SIOP CNS GCT II
Prospective Trial for the diagnosis and treatment of children, adolescents and young adults with Intracranial Germ Cell Tumours

Study period: 5 years from start date

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INTERNATIONAL VERSION
EudraCT number 2009-018072-33
Sponsor’s study number UKM08_0057

Gefördert durch die Deutsche Kinderkrebsstiftung
Projekt-Nr. 2010.19
INITIAL ACTION IN INTRACRANIAL TUMOURS
- GERM CELL TUMOUR SUSPECTED (e.g. PINEAL OR SUPRASELLAR TUMOUR) -

PLEASE NOTE
- In any cases receiving neurological intervention, CSF should be sampled for markers and cytology before ventriculoscopy or biopsy is undertaken.
- * biopsy is not required when markers are positive
- Retaining (i.e. spine if not already done) should be carried out within 48 h of surgical resection.

0.1 Flowsheets (see also appendix C)

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GROUPING FOR DIAGNOSIS

**Abbreviations:**
- CCA = Choriocarcinoma
- YST = Yolk Sac Tumour
- ECT = Embryonal Carcinoma

- Serum AFP > 25 ng/ml or
  - Serum HCG > 50 IU/l or
  - CSF AFP > 25 ng/ml or
  - CSF HCG > 50 IU/l

- NCT: Non-Germinoma (NG6CT)
- Germinoma (ger)
- Teratoma (TER)

GROUPING FOR DISSEMINATION

- Cerebral MRI: two or more foci?
  - yes
    - MRI spinal
    - CSF cytology
    - Metastatic disease
  - no
    - Spinal MRI: positive?
      - yes
        - CSF cytology
        - Metastatic disease
      - no
        - CSF cytology: positive?
          - yes
            - Metastatic disease
          - no
            - Non-metastatic disease

* In case of bitemporal tumor (only pineal+suprasellar) and negative spinal MRI and negative CSF-cytology, disease is classified as non-metastatic.
0.2 Confidentiality and important information

**Confidentiality:** The content of the protocol and the case report forms must be treated confidentially and may not be imparted to uninvolved persons without consent of the study chief investigators neither in oral nor in written form.

**Important information:** The protocol was written by the trial steering committee to the best of their knowledge and belief. Nevertheless mistakes can never be completely excluded. Therefore every doctor is responsible for checking the treatment plans of the protocol before treating a patient.

**Trial related committees**

The SIOP CNS GCT II trial steering committee is responsible for writing the protocol and organizing the study in the participating countries. The SIOP CNS GCT II trial steering committee consists of the coordinating chief investigator, a representing member of the Co-ordinating Centre for Clinical Trials Münster (ZKS), the different country-specific chief investigators and the responsible biometrician. The international trial office is responsible for the minutes of SIOP CNS GCT II trial steering committee meetings and other communication between the steering committee members, e.g. by electronic mail. Further experts can be invited to participate as consultants.

**SIOP CNS GCT II study group**

The SIOP CNS GCT II study group is responsible for deciding on the therapeutic outlines and design of the present SIOP CNS GCT II protocol as well as about premature termination of the trial. Furthermore, all members are also responsible for endorsing and implementing the SIOP CNS GCT II protocol. The members of the SIOP CNS GCT II study group are listed in the Appendix M.

**Data Monitoring and Safety Committee (DMSC)**

An independent DMSC composed of 3 international experts will monitor the progress of the trial on ethical and scientific backgrounds. The role of the DMSC will be to review accrual rate, to examine interim analyses, to monitor toxicities and to examine other trials (Details see chapter 11).
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### Abbreviations

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<td>AE</td>
<td>adverse event</td>
</tr>
<tr>
<td>AFP</td>
<td>Alpha-Fetoprotein</td>
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<tr>
<td>ALT</td>
<td>alanine aminotransferase</td>
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<tr>
<td>AR</td>
<td>adverse reaction</td>
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<tr>
<td>AST</td>
<td>aspartate aminotransferase</td>
</tr>
<tr>
<td>BEP</td>
<td>bleomycin/etoposide/cisplatin</td>
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<tr>
<td>β-HCG</td>
<td>β-Human Chorionic Gonadotropin</td>
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<tr>
<td>BSID</td>
<td>Bayley Scales of Infant and Toddler Development</td>
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<tr>
<td>carboP</td>
<td>carboplatin</td>
</tr>
<tr>
<td>carboPE</td>
<td>carboplatin/etoposide</td>
</tr>
<tr>
<td>carboPEI</td>
<td>carboplatin/etoposide/ifosfamide</td>
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<tr>
<td>CHC</td>
<td>choriocarcinoma</td>
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<tr>
<td>CNS</td>
<td>central nervous system</td>
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<tr>
<td>CPM</td>
<td>coloured progressive matrices</td>
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<tr>
<td>CPT</td>
<td>continuous performance test</td>
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<tr>
<td>CR</td>
<td>complete remission</td>
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<tr>
<td>CCR</td>
<td>complete continuous remission</td>
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<tr>
<td>CRF</td>
<td>case report form (documentation forms)</td>
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<tr>
<td>CSA</td>
<td>craniospinal axis</td>
</tr>
<tr>
<td>CSF</td>
<td>cerebrospinal fluid</td>
</tr>
<tr>
<td>CSI</td>
<td>craniospinal irradiation</td>
</tr>
<tr>
<td>CT</td>
<td>computed tomography</td>
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<tr>
<td>CTC</td>
<td>common terminology criteria</td>
</tr>
<tr>
<td>db</td>
<td>decibel</td>
</tr>
<tr>
<td>DI</td>
<td>diabetes insipidus</td>
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<tr>
<td>DICOM</td>
<td>digital imaging and communications in medicine</td>
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<tr>
<td>DMSC</td>
<td>Data Monitoring and Safety Committee</td>
</tr>
<tr>
<td>DOC</td>
<td>dead of other cause</td>
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<tr>
<td>E</td>
<td>etoposide</td>
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<tr>
<td>EC</td>
<td>embryonal carcinoma</td>
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<tr>
<td>EFS</td>
<td>event free survival</td>
</tr>
<tr>
<td>EI</td>
<td>etoposide/ifosfamide</td>
</tr>
<tr>
<td>EORTC</td>
<td>European Organisation for Research and Treatment of Cancer</td>
</tr>
<tr>
<td>FLAIR</td>
<td>fluid-attenuated inversion recovery</td>
</tr>
<tr>
<td>FU</td>
<td>follow up</td>
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<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>GCSF</td>
<td>granulocyte-colony stimulating factor</td>
</tr>
<tr>
<td>GCTs</td>
<td>germ cell tumours</td>
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<tr>
<td>GER</td>
<td>germinoma</td>
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<tr>
<td>GFR</td>
<td>glomerular filtration rate</td>
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<tr>
<td>GH</td>
<td>growth hormone</td>
</tr>
<tr>
<td>GHD</td>
<td>growth hormone deficiency</td>
</tr>
<tr>
<td>GTS</td>
<td>growing teratoma syndrome</td>
</tr>
<tr>
<td>HCG</td>
<td>human chorionic gonadotrophin</td>
</tr>
<tr>
<td>HD</td>
<td>high dose</td>
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<tr>
<td>HPLAP</td>
<td>human placenta-like alkaline phosphatase</td>
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<tr>
<td>HUI</td>
<td>Health Utilities Index</td>
</tr>
<tr>
<td>I</td>
<td>ifosfamide</td>
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<tr>
<td>ICE</td>
<td>Ifosfamide, Cisplatin &amp; Etoposide</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonisation</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>IMP</td>
<td>Investigational Medicinal Product</td>
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<tr>
<td>K-ABC</td>
<td>Kaufman Assessment Battery for Children</td>
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<tr>
<td>LDH</td>
<td>lactate dehydrogenase</td>
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<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>NCI</td>
<td>National Cancer Institute</td>
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<tr>
<td>nd</td>
<td>not done</td>
</tr>
<tr>
<td>NGGCTs</td>
<td>non-germinomatous germ cell tumours</td>
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<tr>
<td>OCT</td>
<td>transcription factor</td>
</tr>
<tr>
<td>OS</td>
<td>overall survival</td>
</tr>
<tr>
<td>P</td>
<td>cisplatin</td>
</tr>
<tr>
<td>PEI</td>
<td>cisplatin/etoposide/ifosfamide</td>
</tr>
<tr>
<td>PD</td>
<td>progressive disease</td>
</tr>
<tr>
<td>PLAP</td>
<td>placenta-like alkaline phosphatase</td>
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<tr>
<td>PNETs</td>
<td>primitive neuroectodermal tumours</td>
</tr>
<tr>
<td>PR</td>
<td>partial response</td>
</tr>
<tr>
<td>pt</td>
<td>patient</td>
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<tr>
<td>PTA</td>
<td>Pure tone audiogram</td>
</tr>
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<tr>
<td>QLQ</td>
<td>quality of life questionnaire</td>
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<tr>
<td>QOS</td>
<td>quality of survival</td>
</tr>
<tr>
<td>RT</td>
<td>radiotherapy</td>
</tr>
<tr>
<td>SAE</td>
<td>serious adverse event</td>
</tr>
<tr>
<td>SAR</td>
<td>serious adverse reaction</td>
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<tr>
<td>SAS</td>
<td>statistics analysis system</td>
</tr>
<tr>
<td>SD</td>
<td>stable disease</td>
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<tr>
<td>SDQ</td>
<td>strength and difficulties questionnaire</td>
</tr>
<tr>
<td>SGC</td>
<td>syncytiotrophoblastic giant cells</td>
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<tr>
<td>SIOP</td>
<td>International Society of Paediatric Oncology</td>
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<tr>
<td>SOP</td>
<td>Standard Operating Procedure</td>
</tr>
<tr>
<td>SPM</td>
<td>standard progressive matrices</td>
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<tr>
<td>SUSAR</td>
<td>suspected unexpected serious adverse reaction</td>
</tr>
<tr>
<td>TB</td>
<td>tumour bed</td>
</tr>
<tr>
<td>TER</td>
<td>teratoma</td>
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<tr>
<td>TSH</td>
<td>thyroid stimulating hormone</td>
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<tr>
<td>UAR</td>
<td>unexpected adverse reaction</td>
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<tr>
<td>VIP</td>
<td>vinblastine/ifosfamide/cisplatin</td>
</tr>
<tr>
<td>VMI</td>
<td>visual-motor integration</td>
</tr>
<tr>
<td>VP</td>
<td>ventriculo-peritoneal</td>
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<tr>
<td>WHO</td>
<td>World Health Organisation</td>
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<tr>
<td>WV</td>
<td>whole ventricular</td>
</tr>
<tr>
<td>WVI</td>
<td>whole ventricular irradiation</td>
</tr>
<tr>
<td>YST</td>
<td>yolk sac tumour</td>
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0.6 Important notes
Regarding application of the study protocol

With this protocol the SIOP CNS GCT II steering committee presents a prospective trial for the risk-adapted treatment of intracranial Germ Cell Tumours (GCTs) in children, adolescents and young adults.

