CPT STANDARD CLINICAL PRACTICE RECOMMENDATIONS

Choroid Plexus Papilloma WHO grade 1
Atypical Choroid Plexus Papilloma WHO grade 2
Choroid Plexus Carcinoma WHO grade 3

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INTRODUCTORY PAGE

Name of tumour entity: **Choroid Plexus Papilloma WHO grade 1**
Atypical Choroid Plexus Papilloma WHO grade 2
Choroid Plexus Carcinoma WHO grade 3

This document has been developed on behalf of the SIOPE Choroid Pleus Tumour Working Group by:

Radiology	Ulrike Löbel, Brigitte Bison
Surgery	Guirish Solanki, Claudia Faria
Pathology	Christian Thomas
Oncology	Jenny Adamski, Ofelia Cruz, Iwona Filipek, Jonathan Finlay, Miklós Garami, David King, Uwe Kordes, Torben Stamm Mikkelsen, Denise Obrecht-Sturm, Michal Zapotocky
Radiotherapy	Beate Timmerman, Jilly Maclean

Contact: **jenny.adamski@nhs.net**

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ABBREVIATIONS

aCPP	Atypical Choroid Plexus Papilloma
CPC	Choroid Plexus Papilloma
CPP	Choroid Plexus Papilloma
CPT	Choroid Plexus Tumours
CR	Complete Response
CSF	Cerebrospinal Fluid
FD	Fractionated Dose
HPF	High-Power Fields
LFS	Li Fraumeni Syndrome
MRA	Magnetic Resonance Angiography
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
OS	Overall Survival
PD	Progressive Disease
PFS	Progression Free Survival
PR	Partial Response
RT	Radiotherapy
SD	Stable Disease
WHO	World Health Organisation
WT	Wild Type

1 BACKGROUND AND RATIONALE

1.1 Background

Choroid plexus tumours (CPT) are rare brain tumours of the choroid plexus epithelium accounting for 1–4% of all paediatric brain tumours. WHO (World Health Organisation) grading differentiates between benign choroid plexus papilloma (CPP, WHO grade 1), atypical choroid plexus papilloma with increased mitotic activity (aCPP, WHO grade 2) or malignant choroid plexus carcinoma (CPC, WHO grade 3) with frank signs of malignancy. The incidence of aCPP and CPC peaks in the first year of life. DNA-methylation analysis segregates these groups and may help in risk stratification, as some CPP and aCPP cluster with CPCs [1,2]. In paediatric tumours there are two recognised methylation subgroups (Heidelberg Brain Tumour Classifier, current version v11b4): subclass paediatric A and paediatric B. CPTs of the group paediatric B tend to have a worse prognosis. All CPC, some aCPP and very few CPP belong to this group [1].

CPC patients require multimodal therapy for cure [3-14]. In contrast, CPP can be controlled with surgical intervention alone, and metastatic disease requiring consideration of other treatment modalities is rare. aCPP tend to have an enhanced risk of relapse compared to CPP and adjuvant treatment may sometimes be employed in the setting of residual or metastatic disease [15]. Survival rates in CPP and aCPP are excellent, approaching 100% and 97%, but progression-free survival (PFS) is lower at approximately 90% and 70-80% respectively [10,15-17]. In aCPP, prognosis is affected by age with those less than 3 years, and particularly less than 12 months, having an improved progression-free survival [18]. Conversely and reflective of their more aggressive biology, CPC have an overall survival in the region of 60% (see Table 1).

The biology of CPC suggests a pivotal role for the tumour suppressor gene *p53* with somatic or germline pathogenic variants of the *TP53* gene occurring in 36 to 60% of patients with CPC [16,19]. Such pathogenic variants are much rarer in CPP and aCPP. *TP53* pathogenic variants appear to strongly predict survival in CPC in most published cohorts [5,16,20,21]. Patients with either somatic or germline mutations typically have a PFS of zero to 28%, while those with wildtype *TP53* have a PFS of 82 to 100% [5,20].

A significant proportion of patients with *TP53* pathogenic variants in their tumours have constitutional (germline) mutations associated with Li-Fraumeni Syndrome (LFS). The frequency of LFS in patients with CPC varies between approximately 20% (16 of 84 CPC patients; CPT registry) and 100% (8 of 8 CPC patients [22]). Li-Fraumeni patients generally have a poor prognosis, not only due to CPC, but also because of an increased risk of second malignancies, both inherently and as a consequence of DNA-damaging chemotherapy or radiotherapy [23,24]. Although *TP53* mutations generally confer chemoresistance, cell studies have shown the least resistance to methotrexate [25]. This suggests regimes such as Headstart II which include methotrexate may be more effective in patients with germline and/or somatic *TP53* mutations.

Considering these findings, specific testing for somatic and germline *TP53*-mutation is highly recommended for all patients with CPC at initial diagnosis. Germline *TP53* testing in all CPP and aCPP patients should also be considered as mutations rarely occur without additional risk factors but is particularly valid if there is a family cancer history or *p53* tumour immunohistochemistry positivity.

The rarity of CPT has led to a lack of standardised treatment protocols. Treatment is mainly informed by data from retrospective case series or trials with only a small number of participants. Maximal safe surgical resection remains a key part of therapy. Adjuvant chemotherapy has been demonstrated to be beneficial in selecting patients with aCPP and confers a survival benefit in patients with CPC [15,26-28]. Although chemotherapy has been employed in CPP, there is limited evidence for its benefit with only one case report showing a clear chemotherapy response [29]. The most effective agents are etoposide, carboplatin and cyclophosphamide with a variety of different regimens employed. The use of radiotherapy in CPC is more contentious due to the young age of the patients and the often supratentorial location of the tumour, with the potential for severe neurological sequelae. There is also a significant proportion of patients with LFS, where irradiation incurs a significant risk of secondary malignancies and has been shown to be detrimental to outcomes [23]. Case series suggest that CPC are radiosensitive, and radiotherapy has been widely used in clinical practice, but the effect on long-term outcomes or which patients are most likely to benefit remains uncertain.

The SIOPE-CPT working group integrates the published literature on the management of CPT with the CPT-SIOP-2000 trial (NCT00500890) experience and data from the CPT-SIOP registry (www.uke.de/cpt) to establish risk-adapted treatment guidelines, including a reference review for neuroradiology and neuropathology. The CPT-SIOP registry accepts registration of all CPT patients, following appropriate local ethical approval, as a repository for clinical and biological data. The SIOPE-CPT working group strongly encourages data entry into the CPT-SIOP registry and is grateful for all patient registrations to support this valuable on-going resource. In the appendices are examples of treatment protocols for guidance; however national and institutional administration policies can also be followed. The treatment decisions remain the responsibility of the local medical team.

1.2 Patient Group

Although occurrence is reported at all ages, CPT primarily occur in children [30]. Despite an overall age adjusted incidence of just 0.05 per 100000, they account for approximately 1 to 4% of all paediatric brain tumours and 10 to 20% of tumours in children under one year of age [30,31]. Age distribution varies significantly amongst pathological subtypes. The median age at diagnosis in the CPT registry is 3.4 years for CPP, for aCPP it is 0.6 years and for CPC it is 2.3 years. Whilst rare, adult cases of all pathological subtypes of CPT do occur with CPP being the most common [30].

Age also affects where the tumour is most likely to develop. Infant tumours tend to occur in the lateral ventricles, with tumours in the third ventricle, fourth ventricle and cerebellopontine angle being more common in older patients. When relating malignancy to location, the relative frequency of CPC is highest in the lateral ventricles, a third ventricular origin very rare, with CPP being more frequent in the cerebellopontine angle [32]. Metastatic disease at presentation also varies according to subtype, occurring in 6% of CPP but up to a quarter of CPC [33].

1.3 Diagnostic Criteria

Imaging

SIOPE-BTG imaging guidelines apply, please refer to the European Society for Paediatric Oncology (SIOPE) MRI guidelines for imaging patients with central nervous system tumours - PubMed (nih.gov) [34]. Magnetic Resonance Imaging (MRI) sequences and coils must be adapted to the small body size and volume of the predominantly very young patients.

The optimal management of choroid plexus tumours requires a high index of suspicion from initial imaging to be able to consider the best neurosurgical approach. The whole central nervous system axis (head and spine) should be imaged as there is a chance of dissemination in all CPT. CPT are highly vascular lesions and, as such, they appear as T2/FLAIR hyperintense and vividly contrast enhancing lesions. The tumours are primarily intraventricular and frequently impair the flow of cerebrospinal fluid (CSF) with around 70% of patients presenting with hydrocephalus [35].

The differentiation between papilloma and carcinoma on imaging is currently not conclusive and definitive histology is necessary. The differentiation between aCPP and CPC is particularly challenging. CPP generally appear as lobulated masses which are well demarcated whereas carcinomas are usually heterogeneous with haemorrhage, necrosis, and internal cysts. Carcinomas can be suspected over papilloma by increased brain infiltration and diffusion restriction [36]. They are reported to have a more solid composition, be larger in volume and have more surrounding oedema. Magnetic resonance spectroscopy (MRS) reveals carcinomas to have a higher choline peak and more lactate than papillomas [37], whereas papillomas have significantly higher myo-inositol [38]. Arterial spin labelling has been used to show that carcinomas have a higher relative cerebral blood flow [39]. Although a tissue diagnosis is mandated, these imaging features may lead clinicians to suspect carcinoma over papilloma prior to surgery.

Metastasis within the subarachnoid space or leptomeningeal dissemination (LMD), is well reported in CPTs and can have unusual imaging characteristics, such as a cystic appearance [40]. Of caution, diffuse laminar leptomeningeal enhancement which resolves quickly, either without adjuvant treatment or after limited chemotherapy, is also reported.

Known as pseudo-LMD, this is felt to be due to changes within the arachnoid vasculature and can be misconstrued as metastatic disease. If in doubt, we recommend repeating the MRI scan at a short interval to clarify if true metastasis.

As choroid plexus tumours have a propensity to bleed, a high diagnostic suspicion may allow assessment of the blood supply with magnetic resonance angiography (MRA) prior to surgery (if the clinical status of the patient allows this) and consideration of embolisation or a planned 2-stage approach.

Pathology

SIOPE Pathology guidelines apply.

CPP appear as cauliflower-like masses macroscopically and are adherent to the ventricular wall but often separate from the brain tissue. CPC have a similar appearance but may be locally invasive into the brain parenchyma.

Microscopically, CPP is a benign papillary tumour resembling normal choroid plexus tissue, characterized by cuboidal to columnar epithelial cells overlying a vascularized fibrovascular stroma. Mitotic activity is minimal (≤1 mitosis/10 high-power fields (HPF)). Immunohistochemistry can be a useful adjunct to diagnosis with tumours positive for cytokeratin, Kir7.1, transthyretin vimentin, podoplanin, and S-100 [41,42]. Immunohistochemistry for p53 should also be performed, as increased expression can be predictive of a *TP53* pathogenic variant.. However, itis not not a substitute for *TP53* sequencing [20,43]. Atypical CPP (aCPP) is defined by the 2021 WHO classification solely as a choroid plexus papilloma with increased mitotic activity (≥2 mitoses/10 HPF). While other atypical features—such as increased cellularity, pleomorphism, and necrosis—may be present, these are not required for diagnosis. In contrast, CPC are malignant tumours showing frank signs of malignancy, typically characterized by solid sheets of pleomorphic epithelioid tumour cells with frequent mitoses. For the diagnosis of CPC, at least four of the following five histological features are required: brisk mitotic activity (>5 mitoses per 10 high-power fields), nuclear pleomorphism, high cellularity, blurring of the papillary growth pattern with poorly structured sheets of tumour cells and/or areas of necrosis. Positivity for S100 and transthyretin is less than that seen in CPP whilst carcinoembryonic antigen can be expressed [41]. Retained INI-1 expression is useful for distinguishing poorly differentiated CPC from AT/RT (Atypical Teratoid Rhabdoid Tumour), where it is lost [44]. Importantly, *TP53* mutations, which occur most frequently in CPC but also be found in CPP and aCPP, do not influence the classification of these tumours.

Methylation profiling has emerged as a valuable adjunct to histopathological examination in many central nervous system tumours, improving diagnostic precision and providing insights into prognosis. It has been shown to broadly distinguish CPC from CPP and aCPP [16]. In pediatric tumours, two distinct methylation subgroups have been identified using the v11b4 version of the Heidelberg Brain Tumor Classifier: subclass pediatric A and pediatric B. All CPC and some CPP and aCPP fall into the pediatric B subgroup, with aCPP in this category being associated with a less favourable prognosis [2]. Methylation profiling is expected to play a pivotal role in refining prognostic stratification, becoming an integral part of the neuropathological workup in routine diagnostics.

Germline testing for Li-Fraumeni Syndrome should be performed in all CPC and considered in all aCPP and CPP, especially if additional risk factors or positive p53 immunohistochemistry.

Cerebrospinal Fluid

CPT can seed via the CSF and a lumbar puncture on or after day 14 following surgery should be performed in CPC patients. Although metastatic disease on imaging is accepted as a poor prognostic factor, the prognostic impact of isolated positive CSF (Chang Stage M1 disease [45]) has not been established. CPT differentiation from normal (ependymal) cells may be difficult, especially in low grade tumours where positive CSF results may persist for more than 14 days but can be an innocuous finding [46]. Recent advances in Nanopore sequencing technology may allow the diagnosis of CPT to be made from cell-free DNA in CSF, in addition to cytopathology [47]. Here, even in cases where tumour cells are absent on cytology, copy-number variations could still be detected. Although currently experimental, this may be a valuable addition to diagnostics both at presentation and for surveillance.

2 GENERAL APPROACH TO TREATMENT

2.1 Surgical Approaches

Maximal safe resection is the treatment of choice in choroid plexus tumours and is considered curative in CPP. The extent of surgical resection is a prognostic factor in all histological subtypes. CPC are hyper vascular and there is a considerable risk of bleeding during surgery, which may be catastrophic. Neurosurgeons should be aware of this risk and ensure that appropriate blood product support and critical care facilities are available. The possibility of a choroid plexus tumour should be considered pre-operatively in any young child with a highly contrast-enhancing brain tumour located in the ventricles. Following emergency management of acute hydrocephalus, consideration should be made for imaging of the tumour vasculature with MR-perfusion angiography or techniques that give equivalent information so that embolisation or a multi-stage procedure can be considered.

Pre-operative embolisation of tumours may decrease peri-operative blood loss and increase the chance of gross total resection [48]. If appropriate expertise is available, this could be considered either prior to a biopsy or as part of a two-stage procedure, immediately before attempting surgical resection [49,50]. Embolisation can rarely be associated with haemorrhage or infarction and is not universally advocated, with some authors preferring to emphasise precise haemostasis during resection [51].

Neoadjuvant chemotherapy also has the potential to reduce surgical risks in CPC. In one retrospective case series two to 5 cycles of neo-adjuvant ICE (ifosfamide, carboplatin and etoposide) chemotherapy in children with CPC improved the chances of a near-total or gross-total resection and significantly reduced mean blood loss [49,52]. As part of a staged surgical approach, chemotherapy could be considered following biopsy or limited safe surgery and prior to delayed, second definitive surgery in the case of CPC and rarely aCPP. The authors recommended that surgical resection should be considered after every two cycles of chemotherapy.

In summary, surgery for CPTs must be individualised depending on the case. Pre-operative embolisation of feeding vessels of the tumour after appropriate imaging may be considered providing appropriate expertise is available. Neoadjuvant chemotherapy for CPC following an initial biopsy prior to definitive surgery may also be appropriate. Neurosurgeons should be aware of the risk of catastrophic, life-threatening bleeding when operating on CPT and ensure that appropriate supportive care is available.

2.2 Radiotherapy

Radiotherapy was an integral treatment component in past series, particularly in CPC. However, data regarding the irradiation dose, responsiveness and appropriate target volumes with respect to the histological grade and extent of disease at diagnosis are lacking.

For CPP and aCPP, data on the role of radiotherapy are scarce. Both have been reported to respond to radiotherapy and in patients with incomplete resection, the implementation of adjuvant therapy including radiotherapy can improve the outcome to that seen in patients with complete resection [53,54]. Craniospinal irradiation has been reported to be an effective treatment for disseminated CPP [55]. Amongst aCPP patients in the CPT-SIOP-2000 trial, for irradiated versus unirradiated patients, the 5-year OS and PFS were 75% and 63% versus 100% and 92% respectively, although this was not significant and may reflect that irradiation was reserved for disease which was more difficult to treat [17]. CPP and aCPP are known to have a good outcome and long-term disease control can be achieved with surgery or chemotherapy alone. Therefore, most would reserve radiotherapy for CPP and aCPP with multiply relapsed disease or selected high risk cases.

In CPC patients, radiotherapy has been a key component of most treatment protocols. However, the evidence on its effect on survival is conflicting. Data are limited by small numbers, varying chemotherapy regimens and lack of biological data. Retrospective studies have shown both an advantage and no advantage. Wolff *et al.* (1999) showed that the 5-year overall survival for patients with CPC and irradiation was 68%, whereas the 5-year overall survival for CPC without radiation therapy was 16% [56]. In one study, patients who received craniospinal axis irradiation (CSI) were reported to be associated with better overall survival and progression-free survival than patients who received whole-brain or involved-field irradiation [57]. However, there are also studies that did not observe any benefit from radiotherapy [6,58,59]. Sun *et al.* analysed 135 CPC patients and showed that adding adjuvant therapy was associated with better OS but found no advantage of irradiation and chemotherapy over chemotherapy alone [27]. Prospective studies too are

conflicting, and none evaluate radiotherapy in a randomized design. In the SIOP CPT 2000 study, although the 2-year OS for CPC without and with radiotherapy was 55% versus 96.7% respectively, this was not statistically significant. In the present analysis of radiotherapy data of children with CPC included in the SIOP CPT 2000 and 2009 studies, the 5-year OS after radiotherapy (focal and CSI) was 74.0 % as compared with 51.4 % in those not receiving irradiation (p=0.004) [60]. An advantage in OS was seen in non-metastatic, incompletely resected tumours that were irradiated (87.8% versus 55.4% p: 0.019). In metastatic disease, the 5-year PFS after craniospinal irradiation was 100% as compared with 47.7%. However, likely due to the small numbers of patients, the advantage could not be translated into superior OS [17]. Conversely, in the SJYC07 trial, radiotherapy use was not associated with survival in young children with CPC treated with non-myeloablative therapy, albeit numbers were small [5].

