CLINICAL STUDY

Intraventricular choroid plexus tumors: clinical characteristics and impact of current management on survival

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Abstract

Introduction Choroid plexus tumors (CPTs) represent one of the most common intraventricular tumors. Although most are benign, they often reach considerable sizes before clinical manifestation, challenging their surgical management. We aim to describe the clinical characteristics and the impact of current management on the survival of patients harboring intraventricular CPT.

Methods The National Cancer Database (NCDB) was queried to identify biopsy-proven intraventricular CPT patients (2004–2015). Demographic and patterns of care were described, the log-rank method was used to independently analyze survival according to age, WHO grade and extent of resection (EOR). Multivariate analysis was performed to investigate the impact of prognostic factors on overall survival (OS).

Results A total of 439 CPT patients with known WHO grade were included. WHO grade I tumors were more frequent in adults, while WHO grade III tumors were more common in pediatric population. Most CPTs were benign, with a median tumor size of 3–4 cm. Mean tumor size in pediatric population was greater than in adult population (4.39 cm vs. 2.7 cm; $p < 0.01$). Frequency was similar between males and females (51.7% vs. 48.3%; $p > 0.0.5$). Five- and ten-year OS among all patients was 87% and 84%, respectively. EOR was not associated with survival for any WHO grade. On multivariable analysis, only patient age ($p = 0.022$), WHO grade ($p = 0.003$) and medical comorbidity scores ($p = 0.002$) were independently associated with OS after diagnosis.

Conclusion Patients with CPTs present at different stages of life, with sizable tumor burden and distinct WHO grade prevalence. Considering their favorable survival, efforts to improve tumor control should be meticulously weighed against the long-term risk associated with surgery, radiation, and chemotherapy.

Keywords Choroid plexus papilloma · Atypical choroid plexus papilloma · Choroid plexus carcinoma · Prognostic · Epidemiology

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Introduction

Choroid plexus tumors (CPTs) are rare primary intracranial tumors, comprising < 1% of all brain neoplasms. CPTs are almost entirely located in the ventricle system, where they represent one of the most common neoplasms, especially in younger pediatric population [1, 2]. It has been previously described that the majority of CPTs occur predominantly in children and infants, being diagnosed within the first decade of life in 74% of cases. The average annual incidence for all CPTs is as low as 0.3 out of 1,000,000 per year, which may be related to the scattered number of reports about their management and outcomes [3–6].

CPTs arise from the differentiated epithelial tissue of the choroid plexus. The spectrum of CPTs includes WHO grade I choroid plexus papilloma (CPP), grade II atypical choroid plexus papilloma (aCPP), and grade III choroid plexus carcinoma (CPC). CPPs are considered benign tumors, with a reported 5-year overall survival (OS) rate of 90–100%. On the other hand, CPCs are rare and more aggressive tumors carrying the worst prognosis among the group [4, 5, 7]. Distant metastases from CPTs possess a high impact on patient survival, occurring in 12–50% of cases and being much more common in CPCs than CPPs [1, 8, 9].

Although commonly benign in regard to pathology, CPTs often grow into considerable size before clinical manifestation, which typically occur due to hydrocephalus. However, symptoms are often subtle within the pediatric population due to cranial expansibility. Overall, this fact may lead to challenging and potential dangerous surgical scenarios and morbidity and not clearly defined neuro-oncological managements [3, 4]. Currently, there is only a few numbers of studies reporting on CPTs in the literature, and most of the published series are small and tend to present uneven results [10]. Here, we perform a national registry analysis of biopsy-proven intraventricular CPT patients accumulated from 2004 to 2015. First, we describe the epidemiology of these tumors; then we assess clinical and tumor characteristics; and finally, we look at management patterns to identify associations with survival in this specific group of relatively rare tumors.

Material and methods

Data source

Established in 1989, the National Cancer Database (NCBD) is a nationally recognized clinical oncology database, sponsored by the American College of Surgeons and the American Cancer Society. The NCDB collects data from > 1500 facilities accredited by the Commission on Cancer and contains information on treatments and outcomes for patients with malignant disease. The current database gathers > 70% of new cancer diagnoses in the US and contains > 34 million historical records.

