

# Chemotherapy improves the survival of patients with choroid plexus carcinoma: a meta-analysis of individual cases with choroid plexus tumors

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**Abstract** *Background* Choroid plexus carcinomas (CPC) are rare brain tumors with a dismal prognosis. Although the role of surgery has been well established, the question of whether chemotherapy improves the prognosis is still under discussion. *Methods* We created a database of all cases of choroid plexus tumors (CPT) reported in the literature up to the year 2004 to determine prognostic factors and different therapeutic modalities. This database was validated by comparison with an existing database of cases until 1997. *Results* Of 857 documented cases of CPT (median patient age at diagnosis, 3 years), 347 were CPC, 15 atypical choroid plexus papilloma (APP), and 495 choroid plexus papilloma (CPP). Histology was a significant prognostic factor ( $P < .0001$ ; log rank). Within the subgroup of patients with CPC, both surgery and irradiation were linked to a better prognosis ( $P < .005$ ). The 104 CPC patients who received chemotherapy had a statistically better survival than those without chemotherapy ( $P = .0004$ ). When subgroups were defined by radiation treatment, chemotherapy remained beneficial in the subgroup of nonirradiated tumors ( $P = .0001$ ). The benefit of chemotherapy was also

significant when the analysis was restricted to the subgroup of patients with less than completely resected CPC (2-year overall survival (OS)  $54.8 \pm 7\%$  (standard deviation (SD) vs.  $24.4 \pm 7\%$ ,  $P < .0001$ ) and when this subgroup was further divided into smaller subgroups. Likewise, in a multivariate analysis, chemotherapy was highly significantly linked to better prognosis ( $P = .0001$ ). *Conclusion* Patients with less than completely resected CPC should receive chemotherapy.

**Keywords** Choroid plexus tumors · Choroid plexus carcinoma · Treatment · Chemotherapy · Outcome

## Introduction

Choroid plexus tumors (CPT) are rare central nervous system neoplasms accounting for 1–4% of all pediatric brain tumors [1, 2]. Most cases occur in infants and young children, but they are also seen in adults [3–7].

Choroid plexus tumors are categorized on the basis of histological criteria as choroid plexus papilloma (CPP, WHO grade I), choroid plexus carcinoma (CPC, WHO grade III), and an in-between form termed atypical plexus papilloma (APP). The differentiation can be difficult, and some authors report discrepancies between histological appearance and biologic behavior [8–11]. In addition, CPT and the atypical teratoid/rhabdoid tumors (AT/RT) of the central nervous system have overlapping histological features, thereby making the diagnosis of CPT more difficult [12]. Although the hSNF5/INI1 mutation, commonly present in AT/RT, has also been found in CPC [13, 14], more recent data have shown that immunostaining for INI1 is retained in the majority of CPC, which may help to distinguish CPC and AT/RT [12]. By the use of a microarray

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approach, the markers Kir7.1 and stanniocalcin-1 have been found to be expressed in normal and tumor choroid plexus tissue, but not in other brain tumors, and might serve as specific diagnostic markers in the future [15]. All types of CPT can disseminate, and the developments from benign to malignant versions have been described [16].

Choroid plexus carcinomas are highly invasive tumors and are associated with a dismal prognosis. The 5-year survival rates for CPC vary between 10% and 50% [10, 17–20]. Owing to the rarity of CPT, treatments are based only on small case series and expert opinions. For CPC, there is a consensus regarding complete resection as the most important predictor of survival [18, 19, 21, 22]. Surgery is challenging, however, because these tumors are highly vascularized [23–25]. Radiation seems to play a beneficial role, as suggested by retrospective analyses [18, 26], but many patients are too young for this treatment modality.

The role of chemotherapy for CPC is less clear. There are several reports of small series suggesting an effect of postoperative chemotherapy in patients with tumors that are less than completely resected, when the patient is too young to receive radiation [1, 19], whereas the role of neoadjuvant treatment after complete resection and that of chemotherapy in addition to radiation is controversial. In general, the numbers of patients have been too low in previous studies to show a statistically significant effect of chemotherapy on the survival of patients with CPC [27], including our previous study with data for 566 CPT patients extracted from the literature published until 1997 [18]. Since then, further cases have been published, and we therefore repeated the study to include publications from seven more years of literature.