When radiation has been employed, there is considerable variation in fields and doses. Although there is evidence that favours CSI over focal radiation (Mazloom 2010), the SIOP CPT Registry CPC data indicate that focal fields are more commonly employed than craniospinal (63.4%) in localised disease (Reiken abstract). There does not appear to be a survival advantage for craniospinal over focal radiotherapy in M0 disease (unpublished) andtherefore focal fields could be considered. It should be noted that the radiotherapy target volume will usually be very large for CPC, even with focal therapy alone, and therefore and are still likely to be associated with considerable neurocognitive toxicity. Focal radiotherapy may also preclude subsequent CSI and therefore clinicians may wish to employ CSI upfront in selected cases. CSI should be given for metastatic disease. For radiotherapy treatment details, please see table 2.

In general, we recommend CSI should be given for metastatic disease although it is important that the increased toxicities and the limited evidence for such an approach is discussed during the consent process. The principle of restricting CSI to patients aged > 3 years is well established in other tumours such as AT/RT given the significant toxicity of CSI in younger patients [61]. Such an approach is also justified in CPC and CSI should therefore be avoided in patients < 3 years of age. For radiotherapy treatment details, please see table 2.

Radiotherapy is accepted as a component of the standard treatment for patients with CPC. However, the decision to irradiate should consider the extent of disease and residual disease, the age of the child and *TP53* germline status. In patients with LFS or *TP53* tissue mosaicism, for who irradiation confers a significant risk of secondary malignancies, the international consensus is that radiation therapy should be avoided whenever possible. Bahar *et al.* evaluated outcomes in patients with a *TP53* germline mutation and found inferior 2-year survival in patients who had received radiotherapy [23] whilst Bahar *et al*., reported similar findings when reviewing published cases between 1990 and 2013 [23].

In summary, radiation therapy should be considered in all those with high-risk disease for whom irradiation is appropriate, such as CPC and metastatic disease over the age of 3 years. For those patients with *TP53* wild-type tumours, favourable outcomes are leading clinicians to consider a reduction of therapy and avoidance of radiotherapy, which will be investigated in future clinical trials. When the decision to irradiate has been made, it is recommended after two cycles of chemotherapy or as soon as clinically appropriate. It may be more appropriate to delay the timing of irradiation until the end of chemotherapy in younger children or if there is a continued response to chemotherapy. In all cases, proton beam radiotherapy should be considered given the significant late effects of treatment.

Radiotherapy / age, volume, dose prescription, treatment technique

When radiotherapy is to be used, we would recommend following the SIOP CPT protocols as summarised below.

Age	Craniospinal axis (CSI)	Focal	Tumour site/boost	Boost spinal metastases
<1.5 years	-	-	-	-
*>/=1.5 years to <2.5 years	-	50.4 -54.0 Gy	-	-
*>/=2.5 years to <3.0 years	Delay to 3 years	54 Gy	-	-
>/=3.0 years	If not needed	54 Gy	-	-

>/=3.0 years	35.2 Gy / 36.0 Gy FD** : 1.6 / 1.8 Gy	-	19.8 Gy / 18 Gy (55 Gy / 54 Gy) FD**: 1.8 Gy	9.0 Gy at cord, 14.4 Gy at cord FD**: 1.8 Gy

*Patients aged < 3 years will not receive craniospinal RT but focal RT

**FD: fractionated dose

Dose Fractionation

We recommend a standard once daily fractionation of 1.8 Gy, five days a week for each site to be treated. It is reasonable to consider 1.6Gy per fraction for younger patients.

Timing

Radiotherapy should be initiated after recovery of the bone marrow if chemotherapy has been used. The platelet count should be > 50 x 10^9/L with an upward trend and the absolute neutrophil count should be > 1.0 x 10^9 /L before starting irradiation. Haemoglobin levels should be maintained at greater than 10 g/dL. During craniospinal radiotherapy, blood counts should ideally be maintained with transfusion and G-CSF as required.

Modality

New and highly conformal technologies such as proton beam therapy or intensity-modulated radiotherapy (IMRT) (i.e., volumetric modulated arc therapy (VMAT), tomotherapy etc.) should be considered and can be discussed with national representatives for radiotherapy and respective experts. The use of proton beam therapy is encouraged, whenever available and able to cover the target safely. In cases of megavoltage photon therapy, the cranial (whole brain) fields should be treated with energies in the range of 4-6 MV. Energies greater than 6 MV should be avoided because of under-dosage to the lateral meninges due to dose build-up effect. Photons of energy 4-6 MV are advisable for spinal irradiation; however, electrons of suitable energy can be used as an alternative. A combination of photon and electron fields with sufficient energy to cover the brain and spine is allowed.

Target volume and organ at risk definitions

The target definitions will adhere as closely as possible to the ICRU Report 50.

The radiation therapy volumes will consider the extent of the disease at the time of diagnosis and/or progression and prior to the irradiation. If there are questions regarding a particular patient, the treating physician should contact the reference radiotherapy co-coordinator.

Gross Tumour Volume (GTV)

The GTV includes all gross residual tumour and/or the surgical cavity at the primary site after the initial imaging examination and on subsequent imaging performed prior to radiotherapy if there has been disease progression or anatomic changes because of resolution of post-operative changes. Typically, according to the ICRU-50, contrast enhanced MRI scans are used to determine the GTV; however, the most informative imaging, possibly CT scans, PET scans, MR spectroscopy etc. can be used to delineate the GTV as necessary.

Clinical and Planning Target Volumes (CTV/PTV) for local-only treatment

CTV= GTV + 1cm (anatomically constrained), PTV margins as per institution.

Clinical and Planning Target Volumes (CTV/PTV) for craniospinal irradiation

The Clinical Target Volume for CSI comprises the entire brain, spinal cord and thecal sac. CTV delineation should follow the SIOPE Brain Tumour Group consensus guideline available at https://doi.org/10.1016/j.radonc.2018.04.016 and includes a practical CT based delineation atlas with the manuscript [62]. The PTV margin will be defined according to institutional policies.

Organs at risk (OAR)

At least the following organs should be defined for 3DCRT, IMRT or PBT:

Supratentorial brain (left and right)
Brainstem
Hypothalamus
Pituitary gland
Eyes/ lens (left and right)
Optic nerves (left and right)
Optic chiasm
Cochlea (right and left)
Cervical spinal cord
Whole brain

2.3 Chemotherapy

Adjuvant chemotherapy has been shown to be effective in high-risk aCPP and confers a definite survival benefit in CPC [15,26-28]. Several different treatment regimens have been reported, but it is difficult to demonstrate any as obviously superior due to the small number of patients and heterogeneity regarding the types of tumours, the age of patients and the use of irradiation (see Table 1). Often the *TP53* status has not been either evaluated or reported, making comparisons challenging. Many of these studies are retrospective and, although a few prospective trials have been completed, there has only been one completed randomised trial: the SIOP CPT 2000 trial [17]; a second randomised trial closed early due to lack of accrual (SIOP CPT 2009).Whilst different groups may have preferences based on prior experience or familiarity with specific protocols, it is not possible to recommend one chemotherapy strategy over another based on the current literature. Three regimens CarbEV [17], ICE [4] and Head Start II [63]) are the most widely used worldwide and can be considered standard of care for the treatment of CPC. The choice of which treatment to use will, to some extent, depend on national and local familiarity with a protocol but should also be tailored to the individual patient. There is some evidence that the Head Start protocols may be more beneficial in patients with somatic or germline *TP53* mutated tumours [25,64]. In patients with *TP53* wild-type tumours, where outcomes are superior, the lower intensity of CarbEV or ICE may be more appropriate. Information regarding administration is given in detail in the appendices; however, this is provided for guidance only, and institutional or national administration protocols can be used. Clinicians should be guided by their national guidelines and advisory groups, and choices tailored to the individual patient. A summary of the evidence for the commonly used chemotherapy regimens, including those recommended, are below.

Carboplatin, etoposide and vincristine (CarbEV) [15,17]:

A quantitative literature review in 2011 comparing chemotherapy agents suggested a benefit of etoposide, carboplatin, cyclophosphamide and vincristine[26]. These agents were also investigated in the SIOP CPT 2000 trial, which is the only completed prospective randomised trial of chemotherapy in CPTs. Here, patients with high-risk CPT were randomised to six cycles of adjuvant treatment with either CarbEV or CycEV (cyclophosphamide, etoposide and vincristine)[17]. High-risk CPT was defined as CPC, incompletely resected aCPP, and all metastatic CPT. Radiotherapy was recommended after two cycles of chemotherapy and restricted to patients who were at least 3 years of age.

Initial results suggested no difference between the two chemotherapy arms; however, subsequent analysis of the CPT registry showed more disease-related events in the alternating therapy arm than previously seen in either of the previous chemotherapy arms [23]. Final analysis of the SIOP CPT trial confirmed that patients with CPC treated with CarbEV had a significantly superior PFS and OS compared to those treated with CycEV with a 5-year PFS of 62% versus 27% [17]. The current recommendation is therefore six cycles of adjuvant CarbEV. CarbEV is the most widely utilised chemotherapy regimen for high-risk CPT, including CPC, in Europe. This regimen is well tolerated, and for patients with CPP or aCPP, the SIOPE CPT Group would recommend CarbEV as the treatment of choice. In the SIOP CPT trial and registry, most CPC patients received radiotherapy, however 12 out of 33 patients survived without irradiation and 8 patients were rescued with irradiation following progression ([17] and SIOP registry data, unpublished).

Ifosfamide, carboplatin and etoposide (ICE)[4]:

A single centre review from Toronto examined 14 patients with CPC diagnosed between 1985 and 2007, none of whom were irradiated [4]. Twelve patients were given ICE chemotherapy with curative intent. In 11 patients with measurable disease, five demonstrated an objective response. Second look surgery was undertaken in ten patients after a median of four cycles. The 5-year PFS was 53% and OS was 74%, with a mean follow up of 6.9 years.

This regimen is widely used across North America and in some places in Europe. Although intensive, it is deliverable in young children with appropriate dose adjustments and has the most evidence for efficacy without the use of irradiation or high-dose myeloablative chemotherapy. Some variations of ICE regimens are used; the recommended regimen is published [4].

The Head Start protocols [63]:

The Head Start studies were a series of trials conducted between 1991 and 2009 utilising intensive chemotherapy to spare or postpone irradiation therapy in young children (under 6 years of age) with malignant brain tumours. The treatment backbone consists of maximal surgical resection followed by five cycles of intensive induction chemotherapy (cisplatin, cyclophosphamide, vincristine, etoposide +/- high dose methotrexate +/- temozolomide) followed by consolidation myeloablative chemotherapy (thiotepa, carboplatin and etoposide) with autologous hematopoietic progenitor cell rescue. Zaky *et al*. (2015) reported 12 young children with CPC treated with Head Start regimens without irradiation [63]. The 5-year PFS was 38% with an overall survival at 5 years of 62%, although late relapses were also noted. Five patients received irradiation, one for residual disease and 4 at progression or relapse, of whom one survived.

The Head Start II chemotherapy regimen (vincristine, cisplatin, cyclophosphamide and etoposide, with the addition of high-dose methotrexate) is a commonly used regimen across Europe and the United States for high-risk malignant brain tumours in infants. The interest in this regimen in CPC is due to the addition of methotrexate, to which *TP53* mutant cells theoretically retain sensitivity [25]. Although small numbers, outcomes are comparable, and it may therefore be considered as an irradiation-sparing treatment in high-risk CPC. In particular, very limited data in a recent report suggest that the previously reported differential in survival between patients with *TP53* mutated tumours and those with wild-type *TP53* tumours was not seen in this cohort, with the 10-year CPC-free survival being 58% and 50% respectively [64].This is notably improved compared to the previous reported survival of 0-28% in patients with *TP53* mutated tumours [5,20]. Of note, CPC LFS patients may particularly benefit from marrow-ablative chemotherapy and autologous stem cell rescue and the 10-year CPC-free survival was 62% (n=12) [64].

SJYC07 therapy

The prospective SJYC07 trial enrolled 13 patients with CPC for risk-stratified, multi-modal treatment using non-myeloablative high-dose methotrexate–containing induction therapy (methotrexate, cisplatin, cyclophosphamide, vincristine +/- vinblastine) and consolidation with radiotherapy or further chemotherapy [5]. Only patients less than 3 years of age were included, and they were stratified according to risk based on whether they had localised or metastatic disease. Patients with localised disease were eligible for focal radiotherapy if greater than 12 months old whilst craniospinal radiotherapy was delayed until patients were greater than 3 years of age if they were high risk. The 5-year PFS rate was 61.5% with an overall survival rate of 68.4%. All patients with *TP53* wild-type tumours survived compared to only 28.6% of patients with *TP53* mutant tumours. Survival rates compare favourably with other regimens and the authors suggest that *TP53* mutation status should be used to risk-stratify in future trials.

Other chemotherapy regimens

A variety of other chemotherapy regimens have been reported in small case series, the details of which are presented in Table 1. The UK CCSG / SIOP CNS 9204 study included 15 children with CPC, four of whom presented with metastatic disease [3]. Children were treated with 12 months of alternating cycles of myeloablative and non-myeloablative chemotherapy, every 14 days for 7 cycles. Patients did not receive radiotherapy until they had progressive disease. The PFS and overall survival was 21%.

A retrospective review of French data included 102 patients with CPT (54 CPP, 26 aCPP, 22 CPC). Eight of 22 CPC patients were metastatic. The chemotherapy received (6 aCPP, 21 CPC) was very variable and included BB-SFOP chemotherapy (see Table 1) ICE and carboplatin / vincristine / cyclophosphamide chemotherapy (VEC). Eleven patients received irradiation (2 aCPP, 9 CPC). The 5-year EFS was 96% for CPP, 72.9% for aCPP and 25.2% for CPC. The 5-year OS was 100% for CPP, 96.2% for aCPP and 64.7% for CPC [10].

A retrospective review of patients treated at St. Jude's Research Hospital included four CPP and 10 CPC patients [13]. Seven of the CPC patients were metastatic at presentation. Seven CPC patients underwent a gross total primary tumour resection (including all 3 localised patients). All but one CPC patient received chemotherapy with cyclophosphamide, etoposide, vincristine and carboplatin or cisplatin and five received irradiation. Response to chemotherapy was seen in three out of seven evaluable patients. Three patients progressed on chemotherapy, one of which was salvaged with CSI. Eight patients were alive at 3 to 153 months following treatment, six without evidence of disease and five without irradiation. Two CPP patients had a subtotal resection and recurred locally with evolution to CPC; one patient was treated with chemotherapy and CSI and one with CSI alone, with both surviving.

2.4 Intraventricular or intrathecal chemotherapy

As CPC occurs in very young children, often precluding irradiation, and is frequently metastatic, there has been some interest in the use of intraventricular or intrathecal chemotherapy as whole CNS-directed therapy. Intraventricular or intrathecal chemotherapy has been utilised as a CNS-directed therapy in childhood malignant brain tumours, primarily in metastatic relapsed or refractory settings [65]. Although some efficacy has been shown in relapsed CPC, this is restricted to single case reports [66,67]. There is no current evidence to show an additional benefit of intrathecal therapy in the up-front treatment of CPC. In the SIOP CPT 2000 trial, in which some metastatic patients received intrathecal cytosine, arabinoside or etoposide, no survival benefit was observed (unpublished, SIOP CPT Registry). Given its additional toxicity and in the absence of clear data or a clinical trial, it is recommended that intraventricular or intrathecal chemotherapy is reserved for second line treatment.