Data was obtained from the NCDB for patients diagnosed with brain tumors between January 1, 2004 to December 31, 2015 (223,404 patients). Patients excluded were those with non-CPT histology confirmation, non-purely intraventricular tumor, or unknown WHO grade (Fig. 1). The remaining 439 patients were then stratified and analyzed based on available database information.
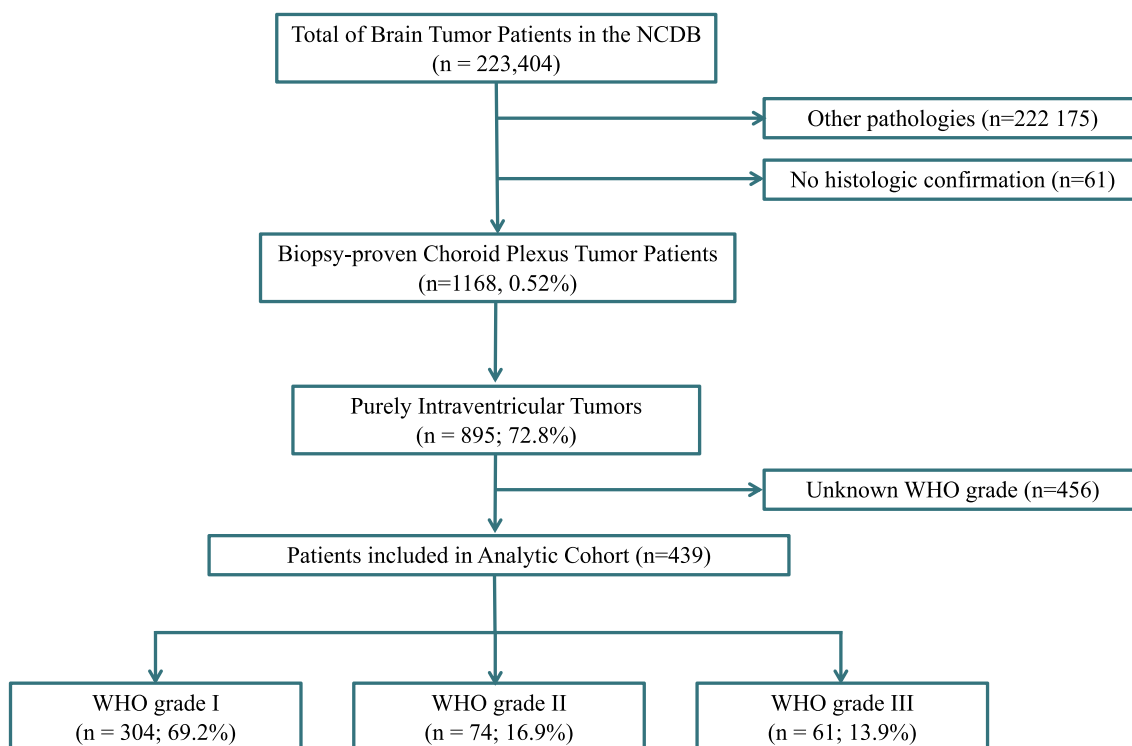

Fig. 1 National Cancer Database (NCDB) cohort selection diagram. *WHO* World Health Organization

Statistical analyses

The primary outcome for this study was overall survival (OS) measured from date of diagnosis. Secondary goals included the description of the baseline clinical characteristics of patients with intraventricular CPTs, as well as the patterns of care that they received. In order to prevent bias based on sites with underreporting of data (favoring the inclusion of some centers over others) and improve result validity, all patients complying with the previously described criteria were evaluated, even if they contained one or more missing data elements. Important prognostic factors including gender, age, race, median income, distance to hospital, Charlson/Deyo score, WHO tumor grade, tumor size, extent of resection, radiation therapy, and chemotherapy were evaluated. The Kaplan Meier method, with log-rank test, was used to independently analyzed the impact of specific variables on survival distribution. Multivariable analysis was performed via Cox proportional hazards models to further investigate factors associated with OS. The Welch t-test was run to determine if there were differences between tumor size of pediatric and adult population. Chi-square test or Fisher-exact test were used to compare categorical variables. All statistical analyses were performed using the SPSS program (SPSS, version 24.0; SPSS Inc., Chicago, IL) and $p < 0.05$ was considered statistically significant.