## Methods

A new database registering all cases of CPT recorded in the National Library of Medicine (“Medline-Database”) until 2004 was created using the method previously described but starting the analysis completely anew [18, 26, 28]. Briefly, the terms “choroid plexus”, “CPT”, “CPC”, and “CPP” were used as search terms, and limitations used were “human” and the English, French, or German language. This resulted in 5938 titles. These were screened by reading the titles and abstracts, and 935 were selected for further analysis. Reading these articles, and additional cases from older publications and book chapters that were cited in these articles, resulted in 251 articles with extractable patient data.

The database had a classical clinical database design with one line per patient. It included the following variables: first author, publication year, patient age at

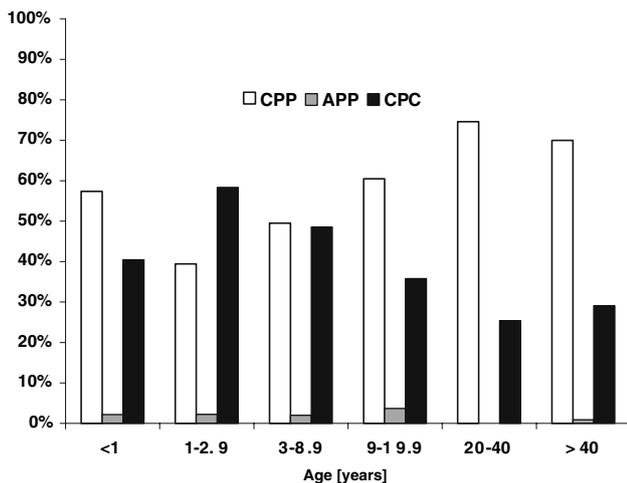
diagnosis, sex, duration of symptoms until diagnosis, tumor location, histology, presence of metastases, metastases location, extent of first surgery, extent of second surgery (biopsy, subtotal or partial, complete resection), radiotherapy and chemotherapy, event-free time, type of event, observation time, vital status, and cause of death. Only publications with extractable information for three or more variables were included in the database. When there were several publications from the same group, only the most recent publication was used for data entry. Observation time was set to zero and the vital status became “death” when patients died during the first surgery or when the tumors were diagnosed at autopsy. Patients with data published without observation time and outcome description were encoded as observation time = 0, vital status = survival. Events were defined as relapse, progression, or death. The new database was validated by comparing the number of extracted patient data with the previous one, which had been generated by different authors and which recorded data until 1997 [18, 26], resulting in a 99% concordance between the databases until 1997.

Statistical evaluations were performed using the SPSS statistical package for social studies, version 12.0.1 (SPSS Inc., Chicago, Illinois, USA). Qualitative parameters such as age, sex, histology, tumor location, metastases, chemotherapy, and radiation were used to divide the database into various subgroups, which were evaluated by analysis of variance and  $\chi^2$  tests. Overall survival (OS) was defined as the time from diagnosis to death or the last observation of patients alive and was plotted by Kaplan-Meier curves. Differences in OS were compared using log-rank tests. For the group of patients with subtotally or partially resected CPC, possible prognostic factors for the risk of death were identified by the Cox proportional hazards regression model. 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 < .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.

## Results

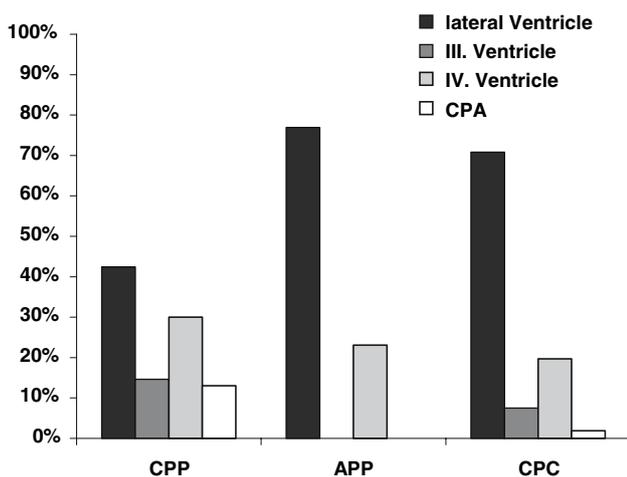
The 251 publications that had sufficient data about individual cases of CPT each reported between one and 49 patients, resulting in a database of 857 patients. Of these 857 patients, 70% were identified from journals published between 1981 and 2004.