Table 1. Summary of chemotherapy for choroid plexus carcinomas

Publication	Patients	Treatment	Comments	EFS / PFS (5 year)	OS (5 year)
Prospective Studies					
SIOP 2000 CPT (Wrede et al. 2009)[15]	29	CarbEV VEC	Randomised controlled trial RT detailed in RT section	28%	36%
SJYC07 trial (Liu et al., 2021)[5]	13	Methotrexate, cisplatin, cyclophosphamide, vincristine +/- vinblastine	Prospective Risk stratified - high risk if metastatic RT varied	61.5%+/- 13.5%	68.4 ± 13.1%
CPT-SIOP-2000 final results (Wolff et al.2022)[17]	55	CarbEV vs VEC (+ 11 other - site decision)	Randomised controlled trial RT detailed in RT section	51% (CarbEV) vs 53% (VEC)	73% (CarbEV) vs 27% (VEC)
CCG 9921 (Geyer et al. 2005)[8]	9	Vincristine / cisplatin / cyclophosphamide / etoposide carboplatin / ifosfamide / etoposide	Phase II randomised controlled trial Very little details on CPC published No upfront RT	7 progressed 33+/-16% (3 years)	 3 patients died 63+/-17% (3 years)
Fouladi (Fouladi et al. 2009)[7]	5	Carboplatin / cyclophosphamide / etoposide /	Phase II, limited institution study 1 metastatic disease, all GTR RT for M+ or PD	1 progressed 60+/-19%	1 died disease, 1 died secondary malignancy 80+/-18%
UKCCSG/SIOP CNS 9204 (Grundy et al. 2010)[3]	15	Alternating: carboplatin / vincristine / cisplatin / methotrexate	Phase II clinical trial. 11/14 progressed on treatment. No RT until PD	21%	21%
Retrospective Studies					
St. Jude's (Chow et al. 1999)[13]	10	Cyclophosphamide / etoposide / vincristine / platinum agent	Retrospective review RT varied	3 progressed	2 died
SickKids (Lafay-Cousin et al. 2010)[4]	12	ICE	Retrospective review No upfront RT	53.3 +/- 16.1% (0 salvaged with radiation)	74.1 +/- 12.9%
John Hopkins (Bettegowda et al., 2012)[6]	7	Not detailed	Retrospective review. 6 received chemotherapy and 3 RT		71% (5 of 7 patients survived)
Seoul (Koh et al., 2014)[9]	8	Variable: Carboplatin / cisplatin /cyclophosphamide / ifosfamide / vincristine / etoposide 4 received High dose	Retrospective review RT varied	8 patients progressed	3 patients survived (all received High dose chemo and 2 received focal RT)

		chemotherapy and PBSC rescue			
Head Start I-III (Zaky et al. 2015)[63]	12	HS I-III chemotherapy	Retrospective review No upfront RT	38%	62%
Cleveland Clinic (Bahar et al., 2017)[23]	7	According to SIOP 2009 Cyclophosphamide / carboplatin / vincristine / etoposide / intrathecal cytarabine / HD methotrexate	Retrospective study Includes 1 adult patient (transformed CPP), median age 4.5 years 2 patients metastatic RT as per SIOP 2009 (below)	3 recurred (all salvaged with CSRT and chemo)	All survived
French experience (Siegfried et al., 2017)[10]	22	Variable: Mainly CarbEV VEC ICE BB-SFOP	Retrospective review Central pathology review (ATRT excluded) RT varied	25.2 +/- 10.6%	64.7 +/- 12.1 %
SIOP Registry (Kordes et al. 2018; Kordes et al. 2014a)[33,68]	77	Variable: Mainly CarbEV VEC	Trial patients RT varied	32%	59 %
Vienna Experience (Hosmann et al., 2019)[51]	4	Variable: etoposide +/- vincristine/ifosfamide +/- cisplatin/carboplatin	RT variable, wide age range of patients	33.3%	100%

CarbEV: Carboplatin / Etoposide / Vincristine
VEC: Vincristine / Etoposide / Cyclophosphamide
ICE: Ifosphamide / Carboplatin / Etoposide
BB-SFOP: Cure 1 Carboplatin/Procarbazine, Cure 2 Etoposide/Cisplatin, Cure 3 Vincristine / Cyclophosphamide, every 21 days total 21 cures
HS I, II and III: A: (5 cycles) Cisplatin / vincristine / etoposide / cyclophosphamide, A2 (5 cycles) Cisplatin / vincristine / etoposide / cyclophosphamide / high dose methotrexate, D/D2 (cycles 1,3,5) cisplatin / vincristine / etoposide / cyclophosphamide / high dose methotrexate and (cycles 2,4) temozolomide / etoposide / vincristine / cyclophosphamide then high dose thiotepa / etoposide / carboplatin and stem cell rescue.
9204: Cycle 1 vincristine / carboplatin, cycle 2 vincristine / methotrexate, cycle 3 vincristine / methotrexate, cycle 4 cisplatin
COG 9921: Randomised vincristine / cisplatin / cyclophosphamide / etoposide or vincristine / carboplatin / ifosfamide / etoposide

3. PATIENT FOLLOW-UP

There are no published data supporting specific surveillance protocols after treatment and the rationale and limitations should be discussed with the patient / family. Recommendations of national groups or institutional practice should be used. Follow-up should be discussed with the patient (if appropriate) and family with the rationale and limitations explained. Factors which may affect follow-up frequency could include age, the need for general anaesthetics or sedation for imaging, co-morbidities, tumour grade, previous treatments given and the available treatment options if relapse is detected.

Most children with CPC relapse shortly after treatment with a median progression free survival of 13 months and we therefore recommend more frequent surveillance in the first two years [69]. A suggested schedule could include an MRI of the head and spine every three to four months for the first two years, spacing to every six months until 5 years off treatment. Less frequent imaging of the spine could be considered if there was no spinal disease at presentation. Annual surveillance may be considered after this. CPP and aCPP tend to grow more slowly and surveillance imaging could be less frequent and, depending on the extent of resection, scanning intervals increased more quickly.

The length of follow-up is also difficult to recommend but it is difficult to mandate for more than five years, despite reported cases of recurrence many years after treatment for CPC [70]. Likewise, CPP and aCPP are reported to have late recurrences and evolution from CPP to CPC is described [71]. Clinicians should therefore still have a low threshold for imaging if new symptoms develop after routine imaging surveillance has been completed.

As well as tumour surveillance, clinicians should undertake late effects surveillance appropriate to the treatment protocol used. Particular to choroid plexus tumours is an awareness of the likely neurocognitive damage as a consequence of the often large, supratentorial tumour, hydrocephalus, high surgical morbidity and chemotherapy or radiotherapy received, often at an extremely young age [72]. Many have neurocognitive impairment, even if not irradiated, and more than half have an intelligence quota significantly below age expectations and display impairment of behaviour and adaptive functions [4,5]. Increased awareness is vital to instigate active rehabilitation and life-long educational support, allowing these children to reach their maximum potential. Children who have received irradiation are also at considerable risk of pituitary dysfunction and should have regular endocrine surveillance.

As a considerable proportion of patients will have LFS, it is highly recommended to follow appropriate international tumour surveillance protocol in addition to CPC tumour surveillance [73,74].

4. SECOND LINE THERAPY IN RELAPSED CHOROID PLEXUS TUMOURS

The choice of second line treatment in progressive or relapsed choroid plexus tumours will be influenced by the child's age, the histology and grade, the extent of disease and the previous treatment strategy, particularly whether they have received radiation therapy or are eligible to receive irradiation. Second line treatment for CPP and aCPP may consist of reconsidering primary treatment modalities such as re-surgery, chemotherapy or radiotherapy determined by the previous treatment, the number of previous progressions and the risk of the disease. The outcome would still be considered favourable and some guidelines are given in the flow sheets (Figure 1 and Figure 2). In multiply relapsed disease, consultation with the appropriate national special interest group is advised.

Although some case reports exist of successful salvage, most consider relapsed CPC to have an extremely poor prognosis without hope of cure. There is no consistent approach and little data available. Discussion of all patients with the appropriate national special interest group is recommended.

Trying to achieve a surgical complete resection, including second look surgery if needed, is important if curative treatment is attempted.

If adjuvant radiotherapy has not been given, it should be considered, again depending on the age, histology and extent of disease. Radiotherapy, where possible, is particularly recommended for patients with choroid plexus carcinoma as a few patients salvaged with irradiation are reported in most series. There are also reports of successful reirradiation in aCPP and stereotactic radiosurgery has been utilised in occasional cases of recurrent CPT including CPC [75-77].

Considering the overlapping nature of various chemotherapy strategies, adjuvant second line chemotherapy cannot be easily recommended and will need further discussions within national choroid plexus interest groups. Data on the benefit of different approaches is limited to single case reports and reported salvage strategies include; myeloablative high dose chemotherapy and stem cell rescue [78], intraventricular therapy [66], targeted agents [79] and standard chemotherapy [80]. Discussion within national advisory groups is strongly advised. Innovative treatment through early phase clinical trials should be considered where available and we encourage discussion with national groups and the Innovative Therapies for Children and Adolescents with Cancer (ITCC) consortium.

5 SPECIFIC TREATMENT RECOMMENDATIONS FOR EACH CHOROID PLEXUS TUMOUR SUBTYPE

5.1 Choroid Plexus Papilloma

Surgery

After emergency correction of the hydrocephalus (if present), maximal safe surgical resection is the treatment of choice. Surgical planning should include careful assessment of the tumour vasculature and consideration of the use of embolisation pre-surgery where possible to minimise the risk of life-threatening bleeds. Following surgery, a watch and wait strategy should be adopted for localised CPP. If local progression is observed, second surgery should be considered.

Chemotherapy:

If there is progressive, inoperable residual disease or it is the third or subsequent resection, then chemotherapy could be considered accepting there is little data on the benefit of chemotherapy in CPP. Patients with metastatic tumours should undergo surgical resection of the primary tumour. A period of observation may be considered in some patients with metastatic CPP prior to initiating chemotherapy as progression may not occur. Central review and methylation profiling to confirm the molecular subgroup diagnosis is recommended if a watch-and-wait approach is considered for metastatic CPP patients.

If chemotherapy is initiated, patients should receive four cycles of CarbEV chemotherapy. If there is complete remission, then consider a watch-and-wait policy. If there is a partial response or stable disease, then complete six cycles of CarbEV, then watch-and-wait without giving irradiation. Assessment should be performed every two cycles and, in cases where a complete response is achieved, discontinuation of chemotherapy considered. If disease progression is identified, consider further surgery and second line chemotherapy, with irradiation only in exceptional cases. Discussion with the national special interest group is strongly recommended.

Radiotherapy indications:

Radiotherapy advice refers to patients without *TP53* germline mutations therefore excluding those with LFS. Consider radiotherapy only in rare situations once surgical and chemotherapy options exhausted. When radiotherapy is delivered with curative intent, refer for consideration of proton therapy.

It is important to note that there is no robust evidence to dictate a radiotherapy approach for CPP and irradiation-related toxicity is considerable. In non-metastatic CPP, locally progressing after repeated surgical procedures and chemotherapy, focal radiotherapy may be indicated in those greater than 1.5 years of age. If metastatic CPP progresses through surgery and chemotherapy, CSI may be indicated in patients greater than 3 years of age although the increased toxicities and lack of evidence for such an approach should be discussed during the consent process.

The recommended treatment for CPP, is summarised in Figure 1.

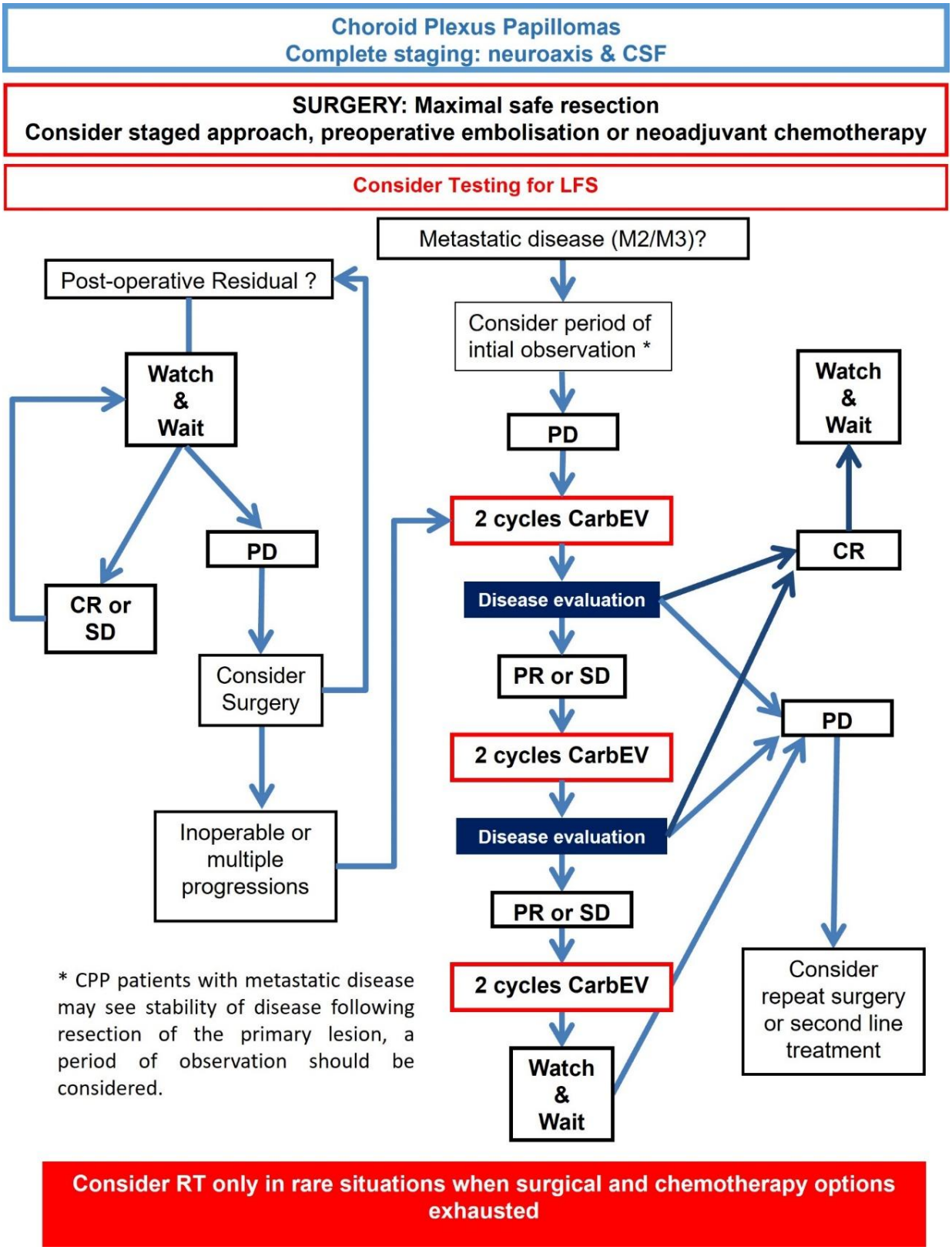

Figure 1. Flow chart for treatment of choroid plexus papillomas (CPP).

Key: CSF: cerebrospinal fluid; LFS: Li Fraumeni syndrome; PD: progressive disease; CR: complete response; SD: stable disease; CarbEV: carboplatin, etoposide, vincristine; PR: partial response; RT: radiotherapy.

5.2 Atypical Choroid Plexus Papilloma

Surgery

After emergency correction of the hydrocephalus, maximal safe surgical resection is the treatment of choice.. Surgical planning should include careful assessment of tumour vasculature and consideration of the use of embolisation pre-operatively where possible. If complete surgical resection is achieved in localised aCPP, a watch-and-wait strategy may be adopted, regardless of the CPT methylation subgroup. If there is subsequent recurrence or progression, a second surgery should be considered.

Chemotherapy

If there is residual localised disease following primary surgery and the patient is less than 3 years of age and/or methylation analysis of the tumour shows it is CPT paediatric subgroup A, a watch-and-wait strategy is recommended.

If there is residual localised disease following primary surgery and the patient is older than 3 years and/or methylation analysis of the tumour shows it is CPT paediatric subgroup B, chemotherapy with six cycles of CarbEV is recommended. Response assessment should be performed every two cycles and second look surgery should be considered.

Following surgery for metastatic aCPP, six cycles of CarbEV chemotherapy should be administered. Response should be assessed after every two cycles and second look surgery should be considered. For patients with metastatic disease who are less than 3 years of age and in CPT paediatric subgroup A, although it is likely that these tumours will behave as CPP, there is not yet enough evidence to de-escalate treatment.

Radiotherapy

Radiotherapy advice refers to patients without LFS and active exclusion of germline *TP53* mutations. Consider radiotherapy only in situations where multiple surgical procedures and chemotherapy options are exhausted without achieving a complete response or with disease progression. When radiotherapy is to be given with curative intent, refer for consideration of proton therapy.

In localised aCPP progressing locally after repeated surgical procedures and chemotherapy in children less than 3 years of age, focal radiotherapy may be indicated in those greater than 1.5 years of age. There is no robust evidence to dictate a radiotherapy approach and irradiation-related toxicity is considerable.

In localised aCPP with unresectable residual tumour in children less than 3 years of age, there is no robust evidence to dictate a radiotherapy approach and irradiation-related toxicity is considerable. Residual disease may remain stable for prolonged periods and watch-and-wait is preferred.

In localised aCPP with unresectable residual disease in children greater than 3 years of age or locally progressive disease post chemotherapy without surgical options, there is no robust evidence to dictate a radiotherapy approach and irradiation-related toxicity is considerable. Watch-and-wait is a reasonable option in those with stable unresectable residual at the end of treatment. Upfront radiotherapy is also acceptable and most European centres tend towards focal radiotherapy. Focal radiotherapy is recommended for patients with progressive disease.

In metastatic aCPP consider craniospinal radiotherapy in patients greater than 3 years of age with progressive disease post chemotherapy, acknowledging such an approach is associated with increased toxicity and is supported by limited evidence.. It is reasonable to watch-and-wait for patients with metastatic aCPP with a complete response to surgery and chemotherapy, with radiotherapy reserved for progressive disease. For patients less than 3 years of age, watch-and-wait would be preferred.

The recommended treatment for aCPP, is summarised in Figure 2.

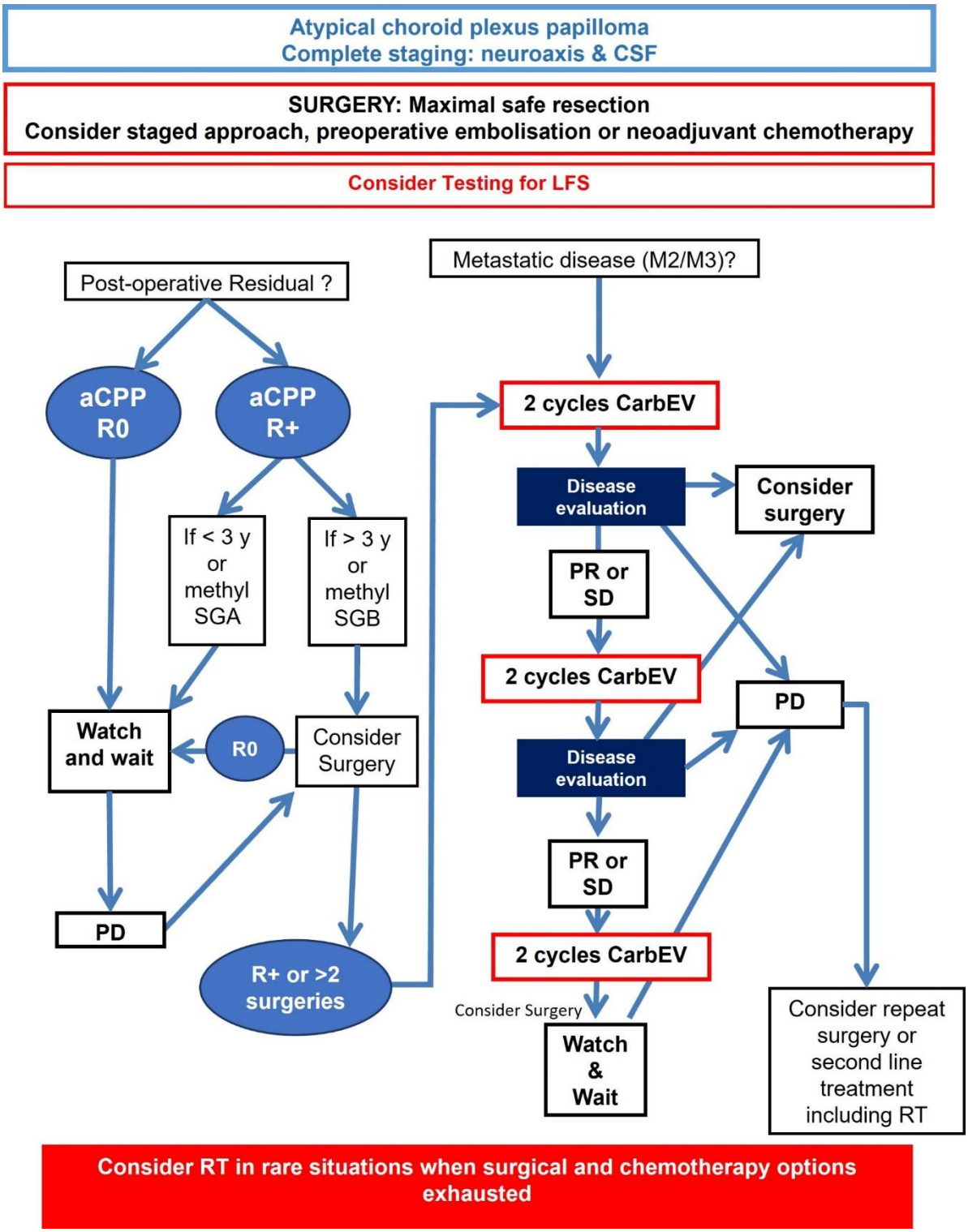

Figure 2. Flowchart for treatment of atypical choroid plexus papillomas (aCPP).