Results

Clinical characteristics

Patient characteristics are shown in Table 1. Among 223,404 patients with brain tumors in the National Cancer Database (NCDB), cases of biopsy-proven CPT represent 0.52% of the total population. From these patients, 439 were diagnosed with an intraventricular CPT and known WHO grade classification (Fig. 1). Although patients under 11 years concentrated almost 40% of the total population, it was noteworthy that 54.4% were non-pediatric patients (> 18 years old). Eighteen percent of patients were diagnosed at 1 year old or younger. WHO grade I tumors were more frequent in the adult population (> 18 years old), while both WHO grade II and III were more common in patients less than 1 year old ($p < 0.01$; Fig. 1a of Supplemental Material). Median tumor size was 3–4 cm. Mean tumor size in the pediatric population (4.39 ± 0.15 cm) was greater than in the adult population (2.7 ± 0.1 cm), with a statistically significant difference of 1.6 cm between both groups (95% CI 1.25 to 1.96, $p < 0.01$).

Most of the tumors were low grade lesions. In fact, CPP (WHO grade I) accounted for 69.2% of all tumors, whereas aCPP accounted for 16.9% (WHO grade II) and CPC (WHO grade III) for 13.9%. Frequency was similar between males and females in general (51.7% vs 48.3% respectively; $p = 0.066$), but there was a male predominance in WHO grade II and WHO grade III patients ($p = 0.039$, Fig. 1b of Supplemental Material); 71.3% of the tumors appeared in white population ($p = 0.048$).

Treatment characteristics

Surgery and extent of resection

All patients included underwent biopsy or resection (Table 1). EOR was unknown in 163 patients (37.1%), while 166 (37.8%) underwent GTR, 55 (12.5%) underwent subtotal resection (STR), and 55 (12.5%) underwent biopsy alone. As extent of resection is described as cornerstone aspect in the management of CPT patients, we analyzed the known data regarding EOR and found that there were no differences in the distribution of biopsy, STR or GTR among different age groups, WHO grades or tumor sizes ($p > 0.05$; Table 1 of Supplemental Material). Despite the importance of GTR, our data show that this is achieved only in 52.2% to 66.7% of cases. Surprisingly, although GTR seemed to favor 5-year OS in patients with WHO grade I tumors ($p < 0.35$) (Fig. 2d), extent of resection was not associated with improved OS on multivariable analysis ($p > 0.05$). (Table 2).

Radiation and chemotherapy

Among all CPT patients, only a minority received radiotherapy (5.7%) or chemotherapy (7.6%) (Table 1). However, when stratified by WHO grade, it was evident that most of the patients receiving adjuvant therapy had a WHO grade II (aCPP) or III (CPC) tumor ($p < 0.001$). Although only three WHO grade III patients received combined chemotherapy and radiation therapy, 63.9% of them received some type of adjuvant therapy, where radiotherapy was administered in 25% and chemotherapy in 44.3% of cases (Table 2 of Supplemental Material and Fig. 3a). In general, the mean age for patients receiving chemotherapy was 2.3 years old (range, 0 to 15 years old; 54.4% in < 1 year) and for those receiving radiotherapy the mean age was 35.7 years old (range, 1 to 70 years old; 76% in > 18 years old). When the impact of adjuvant therapy on survival distribution was evaluated in the group of WHO grade 3 patients, no survival benefit was found ($p > 0.05$) (Fig. 3b).

Overall survival

Five-year and ten-year OS among all patients was 87% and 84%, respectively (Fig. 2a). The impact of individual factors on 5-year OS was evaluated using the Kaplan–Meier method. According the age groups, patients diagnosed after 60 years old presented with less favorable survival

Table 1 Clinical characteristics of patients with intraventricular choroid plexus tumors from the National Cancer Database 2004–2015