This document is intended to describe the proposed collaborative study in CNS GCTs and to provide information for enrollment of patients. This protocol does not represent recommendations for standard treatment or guidelines for the treatment of unregistered patients, but is solely for the purpose of the study. The national chief investigator is responsible for accreditation of participating hospitals at the national level.

Before entering patients into the study, clinicians must ensure that the study protocol has received ethical and regulatory clearance. The steering committee emphasises that even following ethical approval at participating centres, the members of the committee will not take any legal responsibility for possible adverse consequences that may result from the application of the treatment guidelines in this protocol.

The protocol has been written with the greatest possible care, but amendments may still be required in the future; these will be circulated to known registered participants in the trial, but institutions entering patients are advised to contact the appropriate national chief investigator in order to confirm the correctness of the protocol in their possession. Despite our best efforts the possibility of errors within this document cannot be entirely ruled out and investigators are reminded that the ultimate responsibility for the management of any patient treated with this protocol rests with the treating clinician.

The content of the protocol is confidential and may not be divulged in any way to centres not involved in the study, without the approval of the International Study Committee.

Protected labels are marked with the symbol ®; the absence of ® does not imply that the term is free.

The SIOP Europe board has agreed that the SIOP logo can be used for the labeling of this study protocol. However, SIOP Europe is not the sponsor, as defined by the ICH Harmonised Tripartite Guidelines of this study, and accepts no legal responsibility for the conduct of the study. In addition, neither the Board nor the Scientific Committee of SIOP accepts responsibility for the overall conduct of this study and has specifically pointed out that implementation of this study requires the approval of the Research Ethics Committee / Institutional Review Board of each participating institution.
**Overview**

Full Title: SIOP CNS GCT II: Prospective Trial for the diagnosis and treatment of children, adolescents and young adults with Intracranial Germ Cell Tumours

Short Title: SIOP CNS GCT II

**Protocol Number:** UKM08_0057  
**Eudract Number:** 2009-018072-33

**Indication:** Intracranial Germ Cell Tumours

**Chief Investigator:** Gabriele Calaminus MD  
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**Co-ordinating Data Centre:**  
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Dept. of Pediatric Haematology and Oncology,  
Adenauerallee 119  
53113 Bonn  
Germany

**STUDY DURATION:**  
End-point: 2 years following the last patient recruited.  
Duration of recruitment: 5 years are expected to be sufficient to recruit the required number of patients  
Expected start date: 01.06.2011

**STUDY DESIGN:**  
Prospective, non-randomised multicentre study with patients stratified according to risk groups

**PATIENT POPULATION**

**Age of patients:** no lower or upper age limit;  
**Estimated number:** 400 malignant germ cell tumours

**Diagnosis and main criteria for inclusion/exclusion:**  
Intracranial Germ Cell tumours of any histology and intracranial site and dissemination

**Inclusion criteria:**
- Main residence in one of the participating countries
- Primary diagnosis of an intracranial germ cell tumour
- Written consent for trial participation, treatment according to the protocol and consent for data transfer

**Exclusion criteria:**
- Tumour entity other than primary intracranial germ cell tumour or CNS GCT as second malignancy
- Primary diagnosis pre-dating the opening of SIOP CNS GCT II in the participating country of registration
- Medical, psychiatric or social conditions incompatible with trial treatment or treatment according to protocol is not intended
- Participation within a different trial for treatment of germ cell tumours and/or concurrent treatment within any other clinical trial. The only exceptions to this are trials with different endpoints, involving aspects of supportive treatment which can run parallel to SIOP CNS GCT II without influencing the outcome of this trial e.g. trials on antiemetics, antimycotics, antibiotics, strategies for psychosocial support etc.
- Pregnancy and lactation
- Any treatment not given according to protocol prior to registration

**INVESTIGATIONAL MEDICINAL PRODUCTS**

The IMPs on this trial are Carboplatin, Cisplatin, Ifosfamide and Etoposide (as approved by German competent authority).
TREATMENT:

GERMINOMA (± TERATOMA)
Chemotherapy:

- Non-metastatic fully staged germinoma (± teratoma)
  Two courses (1 and 3) of Etoposide and Carboplatin, alternating with two courses (2 and 4) of Etoposide and Ifosfamide

Note: Bifocal germinoma (pineal+suprasellar) are treated as non-metastatic germinoma, if staging shows no additional dissemination

- Metastatic or incompletely staged germinomas (± teratoma)
  Do not receive chemotherapy in this protocol

Radiotherapy:

- Non-metastatic pure germinoma in PR/SD
  After Chemotherapy: 24 Gy (15 fractions) to whole ventricles with a 16 Gy (10 fraction) boost to tumour bed (total tumour dose 40 Gy)

- Non-metastatic germinoma in CR
  After Chemotherapy: 24 Gy (15 fractions) to whole ventricles

- Metastatic or incompletely staged pure germinoma
  24 Gy (15 fractions) to craniospinal axis with a 16 Gy (10 fraction) boost to tumour bed and any intracranial metastases and spinal deposits (total tumour dose 40 Gy)

- Non-metastatic germinoma plus teratoma (incompletely resected)
  After Chemotherapy: 24 Gy (15 fractions) to whole ventricles; 30.4 Gy (19 fraction) boost to tumour bed (total tumour dose 54.4 Gy)

- Metastatic germinoma plus teratoma (incompletely resected)
  24 Gy (15 fractions) to craniospinal axis; 30.4 Gy (19 fraction) boost to tumour bed and 16 Gy (10 fraction) boost to metastases (total tumour dose 54.4 Gy)

NON-GERMINOMA (± TERATOMA)
Chemotherapy:

- Standard risk non-germinomatous malignant GCT
  Four courses of Etoposide, Cisplatin and Ifosfamide (standard treatment)

- High risk non-germinomatous malignant GCT
  Two courses of standard Etoposide, Cisplatin and Ifosfamide, followed by two dose intensified courses of Etoposide, Cisplatin and Ifosfamide with stem cell support

Resection of residual tumour after 3 courses chemotherapy (if indicated), followed by: 4th course. If viable cells are found in the resected tumour specimen patient is transferred to the high risk arm

Radiotherapy for standard and high risk non-germinomatous malignant GCT:

- Patients with localised disease at diagnosis
  After Chemotherapy: 54 Gy focal radiotherapy in 30 fractions

- Patients with metastatic disease at diagnosis
  After Chemotherapy: 30 Gy (20 fractions) to cranio-spinal axis with 24 Gy (15 fraction) boosts to tumour site and any intracranial metastases (total tumour dose 54 Gy) and 20.8 Gy (13 fraction) boosts to spinal deposits (total dose 50.8 Gy)

PRIMARY OBJECTIVES:

Germinoma
- To maintain current high event-free survival (EFS) rates using a risk adapted approach
- In localised germinoma: to omit whole brain and spinal irradiation by using combined treatment with standard chemotherapy and ventricular irradiation (+/- boosts)
- In bifocal tumours (pineal + suprasellar): to treat as non-metastatic disease and to omit whole brain and spinal irradiation by using combined treatment with standard chemotherapy and ventricular irradiation
irradiation (+/- boosts)
- In metastatic disease: to maintain current excellent EFS in metastatic germinoma with craniospinal irradiation

Malignant non-germinoma
To improve EFS:
- by dose escalation of chemotherapy in patients identified as high risk at diagnosis (age < 6 years and/or AFP serum / CSF > 1000 ng/ml)
- by standardising the surgical approach for residual disease after treatment

Teratoma
- To register patients and collect data regarding diagnostics, treatment and outcome in order to develop future treatment strategies

SECONDARY OBJECTIVES:

Germinoma
- To minimise long term effects of irradiation by sparing spinal and whole brain radiotherapy in non-metastatic disease

Malignant non-germinoma
- In standard risk to maintain EFS with chemotherapy and local irradiation

Teratoma
- To evaluate the influence of surgery and treatment on outcome to assist in the development of a future treatment strategy

For all histological subtypes
- To improve accuracy of diagnosis and staging in all registered patients
- To standardise neurosurgical intervention
- For all patients requiring biopsy or resection according to protocol guidelines, to collect and to store tumour material, and CSF where possible, for use in future biological studies.

ENDPOINTS / Criteria for evaluation:

Main end point
Event-free survival, defined as minimum time from the date of diagnosis to:
- Death from any cause
- Relapse
- Progressive disease on therapy
- Or second malignancy

Secondary end points
- Overall survival, defined as time to death from any cause, measured from the date of diagnosis
- Short and long term toxicity.

SPECIAL ASPECTS:

Central response evaluation on a national basis:
Germinoma: In all patients with localised germinoma a central national radiological review is mandatory for response evaluation to chemotherapy and decision if only ventricular irradiation or an additional tumour boost has to be performed.
Non-Germinoma: After three courses of chemotherapy to evaluate response to treatment and to determine necessity of surgery in case of residual before radiotherapy.

Statistical consideration, report to DMSC and stopping rules: see chapter 10 and 11
1 BACKGROUND AND RATIONALE

Intracranial germ cell tumours (GCTs) are rare tumours of childhood and adolescence that are heterogeneous with respect to their primary site, histology, biological profile and response to treatment. Prospective co-operative studies have contributed significantly to our current understanding as well as to success in treating paediatric intracranial GCTs. In malignant GCTs, initial combination platinum-based chemotherapy will be administered prior to risk adapted radiotherapy and delayed tumour resection where required. In tumours with mixed histology, the therapeutic approach depends on the component with the highest grade of malignancy. As a result of improved and standardized therapeutic strategies as well as an optimised multi-disciplinary approach, the overall prognosis of malignant GCTs in the paediatric cohort has increased from around 25% to more than 80%. For teratoma, no standardized treatment approach has been investigated in a multinational protocol to date.

The therapeutic recommendations included in this protocol are based on the data extracted from the published literature and the experience derived from the treatment of patients registered and treated in the SIOP CNS GCT 96 protocol.

1.1 Risk Benefit Assessment

The intended benefit of SIOP CNS GCT II is to reduce treatment burden in localised germinoma with a view to limiting long term effects of therapy and, for non-germinoma, to intensify treatment in high risk patients, in order to improve survival. The risks and benefits of the clinical management employed will be assessed carefully.