In the total population, the male to female ratio was 1.22:1 and the median age was 3 years (range 0–73 years). Tumor locations were reported in 785 cases, with 54%



**Fig. 1** Patient age and histology. APP = atypical choroid plexus papilloma, CPC = choroid plexus carcinoma, CPP = choroid plexus papilloma

( $n = 425$ ) of these tumors located in the lateral ventricles, 11% ( $n = 87$ ) in the third ventricle, 26% ( $n = 200$ ) in the fourth ventricle, and 8% ( $n = 64$ ) in the cerebello pontine angle. Of the 857 patients, 495 (57.8%) had a CPP, 15 (1.8%) an APP, and 347 (40.5%) a CPC. These parameters were not independent: CPC and APP presented more frequently in the younger age groups (median age at diagnosis, 2 years), whereas patients with CPP were significantly older (median age, 6 years,  $P < .001$ ; Fig. 1) and the more malignant tumors were more frequently supratentorial (lateral and III. ventricle) than infratentorial (IV. ventricle and cerebello pontine angle) (78.4% vs. 21.6% for CPC,  $P < .001$ , Fig. 2).



**Fig. 2** Tumor site and histology. APP = atypical choroid plexus papilloma, CPA = cerebello Pontine angle, CPC = choroid plexus carcinoma, CPP = choroid plexus papilloma

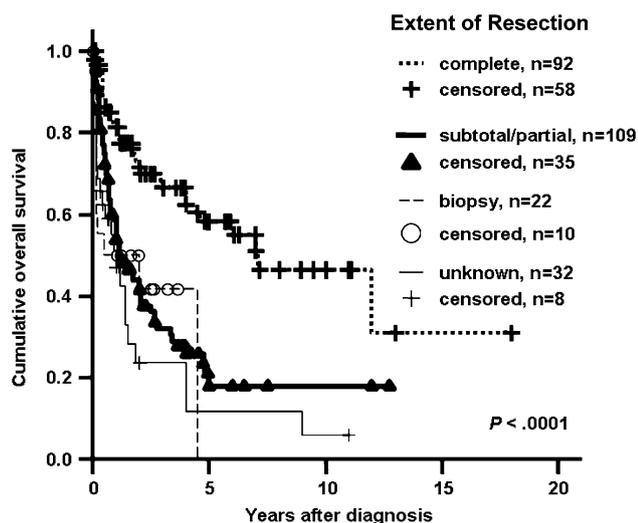
Survival times were significantly dependent on histology. Patients with a CPP had by far a better outcome (1-, 5-, and 10-year OS rates of  $92 \pm 1.5\%$  standard deviation (SD),  $87 \pm 1.9\%$ , and  $82 \pm 2.7\%$ , respectively) compared with patients with a CPC ( $P < .0001$ ; log rank for comparison to  $65 \pm 3\%$  SD,  $51 \pm 3\%$ ,  $34 \pm 4\%$ , and  $25 \pm 4\%$  after 1, 2, 5, and 10 years in CPC) with APP between CPP and CPC.

For further analyses, only patients with CPC were analyzed. OS times were documented in 255 of the 347 patients with CPC. The tumor site influenced the survival significantly, and supratentorial location was linked to a better prognosis ( $P < .0001$ ). Sex or age at diagnosis did not affect survival when analyzed in univariate analyses.

Information about chemotherapy and survival times was reported for 230 of 255 patients with CPC. Of these 230 patients, 45.2% (104 patients) had chemotherapy of various protocols, and 54.8% (126 patients) received no chemotherapy. Males and females were almost equal in number, the tumors were mostly localized supratentorially (73%), and metastases were frequent (14%), without significant differences between the groups with or without chemotherapy. Similar to previous results, patients with chemotherapy were significantly younger than those without chemotherapy (1.5 years compared with 2.1 years,  $P = .003$ ). There was no significant difference in the distribution of the other treatment modalities (surgery and radiation) between the groups.