|	Total		WHO grade I		WHO grade II		WHO grade III	
	n	%	n	%	n	%	n	%
Patient age (years)								
<1	79	18	30	9.9	25	33.8	24	39.3
1–10	90	20.5	62	20.4	8	10.8	20	32.8
11–17	31	7.1	26	8.6	2	2.7	3	4.9
18–40	125	28.5	99	32.6	17	23	9	14.8
41–60	79	18	61	20.1	15	20.3	3	4.9
>60	35	8	26	8.6	7	9.5	2	3.3
Sex								
Male	227	51.7	145	47.7	46	62.2	36	59
Female	212	48.3	159	52.3	28	37.8	25	41
Race								
White	313	71.3	228	75	48	64.9	37	60.7
Black	42	9.6	28	9.2	8	10.8	6	9.8
Hispanic	54	12.3	31	10.2	14	18.9	9	14.8
Others	14	6.8	10	5.6	1	5.4	3	14.8
Median income quartiles								
<$38,000	50	11.4	36	11.8	9	12.2	5	8.2
$38,000–$47,999	107	24.4	72	23.7	21	28.4	14	23
$48,000–$62,999	132	30.1	85	28	22	29.7	25	41
≥$63,000	149	33.9	110	36.2	22	29.7	17	27.9
Unknown	1	0.2						
Distance to hospital (miles)								
<25	241	54.9	164	53.9	40	54.1	37	60.7
25–100	140	31.9	105	34.5	19	25.7	16	26.2
>100	57	13	34	11.2	15	20.3	8	13.1
Unknown	1	0.2	1	0.3	0	0	0	0
Charlson/deyo score								
0	376	85.6	264	86.8	61	82.4	51	83.6
1	40	9.1	26	8.6	9	12.2	5	8.2
2	16	3.6	10	3.3	4	5.4	2	3.3
3	7	1.6	4	1.3	0	0	3	4.9
Tumor size								
≤3 cm	161	36.7	137	45.1	18	24.4	6	9.8
3.01 to 5 cm	129	29.4	78	25.7	30	40.5	21	34.4
>5 cm	67	15.3	26	8.6	13	17.6	28	45.9
Unknown	82	18.7	63	20.7	13	17.6	6	9.8
Extend of resection								
Biopsy only	55	12.5	41	13.5	8	10.8	6	9.8
Subtotal resection	55	12.5	40	13.2	8	10.8	7	11.5
Gross total resection	166	37.8	112	36.8	28	37.8	26	42.6
Unknown	163	37.1	4	1.3	2	2.7	0	0
Radiotherapy								
No	409	93.2	298	98	66	89.2	45	73.8
Yes	25	5.7	2	0.7	8	10.8	15	24.6
Unknown	5	1.1	4	1.3	0	0	1	1.6
Chemotherapy								
No	403	91.8	298	98	71	95.9	34	55.7
Yes	33	7.5	3	1	3	4.1	27	44.3
Unknown	3	0.7	3	1	0	0	0	0