The prognosis for intracranial germ cell tumours is highly dependent on the histological subtype of the tumour present but treatment options including chemotherapy and/or radiotherapy are essential for potential cure of disease.

Germinomas are extremely chemosensitive and radiosensitive. For the last twenty years, craniospinal irradiation has been the gold standard for treatment. But radiation therapy delivered to the whole brain and spine carries the risk of adverse effects. Children and pre-pubertal adolescents are at particular risk of long term sequelae of radiation treatment. The primary rationale for limiting the extent of radiation in young patients is to diminish the potential adverse effects on the CNS, thyroid function and spinal growth. Additional chemotherapy may compensate for a reduction in radiotherapy, but chemotherapy alone is rarely curative when given as a single treatment modality, with a high proportion of tumours relapsing. The combined approach employed in this protocol has a risk of additional toxicity as a result of delivering chemotherapy as well as radiotherapy, but the benefits of decreased radiation field are likely to outweigh side effects of treatment, since a combined approach has been used previously in other studies without excessive morbidity.

For malignant non-germinoma, both chemotherapy and radiotherapy are essential to maximize the chance of curing the disease. They have been seen to respond very well to chemotherapy followed by radiotherapy according to tumour dissemination, in the preceding trial (SIOP CNS GCT 96). This treatment is unchanged compared to SIOP CNS GCT 96 in order to maintain current high event free rates. However, a small number of high risk patients may benefit from a risk-adapted treatment approach. More detailed staging procedures allow identification of patients with certain risk factors. Treatment needs to be strengthened to improve outcome for these high risk patients. The SIOP 96 trial identified a correlation between elevated AFP levels in serum and/or CSF (higher than 1000 ng/ml) and an unfavourable prognosis as well as age < 6 years. Additional toxicity of this intensified chemotherapy may include increased haematological toxicity, requiring greater support, and issues regarding control.
of diabetes insipidus, which should be manageable by following the protocol recommendations. However, improvement of event free survival might justify the consideration of this intensified treatment.

We believe that the potential benefits of the therapy being investigated in this trial outweigh the risks associated with study participation.

1.2 Current knowledge

1.2.1 Epidemiology

Germ cell tumours contribute 3.4% to all malignant tumours in children. The estimated incidence is 0.6 per 100,000 children up to 15 years (Kaatsch et al 2002). In children, the most frequent primary sites of GCTs are the testes (25%), ovaries (25%), the sacrococcygeal region (20%) and the central nervous system (20%) (Figure 1). The histology of GCTs in neonates is almost exclusively mature and immature teratoma, sometimes admixed with subtle foci of yolk sac tumour (YST). During infancy and childhood, YSTs predominate. During childhood, GCTs drop in incidence to < 0.1 per 100,000, and they arise more frequently in girls than in boys. After the onset of puberty, a significant increase in incidence of GCT can be observed, and all histologic entities are more frequent in males (Schneider et al 2004). CNS GCTs predominantly develop around or after the onset of puberty and during the second and third decade of life.

Figure 1: Age and site of malignant GCTs (n= pts per year; MAKEI registry)
Pathobiology of Germ Cell Tumours
According to the holistic concept of Teilum et al (1975), GCTs develop from totipotent primordial germ cells. During early embryogenesis, primordial germ cells can be distinguished as a distinct cell population at the base of the allantoic membrane, and they migrate along the dorsal mesentery to the gonadal streaks and populate the gonads (Anderson 2000). It is assumed that malignant transformation of germ cells occurs during their development and differentiation, but the triggers for this are currently unknown.

GCTs may show pure germ cell differentiation on one hand (seminoma, synonym: dysgerminoma and germinoma) or somatic differentiation on the other (Figure 2). The existence of a common cell of origin may also help to explain the histological heterogeneity within mixed malignant germ cell tumours.

Figure 2: Histogenetic concept of GCTs (modified according to Hawkins et al 1996)

The distinct histological subentities of non-germinomatous GCTs can be distinguished by clinical, morphological and immunohistochemical features (see also pathology appendix F.5 ). Most of these markers do not define a single diagnostic entity but show considerable overlap with other GCTs so that a panel of markers should be employed for diagnostics. Embryonal carcinoma are frequently CD30 positive. Yolk sac tumours are usually alpha fetoprotein (AFP) positive, while choriocarcinoma may be detected by staining for ß-human chorionic gonadotropin (total HCG). On immunhistochemical analysis, germinomatous GCTs are characterized by their positivity for the placenta-like alkaline phophatase (PLAP), detected in most cases; however, the prognostic relevance is currently unclear (Shinoda et al 1988). Like primordial germ cells, germinomas usually express c-Kit (CD117), the receptor for stem cell factor, an important mitogen for normal germ cells. Some germinomas show activating mutations c-Kit similar to seminomas and dysgerminomas. They may express total HCG in a syncytiotrophoblastic component. The homeodomain transcription factor, NANOG, along with OCT3/4 (POU5F1) and SOX2, is part of the core set of transcription factors that maintain embryonic stem cell self-renewal and pluripotency. Expression of NANOG has been detected in fetal germ cells and in gonadal germ cell tumours. NANOG and OCT3/4 can be detected specifically in germinomas and embryonal carcinomas, but they can be distinguished by Sox2 that is negative in germinomas but expressed in embryonal carcinomas and other tumours.

Teratomas may show a higher degree of differentiation with the presence of mature or immature structures derived from all three germ layers, such as hair, squamous and mucous epithelium, teeth, cartilage, bone, glial or thyroid tissue. Immature teratomas present with varying components of...
immature tissue that mostly resemble immature neural tissue with neurotubular structures. Their grade (1 to 3) can be determined according to the relative amount of immature tissue (Gonzalez-Crussi 1982) and some positivity for AFP may be detected.

1.2.2 Molecular biology of GCTs
Studies of imprinting status have helped to substantiate the origins of both gonadal and nongonadal GCTs in primordial germ cells that have failed to populate the gonads normally (Bussey et al. 2001). In addition, imprinting studies have indicated that gonadal and non-gonadal GCTs of different histological subtypes may be derived from different stages of germ cell development. Specific profiles relating to histology and time of onset in relation to puberty have also been described (Schneider et al. 2001). Conventional cytogenetic analysis has revealed differences between GCTs in children and in adults (Perlman et al. 1994, Bussey et al. 1999): Isochromosome 12p (i(12p)), resulting from duplication of the short arm of chromosome 12 and loss of the long arm, is the cytogenetic hallmark of adult GCTs, seen in more than 80% of cases. Adult GCTs without i(12p) usually show gain of part of 12p by other mechanisms, such as double minutes or homogeneously staining regions. In contrast, i(12p) is rarely seen in GCTs arising before the onset of puberty. During childhood, deletions of the short arm of chromosome 1 and the long arm of chromosome 6 can be found more frequently. Unlike in neuroblastoma, the prognostic impact of cytogenetic imbalances in GCTs has not yet been evaluated and the importance of these and other molecular studies in the clinical management of patients is yet to be established for GCTs. A standardized procedure for tissue collection is therefore recommended according to national practice - it is important to emphasise the need for banking of tumour samples for future biological studies whenever there is material available.

1.2.3 Clinical and biochemical characteristics
Malignant non-germinomatous GCTs show specific biological characteristics, irrespective of age, which are reflected in their production of tumour markers according to histological subtype. These have implications for the initial strategy for diagnosis and correlate with response to cytotoxic treatment and radiotherapy (Table 1).

Table 1 Clinical and biological characteristics of germ cell tumours correlated with histology

<table>
<thead>
<tr>
<th>Histology</th>
<th>Clinical behaviour</th>
<th>Tumour markers</th>
<th>Sensitivity to</th>
<th>Chemo</th>
<th>Irrad.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germinoma</td>
<td>malignant</td>
<td>-</td>
<td>(+)</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Embryonal CA Yolk sac tumour Choriocarcinoma</td>
<td>malignant</td>
<td>++</td>
<td>-</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Teratoma</td>
<td>benign (potentially malignant)</td>
<td>-</td>
<td>-</td>
<td>-/?</td>
<td>+/-</td>
</tr>
</tbody>
</table>

Yolk sac tumours secrete alpha-fetoprotein (AFP) and choriocarcinoma secrete human chorionic gonadotropin (here characterized as total HCG) (see appendix F). These markers can be detected in the serum and/or the cerebrospinal fluid and may, in combination with characteristic radiographic findings, be diagnostic of malignant GCTs (Blohm et al. 1998, Schneider et al. 2001). Pure embryonal carcinoma and teratomas are usually not associated with specific tumour markers. Germinoma may be associated with mild elevation of total HCG (less than 50 IU/l in serum and CSF) indicating the presence of syncytiotrophoblastic cells. In approximately 20% of germinoma, serum levels of PLAP may be elevated, and other studies have indicated an association of CNS germinoma with high CSF...
concentrations of soluble c-kit receptor. The relevance of this elevation on treatment and outcome is not yet clear.

1.3 Early experience with treatment of intracranial GCTs

Impact of chemotherapy: Platinum-based chemotherapy was established in the 1970s in the treatment of malignant extracranial GCTs (Einhorn 1977), and cisplatin was subsequently introduced in children with intracranial GCTs (Allen 1987). Subsequent studies have raised questions concerning the most effective dose, the best drug combinations and whether chemotherapy alone was able to cure children with malignant CNS GCTs as effectively as their extracranial counterparts.

Impact of radiotherapy: The use of irradiation in intracranial GCTs has a long history (Rich 1985). Most of the publications relate to CNS germinoma (Sano 1981). For recent years, craniospinal irradiation was the gold standard for these tumours. The focus of the last 15 years has been to reduce the irradiation dose and field in germinomatous and non-germinomatous GCTs, in combination with chemotherapy (Itoyama 1999, Kobayashi 1989, Allen 1987).

Subsequent progress in National cooperative studies in Europe and elsewhere, as reported in the following sections, led to the development of the first European multinational protocol in 1995, SIOP CNS GCT 96, the objectives and findings of which are discussed in detail in sections 1.5.

1.4 Results of previous studies for the treatment of intracranial GCTs

1.4.1 Germinoma

1.4.1.1 European Experience of germinoma

The French SFOP TGM-TC 90-92 was established for treatment of intracranial germinoma, the goal being to treat localised germinoma with chemotherapy and focal RT, thus avoiding irradiation of the craniospinal axis (Baranzelli 1998). All patients with total HCG <50 IU/L and AFP <12 ng/ml and histologically proven germinoma received four alternating courses of etoposide/carboplatin and etoposide/ifosfamide, followed by 40 Gy to the tumour bed. 60 pts with localised germinoma were enrolled. The event-free survival was 83% with a median follow-up time of 36 months (range 10-122 months). The predominant sites of relapse (8/10 cases) were the ventricles, either at the margins or outside the irradiation field (Alapetite 2010).

