was similar to an intend to treat analysis assuming that a patient, who received second surgery, had been in a protocol which had second surgery as a later element of treatment. However, it did not take in account that some patients might have been in such a protocol but expired before they reached the time of the second surgery. Therefore, a second analysis was done, treating second surgery as a time-dependent variable, which changes in every single patient with time. Cox's proportional hazards regression model (22) was used to test the statistical significance of several potential prognostic factors for OS. This modeling was done in an univariate fashion. Five dummy age variables were created to represent the comparison of the 1-2 years, 3-8 years, 9-19 years, 20-39 years and 40+ years age groups *vs*. 0-1 year age group. From this model we estimated the hazard ratio for each potential prognostic factor with a 95% confidence interval. All potential prognostic factors with a p-value <0.25 from the univariate analysis were then included in a saturated model, and backward elimination was used to remove factors from the model based on the likelihood ratio test in the multiple regression analysis. In this model, a patient with second surgery will be included to one of the treatment group being in the "no second surgery" group first and then changing to the "yes, second surgery" group by the time of the second surgery.

Results

Data from 857 patients with CPT were extracted from the literature. The baseline characteristics of these patients are shown in Table I. Four hundred and ninety-five

Table II. *Distribution of risk factors among patients with incomplete resected choroid plexus carcinoma.*

	2nd Surgery			
	Yes	No	Total	Equal distribution?
Number	19 (22.6%)	65 (77.4%)	84 (100%)	-
Age (years)				Yes:
Mean	2.3±4.8	5.9±12.8	5.11±11.5	n.s.
Gender				
Male	11 (57.9%)	37 (56.9%)	48 (57.1%)	Yes:
Female	6 (31.6%)	24 (36.9%)	30 (35.7%)	n.s.
Unknown	2 (10.5%)	4 (6.2%)	6 (7.1%)	
Tumor site				
Supratentorial	16 (84.2%)	44 (67.7%)	60 (71.4%)	Yes:
Infratentorial	2 (10.5%)	20 (30.8%)	22 (26.2%)	n.s.
Unknown	1 (5.3%)	1 (1.5%)	2 (2.4%)	
Metastases				
Yes	3 (15.8%)	10 (16.4%)	13 (16.3%)	Yes:
No	14 (73.7%)	37 (60.7%)	51 (63.8%)	n.s.
Unknown	2 (10.5%)	14 (23.0%)	16 (20.0%)	
Chemotherapy				
Yes	14 (73.7%)	27 (41.5%)	41 (48.8%)	No:
No	5 (26.3%)	37 (56.9%)	42 (50.0%)	$p<0.046$
Unknown	0	1 (1.5%)	1 (1.2%)	
Radiation				
Yes	9 (47.4%)	25 (38.5%)	34 (40.5%)	Yes:
No	10 (52.6%)	40 (61.5%)	50 (59.5%)	n.s.
Unknown	0	0	0	

patients (57.8%) had CPP, 15 patients (1.8%) had APP, and 347 patients (40.4%) had CPC. The male to female ratio of all patients was 1.22:1, without significant differences in the distribution of histologies. The age at diagnosis covered a large range (0-73 years for all patients), but most of the patients were children with a median age at diagnosis of two years for CPC and APP. CPP patients were significantly older (median six years, $p<0.001$). The extent of surgery was known from 635 patients (74.1%). Of those, gross total resection was more frequently achieved in patients with CPP (303/377; 80.4%) than in APP (8/13; 61.5%) or CPC (97/245; 39.6%) (Table I). Complete tumor resection at the first surgery was associated with significantly better outcome in both CPC and CPP. The two-year survival rate of CPC patients was 72.9%±5.0% SD with complete resection (CRes), and 41.9%±4.9% SD with partial resection (PRes; $p<0.001$). For CPP patients, the two-year survival rate was 89.3%±2.6% for CRes and 76.5%±7.4% for PRes, respectively ($p<0.001$; data not shown).