WHO World Health Organization
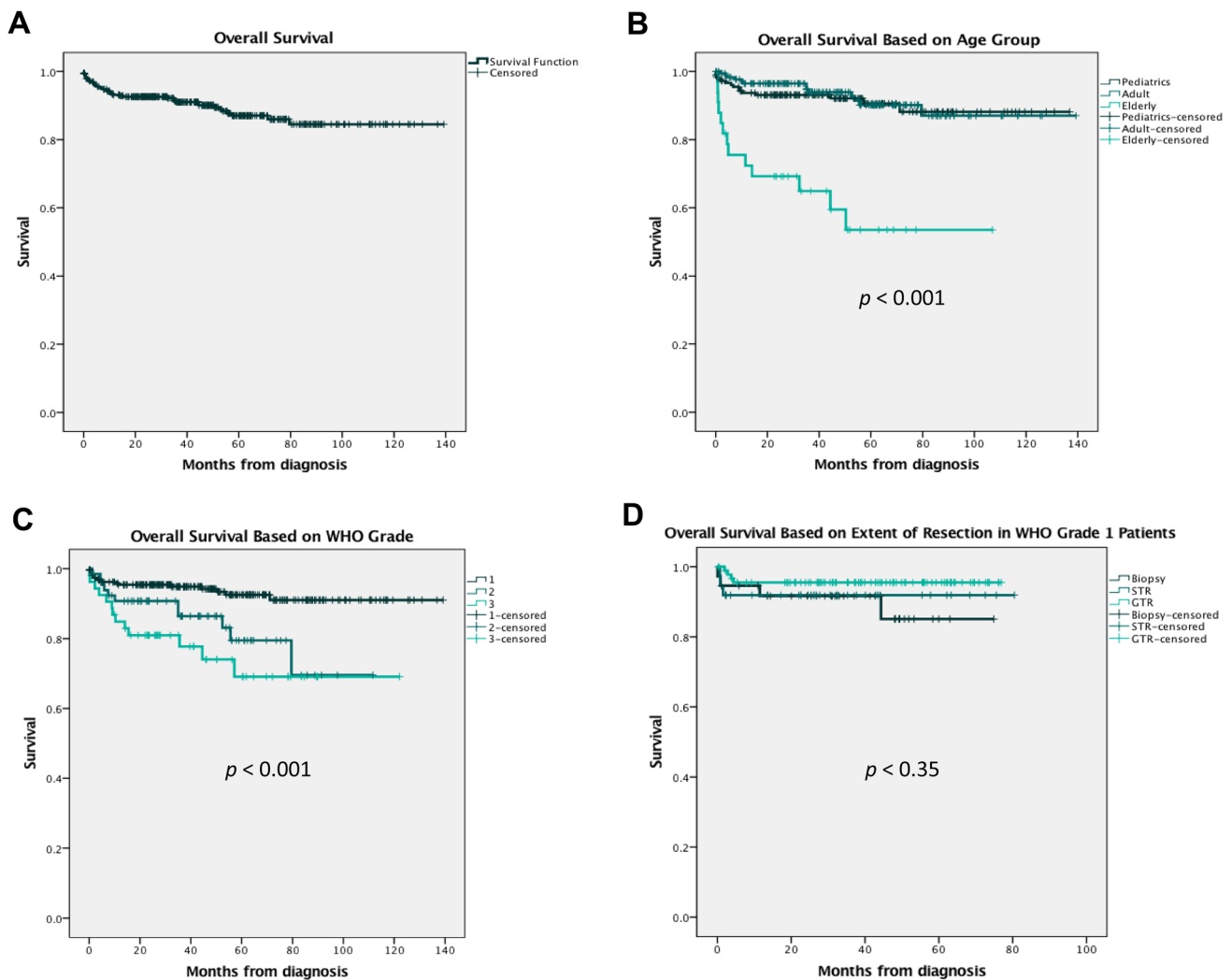
Fig. 2 Kaplan–Meier curves of overall survival among 439 patients diagnosed with intraventricular choroid plexus tumor in the National Cancer Database 2004–2015. Five-year overall survival among all patients was 87%, while 10-year overall survival was 84% (**a**); Kaplan–Meier curve of overall survival following diagnosis of intraventricular choroid plexus tumor based on group of age. Five-year overall survival among patients under 18 years old (pediatrics), between 18 and 60 years old (adults), and older than 60 years old (elderly), was 91%, 90%, and 52%, respectively. Age was independently associated with worse survival after diagnosis (log rank $p < 0.001$) (**b**); Kaplan–Meier curve of overall survival following diagnosis of intraventricular choroid plexus tumor based on WHO grade. Five-year overall survival among patients classified as WHO grade I, WHO grade II, and WHO grade III was 92%, 79%, and 70%, respectively. WHO grade was independently associated with worse survival after diagnosis (log rank $p < 0.001$) (**c**); Kaplan–Meier curve of overall survival following diagnosis of choroid plexus papilloma (WHO grade I) based on extent of resection. Five-year overall survival among patients that underwent biopsy, STR, or GTR was 84%, 91% and 95%, respectively. Extent of resection was not associated to significantly influence overall survival after diagnosis (log rank $p < 0.001$) (**d**). *WHO* World Health Organization, *STR* subtotal resection, *GTR* gross total resection

($p < 0.001$) (Fig. 2b), as well as patients with higher WHO grade ($p < 0.001$) (Fig. 2c). Similarly, impact of EOR was evaluated in each of the WHO grades. For patients diagnosed with CPP (WHO grade I) who underwent GTR, 5-year OS was 95%, whereas it was 91% with STR and 84% with biopsy alone. However, these differences were not significant in this group ($p < 0.35$) (Fig. 2d) and neither in WHO grade 2 nor WHO grade 3 CPT patients (Fig. 2 of Supplemental Material).

On multivariable analysis, neither EOR, utilization of radiotherapy or chemotherapy, or tumor size were predictive for improved survival ($p > 0.05$ for each one). However, accordingly to our previous results, patient age ($p = 0.022$), WHO grade ($p = 0.003$) and medical comorbidity scores ($p = 0.002$) remained independently and significantly

Table 2 Analysis of factors associated with time to death among patients with intraventricular choroid plexus tumors in the National Cancer Database 2004–2015