Key: CSF: cerebrospinal fluid; LFS: Li Fraumeni syndrome; R0: complete resection; R+: residual disease; SGA: methylation subgroup pediatric A; SGB: methylation subgroup pediatric B; PD: progressive disease; CarbEV: carboplatin, etoposide, vincristine; PR: partial response; SD: stable disease; RT: radiotherapy.

5.3 Choroid Plexus Carcinoma

Surgery

After emergency correction of the hydrocephalus, maximal safe surgical resection should be undertaken.. Surgical planning may include careful assessment of the tumour vasculature and consideration of pre-surgery embolisation or open biopsy to confirm the diagnosis. For suspected choroid plexus carcinoma, a conservative approach should also be considered to limit surgical morbidity and mortality, with a planned second stage operation, as resection post chemotherapy has been reported to be technically easier [52].

Chemotherapy

All the following chemotherapy strategies can be considered standard of care as detailed below. Because of emerging data regarding the potential benefit of a methotrexate containing regimen and high dose myeloablative chemotherapy and autologous stem cell rescue in patients with a *TP53* mutation, CarbEV or ICE should be considered preferentially in those with tumours with WT *TP53* and Head Start chemotherapy should be the treatment of choice in patients with *TP53* mutated tumours.

CarbEV

After surgery, six cycles of CarbEV chemotherapy should be administered, with assessment of response after every two cycles of chemotherapy. If complete response is achieved by the end of treatment, a watch-and-wait strategy may be adopted in patients who are too young for radiotherapy. However, irradiation should be carefully considered in all patients. If irradiation is planned, it should be administered as soon as appropriate, with the completion of chemotherapy following radiotherapy. In general, this would be planned after two cycles of chemotherapy, as per the SIOP studies. Clinicians are encouraged to wait until *TP53* testing is performed prior to radiotherapy and delaying until the end of chemotherapy may be preferable. See Appendix 1.

ICE chemotherapy

After surgery up to six cycles of ICE chemotherapy should be administered with assessment of response after every two to three cycles. Second look surgery should be considered after every disease evaluation. Ideally, radiation therapy should be delayed until after five to six cycles. A six-week break should be given before resuming chemotherapy after radiotherapy. See Appendix 2.

Head Start chemotherapy

Head Start chemotherapy could be considered if irradiation should ideally be avoided or delayed. Therefore, it may be appropriate in very young children, particularly for those with *TP53* mutated tumours. Disease evaluation should be performed after the initial two cycles of Head Start induction therapy and then prior to high-dose myeloablative chemotherapy. Peripheral blood haematopoietic cell collection can take place at any point but is ideally performed after the first and/or second cycles of chemotherapy. Radiotherapy would not be administered until treatment has been completed, and then only in those with radiographic and/or cerebrospinal fluid (CSF) cytological residual disease, unless there was progressive disease prior to completion of all chemotherapy. See Appendix 3.

Radiotherapy indications in localised disease

Radiotherapy advice refers to patients without LFS after the active exclusion of germline *TP53* mutations. When radiotherapy is to be given with curative intent, refer for consideration of proton therapy..

Complete remission – (either before or after chemotherapy):

There is no robust evidence to dictate a radiotherapy approach and irradiation-related toxicity is considerable. Watch-and-wait is a reasonable option, especially for younger children. Upfront radiotherapy is standard practice in most European centres as per the SIOP CPT studies. In recent years, most European centres have moved towards focal radiotherapy rather than CSI in view of the toxicity associated with CSI. Focal radiotherapy has been used in children without metastatic disease. Although a reduction in survival has not been observed, the data are not yet robust enough

to determine whether omitting CSI in this scenario is deleterious. CSI can be considered in older children on a case-by-case basis as CPC carries a significant risk of metastatic disease and focal irradiation upfront would generally preclude the use of future CSI. This will require careful discussion during the consent process about both the lack of evidence and the increased expected toxicity.

Residual, inoperable disease post-chemotherapy:

Radiotherapy is recommended for those older than 3 years of age. In recent years most European centres have moved towards focal radiotherapy rather than CSI in view of the toxicity associated with CSI. For those 1.5 to 3 years of age, focal radiotherapy would be recommended when the decision to deliver radiotherapy has been made. In recent years, focal radiotherapy has been used in all children without metastatic disease. Although a reduction in survival has not been seen, the data are not yet clear enough to determine whether focal radiotherapy in isolation is sufficient. CSI can be considered in older children on a case-by-case basis as CPC carries a significant risk of metastatic disease and focal irradiation upfront would generally preclude the use of future CSI.

Progressive, inoperable disease on chemotherapy:

Radiotherapy is advised. Most European centres would deliver focal irradiation; however, the data are not yet clear enough to determine whether this is sufficient. CSI can be considered in older children on a case-by-case basis balancing the risk of toxicities with the potential increase in efficacy. Radiotherapy should generally be avoided in patients with LFS and data suggest a worse outcome in those who receive it. However, irradiation may be considered in patients with active disease who have exhausted all other treatment options, after discussion in a national choroid plexus advisory group. Efforts to adapt radiotherapy should be undertaken in patients with LFS to minimise the risk of secondary neoplasms including the reduction of irradiated volumes using proton therapy if possible [81].

Radiotherapy indications in metastatic disease

Radiotherapy advice refers to patients without LFS by excluding *TP53* germline mutations. The decision to administer radiotherapy is made by the local multidisciplinary team, with guidance from national CPT advisory groups to help with the decision-making process. When radiotherapy is to be administered with curative intent, referral for proton therapy is recommended. It should be noted that the SIOP registry data indicated that metastatic status was not a significant predictor of survival.

The SIOP studies delivered irradiation after two cycles of chemotherapy in those older than 3 years of age, i.e., before a response to chemotherapy can be assessed. This is reasonable when the decision to irradiate has been taken upfront, but it may also be reasonable to fully assess the response to chemotherapy prior to a decision to irradiate, particularly in younger children. If the tumour is responding or stable, it may be preferable to delay radiation until chemotherapy is complete.

In patients with complete resection of the primary site who achieve a complete metastatic response to chemotherapy, treatment should be as per localised disease, i.e., watch-and-wait or upfront irradiation may be appropriate. CSI should be considered rather than focal irradiation whilst acknowledging there is limited evidence for such an approach and late effects will be increased. .

In patients with residual or progressive disease post-chemotherapy and surgery, CSI would be favoured in patients greater than 3 years of age, again discussing the expected toxicity and lack of evidence during the consent process. The recommended treatment for CPC, is summarised in Figure 3.

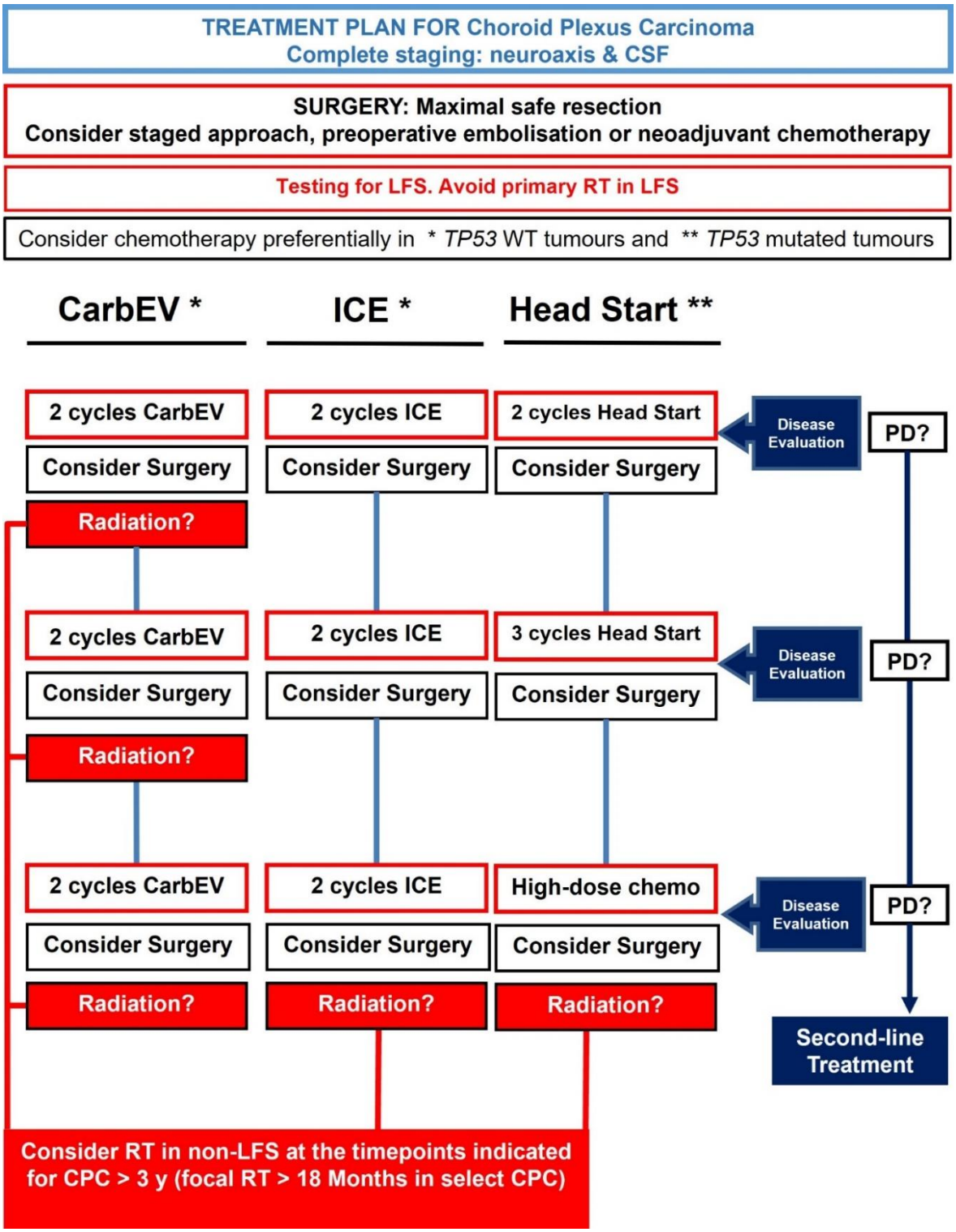

Figure 3. Flowchart for treatment of choroid plexus carcinomas (CPC).

Key: CSF: cerebrospinal fluid; RT: radiotherapy; LFS: Li Fraumeni syndrome; WT: wild type; CarbEV: carboplatin, etoposide, vincristine; ICE: ifosfamide, carboplatin, etoposide; PD: progressive disease.

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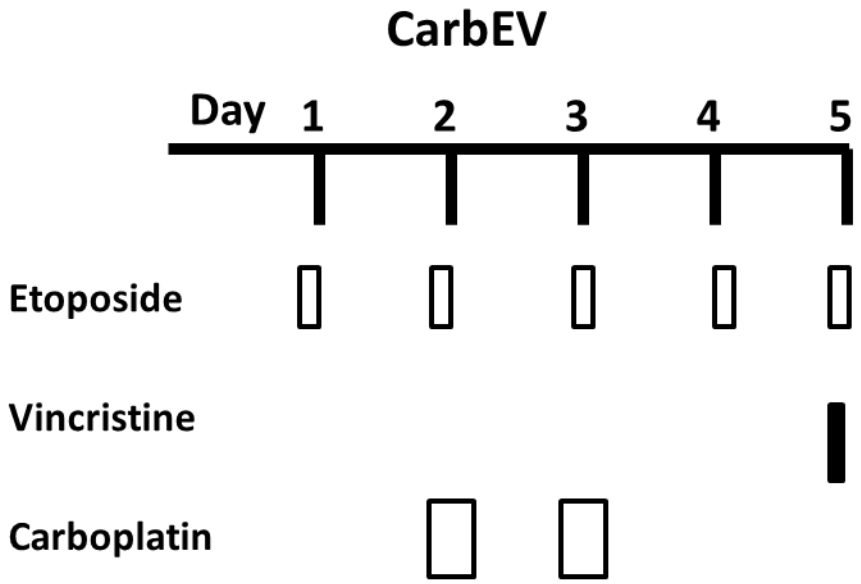
APPENDIX 1. CARBEV CHEMOTHERAPY



CarbEV cycle consists of:

- Etoposide (VP16) 100mg/m2/day as 1-hour infusion on days 1-5
- Carboplatin 350mg/m2/day over 2-hour infusion on days 2 and 3
- Vincristine (VCR) 1.5mg/m2, with a maximum of 2mg, on day 5.

Cycles will be repeated every 28 days. Details of the administration and dose modifications are provided below. Up to 6 cycles should be given.

Radiation, if planned, is ideally given following 2 courses of chemotherapy +/- second look surgery. The exclusion of TP53 mutations is highly recommended and radiation should be delayed until this result is available, with continuation of chemotherapy. A six-week break post radiotherapy should be given before chemotherapy is re-started. A total of 6 courses of first line chemotherapy should be given. In metastatic disease, considering the age of the child, the decision to delay radiation to the end of chemotherapy could be made in the context of an ongoing chemotherapy response.

Consider the use of G-CSF if count recovery is delayed, as per institutional policy.

PJP prophylaxis is recommended, as per the institutional policy.

Administration Guidelines for CarbEV (Carboplatin / Etoposide / Vincristine)

Requirements before each course of chemotherapy:

- Neutrophils > 1.0 x 10^9 /L
- Platelets > 100 x 10^9 /L
- Creatinine < 1.5 ULN

The following chemotherapy can be given as an outpatient, based on the clinician's discretion. It does not require additional fluid however the child should remain well hydrated and IV maintenance fluids should be given if there are any concerns. Care should be taken for young children and infants.

Dose reductions should be made for patients less than 10kg or less than 12 months of age as below.

Drug dilutions should be as per local policies.

DAY 1	T=0	Etoposide 100mg/m^2 IV over 1 hour
DAY 2	T=0	Etoposide 100mg/m^2 IV over 1 hour
	T= 1 hour	Carboplatin 350mg/m^2 IV over 2 hours
DAY 3	T=0	Etoposide 100mg/m^2 IV over 1 hour
	T= 1 hour	Carboplatin 350mg/m^2 IV over 2 hours
DAY 4	T=0	Etoposide 100mg/m^2 IV over 1 hour
DAY 5	T=0	Etoposide 100mg/m^2 IV over 1 hour
	T=1 hour	Vincristine 1.5mg/m^2 (maximum dose = 2mg) IV bolus

Dose adjustments according to age and weight:

Patients below 1 year of age or less than 10 kg in weight:	Calculate dose per body weight: Etoposide 3.3 mg/kg Carboplatin 11.7 mg/kg Vincristine 0.05 mg/kg
Patients less than 3 months of age:	Reduce dose calculated by kg by 33%
Patients less than 1 month of age:	Reduce dose calculated by kg by 50%. Please discuss with choroid plexus special interest group. It may be necessary to dose carboplatin based on pharmacokinetics.
Patients younger than 2 weeks of age:	Do not start chemotherapy before 2 weeks of age

Chemotherapy Dose Modifications CarbEV

These guidelines do not replace local practice nor individual responsibility for patient care. Please discuss with the choroid plexus tumour special interest group if significant concerns.

Haematological	
Before each course due:	
Neutrophils < 1.0 x 10^9/L at day 28	Delay chemotherapy until recovery Consider giving G-CSF to recover white blood cell count. Discontinue G-CSF 48 hours prior to restarting the chemotherapy. Give G-CSF after each of the following blocks, starting at day 9 after the start of chemotherapy
Neutrophil recovery delays therapy > 1 week	Delay until recovery. Restart chemotherapy with 20% reduction of Etoposide and 20% reduction of Carboplatin. The Etoposide reduction is done by deleting day 1 of the block and keeping the doses of day 2 to day 5 identical. The Carboplatin reduction is done by reducing the dose every day by 20%. If any of the drugs had been reduced already for other reasons compared to the previous block, do not reduce it further.
Platelets < 100 x 10^9/L	Delay chemotherapy until recovery
Platelet recovery delays therapy > 1 week	Delay until recovery. Restart chemotherapy with 20% reduction of Etoposide and 20% reduction of Carboplatin. The Etoposide reduction is done by deleting day 1 of the block and keeping the doses of day 2 to day 5 identical. The Carboplatin reduction is done by reducing the dose every day by 20%. If any of the drugs had been reduced already for other reasons compared to the previous block, do not reduce it further.
Platelet/Neutrophil recovery delays therapy > 3 weeks	Delay until recovery. Restart chemotherapy with a 40% reduction of Etoposide and 35% reduction in Carboplatin Delete Etoposide on day 1 and day 5 (40% reduction), reduce the dose of carboplatin by 35% each day and give Vincristine one day earlier (day 4 instead of day 5 at 100% of the dose).
Termination of treatment because of delay	

If treatment is delayed >3 weeks	If patient has had 3 or more courses of therapy, consider stopping chemotherapy. If the patient has had less than 3 courses of therapy, reduce the dose as above and discuss with the choroid plexus tumour special interest group.
After episode of significant nadir with complications	
Neutrophils < 0.05 x 10^9/L Multiple platelet transfusions required Significant febrile neutropenic episode with evidence of sepsis or other complication	Reduce Etoposide and Carboplatin by 20% on subsequent courses. The Etoposide reduction is done by deleting day 1 of the block and keeping the doses of day 2 to day 5 identical. The Carboplatin reduction is done by reducing the dose every day by 20%. If any of the drugs had been reduced already for other reasons compared to the previous block, do not reduce it further.