In Germany two consecutive protocols (MAKEI 83/86 and MAKEI 89) were established for the treatment of intracranial germinoma from 1983. The aim was to give craniospinal irradiation alone with a reduced dose to both the tumour bed and the craniospinal axis. All patients with total HCG levels < 100 IU/L and AFP-level <50 ng/ml were treated with craniospinal RT, in a dose of 36 Gy (MAKEI 83/86) or 30 Gy (MAKEI 89) and a tumour boost of 14 Gy (MAKEI 83/86) or 15 Gy (MAKEI 89). The estimated relapse free survival rate was 91% with a median follow-up time of 59.5 months (range 3-180 months). Relapses were mainly outside the CNS. 2 of 5 relapsing patients showed elevation of markers at relapse and, since they were incompletely staged at diagnosis, were suspected to have had non-germinomatic elements present at first diagnosis. It was therefore concluded that the RT dose to both the primary tumour and craniospinal axis could be reduced safely. In addition it was deduced that craniospinal RT is not sufficient to control non-germinomatous components within the germinoma, thus emphasising the importance of complete diagnostic work-up (Bamberg et al 1999).
1.4.1.2 Non-European experience of germinoma

The largest series to date from outside Europe was published by the Japanese group, led by Matsutani (2001). They reported the experience of their first and second multicentre clinical trials, in which they tested the response of germinoma to chemotherapy and whether a combined approach with radiotherapy, using doses adapted to risk groups, could achieve high survival rates. Pure germinoma was regarded as a good prognostic tumour whereas, if syncytiotrophoblastic cells were seen, patients were classified as intermediate risk. Good risk germinoma received 3 courses of post-operative carboplatin/VP16, followed by local RT with 24 Gy. Intermediate risk patients received 30 Gy RT to a generous local field and 20 Gy to the tumour after resection and chemotherapy. Thereafter they received the same chemotherapy for a total of five courses over 3-4 months. 86 germinomas were treated as good prognostic patients and 10 as intermediate risk patients. Most of the relapses were local and outside the irradiation field. The relapse-free survival rate in the good prognostic group was 92.5% and in the intermediate risk group 90%. It was concluded that if combined treatment is given, whole brain irradiation in localised germinoma is not necessary, but that the irradiation field should be larger than focal.

Aoyama (2002) reported a second Japanese series. After surgery patients received 3 - 4 courses of a two drug regimen (Cisplatin/Etoposide). In localised pure germinoma (n=14) 24 Gy focal RT was then delivered, either to the preoperative target volume or whole ventricles. In germinoma with syncytiotrophoblastic giant cells (SGC, n=11) or disseminated germinoma (n=3), 3-4 courses of ICE (Ifosfamide, Cisplatin, and Etoposide) were administered, followed by focal / ventricular (SGC) or whole CNS irradiation (disseminated), to a dose of 24 Gy. In total HCG secreting tumours an additional 10 Gy boost was delivered to the pineal region and a 6 Gy boost to the neurohypophysis. Results revealed a 90% relapse free survival at five years in localised pure germinoma. Five year relapse free survival was 44% in disseminated germinoma or germinoma with SGC. The authors conclude that in pure germinoma a 24 Gy RT to the local field is sufficient if given after chemotherapy with a Cisplatin containing regimen. In SGC-positive germinoma and disseminated germinoma they proposed a higher irradiation dose, which should include the ventricles and the whole CNS respectively.

Two different North American approaches for germinoma were described, both in small series of patients. Buckner and coworkers (1999) reported a series of 9 patients with germinoma of whom 3 were disseminated. Patients with localised disease were treated with 4 cycles of cisplatin and etoposide, followed either by local field irradiation of 30 Gy if complete response was achieved after chemotherapy or with 54 Gy to local field in cases of incomplete response. In disseminated disease patients received 20 Gy craniospinal radiotherapy (CSI) plus 10 Gy boost or, in cases of incomplete response to chemotherapy, 30 Gy CSI and 23 Gy tumour boost. Eight of the nine patients remained in first continuous complete remission. One patient with localised disease relapsed in the spine. The authors concluded that primary chemo and irradiation, delivered according to extent of tumour and response to chemotherapy, is an effective treatment.

The other approach was to treat germinoma with chemotherapy alone as for their extracranial counterparts. Balmaceda and coworkers (Balmaceda et al 1996) reported on the outcome of 45 germinoma in 1996. All patients received four cycles of carboplatin, etoposide and bleomycin, followed by two additional cycles of the same drugs in complete responders, and two cycles intensified by cyclophosphamide in others. Twenty-two patients relapsed, 18 of whom were cured by additional chemotherapy and radiotherapy; and 4 children died of treatment related toxicity. Although a high rate of complete response to chemotherapy has been shown in other series (Kumabe 2002, Kellie 2004), a chemotherapy only treatment approach remains unproven in patients with intracranial germinoma, as responses were not sustained.
1.4.2 Malignant non-germinoma

1.4.2.1 European experience of non-germinomatous GCT

A chemotherapy only approach for treatment of malignant non-germinomatous CNS GCT was employed in France in the 1990s (SFOP-88 and SFGOP TC 90 until December 1992) and enrolled 18 patients. Treatment consisted of 6 cycles of chemotherapy (Vinblastine/Bleomycin Carboplatin, alternating with Ifosfamide/Etoposide or Etoposide/Carboplatin, alternating with Ifosfamide/Etoposide). Patients with incomplete response to chemotherapy or viable tumour cells at the time of surgery also received 55 Gy local RT, and 35 Gy craniospinal RT for disseminated tumours. Response rates were good but 12 of 18 patients relapsed, so the authors concluded that a sustained remission could only be achieved with additional RT (Baranzelli 1998). Further French experiences included chemotherapy followed by RT. Patte and coworkers (2002) reported a series of 38 patients with non-germinomatous GCTs. All of them received three to four cycles of Carboplatin/VP16 and VP16/Ifosfamide followed by a focal RT of 55 Gy (localised disease). The event-free survival of these patients was 67%.

In Germany patients with intracranial non-germinomatous GCTs were treated from 1986 onwards with a combined chemoradiotherapy strategy. 28 patients with non-germinomatous CNS GCT, diagnosed histologically or by markers, received two courses of BEP, followed by resection and two further courses of chemotherapy, using VIP, giving a total cisplatin dose of 400 mg/m². Chemotherapy was followed by craniospinal RT with 30 Gy CSI and a 24 Gy tumour boost. They achieved a relapse-free survival rate of 67% at 5 years with a median follow-up of 110 months (Calaminus 2005).

A European pilot study was initiated in 1993 to test a four course cisplatin containing regimen, followed by craniospinal irradiation with 30 Gy and 24 Gy tumour boost. The cumulative cisplatin dose was 400 mg/m² based on its superiority over 200 mg/m², demonstrated in a comprehensive analysis of the European data (Calaminus 1994). 19 patients were enrolled, and the event-free survival was 81% with a median follow-up of 11 months (Calaminus 1997).

1.4.2.2 Non-European experience of non-germinomatous GCT

The Japanese group published data on 27 non-germinomatous GCTs (Matsutani et al 1997). Between 1983 and 1995 these patients were treated on 2 consecutive protocols. Eighteen patients classified as intermediate risk (Immature Teratoma, teratoma with malignant transformation, mixed tumours) received 3 courses of Carbo-VP or PE followed by local RT of 30 Gy and additional chemotherapy every 3-4 months. A total tumour free rate of 55.6% was achieved after 2 years. Poor risk patients (yolk sac, embryonal carcinoma, mixed malignant) received ICE chemotherapy (3 to 4 cycles) followed by 30 Gy craniospinal RT and 30 Gy tumour boost and further chemo over 3-4 months. In this group of patients treatment failed to control the disease.

In the USA, Buckner and coworkers (1999) reported 11 patients with non-germinomatous GCTs. They received four cycles of VP16 and cisplatin followed by radiotherapy adapted to dissemination; either 59 Gy focal or 30 Gy craniospinal with a 23 Gy tumour boost. All patients remained in remission. In 1997, data on a multicentre American study were reported by Robertson. 18 patients with non-germinomatous malignant GCTs received 3 to 4 cycles cisplatin/VP16 before RT of 55 Gy to the local field and CSI in disseminated tumours. The event-free survival was 67% at 4 years.

Balmaceda (1996) reported 26 patients with non-germinomatous malignant germ cell tumours, treated with chemotherapy alone. All received four cycles of carboplatin, etoposide and bleomycin, with two additional cycles for complete responders and two cycles intensified by cyclophosphamide in others. 13 of 26 relapsed but 6 were salvaged by additional chemotherapy and RT. The authors concurred with
the French in concluding that chemotherapy alone is inadequate to control the disease and that RT is necessary to achieve long term remission.

The role of residual disease prior to radiotherapy has been considered by some groups; persistent macroscopic tumour after chemotherapy is of important prognostic value (Schild et al, 1996, Robertson et al, 1997, Matsutani et al, 1997). The probability of survival in patients with mixed and pure highly malignant germ cell tumours was significantly better after extensive surgical removal as compared to partial removal or biopsy, respectively (10% versus 75%, respectively). It can be assumed that residual disease after treatment will mainly consist of teratoma, which is known to be resistant to radiotherapy, necrotic or scar tissue (Buckner 1999, Weiner 1999).

1.4.3 Teratoma

The incidence of CNS teratomas is unclear as there is no comprehensive registration of this tumour entity in treatment protocols and cancer registries. Only a few observational studies are published, reflecting the rarity of the diagnosis. When these tumours are diagnosed in the newborn period they are often lethal. It appears that only those who undergo a successful surgical intervention survive (Iim 2003).

The impact of immaturity on outcome has also not been systematically evaluated. Garré reported the successful treatment of a patient with immature teratoma with surgery and chemotherapy (Garré 1996).

In the German series 8 patients with teratoma were registered within the MAKEI 89 trial. 6 of 8 patients were operable and two died shortly after birth. Of the operated patients two relapsed. The event free survival was 50% after a follow-up of 51 months (Göbel 1993).