Surgery was reported as complete surgical resection in 92 (36.1%) of the 255 patients (34.6% with and 43.7% without chemotherapy,  $P = .460$ ). Radiotherapy was received by 88 (34.5%) of the 255 patients. With few exceptions, the radiation was given as standard fractionated radiation with 1.5- to 2-Gy fractions once per day, 5 days per week up to a total of 54 Gy locally. Craniospinal radiation was documented in 31 patients. Starting in the eighties, chemotherapy was given in a large variety of multiagent protocols and included such agents as cyclophosphamide, etoposide, vincristine, cisplatin, carboplatin, lomustine, and others. Of those patients receiving chemotherapy, 34.6% also received radiotherapy. The response to chemotherapy was reported in 40 patients: seven patients (18%) had complete remission, 15 (37%) had a partial response, 12 (30%) had stable disease, and six (15%) had progressive disease.

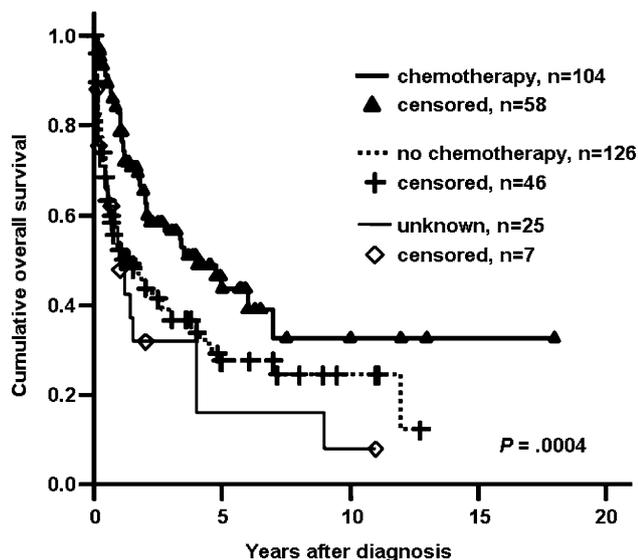
To explore the effect of treatment modalities survival was analyzed first using Kaplan-Meier curves and log rank test for comparison in univariate analyses, addressing each of the major treatment modalities. CPC patients with completely resected tumors had a significantly better outcome than those with subtotally or partially resected tumors: 5-year survival rates were  $58.1 \pm 6.1\%$  SD and  $20.9 \pm 5.1\%$  SD, respectively ( $P < .0001$ , Fig. 3).



**Fig. 3** Cumulative overall survival of patients with choroid plexus carcinoma (CPC) depending on extent of surgery

Radiation was also linked to better survival: the 5-year OS was  $47.4 \pm 6.5\%$  SD in patients receiving radiotherapy compared with  $25.2 \pm 4.3\%$  SD in patients without radiotherapy ( $P = .0002$ , data not shown). Patients who received chemotherapy ( $n = 104$ ) had a significantly better cumulative OS (5-year OS  $46.4 \pm 6.1\%$  SD) than those ( $n = 126$ ) not receiving chemotherapy (5-year OS  $27.6 \pm 4.8\%$  SD,  $P = .0004$ ; Fig. 4).

At this point of the analysis, the apparent benefit of chemotherapy could have been a result of unequal distribution of other parameters influencing survival. Subgroup analyses are one way to address this problem. We defined subgroups by the extent of surgery and radiotherapy in an



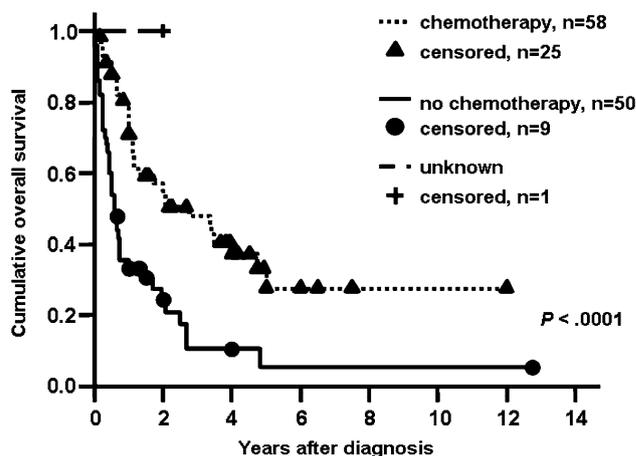
**Fig. 4** Cumulative overall survival of all patients with choroid plexus carcinoma (CPC) treated with and without chemotherapy