Nephrotoxicity

Serum creatinine > higher than 1.5 x normal upper limit prior to chemotherapy	Delay chemotherapy for 1 week and perform isotope GFR
Estimated GFR/Creatinine clearance should be within the normal range for age per 1.73 m^2: ● For children over the age of two years GFR should be > 80 ml/min/1.73 m² ● For children of 18-23 months of age inclusive GFR should be > 70 ml/min/1.73 m² ● For children of 12-17 months of age inclusive GFR should be > 65 ml/min/1.73 m² ● For children of 6-11 months of age inclusive GFR should be > 55 ml/min/1.73 m² ● For children of 0-5 months of age inclusive GFR should be > 40 ml/min/1.73 m².	Delay chemotherapy for 1 week and perform isotope GFR
If Isotope GFR: ● For children over the age of two years GFR > 60 and < 80 ml/min/1.73 m² ● For children of 18-23 months of age inclusive GFR > 60 and < 70 ml/min/1.73 m² ● For children of 12-17 months of age inclusive GFR > 55 and < 65 ml/min/1.73 m²	Reduce Carboplatin by 20% on subsequent courses. The Carboplatin reduction is done by reducing the dose every day by 20%. If any of the drugs had been reduced already for other reasons compared to the previous block, do not reduce it further.

	Perform estimation of GFR by clearance of radioisotope before the next course
If Isotope GFR: ● For children over the age of 18 months GFR < 60 ml/min/1.73 m² ● For children of 6-17 months of age inclusive GFR < 55 ml/min/1.73 m² ● For children of 0-5 months of age inclusive GFR < 40 ml/min/1.73 m².	Omit Carboplatin for the next course. Perform estimation of GFR by clearance of radioisotope before next course
If no recovery	Consider changing chemotherapy to cyclophosphamide-based chemotherapy and discuss with the choroid plexus special interest group

Neurotoxicity of vincristine

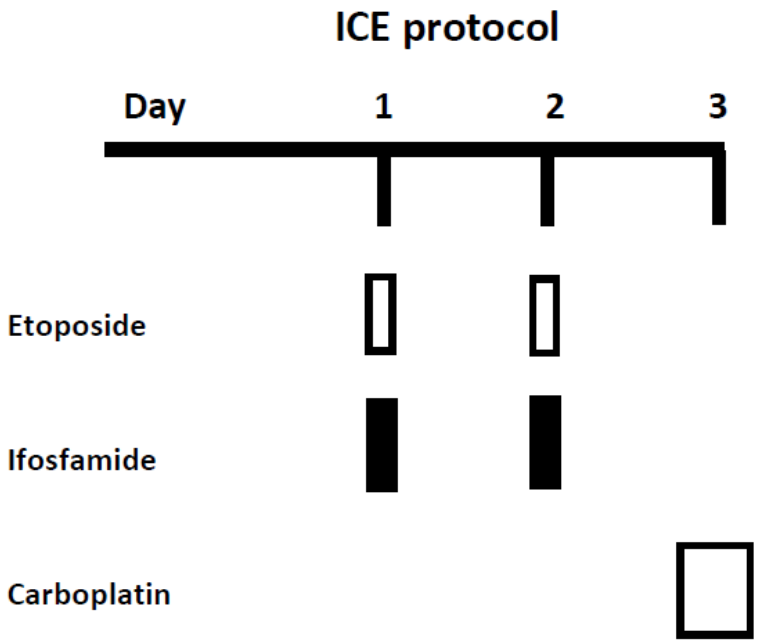
Epileptic seizure or ileus	Stop VCR until recovery
After recovery	Reduce VCR to 1 mg/m² or 66% of previous dose with the next course
In case of further seizures or ileus	Delete Vincristine from the chemotherapy
Significant dysaesthesia or muscular weakness	Omit VCR until recovery
After recovery	Give VCR at 50% doses and increase as tolerated in subsequent courses.
In case of further deterioration	Delete Vincristine from the chemotherapy

Ototoxicity

Grading for Audiometry is based on loss in both ears. Thus, the grading (including that for modification of chemotherapy) is based on the Highest Grading i.e. the “worst ear”.
Pure Tone Audiometry bilateral auditory evoked responses, or otoacoustic emission testing should be performed prior to chemotherapy, after every 2 courses of chemotherapy, at the end of treatment and if any clinical concerns. It should be performed either by air conduction, if necessary combined with a tympanogram to exclude problems with air conduction, or by bone conduction.

Hearing – PTA	Dose Modification
< 16 dB at 1000-3000 Hz or ≤ 40 dB at 4000-8000 Hz	None, Continue Carboplatin
16-30 dB at 1000-3000 Hz or > 40 dB at 4000-8000 Hz	50% dose of Carboplatin
> 30 dB at 1000-3000 Hz and >40 dB at 4000-8000 Hz	Omit Carboplatin and consider changing to cyclophosphamide-based chemotherapy on discussion with the choroid plexus special interest group

APPENDIX 2: ICE PROTOCOL



ICE chemotherapy cycle consists of:

- Etoposide (VP16) 5mg/kg/dose (150mg/m2/day ≥ 36 months) as 2-hour infusion on days 1-2
- Ifosfamide 100 mg/kg/dose (3000mg/m2/day ≥ 36 months) over 3-hour infusion on days 1-2
- Carboplatin 16.6 mg/kg (500mg/m2/day ≥ 36 months) over 2-hour infusion on day 3

Cycles will be repeated every 28 days. Details of the administration and dose modifications are provided below. Up to 6 cycles should be given.

Second look surgery should be considered at every disease evaluation. Irradiation, if planned, is ideally delayed and given after 5 or 6 cycles of chemotherapy +/- second look surgery. The exclusion of TP53 mutations is highly recommended and therefore irradiation should be delayed until this result is available, with continuation of chemotherapy. A six-week break post radiotherapy should be given before chemotherapy is re-started. A total of 6 courses of first line chemotherapy should be given. In metastatic disease, or in consideration of the age of the child, the timing of radiotherapy may be dependent on the ongoing chemotherapy response and might be considered earlier.

Consider the use of G-CSF if count recovery is delayed, as per institutional policy.

PJP prophylaxis is recommended, as per the institutional policy.

Administration Guidelines for ICE (Ifosfamide / Etoposide / Carboplatin)

Requirements before each course of chemotherapy:

- Neutrophils > 1.0 x 10^9 /L
- Platelets > 100 x 10^9 /L
- Creatinine < 1.5 ULN

Subsequent chemotherapy requires additional hydration. The use of a central catheter is recommended for chemotherapy administration. Care should be taken for young children and infants and therapeutic drug monitoring is recommended where available, especially in those less than 3 months of age.

Chemotherapy dose will be calculated in mg/kg for patients <36 months of age at start of each cycle. For patients with ≥36 months of age, chemotherapy dosage will be calculated in mg/m2.

All chemotherapy doses should be based upon actual weight and not modified in obese children to lean or ideal body mass

Dose reductions should be made for those less than 10kg..

Drug dilutions and hydration should be as per local policies.

DAY 1	T=0	Etoposide 5 mg/kg (150mg/m^2 IV ≥ 36 months) over 2 hours
	T= 4 hours	Ifosfamide 100 mg/kg (3000mg/m2 IV ≥ 36 months) over 2 hours*
DAY 2	T=0	Etoposide 5 mg/kg (150mg/m^2 IV ≥ 36 months) over 2hours
	T= 4 hours	Ifosfamide 100 mg/kg (3000mg/m^2 IV ≥ 36 months) over 2 hours*
DAY 3	T=0	Carboplatin 16.6 mg/kg (500mg/m^2 IV ≥ 36 months) over 2 hours (Target AUC of 5.0)

*Ifosfamide administration requires 3000 ml/m^2/d , 24 h-hydration (or per institutional preference) on days 1-3 and mesna administration

DAY 1 MESNA 33 mg/kg or 1000 mg/m^2 IV before ifosfamide administration with prehydration

MESNA 100 mg/kg/day or 3000 mg/m^2 IV in continuous infusion with concomitant hydration

DAY 2 MESNA 100 mg/kg/day or 3000 mg/m^2 IV in continuous infusion with concomitant hydration

DAY 3 MESNA 100 mg/kg/day or 3000 mg/m^2 IV in continuous infusion with concomitant hydration

Dose adjustments according to age and weight:

Patients less than 10 kg in weight:	Calculate dose per body weight in mg/kg

Patients less than 3 months of age:	Reduce dose calculated by kg by 33%
Patients less than 1 month of age:	Reduce dose calculated by kg by 50%. Please discuss with choroid plexus special interest group. It may be necessary to dose carboplatin based on pharmacokinetics done at Newcastle.
Patients younger than 2 weeks of age:	Do not start chemotherapy before 2 weeks of age

Haematological	
Before each course due:	
Neutrophils < 1.0 x 10^9/L at day 28	Delay chemotherapy until recovery Consider giving G-CSF to recover white blood cell count. Discontinue G-CSF 48 hours prior to restarting the chemotherapy. Give G-CSF after each of the following blocks, starting at day 9 after the start of chemotherapy
Neutrophil recovery delays therapy > 1 week	Delay until recovery. Restart chemotherapy with 15% reduction of Etoposide, Ifosfamide and Carboplatin. If any of the drugs had been reduced already for other reasons compared to the previous block, do not reduce it further.
Platelets < 100 x 10^9/L	Delay chemotherapy until recovery
Platelet recovery delays therapy > 1 week	Delay until recovery. Restart chemotherapy with 15% reduction of Etoposide, Ifosfamide and Carboplatin. If any of the drugs had been reduced already for other reasons compared to the previous block, do not reduce it further.
Platelet/Neutrophil recovery delays therapy > 3 weeks	Delay until recovery. Restart chemotherapy with a 35% reduction of Etoposide, Ifosfamide and Carboplatin
Termination of treatment because of delay	
If treatment is delayed >3 weeks	If patient has had 3 or more courses of therapy, consider stopping chemotherapy. If the patient has had less than 3 courses of therapy, reduce the dose as above and discuss with the choroid plexus tumour special interest group.
After episode of significant nadir with complications	

Neutrophils < 0.05 x 10^9/L Multiple platelet transfusions required Significant febrile neutropenic episode with evidence of sepsis or other complication	Reduce Etoposide, Ifosfamide and Carboplatin by 20% on subsequent courses. If any of the drugs had been reduced already for other reasons compared to the previous block, do not reduce it further.

Nephrotoxicity

Serum creatinine > higher than 1.5 x normal upper limit prior to chemotherapy	Delay chemotherapy for 1 week and perform isotope GFR
Estimated GFR/Creatinine clearance should be within the normal range for age per 1.73 m^2: • For children over the age of two years GFR should be > 80 ml/min/1.73 m² • For children of 18-23 months of age inclusive GFR should be > 70 ml/min/1.73 m² • For children of 12-17 months of age inclusive GFR should be > 65 ml/min/1.73 m² • For children of 6-11 months of age inclusive GFR should be > 55 ml/min/1.73 m² • For children of 0-5 months of age inclusive GFR should be > 40 ml/min/1.73 m².	Delay chemotherapy for 1 week and perform isotope GFR
If Isotope GFR: • For children over the age of two years GFR > 60 and < 80 ml/min/1.73 m² • For children of 18-23 months of age inclusive GFR > 60 and < 70 ml/min/1.73 m² • For children of 12-17 months of age inclusive GFR > 55 and < 65 ml/min/1.73 m²	Reduce Ifosfamide by 20% on subsequent courses. Consider therapeutic drug monitoring for Carboplatin dosing or calculate the dose using the modified Calvert formula. If any of the drugs had been reduced already for other reasons compared to the previous block, do not reduce it further. Perform estimation of GFR by clearance of radioisotope before the next course
If Isotope GFR: • For children over the age of 18 months GFR < 60 ml/min/1.73 m² • For children of 6-17 months of age inclusive GFR < 55 ml/min/1.73 m² • For children of 0-5 months of age inclusive GFR < 40 ml/min/1.73 m².	Consider changing chemotherapy and discuss with the choroid plexus special interest group
If no recovery	Consider changing chemotherapy and discuss with the choroid plexus special interest group

Neurotoxicity of ifosfamide (Ifosdfamide Induced Encephalopathy

Somnolence or agitation (grade I/II)	Follow-up, no dose reduction required
Sever somnolence, agitation, confusion, disorientation or hallucinations (grade III) Coma, seizures, toxic psychosis (grade IV)	Stop ifosfamide infusion, continue Mesna and hydration, methlythionium chloride (methylene blue)
After recovery	Consider prolonged ifosfamide infusion and prophylaxis with methylene blue
In case of further deterioration	Consider changing chemotherapy (CarbEV) and discuss with the choroid plexus special interest group

Ifosfamide induced hemorrhagic cystitis

Microscopic hematuria Macroscopic hematuria	Hydration, mesna. No ifosfamide dose reduction
Macroscopic hematuria with clots	Hyperhydration, increase mesna dose. Ifosfamide dose reduction not required if recovered
Macroscopic hematuria with clots and an elevated creatinine secondary to obstruction	Hyperhydration, forced duresis, increase mesna dose. Ifosfamide dose reduction not required if recovered
Repeated episodes/no recovery	Omit Ifosfamide and consider changing chemotherapy on discussion with the choroid plexus special interest group

Ototoxicity

Grading for Audiometry is based on loss in both ears. Thus the grading (including that for modification of chemotherapy) is based on the Highest Grading i.e. the “worst ear”.

Pure Tone Audiometry bilateral auditory evoked responses, or otoacoustic emission testing should be performed prior to chemotherapy, after every 2 courses of chemotherapy, at the end of treatment and if any clinical concerns. It should be performed either by air conduction, if necessary combined with a tympanogram to exclude problems with air conduction, or by bone conduction.

Hearing – PTA	Dose Modification
< 16 dB at 1000-3000 Hz or ≤ 40 dB at 4000-8000 Hz	None, Continue Carboplatin
16-30 dB at 1000-3000 Hz or > 40 dB at 4000-8000 Hz	50% dose of Carboplatin

> 30 dB at 1000-3000 Hz and >40 dB at 4000-8000 Hz	Omit Carboplatin and consider changing chemotherapy on discussion with the choroid plexus special interest group

APPENDIX 3: ADAPTED HEAD START II PROTOCOL

Head Start II chemotherapy consists of:

- 5 induction cycles given every 21-28 days:
  - Vincristine 0.05 mg/kg (max 2mg) as a slow injection on days 1, 8 and 15
  - Cisplatin 3.5 mg/kg as a 6 hour infusion on day 2
  - Cyclophosphamide 65 mg/kg as a one-hour infusion on day 2 and 3
  - Etoposide 4 mg/kg as a 2-hour infusion on day 2 and 3
  - Methotrexate 400mg/kg (max 20g) as a 4-hour infusion on day 4

- A single cycle of consolidation high-dose myeloablative chemotherapy with stem cell rescue given 21-28 days after the final cycle of induction chemotherapy:
  - Carboplatin
  - Etoposide
  - Thiotepa

Induction Cycles will be repeated every 21-28 days. HDC should be given 21-28 days after recovery from cycle 5 of induction chemotherapy. Details of the administration and dose modifications are provided below.

Second look surgery should be considered at every disease evaluation. Irradiation, if planned, is delayed until the treatment is completed. The exclusion of TP53 mutations is strongly recommended.

G-CSF should be administered following each cycle of chemotherapy as per the institutional policy. Please see the supportive care guidelines below.

Administration Details:

Induction chemotherapy:
The cycles should be given every 21-28 days.

Drug	Dose	Route	1	2	3	4	5	6	7	8	15
Vincristine *	0.05 mg/kg (max 2mg)	IV	●							●	●
Cisplatin	3.5 mg/kg	IVI 6hr	●								
Cyclophosphamide	65 mg/kg	IVI 1hr		●	●						
Etoposide	4 mg/kg	IVI 2hr		●	●						
Methotrexate	400mg/kg (max 20g)	IVI 4hr				●					

***Cycles 1-3: vincristine in cycles 1,2 and 3 (total of 9 doses of vincristine). Cycle 4 and 5: no vincristine**

If the serum MTX concentration is lower than the target level, as expected, folinic acid rescue should continue until MTX-serum concentration is ≤0.1µmol/l.

Hour	MTX-serum concentration in µmol/l	Folinic acid-rescue
24	< 10	15mg/m^2 IV q6 hourly
48	< 1	15mg/m^2 IV q6 hourly
72	≤ 0.1	Stop rescue and hydration

If the serum MTX concentration is not below the target levels as expected, folinic acid rescue should follow guidelines in Appendix 4.

Start Granulocyte colony stimulating factor (GCSF) 5 micrograms/kg/day IV/SC daily from day 5 until count recovery or pegylated GCSF 0.1mg/kg (maximum single dose 6mg) on day 5, as per the institutional practice.