1.5 The first SIOP CNS GCT study (SIOP CNS GCT 96)

For diagnosis, a MRI of head and spine, CSF cytology and measurement of AFP and total HCG in both serum and CSF were mandatory. The thresholds for AFP and total HCG were set at 25 ng/ml and 50 IU/L respectively. Values above these levels indicated the presence of malignant non-germinomatous elements (yolk sac tumour or choriocarcinoma). Histological verification was recommended for diagnosis of all cases with markers below these levels. The diagnosis of germinoma could be considered proven in such cases if the biopsy demonstrated germinoma only. Patients with additional components of only teratomatous tissue were treated as germinoma.

Metastatic disease was defined as the presence of more than one intracranial tumour focus, presence of spinal metastases, tumour cells in CSF or metastases outside CNS. An exception to this was a tumour involving pineal and suprasellar sites without any other dissemination, defined as non-metastatic, bifocal disease.

1.5.1 Aims

Aims in Germinoma:

- to compare two treatment options:
  - Option A: craniospinal irradiation with 24 Gy (1.6 Gy fractions) and a 16 Gy tumour boost
  - Option B: systemic chemotherapy with two cycles of CarboPEI and exclusively focal irradiation with 40 Gy for non-metastatic disease and craniospinal (24 Gy and 16 Gy tumour boost) irradiation for metastatic tumours
These two therapeutic options were not compared in a randomised fashion, following concerns regarding the high rate of registered protocol violations in the previous MAKEI 86 and 89 studies. Instead, participating countries selected one of the options based on national preference, Germany and UK choosing option A, and France and Italy, option B.

- to evaluate if the reduced RT-dosage in option A would produce comparable results to those of MAKEI 89

**Aims in malignant non-germinoma**

- to improve outcome in comparison to MAKEI 89 and SFOP TGM-TC 90-92

Therapy consisted of a combination of chemotherapy and irradiation. For chemotherapy four cycles of Cisplatin, Etoposide, Ifosfamide (PEI) were administered. In cases of non-metastatic disease, focal irradiation with 54 Gy was then administered. In patients with evidence of metastases (CSF cytology or MRI), craniospinal irradiation with 30 Gy was followed by a boost of 24 Gy to all sites of tumour visible on MRI (Calaminus et al 1997).
1.5.2 Registration in SIOP CNS GCT 96

A total of 511 patients diagnosed up to 31st December 2003 had been registered in SIOP CNS GCT 96 by 30th September 2005. Of these, 319 patients had been treated according to the protocol and 192 were non-study patients (including 46 for which essential data was missing).

Table 2: Registration within the participating European countries

<table>
<thead>
<tr>
<th></th>
<th>Germinoma</th>
<th>Non-germinoma</th>
<th>Teratoma</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>37</td>
<td>25</td>
<td>2</td>
<td>64</td>
</tr>
<tr>
<td>Germany</td>
<td>135</td>
<td>82</td>
<td>14</td>
<td>231</td>
</tr>
<tr>
<td>Italy</td>
<td>27</td>
<td>13</td>
<td>2</td>
<td>42</td>
</tr>
<tr>
<td>UK</td>
<td>65</td>
<td>38</td>
<td>4</td>
<td>107</td>
</tr>
<tr>
<td>Other</td>
<td>33</td>
<td>31</td>
<td>3</td>
<td>68</td>
</tr>
<tr>
<td>Total</td>
<td>297</td>
<td>189</td>
<td>25</td>
<td>511</td>
</tr>
</tbody>
</table>

Figure 3: Age and histology of intracranial GCTs

Table 3: SIOP CNS GCT 96: Reported patients with CNS GCT treated and not treated according to the protocol guidelines

<table>
<thead>
<tr>
<th></th>
<th>Germinoma</th>
<th>Non-germinoma</th>
<th>Teratoma</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>protocol pts</td>
<td>196</td>
<td>122</td>
<td>-</td>
<td>318</td>
</tr>
<tr>
<td>missing info</td>
<td>31</td>
<td>15</td>
<td>-</td>
<td>46</td>
</tr>
<tr>
<td>non-protocol pts</td>
<td>70</td>
<td>51</td>
<td>25</td>
<td>146</td>
</tr>
<tr>
<td>total</td>
<td>297</td>
<td>189</td>
<td>25</td>
<td>511</td>
</tr>
</tbody>
</table>
Table 4: Reasons for classification of a non-protocol patient

<table>
<thead>
<tr>
<th>Reason</th>
<th>Germinoma</th>
<th>Non-germinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>no therapy at all (inoperable) or resection only</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>unclear or changed histology</td>
<td>17</td>
<td>3</td>
</tr>
<tr>
<td>changes in chemotherapy or start with other protocol</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>insufficient treatment</td>
<td>11</td>
<td>16</td>
</tr>
<tr>
<td>Overtreatment</td>
<td>34</td>
<td>27</td>
</tr>
<tr>
<td>Total</td>
<td>70</td>
<td>51</td>
</tr>
</tbody>
</table>

1.5.3 Results in germinoma patients registered in SIOP CNS GCT 96

297 patients diagnosed with germinoma up to 31st December 2003 were enrolled and detailed information is available for 196 of these, treated according to protocol guidelines.

1.5.3.1 Comparison of Option A with MAKEI 89

Table 5: EFS of study patients with non-metastatic disease and irradiation dosage according to Option A (pts with RT-deviation of more than 2 Gy are excluded)

<table>
<thead>
<tr>
<th></th>
<th>SIOP CNS GCT 96 option A</th>
<th>MAKEI 89</th>
<th>log-rank p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFS (10 years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>0.93±0.03</td>
<td>0.82±0.07</td>
<td>0.25</td>
</tr>
<tr>
<td>FU-time (months)</td>
<td>86/91</td>
<td>25*/30</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3-122, median 47</td>
<td>3-154, median 97</td>
<td></td>
</tr>
<tr>
<td>Survival (10 years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>alive</td>
<td>0.94±0.03</td>
<td>0.92±0.05</td>
<td>0.85</td>
</tr>
<tr>
<td>FU-time (months)</td>
<td>87/91</td>
<td>28/30</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3-122, median 47</td>
<td>3-161, median 100</td>
<td></td>
</tr>
</tbody>
</table>
* two more events after 122 and 151 months

Despite the reduced irradiation dose, the results are slightly better than in the MAKEI 89 protocol.

1.5.3.2 Comparison of Option A with Option B

Table 6: EFS and survival of protocol pts with intracranial germinoma (SIOP CNS GCT 96)

<table>
<thead>
<tr>
<th></th>
<th>SIOP CNS GCT 96 option A</th>
<th>SIOP CNS GCT 96 option B combined treatment</th>
<th>log-rank p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>0.94±0.02</td>
<td>0.84±0.05</td>
<td>0.03</td>
</tr>
<tr>
<td>FU-time (months)</td>
<td>122/128</td>
<td>59/68</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3-122, median 49</td>
<td>5-85, median 42</td>
<td></td>
</tr>
<tr>
<td>Overall survival (OS)</td>
<td>0.95±0.02</td>
<td>0.86±0.09</td>
<td>0.77</td>
</tr>
<tr>
<td>alive</td>
<td>123/128</td>
<td>65/68</td>
<td></td>
</tr>
<tr>
<td>FU-time (months)</td>
<td>132/128</td>
<td>5-85, median 45</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3-122, median 49</td>
<td>5-85, median 45</td>
<td></td>
</tr>
</tbody>
</table>

The EFS of the combined therapy (option B) is slightly inferior to option A, but OS is comparable for both treatment options.
1.5.3.3 Comparison of unifocal, bifocal and metastatic germinoma

EFS of patients with bifocal or metastatic disease was compared retrospectively with localised unifocal disease, treated according to option A or B (Table 7).

31 patients presented with bifocal disease, i.e. tumour manifestation in both the pineal and suprasellar regions, and 40 patients had metastatic tumours.

Table 7: EFS of patients with germinoma and unifocal, bifocal or metastatic tumours and therapy according to option A or B of the SIOP CNS GCT-96 protocol

<table>
<thead>
<tr>
<th></th>
<th>unifocal</th>
<th>bifocal</th>
<th>metastatic</th>
<th>log-rank p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Option A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>0.94±0.03</td>
<td>0.95±0.05</td>
<td>0.96±0.04</td>
<td>0.98</td>
</tr>
<tr>
<td>FU-time (months)</td>
<td>78/82</td>
<td>19/20</td>
<td>25/26</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3-122, med. 48</td>
<td>10-116, med. 47</td>
<td>3-111, med. 50</td>
<td></td>
</tr>
<tr>
<td>Option B</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>0.77±0.07</td>
<td>0.89±0.10</td>
<td>1.00</td>
<td>0.14</td>
</tr>
<tr>
<td>FU-time (months)</td>
<td>35/43</td>
<td>10/11</td>
<td>14/14</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5-85, med. 38</td>
<td>10-84, med. 58</td>
<td>20-78, med. 44</td>
<td></td>
</tr>
<tr>
<td>log-rank p-value</td>
<td>&lt;0.01</td>
<td>0.69</td>
<td>0.46</td>
<td></td>
</tr>
</tbody>
</table>

- Option A and B: The comparison of patients with unifocal tumours with patients with bifocal or metastatic disease does not show any significant differences.
- Metastatic disease: Chemo + craniospinal irradiation and craniospinal irradiation alone are comparable
- Non-metastatic disease: patients receiving combined treatment show inferior results to those receiving radiotherapy alone.

Implications of the results for SIOP CNS GCT II:
Since the presence of metastatic or bifocal disease does not constitute a significant risk factor, all germinoma patients with metastatic disease will receive craniospinal irradiation without chemotherapy in SIOP CNS GCT II. Patients with bifocal disease will receive treatment according to non-metastatic disease with chemotherapy and ventricular irradiation and a boost to both primaries in the event of incomplete response.

1.5.3.4 Completeness of staging and pattern of relapse in germinoma

Further analysis was undertaken to assess the impact of completeness of diagnostic work-up and staging on outcome. Complete diagnostic work-up includes imaging of the brain and spine, measurement of the tumour markers AFP and total HCG in both serum and CSF, and CSF cytology.

Of the 196 patients, work-up was complete in only 120 cases, while in 76 patients one or more investigations were omitted. The occurrence of events correlated with incompleteness of diagnostic work-up with events in 7% and 24% in completely and incompletely worked up patients respectively (Calaminus et al 2002) (Table 8).