	Multivariable analysis			
	p-value	OR	Lower 95% CI	Upper 95% CI
Age	**0.022**	1.028	1.004	1.052
Sex				
Male		1.00*		
Female	0.718	1.233	0.396	3.834
Charlson/deyo score				
0		1.00*		
1	0.43	0.363	0.029	4.516
2	**0.002**	23.353	3.063	178.056
3	0.209	3.475	0.497	24.298
WHO grade				
I		1.00*		
II	0.09	3.271	0.832	12.866
III	**0.003**	12.492	2.321	67.228
Median income quartiles				
<$38,000		1.00*		
$38,000–$47,999	0.568	1.846	0.226	15.088
$48,000–$62,999	0.074	0.124	0.012	1.224
≥$63,000	0.503	0.502	0.067	3.783
Tumor size				
≤3 cm		1.00*		
3.01 to 5 cm	0.834	1.169	0.271	5.034
>5 cm	0.297	2.883	0.394	21.117
Resection				
Biopsy only		1.00*		
Subtotal resection	0.443	1.914	0.364	10.063
Gross total resection	0.753	0.766	0.145	4.048
Radiotherapy				
No		1.00*		
Yes	0.9	0.891	0.145	5.464
Chemotherapy				
No		1.00*		
Yes	0.198	0.162	0.01	2.58

Bold values are statistically significant

*Reference value

WHO World Health Organization, *OR* odds ratio, *CI* confidence interval

associated with OS after diagnosis (Table 2). Overall, although the use of radiotherapy and chemotherapy was significantly associated with WHO grade, the use of adjuvant therapy was not predictive of improved survival (Table 2; and Table 2 of Supplemental Material).

Discussion

CPTs are rare intracranial tumors that often represent challenging clinical scenarios. Biopsy proven CPTs account for 0.52% of all brain tumors within this large patient cohort. As expected, patients with advanced age (particularly those over 60 years old), higher medical comorbidities, or higher WHO grade presented a worsened OS after diagnosis. However, despite the median tumor size being around 3–4 cm, OS was excellent (87% and 84% for all at 5 and 10 years, respectively) and particularly favorable for those diagnosed with CPP who underwent GTR (95% at 5 years). Considering the long-term survival of patients with CPT demonstrated in the present study, therapies that aim to maximize tumor control and limit further complications are critical for the overall management in these patients.

It is worth mentioning some key epidemiological findings of our study given the large cohort that was studied. First, 54.4% of patients were older than 18 years, contrary to the current belief that most of these tumors occur in children [11]. Although there exist multiple reports on CPTs presenting in the adult population, most of them consist of small series and they may be more commonly distributed in this age group than what it is currently described in the literature [12–15]. However, it is fair to say that patients before adolescence concentrated almost 40% of the total population (< 11 years old).

Second, we found nearly identical incidence of males and females patients for the whole series of CPTs, which is in contrast with the current series suggesting a male preponderance [6] with a male to female ratio of 1.4:1 for the same group of patients. On the other hand, our results support a Surveillance Epidemiology and End Results (SEER) data report of 349 CPTs that found no gender predilection but a significant association between male gender and worse OS [7]. In our study, after performing a stratified analysis according to WHO grade, we show a statistically significant male preponderance only for the more aggressive WHO grade II and III tumors, which may connect and explain all the previously reported results. Third, the frequency of CPTs was confirmed in our series, representing 0.52% of all brain tumors. Similar to our findings, CPTs have been reported at rates of < 1% of all brain tumors [16, 17]. Fourth, most of CPTs have been reported to appear in white patients. In fact, previous reports of malignant brain tumors in children less than 1 year old also show higher incidence in white patients than in other races [18]. Although we also report a higher incidence of CPTs in white patients, this information must be contextualized with the country's racial distribution.