Since complete resection in the initial surgery was associated with better outcome, the influence of second surgery in patients with incompletely resected CPC was analyzed. Information about second surgery was available for 84 out of 97 patients with less than completely resected CPC. Of the 84 patients, 19 (22.6%) underwent second surgery, whereas 65 (77.4%) did not. Patients with second surgery were treated significantly more often with chemotherapy (73.7% *versus* 41.5%; $p<0.05$). However, there was no significant difference between those groups regarding age, gender, tumor site, radiation therapy or presence of metastases (Table II). The Kaplan-Meier curve of CPC patients with second surgery after incomplete primary resection appears far superior to the one with no second surgery (two-year overall survival 69%±11% *versus* 30%±6%, Figure 1); this appeared to be significant when treating the groups as intend to treat analysis ($p<0.005$). However, when treating second surgery as a time-dependent parameter, the significance was lost ($p=0.13$, see Methods). This does not change, when comparing only patients who received chemotherapy in a subgroup analysis: the better survival of patients with second surgery results in a low p-value in the intend to treat approach ($p<0.05$; data not shown), but using the Cox model as a multivariate approach did not confirm statistical significance. For CPP, second surgery did not significantly affect the outcome of these patients (Figure 2), regardless of how the analysis was done.

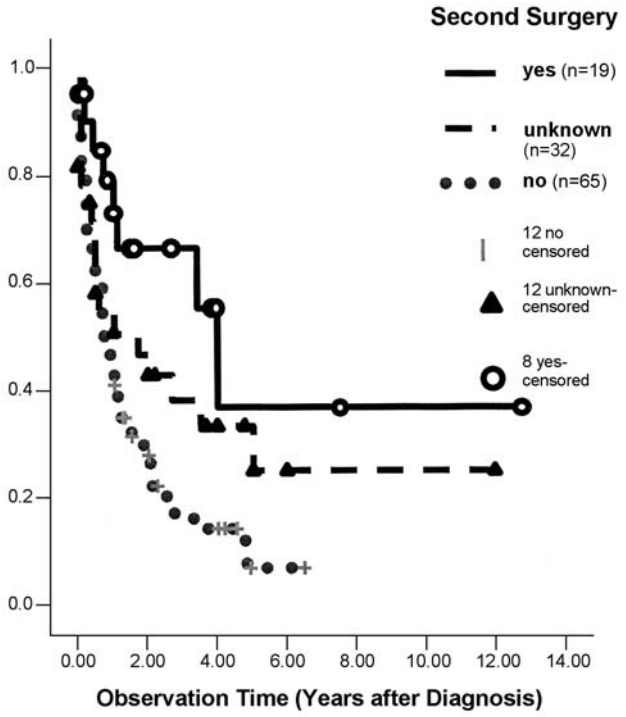

Figure 1. *Choroid plexus carcinoma: cumulative overall survival of patients with partially resected CPC with, without and with unknown second surgery. The survival of patients, who were operated a second time, appeared superior to those operated only once. When treating second surgery as a time-dependent variable, this difference was not statistically significant. See text for a more detailed discussion.*

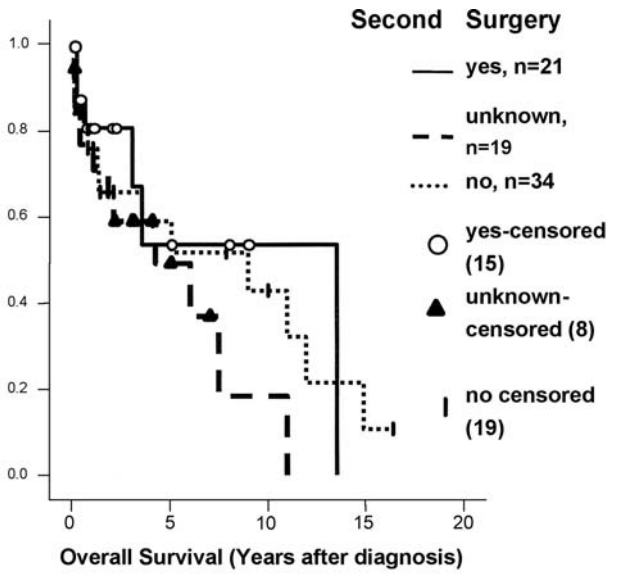

Figure 2. *Choroid plexus papilloma: cumulative overall survival of patients with less than completely resected CPP (combining biopsy and partial resection) with, without and with unknown second surgery. There was no apparent difference between these subgroups in patients with CPP.*