Supportive Care during induction chemotherapy:

- Steroids for anti-emesis must be avoided (hydrocortisone replacement as required). This chemotherapy is a highly emetogenic treatment. Aggressive anti-emetics upfront are essential.
- Care should be taken for patients who develop febrile neutropenia while being treated with and rescued from HD MTX. Avoid drugs that may interact with methotrexate and nephrotoxic drugs according to local guidelines. Meropenem should be considered the antibiotic of choice in the management of febrile neutropenia during high dose methotrexate administration.
- Irradiated blood products as per institutional policy
- PJP prophylaxis as per local policy
- Fungal prophylaxis as per local policy
- Blood product support as per local policy

Investigations required before each phase/cycle:

	Diagnosis	Post-op	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Prior to HDC
Physical examination	X	X	X	X	X	X	X	X
Biochemistry, haematology *			X	X	X	X	X	X
GFR			X		X		X	X
CSF cytology*		X			X			X
MRI Head	X	X			X			X
MRI spine	X				X			X
Audiology			X	X	X	X	X	X
Stem cell collection		***						X
Echocardiogram								X
Pulmonary assessment								X

*Blood tests: renal function, bicarbonate, Ca, Mg, Phosphate, LFT, tubular resorption phosphate, FBC

** If CSF abnormal at diagnosis, repeat LP after alternate courses of chemotherapy and prior to high chemotherapy

*** consider stem cell collection prior to cycle 1 chemotherapy

Investigations prior to starting each cycle of induction chemotherapy:

Physical	Clinically well **No evidence of active infection**
Haematology	ANC > 1 x 10^9/L and WBC > 2 x 10^9/L Platelets > 100 x 10^9/L (unsupported)
Biochemistry	Normal renal function GFR/eGFR >80 ml/min/1.73 m^2 Transaminases <1.5 x upper limit normal Bilirubin < 30 µmol/L
Audiogram	<16–30 dB at 1,000–3,000Hz and/or <40 dB at 4,000–8,000Hz

Administration of induction chemotherapy:

Hydration and Mannitol may be altered as per local policy.

Day	Lumen 1	Lumen 2	Notes
Day 1 T=0hr		Glucose 2.5% Sodium Chloride 0.45% containing 20mmol Potassium/L at 200ml/m2/hr for 3 hours	
Day 1 T=3hr	**Vincristine** 0.05mg/kg (max 2mg) IV Slow Bolus **Cisplatin** 3.5mg/kg IV Infusion in Sodium Chloride 0.9% for 6 hours	Glucose 2.5% Sodium Chloride 0.45% containing Potassium Chloride 20mmol/L and 60mL/L Mannitol 20% for 6 hours **Total hydration rate including cisplatin: 125ml/m^2/hr**	**No vincristine in cycles 4 and 5** Diuresis: If at any time the urine output falls below 3 ml/kg/hr for 2 hours give Mannitol 0.5g/kg (2.5ml/kg mannitol 20%) over 15-30 minutes. Avoid Furosemide.
Day 1 T=9hr		Glucose 2.5% Sodium Chloride 0.45% containing Potassium Chloride 20mmol/L and 60mL/L Mannitol 20% for 6 hours at **125**ml/m^2/hr	
Day 1 T=15hr		Glucose 2.5% Sodium Chloride 0.45% containing Potassium Chloride 20mmol/L, Magnesium Sulphate 10mmol/L, Calcium Chloride 0.6mmol/L for 12 hours at **125**ml/m^2/hr	
Day 2 T=3hr	**Etoposide** 4mg/kg IV Infusion in Sodium Chloride 0.9% for 2 hours	Glucose 2.5% Sodium Chloride 0.45% containing Potassium Chloride 20mmol/L and 78mg/kg Mesna for 24 hours at 125ml/m^2/hr	*****Monitor fluid balance. Reduce rate of infusion so hydration rate plus drugs provides at least 125ml/m^2/hr*** ***Dipstick urine for signs haematuria***
Day 2 T=5hr	**Cyclophosphamide** 65mg/kg IV Infusion in Sodium Chloride 0.9% for 1 hour		
Day 3 T=3hr	**Etoposide** 4mg/kg IV Infusion in Sodium Chloride 0.9% for 2 hours	Glucose 2.5% Sodium Chloride 0.45% containing Potassium Chloride 20mmol/L and 78mg/kg Mesna for 24 hours at 125ml/m^2/hr	
Day 3 T=5hr	**Cyclophosphamide** 65mg/kg IV Infusion in Sodium Chloride 0.9% for 1 hour		
Day 4 T=3hr		Glucose 2.5%/Sodium chloride 0.45% containing Potassium Chloride 20mmol/litre and Sodium Bicarbonate 50mmol/litre at 125ml/m^2/hr	
Day 4 T=7hr*	**High Dose Methotrexate** 400mg/kg IV Infusion in Sodium Chloride 0.9% for 4 hours	**Continue hydration until Folinic acid rescue complete**	*See Appendix D for requirements to start MTX infusion.

Day 5		**Folinic acid** 15mg/m^2 IV 6 hourly starting 24 hours after the start of the IV methotrexate infusion	See Folinic acid Rescue for further details – Appendix D.
Day 5	**Start GCSF 5 micrograms/kg/day IV/SC**		
Day 8	**Vincristine** 0.05mg/kg (max 2mg) IV Slow Bolus		**No vincristine in cycles 4 and 5**
Day 15	**Vincristine** 0.05mg/kg (max 2mg) IV Slow Bolus		

Dose modification for toxicity during induction chemotherapy:

Haematological	
Before each course due:	
Neutrophils < 1.0 x 10^9/L WBC < 2 x 10^9/L Platelets < 100 x 10^9/L	Delay chemotherapy until recovery No dose modifications in subsequent cycles made for infections or delayed recovery. GCSF support recommended.
Nephrotoxicity	
Serum creatinine > higher than 1.5 x normal upper limit prior to chemotherapy	Delay chemotherapy for 1 week and perform isotope GFR
Estimated GFR/Creatinine clearance should be within the normal range for age per 1.73 m^2: • For children over the age of two years GFR should be > 80 ml/min/1.73 m² • For children of 18-23 months of age inclusive GFR should be > 70 ml/min/1.73 m² • For children of 12-17 months of age inclusive GFR should be > 65 ml/min/1.73 m² • For children of 6-11 months of age inclusive GFR should be > 55 ml/min/1.73 m² • For children of 0-5 months of age inclusive GFR should be > 40 ml/min/1.73 m².	Delay chemotherapy for 1 week and perform isotope GFR
If Isotope GFR: • For children over the age of two years GFR > 60 and < 80 ml/min/1.73 m² • For children of 18-23 months of age inclusive GFR > 60 and < 70 ml/min/1.73 m² • For children of 12-17 months of age inclusive GFR > 55 and < 65 ml/min/1.73 m²	Replace cisplatin with carboplatin 12mg/kg Perform estimation of GFR by clearance of radioisotope before the next course

If Isotope GFR: • For children over the age of 18 months GFR < 60 ml/min/1.73 m² • For children of 6-17 months of age inclusive GFR < 55 ml/min/1.73 m² • For children of 0-5 months of age inclusive GFR < 40 ml/min/1.73 m².	Omit all platinum chemotherapy Consider 25% dose reduction of etoposide and cyclophosphamide

Ototoxicity

Grading for Audiometry is based on loss in both ears. Thus the grading (including that for modification of chemotherapy) is based on the Highest Grading i.e. the "worst ear".

Pure Tone Audiometry bilateral auditory evoked responses, or otoacoustic emission testing should be performed prior to chemotherapy, after every 2 courses of chemotherapy, at the end of treatment and if any clinical concerns. It should be performed either by air conduction, if necessary combined with a tympanogram to exclude problems with air conduction, or by bone conduction.

Hearing – PTA	Dose Modification
< 16 dB at 1000-3000 Hz or ≤ 40 dB at 4000-8000 Hz	None, Continue Carboplatin
16-30 dB at 1000-3000 Hz or > 40 dB at 4000-8000 Hz	Replace cisplatin with carboplatin 12mg/kg
> 30 dB at 1000-3000 Hz and >40 dB at 4000-8000 Hz	Withhold platinums

Neurotoxicity of vincristine

Epileptic seizure or ileus	Stop VCR until recovery
After recovery	Reduce VCR to 0.03mg/kg with the next course. If seizures do not recur, then escalate to full dosage
In case of further seizures or ileus	Delete Vincristine from the chemotherapy
Significant dysaesthesia or muscular weakness	Omit VCR until recovery
After recovery	Reduce VCR to 0.03mg/kg with the next course. Increase as tolerated in subsequent courses.
In case of further deterioration	Delete Vincristine from the chemotherapy
Jaw pain	Treat with analgesics; do not modify vincristine dose.
Constipation (in absence of ileus)	Follow local policy to treat constipation but continue vincristine

Liver Toxicity

Vincristine induced Hyperbilirubinaemia	Assess LFTs only if patient is jaundiced. Bilirubin >50mmol: hold next dose vincristine Bilirubin 25 – 49mmol/l: administer Vincristine 0.03mg/kg, escalate to full dose if bilirubin falls below 25mmol/l

Probable MTX induced i.e. up to 3 weeks after MTX	It is expected that patients receiving high dose Methotrexate will develop hypertransaminasemia and occasionally hyperbilirubinemia. These elevations can last up to two weeks following the methotrexate infusion and will not be considered toxicity requiring discontinuation of the drug
Post – methotrexate: ALT > 20 x ULN for > 2 weeks **Bilirubin > 1.25 x ULN > 3 weeks**	Consider additional aetiology. Discuss with national advisory group
Not MTX induced	Delay one week. Give if ALT < 10 x ULN and normal bilirubin

Autologous stem cell collection:

This should be undertaken as per the local guidance for stem cell collection in accordance with national regulations. Peripheral stem cells collection should be considered during steady-state, harvesting prior to commencing chemotherapy or following the first or second cycle of chemotherapy. Delay of chemotherapy should be avoided. Use G-CSF 10 micrograms/kg/day subcutaneously to prime bone marrow for stem cell collection or according to institutional guidelines. Irradiated blood products as per institutional policy. Target >6 x 10^6 CD34+ cells/kg should be collected and stored in at least 2 aliquots (3x10^6 CD34+ cells/kg) as per local policy.

High dose chemotherapy (HDC) with autologous stem cell rescue (ASCR):

Treatment outline:

Following completion of induction chemotherapy, if there is radiographic evidence of residual tumour on disease evaluation second-look surgery (SLS) should be considered. A second opinion from national neurosurgical leads should be sought. Post-SLS, or if SLS is not deemed safe/possible, the patient should proceed to consolidation myeloablative chemotherapy. These patients should be discussed with the national advisory group regarding possible irradiation following recovery from consolidation chemotherapy.

High-dose chemotherapy should start 3-4 weeks after the last course of intensive induction chemotherapy if there is no evidence of progressive disease.

Timeline for HDC and ASCR:

	Route	-8	-7	-6	-5	-4	-3	-2	-1	0	1	2	3	4	5
Hydration	**IV**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**				
Carboplatin	**IV**	**X**	**X**	**X**											
Etoposide	**IV**				**X**	**X**	**X**								
Thiotepa	**IV**				**X**	**X**	**X**								
Stem cells	**IV**									**X**					
GCSF	**sc/IV**														**X**

Investigations before the course of High Dose Chemotherapy (HDC):

Physical examination	Clinically well Dental assessment
Tumour assessment	No evidence of progressive disease on MRI and CSF cytological assessment
Cardiology assessment	Normal echocardiogram FS >29% No evidence of pulmonary hypertension
Respiratory assessment	Normal chest x-ray and oxygen saturations Lung functions, if old enough and possible
Haematology	ANC > 0.8 x 10^9/L and unsupported platelet count > 80 x 10^9/L
Liver assessment	Normal liver function defined as < 1.5 x upper limit of normal and bilirubin < 30 µmol/L
Renal assessment	GFR >60 ml/min/1.73m^2 No significant tubulopathy
Audiology	If significant deafness, consider discussion with Embryonal Tumour Group
Concomitant medications	Review concomitant nephrotoxic drugs

Administration of High Dose Chemotherapy:

Day/Time	**Drug**
Day -8 T = -3 hrs	**Hydration** 125ml/m^2/hr for 3 hours Sodium chloride 0.9% or as per local practice Continue hydration until at least 24 hours post-stem cell infusion (or as per local policy)
Day -8 T = 0 hrs	**Carboplatin (see dose below)**
Day -7 T = 0 hrs	**Carboplatin**
Day -6 T = 0 hrs	**Carboplatin**
Day -5 T = 0 hrs	**Thiotepa (see dose below)**
Day -5 T = 3 hrs	**Etoposide (see dose below)**
Day -4 T = 0 hrs	**Thiotepa**

Day -4 T = 3 hrs	**Etoposide**
Day -3 T = 0 hrs	**Thiotepa**
Day -3 T = 3 hrs	**Etoposide**
Day 0	Autologous **stem cells** Infuse as per local policy
Day +5	GCSF 5mcg/kg/day SC/IV as per local policy until neutrophils greater than $1x10^9$/L for 2 consecutive days or as per institutional policy

Drug	**Dose**	**Administration**
Carboplatin	AUC 7 mg/ml/min using Newell or Calvert formulae (as per local policy) or 16.6 mg/kg. See appendix E. **Use lower of the calculated doses and maximum dose of 500 mg/m² or 16.6 mg/kg**	IV infusion over 4 hours on Day -8 to Day -6
Thiotepa	300 mg/m² or 10 mg/kg Use lower of the two calculated doses	IV infusion over 3 hours on Day -5 to Day -3
Etoposide	250 mg/m² or 8.3 mg/kg Use lower of the two calculated doses	IV infusion over 4 hours on Day -5 to Day -3

Dose modification of high dose chemotherapy conditioning for toxicity:

Haematological	
Before HDC:	
Neutrophils < 0.8 x 10^9/L Platelets < 80 x 10^9/L	Delay chemotherapy until recovery
Nephrotoxicity	Isotope GFR should be performed prior to HDC as per institutional policy
Serum creatinine > higher than 1.5 x normal upper limit prior to chemotherapy	Delay chemotherapy for 1 week and perform isotope GFR
Estimated GFR/Creatinine clearance should be within the normal range for age per 1.73 m²: • For children over the age of two years GFR should be > 80 ml/min/1.73 m² • For children of 18-23 months of age inclusive GFR should be > 70 ml/min/1.73 m²	Delay chemotherapy for 1 week and perform isotope GFR

• For children of 12-17 months of age inclusive GFR should be > 65 ml/min/1.73 m² • For children of 6-11 months of age inclusive GFR should be > 55 ml/min/1.73 m² • For children of 0-5 months of age inclusive GFR should be > 40 ml/min/1.73 m².	
If Isotope GFR: • For children over the age of two years GFR > 60 and < 80 ml/min/1.73 m² • For children of 18-23 months of age inclusive GFR > 60 and < 70 ml/min/1.73 m² • For children of 12-17 months of age inclusive GFR > 55 and < 65 ml/min/1.73 m²	Delay for 1 week and re-check. Discuss national advisory group and consider reducing Carboplatin to AUC 5.3mg/ml/min IV over 4 hours
If Isotope GFR: • For children over the age of 18 months GFR < 60 ml/min/1.73 m² • For children of 6-17 months of age inclusive GFR < 55 ml/min/1.73 m² • For children of 0-5 months of age inclusive GFR < 40 ml/min/1.73 m².	Discuss with national advisory group and consider

Ototoxicity

Grading for Audiometry is based on loss in both ears. Thus the grading (including that for modification of chemotherapy) is based on the Highest Grading i.e. the “worst ear”.

Pure Tone Audiometry bilateral auditory evoked responses, or otoacoustic emission testing should be performed prior to chemotherapy, after every 2 courses of chemotherapy, at the end of treatment and if any clinical concerns. It should be performed either by air conduction, if necessary combined with a tympanogram to exclude problems with air conduction, or by bone conduction.

Hearing – PTA	Dose Modification
< 16 dB at 1000-3000 Hz or ≤ 40 dB at 4000-8000 Hz	None, Continue Carboplatin
16-30 dB at 1000-3000 Hz or > 40 dB at 4000-8000 Hz	Discuss with national advisory group and consider reducing Carboplatin to AUC 5.3mg/ml/min IV over 4 hours
> 30 dB at 1000-3000 Hz and >40 dB at 4000-8000 Hz	Withhold platinums
Liver Toxicity	
Transaminases > 1.5xULN	Delay chemotherapy until recovery
Bilirubin > 1.5x ULN	Delay chemotherapy until recovery

Supportive care for High Chemotherapy and autologous stem cell rescue:

- Patients must not receive corticosteroids concomitant with chemotherapy administration for the sole purpose of anti-emesis.
- Review concomitant nephrotoxic medications during conditioning.
- Co-trimoxazole as per local policy.
- Use irradiated blood products as per local policy.
- Antifungal prophylaxis as per local policy.
- Antiviral prophylaxis as per local policy.
- Skin care as per local policy for thiotepa.

APPENDIX 4: MANAGEMENT OF HIGH DOSE METHOTREXATE AND FOLINIC ACID RESCUE

Please note:

- Creatinine clearance must be greater than 60ml/min/1.73m^2.
- The dose of high-dose methotrexate is 400mg/kg
- Prehydrate with 125 ml/m^2/hr for a minimum of 4 hours in order to achieve a pH >7 and a urine output > 100 ml/m^2/hr
- Methotrexate is administered over 4 hours
- Methotrexate levels must be measured at 24, 48, 72 hours until MTX <0.1µmol/l

Folinic acid rescue:

- Folinic acid rescue starts at 24 hours after the infusion commenced and continues IV 6 hourly until methotrexate <0.1µmol/l (or the lowest concentration which can be measured locally)*. The dose of folinic acid must be increased if the patient has a toxic methotrexate level as outlined in the table below.
- The upper limits of serum methotrexate:
  - 24 hours is 10µmol/L
  - 48 hours is 1µmol/L
  - 72 hours is 0.1µmol/L

Time from start of MTX	Serum Creatinine Measurement	MTX level measurement	MTX concentration expected	Folinic acid dose	Comments
24 hours	Yes	Yes	<10 µmol/L	15mg/m^2 IV	
48 hours	Yes	Yes	≤ 1µmol/L	15mg/m^2 IV	
72 hours	Yes	Yes	≤ 0.1 µmol/L	15mg/m^2 IV	

Guidelines for adjustment of folinic acid dose during delayed methotrexate excretion:

$$\text{Total daily dose of leucovorin (mg)} = \frac{\text{Patient's actual serum MTX} \times \text{standard daily dose of folinic acid (mg)}^*}{\text{Upper limit of serum MTX for the actual day and time}}$$

*Standard daily dose is 60mg/m^2/day at 6 hourly doses

Example: If the 48 hours methotrexate level was 40µmol/l, the folinic acid dose should be adjusted to:
Total daily dose = 60 mg/m^2 × 40µmol/l /1µmol/l = 2400mg/m^2 /24 hours** of folinic acid (mg)

** Give higher doses of folinic acid q 3 hours

If symptoms suggest excretion problem during infusion:
Assess renal function 12 hours after start of methotrexate infusion, if rise in creatinine > 25% review fluid balance.
Repeat renal function at 24 hr

HYDRATION WHEN CREATININE RISES ABOVE THE BASELINE
If, at 24 hours, the creatinine rises above the baseline but is less than 125% of the baseline level continue fluids at a rate of 125mL/m^2/hr. Keep urinary pH >7. Estimate urine output 4 hourly, and furosemide can be used to aid diuresis.