In accordance with previously described studies, WHO grade III CPT (CPCs) were found more
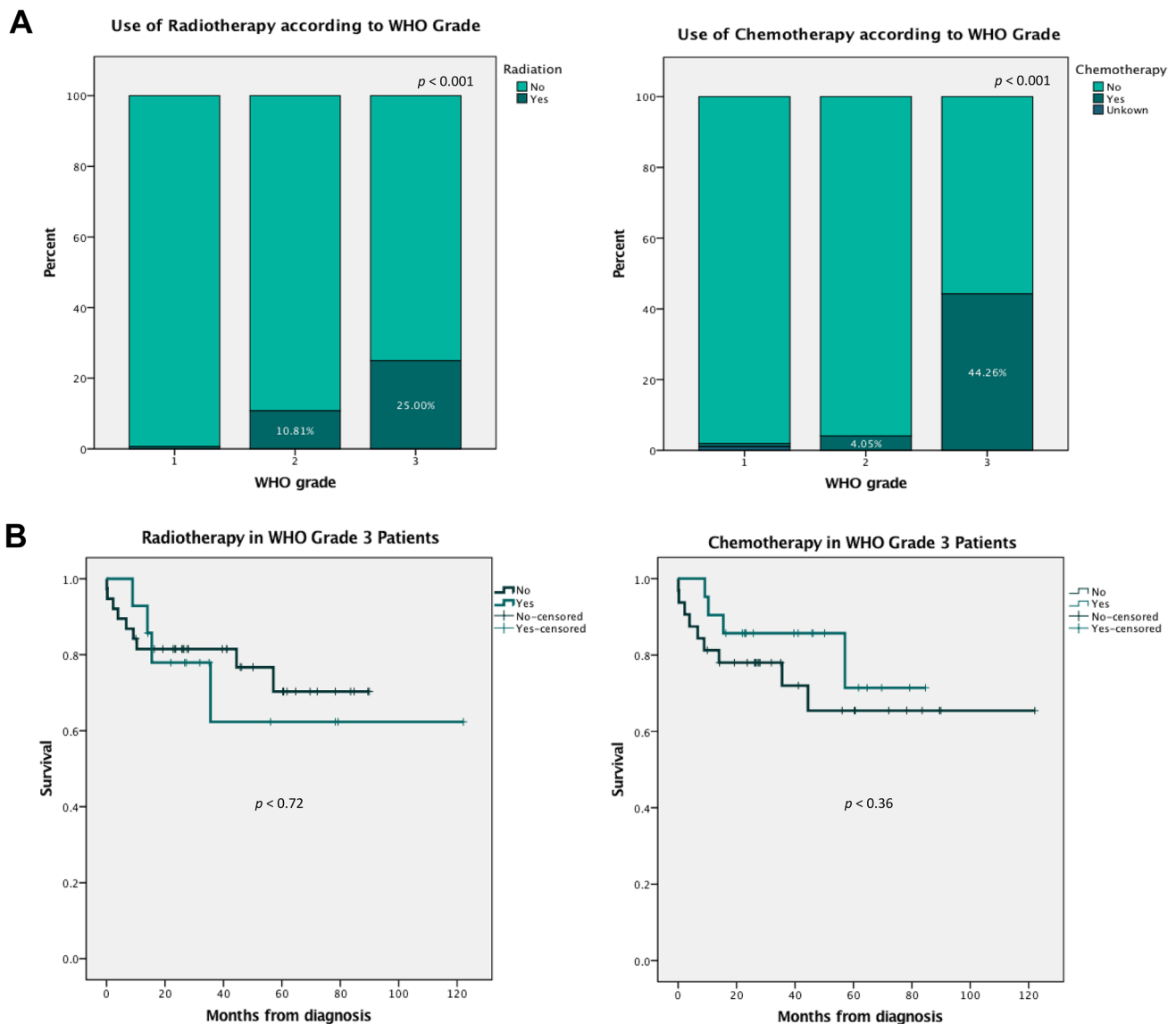
Fig. 3 Use of radiotherapy and chemotherapy according to WHO grade (**a**); Kaplan–Meier curve of overall survival according to treatment in patients with choroid plexus carcinoma (WHO grade III) (**b**). *WHO* World Health Organization

frequently in the pediatric population (77% of the cases in patients < 18 years old, representing 23.5% of the tumors in this age group, but only 5.8% of the tumors in those ≥ 18 years old), with the group of patients < 1 years old accounting for 40% of CPCs cases (Table 1). WHO grade I (CPPs) were observed more frequently in non-pediatric patients and given that CPPs represent almost 70% of all CPTs, this led to the fact that 54.4% of all CPTs patients were non-pediatric [19, 20]. Furthermore, mean tumor size of pediatric patients was significantly greater than mean tumor size of adult population, which may be in line with the higher prevalence of more aggressive disease in pediatric population and also the higher cranial vault

expansibility and subtle symptoms upon the presence of high intracranial pressure and hydrocephalus.

Age older than 60 years, as well as higher medical comorbidities, was significantly associated with worse OS, most probably due to the inherent relationship between these two variables after 60 years complications of surgery remained unknown, and further studies should analyze EOR-associated complications. Since previous studies have analyzed CPT outcomes predominantly in children and there are few reports regarding the adult population, our findings may be important during daily clinical decision making in an attempt to better weigh therapeutic efforts, survival and quality of life.

Although the treatment of intraventricular tumors is controversial due to the challenges presented by their location, size, functionality of surrounded anatomy and presence of hydrocephalus; maximal safe resection remains the mainstay of the treatment. In fact, GTR has been reported as the most important predictor of survival, particularly in WHO grade III CPTs. However, even after complete surgical removal, many patients still experience recurrence, and adjuvant radiation therapy or chemotherapy is often used for optimizing tumor control and patient survival [6, 21].