effort to find out if the presumed influence of chemotherapy remained detectable. When the effect of chemotherapy was analyzed in the subgroups of patients with and without radiation, chemotherapy remained beneficial in those patients without irradiation ( $P = .0001$ ). In the group with radiation, a tendency towards a better survival was observed, but this was not statistically significant (data not shown). For surgery as influencing factor, the picture was similar: In the subgroup of patients with incompletely resected CPC, those patients receiving chemotherapy ( $58/109$ ) had a significantly better median OS ( $2.75 \text{ years} \pm 0.85 \text{ SD}$ ) than the patients without chemotherapy ( $0.58 \text{ years} \pm 0.1 \text{ SD}$ ;  $P < .01$  log rank; Fig. 5). For the subgroup of patients with completely resected CPC, chemotherapy did not make an apparent difference ( $P = .487$ , log rank).

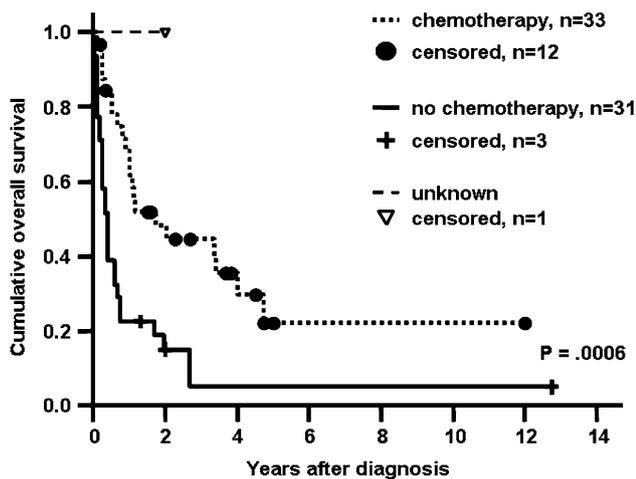
Splitting of these subgroups further into groups of patients uniform with regards to both success of surgery and radiation continued to support the benefit of chemotherapy with significant differences within the subgroups of incompletely resected and irradiated (2-year OS  $63.0 \pm 10.5\%$  SD with chemotherapy versus  $31.8 \pm 10.5\%$  SD without chemotherapy;  $P < .012$ ), and incompletely resected and not irradiated tumors (2-year OS  $44.5 \pm 9.0\%$  SD with chemotherapy versus  $15.0 \pm 6.6\%$  SD;  $P = .0006$ ; Fig. 6).

However, there was only a trend without statistical significance towards a better survival with chemotherapy in the group of completely resected and not irradiated tumors, and there was no difference in the group of completely resected and irradiated tumors (data not shown).

Since the distribution of age was not equal in the two groups (with and without chemotherapy), a Cox regression analysis was performed to elucidate which factors independently affected survival and to rule out a bias.



**Fig. 5** Cumulative overall survival of patients with subtotally or partially resected choroid plexus carcinoma (CPC) with and without chemotherapy



**Fig. 6** Cumulative overall survival of patients with subtotaly/partially resected choroid plexus carcinoma without irradiation. Log rank test to compare survival of patients with or without chemotherapy within this subgroup

A univariate analysis for patients with incompletely resected CPC was performed first, testing age, sex, chemotherapy, radiation, and tumor site. Potential prognostic factors with a  $P$ -value  $< 0.25$  (chemotherapy,  $P < .0001$ ; radiotherapy,  $P = .003$ ; tumor site,  $P = .01$ ; and age,  $P = .12$ ) were subsequently analyzed in a multivariate analysis. Chemotherapy ( $P = .0001$ ) and radiotherapy ( $P < .0007$ ) remained significantly associated with survival, indicating that the distribution of age did not result in a bias.

In summary both, the subgroup analyses and the Cox multiple regression analysis, confirmed the better prognosis of CPC patients after receiving chemotherapy.