If, at 24 hours, the creatinine rises to 125% of the baseline level or above, then increase fluids to a rate of 200mL/m^2/hr. Keep urinary pH >7. Estimate urine output 4 hourly, and furosemide can be used to aid diuresis. If urine output is less than 80% of fluid intake, (despite use of furosemide) consider Glucarpidase.

Renal disruption of the MTX clearance:

Methotrexate-induced renal dysfunction with prolonged methotrexate clearance is a medical emergency. Disruption of the methotrexate clearance may occur, if after the first day of MTX therapy:

- The urine pH drops < 6.0: give sodium bicarbonate (1 mmol/kg) over short infusion over 30-60 min.
- The creatinine (serum) rises > 25% of the base level
- Despite therapy with furosemide, diuresis is dropping
- MTX level is above the target level

The alkaline diuresis will be forced by elevating the input to 4500 ml/m²/24 h and continuing alkalinisation (urine pH ≥ 7.0) and tight fluid equilibration.

Caution: Folinic acid doses > 20 mg/kg/dose should be given as a 1 hr infusion, because of saturable enteral resorption. Due to the content of Calcium, repeated measurements of serum Calcium levels are necessary

Glucarpidase could be considered when:

- Serum creatinine rise >100% within 24 hrs of MTX administration
- Delayed excretion when plasma MTX levels plateau

APPENDIX 5: RENAL DOSING OF CARBOPLATIN FOR HIGH DOSE CHEMOTHERAPY

The carboplatin target AUC is 7mg/ml.min per dose x 3 days (total AUC 21 mg/ml.min). It is recommended to dose Carboplatin for D3 based on the patients Carboplatin pharmacokinetics on D1 where possible.

Calvert formula:

Carboplatin dose (mg) = Target AUC x (uncorrected GFR {ml/min} + [0.36 x weight (kg)])

Newell formula and dosing charts for:

- **Carboplatin AUC: 7mg/ml.min and**
- **Carboplatin AUC: 5.3mg/ml.min**

The tables in the following pages provide the dose of carboplatin in milligrams (mg) to be administered during high dose chemotherapy and autologous stem cell rescue. The dose is calculated using the patient 's weight in kg and the t1/2 (mins) of the EDTA GFR using the following formula:

Carboplatin dose (mg) =

AUC (mg/ml.min) x {[0.693 / t ½ (min)] x [0.52 x (843 x body weight (kg)$^{0.891}$)] + (0.36 x body weight (kg))

Newell Chart A: Carboplatin AUC 7mg/ml.min Weight: 0.5-31kg EDTA t½ (30-115)

	Half life EDTA (min)																	
Body Wt (kg)	**30**	**35**	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**	**85**	**90**	**95**	**100**	**105**	**110**	**115**
0.5	39	34	30	27	24	22	20	19	18	17	16	15	14	13	13	12	12	11
1	73	63	56	50	45	41	38	35	33	31	29	28	26	25	24	23	22	21
1.5	106	91	80	72	65	59	55	51	47	44	42	40	38	36	34	33	32	30
2	136	118	104	93	84	77	71	66	61	58	54	51	49	47	44	43	41	39
2.5	167	144	127	113	103	94	86	80	75	70	66	63	60	57	54	52	50	48
3	196	169	149	133	121	110	102	95	88	83	78	74	70	67	64	61	59	57
3.5	225	194	171	153	139	127	117	109	102	95	90	85	81	77	74	71	68	65
4	254	219	193	173	156	143	132	123	115	108	101	96	91	87	83	80	77	74
4.5	282	243	214	192	174	159	147	136	127	120	113	107	102	97	93	89	85	82
5	310	268	236	211	191	175	161	150	140	132	124	118	112	107	102	98	94	90
5.5	338	291	257	230	208	190	176	163	153	143	135	128	122	116	111	106	102	98
6	365	315	278	248	225	206	190	177	165	155	146	139	132	126	120	115	111	106
6.5	392	338	298	267	242	221	204	190	177	167	157	149	142	135	129	124	119	114
7	419	362	319	285	258	237	218	203	190	178	168	159	151	144	138	132	127	122
7.5	446	385	339	303	275	252	232	216	202	190	179	170	161	154	147	141	135	130
8	472	408	359	322	291	267	246	229	214	201	190	180	171	163	156	149	143	138
8.5	499	430	379	340	308	282	260	242	226	212	200	190	180	172	165	158	152	146
9	525	453	399	357	324	297	274	254	238	224	211	200	190	181	173	166	160	154
9.5	551	476	419	375	340	311	287	267	250	235	222	210	200	190	182	174	168	161
10	577	498	439	393	356	326	301	280	262	246	232	220	209	199	191	183	176	169
11	628	542	478	428	388	355	328	305	285	268	253	240	228	217	208	199	191	184
12	679	586	517	463	420	384	355	330	308	290	274	259	246	235	225	216	207	199
13	729	630	555	497	451	413	381	354	331	311	294	279	265	253	242	232	223	215
14	780	673	593	531	482	441	407	379	354	333	314	298	283	270	259	248	238	229
15	829	716	631	565	513	470	434	403	377	354	335	317	302	288	275	264	254	244
16	879	759	669	599	543	498	459	427	400	376	355	336	320	305	292	280	269	259
17	928	801	706	633	574	525	485	451	422	397	375	355	338	322	308	296	284	274
18	976	843	744	666	604	553	511	475	444	418	395	374	356	339	325	311	299	288
19	1025	885	781	699	634	581	536	499	467	439	414	393	374	356	341	327	314	303
20	1073	927	817	732	664	608	562	522	489	459	434	411	391	373	357	343	329	317
21	1121	968	854	765	694	636	587	546	511	480	453	430	409	390	373	358	344	332
22	1169	1010	890	798	723	663	612	569	533	501	473	448	427	407	389	374	359	346
23	1216	1051	927	830	753	690	637	593	554	521	492	467	444	424	405	389	374	360
24	1264	1092	963	863	782	717	662	616	576	542	512	485	462	440	421	404	389	374
25	1311	1132	999	895	812	744	687	639	598	562	531	503	479	457	437	419	403	388
26	1358	1173	1035	927	841	770	712	662	619	582	550	522	496	474	453	435	418	403
27	1404	1213	1070	959	870	797	736	685	641	603	569	540	513	490	469	450	432	417
28	1451	1254	1106	991	899	823	761	708	662	623	588	558	531	506	485	465	447	431
29	1497	1294	1141	1022	928	850	785	730	683	643	607	576	548	523	500	480	461	445
30	1543	1334	1176	1054	956	876	809	753	705	663	626	594	565	539	516	495	476	458
31	1589	1374	1212	1086	985	902	834	776	726	683	645	612	582	555	532	510	490	472

Newell Chart B: Carboplatin AUC 7mg/ml.min Weight: 32-70kg EDTA t½ (30-115)

	Half life EDTA (min)																	
Body Wt (kg)	**30**	**35**	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**	**85**	**90**	**95**	**100**	**105**	**110**	**115**
32	1635	1413	1247	1117	1013	929	858	798	747	702	664	629	599	572	547	525	505	486
33	1681	1453	1282	1148	1042	955	882	821	768	722	682	647	616	588	563	540	519	500
34	1727	1492	1316	1180	1070	981	906	843	789	742	701	665	633	604	578	555	533	514
35	1772	1532	1351	1211	1099	1007	930	865	810	762	720	683	649	620	593	569	547	527
36	1817	1571	1386	1242	1127	1033	954	888	831	781	738	700	666	636	609	584	562	541
37	1863	1610	1420	1273	1155	1058	978	910	852	801	757	718	683	652	624	599	576	555
38	1908	1649	1455	1304	1183	1084	1002	932	872	821	775	735	700	668	639	613	590	568
39	1953	1688	1489	1334	1211	1110	1025	954	893	840	794	753	716	684	655	628	604	582
40	1997	1726	1523	1365	1239	1135	1049	976	914	859	812	770	733	700	670	643	618	596
41	2042	1765	1557	1396	1267	1161	1073	998	934	879	830	788	750	716	685	657	632	609
42	2087	1804	1591	1426	1294	1186	1096	1020	955	898	849	805	766	731	700	672	646	623
43	2131	1842	1625	1457	1322	1212	1120	1042	975	917	867	822	783	747	715	686	660	636
44	2176	1881	1659	1487	1350	1237	1143	1064	996	937	885	840	799	763	730	701	674	649
45	2220	1919	1693	1518	1377	1262	1167	1086	1016	956	903	857	816	779	745	715	688	663
46	2264	1957	1727	1548	1405	1288	1190	1107	1037	975	921	874	832	794	760	730	702	676
47	2308	1995	1761	1578	1432	1313	1213	1129	1057	994	940	891	848	810	775	744	716	690
48	2352	2033	1794	1608	1460	1338	1237	1151	1077	1013	958	908	865	826	790	758	729	703
49	2396	2071	1828	1638	1487	1363	1260	1172	1097	1032	976	926	881	841	805	773	743	716
50	2440	2109	1861	1669	1514	1388	1283	1194	1118	1052	994	943	897	857	820	787	757	730
51	2483	2147	1895	1699	1542	1413	1306	1215	1138	1071	1012	960	914	872	835	801	771	743
52	2527	2185	1928	1728	1569	1438	1329	1237	1158	1089	1030	977	930	888	850	816	785	756
53	2571	2222	1961	1758	1596	1463	1352	1258	1178	1108	1047	994	946	903	865	830	798	769
54	2614	2260	1995	1788	1623	1488	1375	1280	1198	1127	1065	1011	962	919	879	844	812	783
55	2657	2298	2028	1818	1650	1513	1398	1301	1218	1146	1083	1028	978	934	894	858	826	796
56	2701	2335	2061	1848	1677	1537	1421	1322	1238	1165	1101	1045	994	949	909	872	839	809
57	2744	2372	2094	1877	1704	1562	1444	1344	1258	1184	1119	1061	1010	965	924	887	853	822
58	2787	2410	2127	1907	1731	1587	1467	1365	1278	1203	1137	1078	1026	980	938	901	866	835
59	2830	2447	2160	1936	1758	1611	1489	1386	1298	1221	1154	1095	1042	995	953	915	880	848
60	2873	2484	2193	1966	1784	1636	1512	1407	1318	1240	1172	1112	1059	1011	968	929	894	861
61	2916	2521	2225	1995	1811	1660	1535	1429	1338	1259	1190	1129	1074	1026	982	943	907	874
62	2959	2558	2258	2025	1838	1685	1558	1450	1357	1277	1207	1145	1090	1041	997	957	921	887
63	3002	2595	2291	2054	1864	1709	1580	1471	1377	1296	1225	1162	1106	1057	1012	971	934	900
64	3044	2632	2324	2083	1891	1734	1603	1492	1397	1314	1242	1179	1122	1072	1026	985	948	913
65	3087	2669	2356	2113	1918	1758	1625	1513	1417	1333	1260	1195	1138	1087	1041	999	961	926
66	3129	2706	2389	2142	1944	1783	1648	1534	1436	1352	1278	1212	1154	1102	1055	1013	974	939
67	3172	2743	2421	2171	1971	1807	1670	1555	1456	1370	1295	1229	1170	1117	1070	1027	988	952
68	3214	2780	2454	2200	1997	1831	1693	1576	1476	1389	1312	1245	1186	1132	1084	1041	1001	965
69	3257	2816	2486	2229	2024	1855	1715	1597	1495	1407	1330	1262	1202	1147	1099	1055	1015	978
70	3299	2853	2518	2258	2050	1880	1738	1618	1515	1425	1347	1279	1217	1162	1113	1069	1028	991

Newell Chart C: Carboplatin AUC 7mg/ml.min Weight: 0.5-31kg EDTA t½ (130 -200

	Half life EDTA (min)																
Body Wt (kg)	**120**	**125**	**130**	**135**	**140**	**145**	**150**	**155**	**160**	**165**	**170**	**175**	**180**	**185**	**190**	**195**	**200**
0.5	11	10	10	10	9	9	9	9	8	8	8	8	8	7	7	7	7
1	20	20	19	18	18	17	17	16	16	15	15	15	14	14	14	13	13
1.5	29	28	27	26	26	25	24	23	23	22	22	21	21	20	20	19	19
2	38	37	35	34	33	32	31	30	30	29	28	28	27	26	26	25	25
2.5	46	45	43	42	41	39	38	37	36	35	35	34	33	32	32	31	30
3	55	53	51	49	48	47	45	44	43	42	41	40	39	38	37	37	36
3.5	63	61	59	57	55	54	52	51	49	48	47	46	45	44	43	42	41
4	71	69	66	64	62	61	59	57	56	54	53	52	51	50	49	48	47
4.5	79	76	74	72	69	67	65	64	62	61	59	58	56	55	54	53	52
5	87	84	81	79	76	74	72	70	68	67	65	64	62	61	60	58	57
5.5	95	92	89	86	83	81	79	77	75	73	71	69	68	66	65	64	62
6	103	99	96	93	90	88	85	83	81	79	77	75	73	72	70	69	68
6.5	110	107	103	100	97	94	92	89	87	85	83	81	79	77	76	74	73
7	118	114	110	107	104	101	98	95	93	91	88	86	85	83	81	79	78
7.5	126	121	117	114	110	107	104	102	99	96	94	92	90	88	86	85	83
8	133	129	124	121	117	114	111	108	105	102	100	98	96	93	92	90	88
8.5	141	136	132	127	124	120	117	114	111	108	106	103	101	99	97	95	93
9	148	143	139	134	130	127	123	120	117	114	111	109	106	104	102	100	98
9.5	156	150	146	141	137	133	129	126	123	120	117	114	112	109	107	105	103
10	163	158	152	148	143	139	135	132	129	125	123	120	117	115	112	110	108
11	178	172	166	161	156	152	148	144	140	137	134	131	128	125	123	120	118
12	192	186	180	174	169	164	160	156	152	148	145	141	138	135	133	130	128
13	207	200	194	188	182	177	172	168	163	159	156	152	149	146	143	140	137
14	221	214	207	201	195	189	184	179	175	171	167	163	159	156	153	150	147
15	236	228	220	214	207	202	196	191	186	182	177	173	170	166	163	160	157
16	250	242	234	227	220	214	208	203	198	193	188	184	180	176	173	169	166
17	264	255	247	239	232	226	220	214	209	204	199	195	190	186	183	179	176
18	278	269	260	252	245	238	232	226	220	215	210	205	201	196	192	189	185
19	292	282	273	265	257	250	243	237	231	226	220	215	211	206	202	198	194
20	306	296	286	278	270	262	255	248	242	236	231	226	221	216	212	208	204
21	320	309	299	290	282	274	267	260	253	247	241	236	231	226	222	217	213
22	334	323	312	303	294	286	278	271	264	258	252	246	241	236	231	227	222
23	348	336	325	315	306	298	290	282	275	269	262	257	251	246	241	236	232
24	361	349	338	328	318	309	301	293	286	279	273	267	261	256	250	246	241
25	375	362	351	340	330	321	313	304	297	290	283	277	271	265	260	255	250
26	389	376	364	353	342	333	324	316	308	300	294	287	281	275	270	264	259
27	402	389	376	365	354	345	335	327	319	311	304	297	291	285	279	274	268
28	416	402	389	377	366	356	347	338	329	322	314	307	301	294	288	283	278
29	429	415	402	390	378	368	358	349	340	332	324	317	310	304	298	292	287
30	443	428	414	402	390	379	369	360	351	342	335	327	320	314	307	301	296
31	456	441	427	414	402	391	380	371	361	353	345	337	330	323	317	311	305

Newell Chart D: Carboplatin AUC 7mg/ml.min. Weight: 32-70kg EDTA t½ (120-200)

	Half life EDTA (min)																
Body Wt (kg)	**120**	**125**	**130**	**135**	**140**	**145**	**150**	**155**	**160**	**165**	**170**	**175**	**180**	**185**	**190**	**195**	**200**
32	469	454	439	426	414	402	392	382	372	363	355	347	340	333	326	320	314
33	483	467	452	438	426	414	403	392	383	374	365	357	349	342	335	329	323
34	496	480	464	450	437	425	414	403	393	384	375	367	359	352	345	338	332
35	509	492	477	462	449	437	425	414	404	394	385	377	369	361	354	347	341
36	522	505	489	474	461	448	436	425	414	405	395	387	378	371	363	356	350
37	536	518	502	486	472	459	447	436	425	415	405	397	388	380	373	365	359
38	549	531	514	498	484	471	458	446	435	425	416	406	398	390	382	375	368
39	562	543	526	510	496	482	469	457	446	435	426	416	407	399	391	384	376
40	575	556	538	522	507	493	480	468	456	446	435	426	417	408	400	393	385
41	588	569	551	534	519	504	491	479	467	456	445	436	426	418	409	402	394
42	601	581	563	546	530	516	502	489	477	466	455	445	436	427	419	411	403
43	614	594	575	558	542	527	513	500	488	476	465	455	445	436	428	420	412
44	627	606	587	570	553	538	524	510	498	486	475	465	455	446	437	429	421
45	640	619	600	582	565	549	535	521	508	496	485	475	464	455	446	437	429
46	653	631	612	593	576	560	546	532	519	506	495	484	474	464	455	446	438
47	666	644	624	605	588	571	556	542	529	517	505	494	483	474	464	455	447
48	679	656	636	617	599	583	567	553	539	527	515	503	493	483	473	464	456
49	692	669	648	628	610	594	578	563	550	537	525	513	502	492	482	473	464
50	704	681	660	640	622	605	589	574	560	547	534	523	512	501	491	482	473
51	717	694	672	652	633	616	600	584	570	557	544	532	521	510	500	491	482
52	730	706	684	664	644	627	610	595	580	567	554	542	530	520	509	500	490
53	743	718	696	675	656	638	621	605	591	577	564	551	540	529	518	508	499
54	756	731	708	687	667	649	632	616	601	587	573	561	549	538	527	517	508
55	768	743	720	698	678	660	642	626	611	597	583	570	558	547	536	526	516
56	781	755	732	710	690	671	653	637	621	607	593	580	568	556	545	535	525
57	794	768	744	721	701	682	664	647	631	616	603	589	577	565	554	544	534
58	806	780	756	733	712	693	674	657	641	626	612	599	586	574	563	552	542
59	819	792	767	745	723	703	685	668	651	636	622	608	596	584	572	561	551
60	832	804	779	756	734	714	696	678	662	646	632	618	605	593	581	570	559
61	844	817	791	768	746	725	706	688	672	656	641	627	614	602	590	579	568
62	857	829	803	779	757	736	717	699	682	666	651	637	623	611	599	587	577
63	869	841	815	791	768	747	727	709	692	676	660	646	633	620	608	596	585
64	882	853	827	802	779	758	738	719	702	685	670	656	642	629	616	605	594
65	895	865	838	813	790	769	748	730	712	695	680	665	651	638	625	614	602
66	907	877	850	825	801	779	759	740	722	705	689	674	660	647	634	622	611
67	920	890	862	836	812	790	769	750	732	715	699	684	669	656	643	631	619
68	932	902	874	848	823	801	780	760	742	725	708	693	679	665	652	640	628
69	945	914	885	859	834	812	790	771	752	734	718	702	688	674	661	648	636
70	957	926	897	870	846	822	801	781	762	744	727	712	697	683	669	657	645