The main explanation for this difference is the incomplete diagnostic evaluation of the CSF (neither cytology nor tumour markers) in 23 patients, among whom five developed an event. One of these patients died as a result of treatment related complications. Two of the three relapsed cases appeared to contain components of choriocarcinoma based on elevated markers (Table 9).
Table 8: Completeness of the pretherapeutic diagnostic work-up in relation to tumour spread (staging: cranial and spinal MRI, CSF cytology), histologic differentiation (tumour markers in serum and CSF) and occurrence of events according to therapeutic option and site of relapse

<table>
<thead>
<tr>
<th>CCR</th>
<th>event</th>
<th>option, site and kind of event</th>
</tr>
</thead>
</table>
| staging complete marker complete | 112 | 8 | A local  
| | | | A DOC metabolic failure during septicemia after therapy  
| | | | A local YST  
| | | | B ventricular  
| | | | B local/ventricular  
| | | | B 2nd malignancy (mal. melanoma)  
| | | | B spinal  
| | | | B local |
| staging complete marker incomplete | 24 | 1 | A local YST (marker increased) |
| staging incomplete marker complete | 22 | 1 | B local+ventricular |
| staging incomplete marker incomplete | 23 | 5 | A DOC sickle cell anemia  
| | | | A local  
| | | | B ventricular CHC (marker increased)  
| | | | B ventricular CHC (marker increased) |
| Total | 181 | 15 |

Table 9: EFS correlated with completeness of the diagnostic evaluation of the CSF

<table>
<thead>
<tr>
<th>SIOP CNS GCT 96</th>
<th>CSF-diagnostics Complete or partially complete</th>
<th>no CSF diagnostics</th>
<th>log-rank p-value</th>
</tr>
</thead>
</table>
| EFS Option A CR | 0.94±0.03  
| FU-time (months) | 106/111  
| | 3-122, median 47  
| | 0.94±0.06  
| | 16/17  
| | 3-99, median 55 |
| EFS Option B CR | 0.88±0.05  
| FU-time (months) | 56/62  
| | 5-85, median 43  
| | 0.42±0.22  
| | 3/6  
| | 8-78, median 18 |
| EFS total CR | 0.92±0.02  
| FU-time (months) | 162/173  
| | 3-122, median 46  
| | 0.80±0.09  
| | 19/23  
| | 3-99, median 49 |

Even after complete diagnostic evaluation, relapses have been observed. However, the recurrent tumours were all germinoma except for one case. In contrast, the diagnosis at relapse was different to that at first diagnosis in three of seven patients with incomplete diagnostic work-up. The implication is that components of yolk sac tumour (n=1) and choriocarcinoma (n=2) might have been detected with a complete diagnostic evaluation, which would have resulted in treatment according to a different and more intensive strategy.

The sites of relapse are mainly local (n=6), ventricular (n=3) or combined (n=2). An isolated spinal relapse has been documented only once. Since the ventricular relapses have developed only in
patients treated according to option B, it may be concluded that even after systemic chemotherapy, focal irradiation may not be sufficient to control disease in the ventricles (Alapetite et al. 2002).

Implications for SIOP CNS GCT II:
Localised germinoma can be treated effectively with chemotherapy and limited field radiotherapy, to spare radiation effects on spinal axis and whole brain. In SIOP CNS GCT 96, this option was implemented for patients with localised germinoma. The results show that complete staging is crucial if craniospinal irradiation (CSI) is not used and that combined treatment can be employed in non-metastatic disease to avoid CSI, but suggest that chemotherapy + focal irradiation might be insufficient to control subclinical disease in the ventricular area. Therefore, ventricular irradiation will be established in SIOP CNS GCT II. As most of the relapses occurred in incompletely staged patients, complete staging is of crucial importance.

1.5.4 Residual disease at the end of treatment
The presence of residual tumour at the end of treatment is a recognised risk factor for most malignant brain tumours. The impact of residual disease for intracranial germinoma has therefore also been analysed retrospectively (Calaminus 2004). Time points for evaluation were after surgery, three to six months after radiotherapy and at follow-up (1, 2 and 5 years after diagnosis). Residual lesions were defined as any abnormal contrast enhancement persisting in the former tumour region.

107 study patients were evaluated. Thirteen had been completely resected and could therefore not be analysed according to response to treatment. 54 patients had a subtotal or partial resection of whom 39 received craniospinal irradiation (option A) and 15 patients had combined treatment (option B). A stereotactic biopsy was performed in 40 patients, of whom 31 received option A and 9 option B (Figure 4).

**Figure 4: Surgery, therapy option and residual lesions (rl+) in CNS germinoma**

<table>
<thead>
<tr>
<th>Complete resection</th>
<th>Partial resection</th>
<th>Stereotactic biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>54</td>
<td>40</td>
</tr>
<tr>
<td>Option A</td>
<td>Option B</td>
<td></td>
</tr>
<tr>
<td>39</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Option A</td>
<td>Option B</td>
<td></td>
</tr>
<tr>
<td>31</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Residual lesions</td>
<td>Residual lesions</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In summary, 30 patients (28%) had residual tumour after radiotherapy. Residual lesions were between 0.2 cm and 2.0 cm in diameter. No patient underwent surgery or any other treatment for this residual disease. In follow-up, 13 tumours resolved spontaneously (43%), the others remained stable and only one of the 30 patients developed a progression / relapse.

In comparison to the group of patients without residual lesion at the end of therapy (n=64, 5 events), no difference in event-free survival could be detected (no residual: EFS 0.88±0.06 versus residual lesion: EFS 0.97±0.03) (Calaminus et al 2004). It is therefore concluded that germinoma patients with residual tumour at the end of treatment do not require further therapy.
1.6 Results in malignant non-germinoma patients registered in SIOP CNS GCT 96

1.6.1 Comparison with MAKEI 89

189 patients diagnosed up to 31st December 2003 were registered in SIOP CNS GCT 96 and sufficient information is available for analysis of 123 of these, treated according to protocol guidelines. In comparison to MAKEI 89, the international multi-centre study resulted in a 10% increase in EFS. There are two possible explanations for this: two DOCs occured during chemo in SIOP CNS GCT 96. In MAKEI 89, only one DOC was caused by chemo, but 3 DOCs were observed as a result of surgery. The proportion of patients diagnosed without biopsy increased considerably and, as a result, no perioperative deaths prior to the start of chemotherapy occurred. In addition, chemotherapy has been intensified as a result of replacing bleomycin with ifosfamide (Table 10).

Table 10. EFS of protocol pts with malignant non-germinoma

<table>
<thead>
<tr>
<th></th>
<th>SIOP CNS GCT 96</th>
<th>MAKEI 89</th>
<th>log-rank p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFS (10 years)</td>
<td>0.70±0.05</td>
<td>0.56±0.10</td>
<td>0.06</td>
</tr>
<tr>
<td>CR</td>
<td>91/123</td>
<td>14/25</td>
<td></td>
</tr>
<tr>
<td>FU-time (months)</td>
<td>0-103, median 35</td>
<td>0-142, median 66</td>
<td></td>
</tr>
<tr>
<td>Survival (10 years)</td>
<td>0.67±0.09</td>
<td>0.56±0.10</td>
<td>0.02</td>
</tr>
<tr>
<td>alive</td>
<td>100/123</td>
<td>14/25</td>
<td></td>
</tr>
<tr>
<td>FU-time (months)</td>
<td>0-106, median 40</td>
<td>0-142, median 66</td>
<td></td>
</tr>
</tbody>
</table>

1.6.1.1 The impact of dissemination on survival

Figure 5: EFS of study patients with non-metastatic versus metastatic NGGCT

Ninety-two patients with non-metastatic NGGCT received chemotherapy and focal irradiation, and 69 of these patients are in continuous remission. Five additional patients with local disease but incomplete workup and 26 patients with metastatic tumours received chemotherapy and craniospinal irradiation; of these 31 patients, 22 are in continuous first remission (follow-up time 0-103, median 35 months). Patients with non-metastatic disease and metastatic disease are compared, regardless of extent of radiotherapy, in figure 5. One patient from each group died during chemotherapy, due to complications.
Implications for SIOP CNS GCT II:
Radiotherapy strategy will continue unchanged.

1.6.1.2 Incomplete staging
Analysis was undertaken to assess the impact of incomplete staging (CSF cytology, spinal MRI) on prognosis. Among the 92 study patients with non-metastatic disease and chemotherapy + focal irradiation, tumour staging was evaluated (Table 11).

Table 11: Workup and outcome in NGGCTs

<table>
<thead>
<tr>
<th>SIOP CNS GCT 96</th>
<th>CR</th>
<th>Event</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Workup complete (w.r.t. dissemination)</td>
<td>57</td>
<td>19</td>
<td>76</td>
</tr>
<tr>
<td>Workup incomplete (w.r.t. dissemination)</td>
<td>12</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>Total</td>
<td>69</td>
<td>23</td>
<td>92</td>
</tr>
</tbody>
</table>

p=1.00 (w.r.t. = with respect to)

Implications for SIOP CNS GCT II:
Based on the data available, incomplete tumour staging in NGGCTs does not carry an unfavourable prognosis in terms of survival, as only four of these 16 patients relapsed in comparison to 19 of 76 with complete staging according to dissemination. However, a complete staging is recommended to detect high risk patients (see section 5.2) and to treat patients appropriately according to dissemination.

1.6.1.3 Levels of tumour markers at diagnosis

The prognostic impact of the levels of tumour markers was evaluated retrospectively. Levels of AFP and total HCG were measured in at least one compartment (CSF or serum) in 120 patients.

Table 12: Rate of relapse of intracranial malignant non-germinomatous GCTs correlated with the levels of the tumour markers AFP and total HCG in CSF and/or serum

<table>
<thead>
<tr>
<th></th>
<th>CR</th>
<th>Event</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Both within defined limits</td>
<td>7</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Only AFP elevated (&gt;25 ng/ml)</td>
<td>23</td>
<td>16</td>
<td>39</td>
</tr>
<tr>
<td>Only total HCG elevated (&gt;50 IU/l)</td>
<td>36</td>
<td>6</td>
<td>42</td>
</tr>
<tr>
<td>Both elevated</td>
<td>22</td>
<td>9</td>
<td>31</td>
</tr>
<tr>
<td>Total</td>
<td>88</td>
<td>32</td>
<td>120</td>
</tr>
</tbody>
</table>

Chi-squared (X²) Test p=0.04

Normal tumour markers (within defined limits) were measured in only eight patients, and one of these patients relapsed. An isolated elevation of total HCG did not affect prognosis, whereas more than half of the patients with isolated or combined elevation of AFP suffered an event.