## Discussion

Choroid plexus carcinomas are highly invasive and disseminate frequently, and therefore the prognosis of patients with these tumors is still poor. Owing to the rarity of these tumors, treatment recommendations are based on scant evidence. Surgical treatment of CPC is generally considered the most important prognostic factor [10, 22, 29], and this was confirmed in our analysis. The 5-year survival rate of 58% after complete tumor resection (versus 20% after partial resection) was in agreement with previous reports [10, 17]. This is far from satisfactory, as it leaves almost half of the patients with a dismal outcome even after complete resection. Adjuvant treatment of CPC may therefore be important not only for patients with partially resected CPC but also for patients with completely resected CPC.

The role of radiotherapy is controversial. In some small series [30, 31], an objective response to radiotherapy was

reported, showing that CPC is a radiosensitive tumor. Several case reports in the literature describe children with long-term survival that had received radiotherapy [1, 17, 31–34]. Larger analyses, including our own, showed that radiotherapy improves the survival outcome of patients with CPC for incompletely and completely resected tumors [26]. However, the late neurological sequelae of radiotherapy given to children under 3 years of age exclude this modality, leaving only chemotherapy as an adjuvant treatment for the majority of patients with CPC.

Chemotherapy appeared superior in some previous reports [1, 35, 36], but the influencing factors could not be addressed yet due to low numbers, and the relevance of these findings had therefore remained uncertain. In our analysis, chemotherapy significantly improved the cumulative OS of all patients with CPC. In subgroup analyses, we could show for the first time that chemotherapy significantly improved the survival of patients with partially resected CPC, which adds evidence to the frequent recommendation to treat these children [19, 21, 22, 37, 38]. In further subgroup analyses, we showed that this benefit of chemotherapy was independent of the use of radiotherapy. Patients with incompletely resected CPC receiving combined radiochemotherapy had the best 2-year OS (63%), followed by those with chemotherapy alone (45%), radiotherapy alone (32%), and those without further therapy (15%). These data strongly support the use of combined radiochemotherapy in patients over the age of 3 years and chemotherapy alone if the patients are younger. The total amount of necessary adjuvant treatment, and the order in which the modalities are used, still have to be determined.

The initial surgery is a challenge for the neurosurgeon due to the extreme vascularity of the tumor, the tendency of the tumors to invade adjacent brain, and the often large tumor size. Perioperative excessive blood loss contributes to the high perioperative morbidity and mortality, and attempts of complete tumor resection might have been abandoned for this reason [10, 19, 23]. Presurgical chemotherapy reduces the high degree of tumor vascularity, which may in turn facilitate complete resection. St Clair et al. [39] described four patients with inoperable CPC, in whom an initial surgery was limited to biopsy or partial resection but after chemotherapy a gross total resection could be achieved. The average blood loss in the first operation was 390 ml, and only 105 in the second. Histologically there was a dramatic increase in fibrosis and collagen deposition, when comparing the tumor prior to chemotherapy to those after chemotherapy [40]. Because the importance of complete surgical resection in patients with CPC is even greater than for other brain tumors [22], second surgery may be another approach to facilitate complete resection [28, 41].

Even after primary complete resection of CPC, there are significant relapse rates [2, 17], which might be due to microscopic residual tumor after macroscopically complete tumor resection. However, the use of adjuvant treatment is controversial [21, 26]. In our analysis, chemotherapy did not significantly improve the outcome of these patients. However, in the subgroup of patients not receiving radiotherapy, there was a trend towards better survival with chemotherapy, suggesting the use of chemotherapy as an adjuvant treatment in completely resected CPC, too.

We acknowledge that a literature review cannot produce the level of evidence of a prospective randomized study, and a bias resulting from publication of results for patients with a favorable outcome cannot be ruled out. Because CPT are rare, however, almost every case is worth publication, and a relevant bias seems to be unlikely. Given the lack of data from prospective studies, this systematic literature analysis provides the best possible evidence. In our opinion, considering the results of this study, randomization to a treatment without chemotherapy seems unethical, and such a study will probably never be performed.

These data also confirm the previous opinions, which have resulted in an international discussion and launching the international randomized CPT-SIOP-2000 study comparing two chemotherapeutic agents. This study is under way, and will answer which chemotherapeutic agents are effective, a question which could not be answered by this literature analysis.

In conclusion, chemotherapy should be given to patients with less than completely resected CPC, if possible in combination with radiotherapy. For completely resected CPC, there is a trend towards a better cumulative OS, and for those patients chemotherapy should be considered.

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