Since EOR is considered a major prognostic factor for CPCs, GTR has been recommended in CPCs even if it is often difficult due to the high risk of intraoperative hemorrhage [22]. Reported CPCs 5-year survival rate reaches around 58% after complete tumor resection and only 20% after partial resection [4, 12, 23]. However, we did not find survival benefits from more aggressive resections when EORs were compared in a stratified manner in each of the WHO grades. Although the number of WHO grade 2 and 3 patients with complete follow-up included in our analysis may have been not big enough to detect significant differences and the data about tumor size did not include tumor volumes, it is important to highlight that the role of EOR has been challenged in CPT and other pathologies [7, 21]. Zhou et al. reported on 96 pediatric patients and describe that GTR did not offer survival benefits probably due to the use of adjuvant therapy in cases of partial tumor resection [21]. Thus, Thompson et al. reevaluated the role of EOR in medulloblastoma surgery, and after a careful analysis according to different molecular subgroups found that it may not be as relevant as claimed before [24, 25]. In this setting, it is worth mentioning, that due to the very vascularized nature of CPCs, a significant cause of morbidity and mortality is the excessive perioperative blood loss [26, 27]. Thus, the benefits of aggressive surgery must be carefully weighed against the risk of causing new neurological deficits and other serious complications [28].

Surgery is also important in cases of WHO grade I CPTs, as the need for both pathologic confirmation and symptom relief is always present [26, 29–31]. Previous reports describe survival benefits from GTR at 5 years for patients with CPPs [5]. Studies show that GTR is associated with a significant increase in OS compared to STR and biopsy alone in either adult or pediatric population [6, 32, 33]. However, our series that contains a largest number of CPT patients, showed no survival benefit from GTR. A careful analysis on the impact of EOR in CPT is necessary in order to determine the role of EOR on survival outcomes of CPT patients.

Furthermore, our series identified similar rates of GTR among different WHO grades, which is in contrast to previous studies reporting increasing rates of GTR with increasing WHO grades [22]. We report rates of GTR of approximately 60% for each of the WHO grades, it assumes that despite the grade, surgeons are resecting the tumor. However; according to the literature and our study WHO grade I CPT patients have excellent prognosis even when adjuvant therapy is often not performed after partial excision, which may suggest that a conservative approach during surgery can still be associated with good outcomes and that there is no reason to risk patient integrity in order to pursue aggressive surgery in this group of patients [11].

Radiotherapy (6.8%) and chemotherapy (8.2%) were less commonly utilized in general, but as expected, their use was positively correlated with higher WHO grade. In fact, 25% of patients diagnosed with WHO grade 3 tumors received radiation therapy and 45% received chemotherapy. Interestingly, when the use of radiation or chemotherapy was analyzed in this group of patients, there were no significant differences in OS. This, together with the fact that WHO grade was a proven prognostic factor in our two separate analyses (Long rank test and Cox regression), lead us to recommend a careful patient selection before treatment initiation.

As with any retrospective study, there is the risk of confounding variables that were not accounted for in our analysis, such as symptomatology, location, radiotherapy dose and technique, and others. The principal limitation of the current study is the number of patients with unknown EOR, which made difficult to determine the impact of EOR for WHO grade 2 and 3 patients, in this regard, we encourage the volumetric studies of EOR in order to elucidate a more precise effect of EOR on patient survival [34–42]. Furthermore, another potential limitation from using the NCDB is that the information is collected directly from the medical records by certified tumor registrars. Thus, although EOR is determined based on neurosurgeons' experience or imaging techniques, we cannot specify which method was used to gather the EOR. Additionally, local tumor control, toxicity following therapy, and cause of death are not available in the NCDB. Regardless, given the limited published data on CPTs, the current study provides a significant contribution to the understanding of clinical characteristics and the impact of the current pattern of management on CPT patients' outcomes.

Conclusion

Patients with CPTs present at different stages of life, often with sizable tumor burden. In our analysis, both WHO grade and age were significantly associated with survival. Considering the favorable survival of CPTs, efforts to improve tumor control should be meticulously weighed against the long-term risk associated with surgery, radiation therapy, and chemotherapy.

Compliance with ethical standards

Conflict of interest There are no conflict of interests to report or financial disclosures related to this manuscript.

Ethical approval There is compliance with ethical standards.

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