Discussion

Based upon a meta-analysis of individual cases, we provide data suggesting that second surgery is beneficial for CPC but not for CPP patients. A meta-analysis of published cases is biased by the interests of authors, journals and readers in a particular case, which will increase the relative frequency of rare and complicated cases. However, this might not affect CPT as much as other diseases since these histological diagnoses are rare already, making every single case interesting. In fact, the distribution of age, histology and outcome of this literature analysis are comparable to other studies (1, 13), and to the prospectively collected data in the international CPT-SIOP study (Société Internationale d' Oncologie Pédiatrique; data not shown), making a relevant bias less likely. For any treatment question, prospectively randomized phase III studies would be preferable. For instance, the question of second surgery, addressed here, may be influenced by the possible bias that those having second surgery are a selected population of those with tumors that appeared resectable and were not too ill to have surgery. Very little of this bias can be addressed analyzing retrospective data. However, the question of second surgery was not successfully answered in a phase III study even for the far more frequent ependymoma, making it virtually impossible to do this in CPT. This leaves a literature meta-analysis as a reasonable way to get at least the best information possible.

Complete tumor resection significantly improves the prognosis of patients with CPC. These previously published findings (1, 12-14, 16, 17) could be confirmed in this recent and larger set of data. In addition, we provide data coming close to answering the question of whether second surgery is beneficial in CPC and CPP. In particular in CPC, with low survival after incomplete resection, second surgery might be important. Indeed, we found higher survival rates in patients receiving second surgery. This was independent of radiotherapy or chemotherapy. By the nature of the original data, the statistical evaluation of this finding was difficult. When simulating an intend to treat analysis, the finding appeared statistically significant. However, this contains a bias: patients who expired prior to the time of second surgery will be counted in the "no second surgery" group even when the intent had been to operate a second time. Treating second surgery as a time-dependent variable and using the Cox analysis eliminates this problem, but then a patient treated with chemotherapy followed by second surgery will first be counted as "no second surgery" switching group after second surgery has occurred. This might cause a

bias in the opposite direction. With this analysis, the survival was still higher in the second surgery group, but the *p*-value was 0.13, indicating no statistical significance. The truth has to be assumed to be somewhere in the middle between the two analyses. The fact that the curve of patients with unknown second surgery ends up in the middle between the other curves (Figure 1) further suggests that second surgery is meaningful: this population is a mixture of patients belonging to one or the other group. If second surgery is indeed important for survival, the curve should come out in the middle – as it does; if second surgery was not relevant, there would be no reason for the position of the third curve. In summary, these data are strongly suggestive of a relevant difference with second surgery, but statistical significance was not reached completely.

One might hypothesize that chemotherapy might make second surgery possible. Unfortunately, the data were insufficient to analyze this hypothesis: second surgery remained a positive prognostic factor in the subgroup of patients who received chemotherapy, but there were only 5 patients with no second surgery and no chemotherapy, making the reverse analysis meaningless. Similarly, there were not enough data about quality of life and possible negative effects of radical surgery. This will need to be addressed in the prospective registry.

In contrast to CPC, the CPP data did not support second surgery; none of the different ways to analyze the data indicated a benefit, the Kaplan Meier curves cross and the curve of patients with unknown information comes out far away from the other two. This suggests no influence of second surgery in this population. The reason remains unclear. Nonsurgical treatment options could be the reason, but the data do not support this either: very few CPP patients received chemotherapy or radiation, and there was no significantly detectable benefit for the patients in this data. Therefore, these data are suggestive of supporting second surgery in CPC but not in CPP.

When considering all possible biases, the question, of whether second surgery should be performed on a patient with incompletely resected CPC remains unanswered, if insisting on a level of evidence comparable to phase III studies. However, the decision still has to be made for individual patients. This study supports that second surgery should be seriously considered. On the contrary, for CPP it suggests that infants may benefit from a waiting time to allow the brain to grow.

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