Newell Chart E: Carboplatin AUC 5.3mg/ml.min Weight: 0.5-31kg EDTA t½ (30-115)

	Half life EDTA (min)																	
Body Wt (kg)	**30**	**35**	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**	**85**	**90**	**95**	**100**	**105**	**110**	**115**
0.5	30	26	23	20	18	17	15	14	13	13	12	11	11	10	10	9	9	9
1	56	48	42	38	34	31	29	27	25	23	22	21	20	19	18	17	17	16
1.5	80	69	61	54	49	45	41	38	36	34	32	30	29	27	26	25	24	23
2	103	89	78	70	64	58	54	50	46	44	41	39	37	35	34	32	31	30
2.5	126	109	96	86	78	71	65	61	57	53	50	48	45	43	41	39	38	36
3	149	128	113	101	91	84	77	72	67	63	59	56	53	51	49	47	45	43
3.5	171	147	130	116	105	96	89	82	77	72	68	65	61	58	56	53	51	49
4	192	166	146	131	118	108	100	93	87	81	77	73	69	66	63	60	58	56
4.5	214	184	162	145	132	120	111	103	96	91	85	81	77	73	70	67	64	62
5	235	203	178	160	145	132	122	113	106	100	94	89	85	81	77	74	71	68
5.5	256	221	194	174	158	144	133	124	116	109	102	97	92	88	84	81	77	74
6	276	238	210	188	170	156	144	134	125	117	111	105	100	95	91	87	84	81
6.5	297	256	226	202	183	168	155	144	134	126	119	113	107	102	98	94	90	87
7	317	274	241	216	196	179	165	154	144	135	127	121	115	109	105	100	96	93
7.5	337	291	257	230	208	191	176	163	153	144	135	128	122	116	111	107	102	99
8	358	309	272	243	221	202	186	173	162	152	144	136	129	123	118	113	109	105
8.5	377	326	287	257	233	213	197	183	171	161	152	144	137	130	125	119	115	110
9	397	343	302	271	245	225	207	193	180	169	160	151	144	137	131	126	121	116
9.5	417	360	317	284	257	236	218	202	189	178	168	159	151	144	138	132	127	122
10	437	377	332	297	270	247	228	212	198	186	176	166	158	151	144	138	133	128
11	476	411	362	324	294	269	248	231	216	203	191	181	173	165	157	151	145	140
12	514	444	391	350	318	291	269	250	233	219	207	196	187	178	170	163	157	151
13	552	477	420	376	341	313	289	268	251	236	223	211	201	191	183	176	169	162
14	590	510	449	402	365	334	308	287	268	252	238	226	215	205	196	188	180	174
15	628	542	478	428	388	355	328	305	285	268	253	240	228	218	208	200	192	185
16	665	575	507	454	411	377	348	323	303	284	269	255	242	231	221	212	204	196
17	702	607	535	479	434	398	367	342	320	300	284	269	256	244	233	224	215	207
18	739	639	563	504	457	419	387	360	336	316	299	283	269	257	246	236	227	218
19	776	670	591	529	480	440	406	378	353	332	314	297	283	270	258	248	238	229
20	813	702	619	554	503	461	425	396	370	348	329	311	296	283	270	259	249	240
21	849	733	647	579	525	481	444	413	387	364	343	326	310	295	283	271	261	251
22	885	765	674	604	548	502	463	431	403	379	358	339	323	308	295	283	272	262
23	921	796	702	629	570	522	482	449	420	395	373	353	336	321	307	294	283	273
24	957	827	729	653	592	543	501	466	436	410	387	367	349	333	319	306	294	283
25	992	857	756	677	615	563	520	484	453	426	402	381	363	346	331	318	305	294
26	1028	888	783	702	637	583	539	501	469	441	416	395	376	359	343	329	316	305
27	1063	919	810	726	659	603	557	518	485	456	431	409	389	371	355	341	327	315
28	1098	949	837	750	680	623	576	536	501	471	445	422	402	383	367	352	338	326
29	1134	980	864	774	702	643	594	553	517	487	460	436	415	396	379	363	349	337
30	1169	1010	891	798	724	663	613	570	534	502	474	449	428	408	391	375	360	347
31	1203	1040	917	822	746	683	631	587	550	517	488	463	441	420	402	386	371	358

Newell Chart F: Carboplatin AUC 5.3mg/ml.min Weight: 32-70kg EDTA t½ (30-115)

	Half life EDTA (min)																	
Body Wt (kg)	**30**	**35**	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**	**85**	**90**	**95**	**100**	**105**	**110**	**115**
32	1238	1070	944	846	767	703	650	604	566	532	502	476	453	433	414	397	382	368
33	1273	1100	970	869	789	723	668	621	581	547	517	490	466	445	426	409	393	379
34	1307	1130	997	893	810	743	686	638	597	562	531	503	479	457	438	420	404	389
35	1342	1160	1023	917	832	762	704	655	613	577	545	517	492	469	449	431	414	399
36	1376	1189	1049	940	853	782	722	672	629	592	559	530	504	482	461	442	425	410
37	1410	1219	1075	964	874	801	740	689	645	606	573	543	517	494	472	453	436	420
38	1444	1248	1101	987	896	821	758	706	660	621	587	557	530	506	484	464	447	430
39	1478	1278	1127	1010	917	840	776	722	676	636	601	570	542	518	496	476	457	441
40	1512	1307	1153	1034	938	860	794	739	692	651	615	583	555	530	507	487	468	451
41	1546	1336	1179	1057	959	879	812	756	707	665	629	596	568	542	519	498	479	461
42	1580	1366	1205	1080	980	898	830	772	723	680	643	609	580	554	530	509	489	471
43	1614	1395	1231	1103	1001	917	848	789	738	695	656	623	593	566	542	520	500	482
44	1647	1424	1256	1126	1022	937	866	805	754	709	670	636	605	578	553	531	510	492
45	1681	1453	1282	1149	1043	956	883	822	769	724	684	649	617	590	564	542	521	502
46	1714	1482	1308	1172	1064	975	901	838	785	738	698	662	630	601	576	552	531	512
47	1748	1511	1333	1195	1084	994	919	855	800	753	711	675	642	613	587	563	542	522
48	1781	1540	1359	1218	1105	1013	936	871	816	767	725	688	655	625	598	574	552	532
49	1814	1568	1384	1241	1126	1032	954	888	831	782	739	701	667	637	610	585	563	542
50	1847	1597	1409	1263	1147	1051	971	904	846	796	752	714	679	649	621	596	573	552
51	1880	1626	1435	1286	1167	1070	989	920	861	811	766	727	692	660	632	607	584	562
52	1913	1654	1460	1309	1188	1089	1006	937	877	825	780	740	704	672	643	618	594	572
53	1946	1683	1485	1331	1208	1108	1024	953	892	839	793	752	716	684	655	628	604	582
54	1979	1711	1510	1354	1229	1126	1041	969	907	854	807	765	728	696	666	639	615	592
55	2012	1740	1535	1376	1249	1145	1059	985	922	868	820	778	741	707	677	650	625	602
56	2045	1768	1560	1399	1270	1164	1076	1001	937	882	834	791	753	719	688	661	635	612
57	2078	1796	1585	1421	1290	1183	1093	1017	953	896	847	804	765	730	699	671	646	622
58	2110	1825	1610	1444	1310	1201	1110	1034	968	910	860	816	777	742	711	682	656	632
59	2143	1853	1635	1466	1331	1220	1128	1050	983	925	874	829	789	754	722	693	666	642
60	2175	1881	1660	1488	1351	1239	1145	1066	998	939	887	842	801	765	733	703	677	652
61	2208	1909	1685	1511	1371	1257	1162	1082	1013	953	901	855	814	777	744	714	687	662
62	2240	1937	1710	1533	1391	1276	1179	1098	1028	967	914	867	826	788	755	725	697	672
63	2273	1965	1735	1555	1412	1294	1196	1114	1043	981	927	880	838	800	766	735	707	682
64	2305	1993	1759	1577	1432	1313	1214	1130	1058	995	941	893	850	811	777	746	717	692
65	2337	2021	1784	1599	1452	1331	1231	1146	1073	1009	954	905	862	823	788	756	728	701
66	2369	2049	1809	1622	1472	1350	1248	1161	1087	1023	967	918	874	834	799	767	738	711
67	2402	2077	1833	1644	1492	1368	1265	1177	1102	1037	981	930	886	846	810	777	748	721
68	2434	2105	1858	1666	1512	1386	1282	1193	1117	1051	994	943	898	857	821	788	758	731
69	2466	2132	1882	1688	1532	1405	1299	1209	1132	1065	1007	955	910	869	832	799	768	741
70	2498	2160	1907	1710	1552	1423	1316	1225	1147	1079	1020	968	922	880	843	809	778	750

Newell Chart G: Carboplatin AUC 5.3mg/ml.min Weight: 0.5-30kg EDTA t½ (120-200)

	Half life EDTA (min)																
Body Wt (kg)	**120**	**125**	**130**	**135**	**140**	**145**	**150**	**155**	**160**	**165**	**170**	**175**	**180**	**185**	**190**	**195**	**200**
0.5	8	8	8	7	7	7	7	7	6	6	6	6	6	6	6	5	5
1	15	15	14	14	13	13	13	12	12	12	11	11	11	11	10	10	10
1.5	22	21	21	20	19	19	18	18	17	17	16	16	16	15	15	15	14
2	29	28	27	26	25	24	24	23	22	22	21	21	20	20	20	19	19
2.5	35	34	33	32	31	30	29	28	28	27	26	26	25	24	24	23	23
3	41	40	39	37	36	35	34	33	33	32	31	30	30	29	28	28	27
3.5	48	46	44	43	42	41	39	38	37	36	36	35	34	33	33	32	31
4	54	52	50	49	47	46	45	43	42	41	40	39	38	38	37	36	35
4.5	60	58	56	54	53	51	50	48	47	46	45	44	43	42	41	40	39
5	66	64	62	60	58	56	55	53	52	50	49	48	47	46	45	44	43
5.5	72	69	67	65	63	61	60	58	56	55	54	53	51	50	49	48	47
6	78	75	73	70	68	66	64	63	61	60	58	57	56	54	53	52	51
6.5	84	81	78	76	73	71	69	67	66	64	63	61	60	59	57	56	55
7	89	86	83	81	78	76	74	72	70	69	67	65	64	63	61	60	59
7.5	95	92	89	86	84	81	79	77	75	73	71	70	68	67	65	64	63
8	101	97	94	91	89	86	84	82	79	77	76	74	72	71	69	68	67
8.5	107	103	100	97	94	91	88	86	84	82	80	78	76	75	73	72	70
9	112	108	105	102	99	96	93	91	88	86	84	82	81	79	77	76	74
9.5	118	114	110	107	104	101	98	95	93	91	89	87	85	83	81	79	78
10	123	119	115	112	109	105	103	100	97	95	93	91	89	87	85	83	82
11	135	130	126	122	118	115	112	109	106	104	101	99	97	95	93	91	89
12	146	141	136	132	128	125	121	118	115	112	110	107	105	103	100	98	97
13	157	151	147	142	138	134	130	127	124	121	118	115	113	110	108	106	104
14	168	162	157	152	147	143	139	136	132	129	126	123	121	118	116	113	111
15	178	172	167	162	157	153	148	145	141	138	134	131	128	126	123	121	119
16	189	183	177	172	167	162	157	153	150	146	143	139	136	133	131	128	126
17	200	193	187	181	176	171	166	162	158	154	151	147	144	141	138	136	133
18	211	204	197	191	185	180	175	171	167	163	159	155	152	149	146	143	140
19	221	214	207	201	195	189	184	179	175	171	167	163	160	156	153	150	147
20	232	224	217	210	204	198	193	188	183	179	175	171	167	164	160	157	154
21	242	234	227	220	213	207	202	197	192	187	183	179	175	171	168	164	161
22	253	244	237	229	223	216	211	205	200	195	191	186	182	179	175	172	168
23	263	254	246	239	232	225	219	214	208	203	199	194	190	186	182	179	175
24	274	264	256	248	241	234	228	222	217	211	207	202	198	194	190	186	182
25	284	274	266	258	250	243	237	231	225	219	214	210	205	201	197	193	189
26	294	284	275	267	259	252	245	239	233	227	222	217	213	208	204	200	196
27	304	294	285	276	268	261	254	247	241	235	230	225	220	216	211	207	203
28	315	304	295	286	277	270	262	256	249	243	238	233	228	223	218	214	210
29	325	314	304	295	286	278	271	264	258	251	246	240	235	230	226	221	217
30	335	324	314	304	295	287	280	272	266	259	253	248	242	237	233	228	224
31	345	334	323	313	304	296	288	281	274	267	261	255	250	245	240	235	231

Newell Chart H: Carboplatin AUC 5.3mg/ml.min Weight: 32-70kg EDTA t½ (120-200)

	Half life EDTA (min)																
Body Wt (kg)	**120**	**125**	**130**	**135**	**140**	**145**	**150**	**155**	**160**	**165**	**170**	**175**	**180**	**185**	**190**	**195**	**200**
32	355	344	333	323	313	305	296	289	282	275	269	263	257	252	247	242	238
33	365	353	342	332	322	313	305	297	290	283	276	270	265	259	254	249	244
34	375	363	352	341	331	322	313	305	298	291	284	278	272	266	261	256	251
35	386	373	361	350	340	331	322	314	306	299	292	285	279	274	268	263	258
36	396	382	370	359	349	339	330	322	314	306	299	293	287	281	275	270	265
37	406	392	380	368	358	348	339	330	322	314	307	300	294	288	282	277	272
38	415	402	389	377	366	356	347	338	330	322	315	308	301	295	289	284	278
39	425	411	398	386	375	365	355	346	338	330	322	315	308	302	296	290	285
40	435	421	408	395	384	373	364	354	346	337	330	322	316	309	303	297	292
41	445	431	417	404	393	382	372	362	353	345	337	330	323	316	310	304	298
42	455	440	426	413	402	390	380	370	361	353	345	337	330	323	317	311	305
43	465	450	435	422	410	399	388	378	369	361	352	345	337	330	324	318	312
44	475	459	445	431	419	407	397	387	377	368	360	352	344	337	331	324	318
45	485	469	454	440	428	416	405	395	385	376	367	359	352	344	338	331	325
46	494	478	463	449	436	424	413	403	393	383	375	367	359	352	345	338	332
47	504	488	472	458	445	433	421	411	401	391	382	374	366	359	351	345	338
48	514	497	481	467	454	441	429	419	408	399	390	381	373	366	358	351	345
49	524	506	491	476	462	449	438	427	416	406	397	388	380	373	365	358	352
50	533	516	500	485	471	458	446	434	424	414	405	396	387	379	372	365	358
51	543	525	509	494	479	466	454	442	432	421	412	403	394	386	379	372	365
52	553	535	518	502	488	475	462	450	439	429	419	410	402	393	386	378	371
53	562	544	527	511	497	483	470	458	447	437	427	417	409	400	392	385	378
54	572	553	536	520	505	491	478	466	455	444	434	425	416	407	399	392	384
55	582	563	545	529	514	500	486	474	463	452	441	432	423	414	406	398	391
56	591	572	554	538	522	508	494	482	470	459	449	439	430	421	413	405	398
57	601	581	563	546	531	516	503	490	478	467	456	446	437	428	420	412	404
58	611	591	572	555	539	524	511	498	486	474	464	453	444	435	426	418	411
59	620	600	581	564	548	533	519	506	493	482	471	461	451	442	433	425	417
60	630	609	590	572	556	541	527	513	501	489	478	468	458	449	440	432	424
61	639	618	599	581	565	549	535	521	509	497	485	475	465	456	447	438	430
62	649	628	608	590	573	557	543	529	516	504	493	482	472	462	453	445	437
63	658	637	617	599	581	566	551	537	524	512	500	489	479	469	460	451	443
64	668	646	626	607	590	574	559	545	531	519	507	496	486	476	467	458	450
65	677	655	635	616	598	582	567	552	539	526	515	503	493	483	473	465	456
66	687	664	644	624	607	590	575	560	547	534	522	511	500	490	480	471	462
67	696	674	653	633	615	598	583	568	554	541	529	518	507	497	487	478	469
68	706	683	661	642	623	606	591	576	562	549	536	525	514	503	494	484	475
69	715	692	670	650	632	615	598	583	569	556	544	532	521	510	500	491	482
70	725	701	679	659	640	623	606	591	577	563	551	539	528	517	507	497	488