50 of the 122 evaluable patients (AFP measured in serum and/or CSF) showed AFP values < 25 µg/l; 43 of these patients are in continuous first remission. In contrast, 9 of 16 patients with very high levels of AFP (>1000 ng/ml) relapsed (Figure 6, Table 13).
Figure 6: AFP-value and EFS of protocol pts with intracranial malignant NGGCTs

Table 13: AFP-group and outcome in NGGCTs

<table>
<thead>
<tr>
<th></th>
<th>CR</th>
<th>Event</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFP ( &lt; 1000 \text{ ng/ml} )</td>
<td>83</td>
<td>23</td>
<td>106</td>
</tr>
<tr>
<td>AFP ( &gt; 1000 \text{ ng/ml} )</td>
<td>7</td>
<td>9</td>
<td>16</td>
</tr>
<tr>
<td>Total</td>
<td>90</td>
<td>32</td>
<td>122</td>
</tr>
</tbody>
</table>

Chi-squared \((X^2)\) Test \(p<0.01\)

Implications for SIOP CNS GCT II:
Comparison of marker elevation between serum and CSF clearly demonstrated that there is a proportion of patients with elevation of total HCG in CSF in the presence of normal \((<25 \text{ ng/ml})\) serum levels. Conversely for AFP, the marker was elevated earlier in serum than in CSF in some patients. It is therefore essential to evaluate tumour markers in both serum and CSF.

1.6.1.4 Residual lesions at the end of therapy

The presence of residual tumour was analysed as a potential risk factor for relapse. 43 of the 99 patients (43\%) treated according to the protocol and with information about status at the end of therapy had residual tumour at the end of treatment (Figure 7). In 23 patients, no information regarding the status at the completion of therapy is available.

More than every second patient with residual tumour relapsed, whereas relapses were seen in only one out of seven patients in complete remission at the end of therapy (chemo-, radiotherapy, surgery).
Figure 7: Residual tumour and EFS of study patients with intracranial malignant non-germinomatous GCT (log-rank p<0.01) (n=99)

Implications for SIOP CNS GCT II:
As the data confirm that focal RT in addition to induction chemotherapy in non-metastatic patients is sufficient to control subclinical disease, the radiotherapy strategy of SIOP CNS GCT 96 for non-germinomatous malignant CNS GCT will continue unchanged.

Incompletely staged patients will be excluded as protocol treated patients and craniospinal RT will be recommended (see chapter 4).

The AFP level in serum and/or CSF correlates with the risk of relapse and is prognostically unfavourable if it is higher than 1000 ng/ml. These patients will be considered high risk and will receive intensified chemotherapy.

In the presence of residual disease after chemotherapy, resection of residual tumour prior to radiotherapy will be recommended. In the event that surgical intervention at that time point is considered impossible or expected to result in significant morbidity, the possibility of continuing radiotherapy and postponing surgery can be considered in discussion with the national investigator/coordinator. If malignant viable tumour cells are present, an intensified treatment will be delivered (see chapter 7.2).

Age <6 years and outcome:
In the SIOP 96 trial all children (n=3) which were less than 6 years of age with non-germinomatous germ cell tumours relapsed and died, therefore these children will be handled as poor risk patients and receive treatment intensification like the group of patients with AFP >1000 ng/ml
Intracranial teratomas are rare and as they have traditionally been considered as a benign disease the collection of information within previous European studies has been incomplete at best. The SIOP CNS GCT 96 protocol did not include recommendations for treatment of intracranial teratomas, because of a paucity of data on these rare and heterogeneous tumours on which to base guidance. Nevertheless, 25 patients have been registered and followed up prospectively.

In general, among the teratoma patients, the histological diagnosis has rarely been accompanied by a complete diagnostic work-up including measurement of tumour markers in serum and CSF, assessment of CSF cytology or spinal MRI. Therefore, in most cases the assignment of patients to the group of teratomas has been made on the basis of the histopathological diagnosis only. The histological grades of immaturity were diagnosed at the following frequencies: grade 0 n=11, grade 1 n=3, grade 2 n=5 and grade 3 n=4, unclear n=2. The age range of affected girls was 0–8 years (median 0.5 years) and of boys 0-19 years (median 8). Tumours ranged in size from 1.2 to 8 cm in maximum diameter (median 5 cm).

Twenty-three patients underwent tumour resection, which was reported as complete in 15 patients, subtotal in 3 and partial in 5. Two neonates succumbed to their tumours without surgical treatment. Cases can be characterised further as follows:

- Seven of 11 patients with grade 0 teratoma had a complete resection of whom 3 subsequently relapsed but are surviving in second remission. Four patients are surviving with incomplete resection, even though one patient relapsed.
- Only 3 patients underwent complete resection for grade 1 teratoma. One relapse occurred but is in second remission.
- Five children were diagnosed with grade 2 teratoma which was completely resected in 3 cases. All of these patients received chemotherapy and two additional radiotherapy. They are in first remission. Both patients who had an incomplete resection, one of whom had additional chemotherapy, died of disease.
- Two of 4 patients with grade 3 immature teratoma underwent complete resection without further therapy. Both relapsed and one of these died. One of the 2 patients with incomplete resection received additional radiotherapy and survived, whilst the other received unknown additional treatment and is also alive.
- One patient with unclear histology (no resection possible) was treated with one cycle of chemotherapy but died due to progression. One child died without any treatment.

This information supports the importance of immaturity and the role of primary resection (Im et al 2003). Because of the small numbers of patients, the question of whether adjuvant treatment is beneficial in immature teratomas (grade 2/3) remains unanswered. In this context, single case reports have to be taken into account, which include some evidence that patients with relapsed teratomas may benefit from adjuvant chemotherapy (Garré et al 1996).

**Implications for SIOP CNS GCT II**

Patients with intracranial teratomas should be registered in order to obtain more information regarding the epidemiology and biology of this rare disease. A complete diagnostic work-up according to the guidelines for malignant intracranial GCTs (tumour markers in serum and CSF, CSF cytology and complete radiographic assessment including imaging of the spinal axis) is strongly recommended. Central review by reference institutions, particularly pathology, will contribute important information on histological grading and appearance of malignant microfoci.
Treatment for mature and immature teratoma needs to be individualised, based on the age of the patient, clinical status, tumour stage and histology. Thus, no overall therapeutic strategy will be outlined in the protocol but recommendations may be given on an individual basis.

1.8 Conclusions from the data

1.8.1 Germinoma

Large retrospective series and the prospective trials discussed here have shown that craniospinal irradiation alone is a safe therapy yielding high cure rates. In localised disease, radiotherapy alone with restricted treatment volumes (omission of spinal irradiation) may be equally effective (Shibamoto 2001, Wolden et al. 1995). When delivered as combined treatment with chemotherapy, focal radiotherapy fields are associated with an increased risk of ventricular relapse (Alapetite 2002). In this setting ventricular irradiation is the safest treatment, in order to control subclinical disease. A dose of 40 Gy to the primary tumour site achieves high local control rates. In conjunction with chemotherapy, a dose reduction to 24 Gy might be possible based on Japanese data (Matsutani et al, 2001, Aoyama et al, 2002). Because of the excessive relapse rates in some series (Balmaceda 1996), chemotherapy alone cannot be accepted as primary treatment.

In metastatic disease radiotherapy of the CSA followed by a boost to the tumour site remains the mainstay of therapeutic management (Buckner 1999, Ayoama 2002). Additional chemotherapy does not confer any additional benefit.

1.8.2 Nongerminomatous malignant germ cell tumours

These tumours display a high responsiveness to chemotherapeutic agents, although chemotherapy alone is insufficient to achieve cure, being associated with a 50% relapse rate in 26 patients in the Memorial Sloan Kettering Cancer Centre Group cohort (Balmaceda et al. 1996, Baranzelli 1998). The combination of radiotherapy with platinum based chemotherapy plays a key role in achieving optimal outcome and has now become the treatment standard in this group of tumours. Although NGGCTs appear to be relatively radioresistant compared to their germinoma counterparts, there is strong evidence that radiotherapy plays a crucial part in the management of these malignant intracranial tumours. There is a clear dose response relationship indicating that doses in excess of 50 Gy should be given to the primary tumour site (Buckner 1999, Matsutani 2001, Robertson 1997). The data in the published literature also underline the observation made in SIOP CNS GCT 96 that focal irradiation is sufficient for local tumour control in localised disease, if a dose of more than 50 Gy is delivered. The prognostic value of AFP elevation at diagnosis and the persistence of residual disease at the end of treatment has been demonstrated in SIOP CNS GCT 96, and these findings will be carried forward as means of identifying high risk patients.

1.9 Study design and rationale for changes compared to SIOP CNS GCT 96

Specific changes in therapy compared to preceeding SIOP CNS GCT 96 protocol are given below, according to histological subtype.

The diagnostic and therapeutic algorithms for the current study are outlined in the flow-sheets (see Figure 9 and 10). They involve careful diagnostic work-up to establish histological subtype (teratoma, germinoma, malignant NGGCT). This is based on tumour markers with biopsy reserved for cases in which markers are within the defined limits, and staging in order to determine treatment stratification, including fields for delivery of radiotherapy.
1.9.1 Germinoma

Germinoma should be diagnosed based on biopsy performed in the context of levels of the tumour markers AFP and total HCG in both serum and CSF within the defined limits (AFP ≤ 25 ng/ml, total HCG ≤ 50 IU/l).

Positive CSF-cytology and/or positive imaging is defined as metastatic disease and cases with incomplete staging should be treated as metastatic.

Bifocal tumours (pineal and suprasellar only) are considered non-metastatic disease and will be treated in the same way as unifocal tumours. However, in this group of patients, a European consensus has been reached that a biopsy for histological verification is not mandatory if typical appearances are present on imaging and all other diagnostic procedures are complete, particularly the presence of levels of AFP and total HCG within the defined limits.

In localised germinoma, evaluation of response to chemotherapy will need to be made by the national responsible radiologist in real time, according to neuroradiological guidelines, as it will influence dose of radiotherapy to be given. All doubtful cases will be discussed with the international panel.

Detection of biological/genetic features may play a role in the future for treatment stratification. It is therefore also strongly recommended that CSF and tissue samples should be stored and made available to the national tissue banks.

1.9.1.1 Non-metastatic germinoma – Rationale for extended target volume of irradiation (ventricular system) after chemotherapy

The SIOP 96-arm B study and the previous French SFOP 90 study have applied a combined approach to uni- and bifocal germinomas with carboplatin based primary chemotherapy followed by radiation therapy directed to the primary tumour bed only up to 40 Gy. A relapse rate of 11% and 15% at 19 m and 72 m median follow up was seen (Alapetite 2002). Ventricular relapses - mainly at margins or out of RT fields - were the predominant pattern in both series (75%). These results suggest that chemotherapy used in these protocols might be less effective than RT in controlling ventricular dissemination. As it has been shown that focal irradiation is unable to prevent relapses reliably at the edge of the field or within the ventricles, even in the context of two cycles of systemic chemotherapy, the radiotherapy field has to include the whole ventricular system.

This combined modality approach is justified in the pursuit of reduced radiotherapy doses and volumes. However, in germinoma the radiation field will be increased compared to SIOP CNS GCT 96 and the dose of irradiation will be determined according to response to chemotherapy.

1.9.1.2 Non-metastatic germinoma – Rationale for dose reduction of radiotherapy in case of complete remission or residual disease after chemotherapy

Essentially, radiotherapy dose can be based on tumour burden (Shibamoto 2001). Chemotherapy achieves conversion from macroscopic tumour to subclinical disease thereby allowing a dose reduction to the tumour site (Sawamura 1998, Kitamura 1999, Matsutani 2001, Ayoama 2002).

In cases of completely staged non-metastatic disease, combined chemotherapy and radiotherapy will be given in order to achieve a further reduction of radiotherapy dose. In the event of complete remission after chemotherapy (standard risk), patients will receive ventricular irradiation with 24 Gy in order to treat subclinical subependymal or intraventricular spread effectively.
This study addresses the question in patients with a complete response to chemotherapy whether combined treatment in localised germinoma with chemotherapy (Carboplatin / Etoposide / Ifosfamide) together with 24 Gy ventricular radiotherapy is equivalent in terms of survival to that achieved in SIOP CNS GCT 96 with 40 Gy focal RT.

The additional tumour boost of 16 Gy after 24 Gy whole ventricular radiation (WVI) can be omitted when there is no radiological evidence of any residual disease after chemotherapy. Patients with any amount of residual tumour will receive an additional tumour boost of 16 Gy. In case of teratoma component in primary histology and stable disease after chemotherapy, a tumour resection has to be considered. If no resection is performed or the tumour is resected incompletely, a tumour boost up to 54.4 Gy is recommended.

1.9.1.3 Metastatic or incompletely staged germinoma

In the event of metastatic disease (positive CSF cytology and/or positive imaging), or of incomplete staging, craniospinal radiotherapy with 24 Gy CSI and a boost to visible tumour sites up to 40 Gy should be given.

In the presence of a teratoma component in the primary histology and stable disease of the primary tumour after 24 Gy, an increase of the tumour boost up to 54.4 Gy should be discussed with the national chief investigator, if the tumour is not completely resected.
### 1.9.1.4 Summary of changes in the management of germinoma

**Table 14: Changes in the management of germinoma**

<table>
<thead>
<tr>
<th>Histology</th>
<th>Diagnostics</th>
<th>SIOP CNS GCT 96</th>
<th>SIOP CNS GCT II</th>
</tr>
</thead>
<tbody>
<tr>
<td>germinoma (± teratoma) non-metastatic (unifocal)</td>
<td>biopsy* marker serum/CSF: according to definition CSF cytology: negative cranial/spinal MRI: no dissemination</td>
<td>24 Gy craniospinal</td>
<td>Carbo/VP16 ** x 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>16 Gy tumour</td>
<td>if CR: 24 Gy ventricles</td>
</tr>
<tr>
<td></td>
<td></td>
<td>or Carbo/VP16 ** x 2</td>
<td>if PR: 24 Gy ventricles</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40 Gy focal</td>
<td>16 Gy tumour</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>if component of teratoma and SD, incompletely or not resected:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>boost up to 54.4 Gy</td>
</tr>
<tr>
<td>germinoma (± teratoma) non-metastatic (bifocal - only pineal + suprasellar)</td>
<td>biopsy marker serum/CSF: according to definition CSF cytology: negative cranial/spinal MRI: no dissemination</td>
<td>24 Gy craniospinal</td>
<td>Carbo/VP16 ** x 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>16 Gy tumour</td>
<td>if CR: 24 Gy ventricles</td>
</tr>
<tr>
<td></td>
<td></td>
<td>or Carbo/VP16 ** x 2</td>
<td>if PR: 24 Gy ventricles</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40 Gy focal</td>
<td>16 Gy tumour</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>if component of teratoma and SD, incompletely or not resected:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>boost up to 54.4 Gy</td>
</tr>
<tr>
<td>germinoma (± teratoma) metastatic or incompletely staged</td>
<td>biopsy marker serum/CSF: according to definition CSF cytology: positive or cranial/spinal MRI: dissemination</td>
<td>24 Gy craniospinal</td>
<td>Carbo/VP16 ** x 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>16 Gy tumour</td>
<td>if CR: 24 Gy ventricles</td>
</tr>
<tr>
<td></td>
<td></td>
<td>or Carbo/VP16 ** x 2</td>
<td>if PR: 24 Gy ventricles</td>
</tr>
<tr>
<td></td>
<td></td>
<td>24 Gy craniospinal</td>
<td>16 Gy tumour</td>
</tr>
<tr>
<td></td>
<td></td>
<td>24 Gy craniospinal</td>
<td>if component of teratoma and SD: discuss</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+ 16 Gy tumour</td>
<td>boost up to 54.4 Gy</td>
</tr>
</tbody>
</table>

* or resection

**Details for Chemotherapy see chapter 6**

**Details for RT see 6.1.6 (table 19,20,21) and 6.2.2 (table 22,23)**
1.9.2 Malignant non-germinoma

In the previous study, all patients with malignant non-germinoma received pre-operative chemotherapy followed by focal radiotherapy for localised tumours and craniospinal radiotherapy for disseminated disease (positive CSF cytology or imaging). There is no rationale for changing the radiotherapy regimen as it has clearly been shown that radiotherapy according to tumour dissemination is able to control local (focal RT) and disseminated disease (CSI). It is also clear that there is a selected group of poor risk patients (AFP>1000 ng/ml) that may benefit from more intensive chemotherapy and that surgery of residual disease plays an important role. Treatment will therefore be intensified in patients with AFP >1000 ng/ml (in serum or CSF) with the aim of increasing cure rates in this group of patients and surgery will be strongly recommended in patients with residual tumour after chemotherapy. If malignant viable tumour cells are present, intensified treatment will be delivered following bone marrow harvest.

Irrespective of stage, patients with AFP ≤ 1000 ng/ml will receive four cycles of PEI. Response to treatment will be evaluated after the third cycle of chemotherapy. In the event of complete remission (standard risk), patients with non-metastatic tumours at diagnosis will receive a fourth cycle followed by focal irradiation. If partial response has been documented, complete surgical resection of residual tumour tissue has to be considered whenever possible prior to the fourth cycle of PEI chemotherapy. Patients with viable tumour cells in a resection specimen after 3 courses of chemotherapy will receive one cycle of HD PEI before irradiation is administered.

Treatment of patients with disseminated tumours will follow the same strategy. However, instead of focal radiotherapy, craniospinal radiotherapy (30 Gy) will be administered with a tumour boost of 24 Gy to the primary tumour and all metastases visible on MRI at diagnosis.

Patients defined as high risk based on high initial levels of AFP (> 1000 ng/ml) will receive two cycles of PEI chemotherapy followed by two cycles of dose-intensified chemotherapy (HD-PEI) with autologous stem cell support. For this purpose, peripheral hematopoietic stem cells will need to be harvested following either the first or the second cycle of standard PEI. Furthermore, patients in whom the histological evaluation after delayed tumour resection has revealed viable malignant tumour cells will also be considered high risk. In this rare situation, harvesting of autologous bone marrow will be recommended in order to keep the interval between the third PEI cycle and the HD-PEI chemotherapy as short as possible.

In the SIOP 96 trial all children (n=3) who were less then 6 years of age with non-germinomatous germ cell tumours relapsed and died. These children will therefore be treated as high risk patients. In children < 6 years of age at at diagnosis, an intensified treatment strategy is recommended, as for patients with AFP > 1000 ng/ml. Radiotherapy according to dissemination is given only in patients older than or equal 6 years of age at time of radiotherapy. All of these very rare patients should, however, be discussed with the national co-ordinator/investigator.

Detection of biological/genetic features may play a role in the future for treatment stratification. It is therefore also strongly recommended that CSF and fresh tissue samples of cases where biopsies or resections have been undertaken should be stored and made available to the national tissue banks.
### Table 15 Changes in the management of malignant non-germinoma

<table>
<thead>
<tr>
<th>Histology</th>
<th>Diagnostics</th>
<th>SIOP CNS GCT 96</th>
<th>SIOP CNS GCT II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant non-germinoma (± teratoma) (localised)</td>
<td>(biopsy) marker serum/CSF: according to definition CSF cytology: negative cranial/spinal MRI: no dissemination</td>
<td>4 x PEI 54 Gy focal</td>
<td>4 x PEI 54 Gy focal&lt;br&gt;resection of residual after 3 courses of chemotherapy, therapy intensification in case of viable malignant tumour&lt;br&gt;AFP ≤ 1000 ng/ml and age &gt; 6 yrs: 4 x PEI 54 Gy focal&lt;br&gt;AFP &gt; 1000 ng/ml and/or age ≤ 6 yrs: 2 x PEI, 2 x HD PEI 54 Gy focal (only patients aged &gt; 6 yrs) note: &lt; 6 yrs discuss with national co-ordinator resection of residual after chemotherapy</td>
</tr>
<tr>
<td>Malignant non-germinoma (± teratoma), (metastatic or incompletely staged)</td>
<td>(biopsy) marker serum/CSF: according to definition CSF cytology: positive or cranial/spinal MRI: dissemination</td>
<td>4 x PEI 30 Gy craniospinal + 24 Gy tumour</td>
<td>4 x PEI, 30 Gy craniospinal + 24 Gy tumour&lt;br&gt;resection of residual after 3 courses of chemotherapy, therapy intensification in case of viable malignant tumour&lt;br&gt;AFP ≤ 1000 ng/ml and age &gt; 6 yrs: 4 x PEI, 30 Gy craniospinal + 24 Gy tumour (only patients aged ≥ 6 yrs) note: ≤ 6 yrs discuss with national co-ordinator resection of residual after chemotherapy</td>
</tr>
</tbody>
</table>

**Details for chemotherapy see chapter 7**
**Details for RT see 7.1.6 (table 24,25) and 7.2.6 (table 26,27)**
1.9.3 Teratoma

Published evidence available regarding the management of teratomas is sparse. Surgery seems to be the most appropriate step if feasible. The impact of immaturity is unclear and also the value of adjuvant treatment such as chemotherapy or RT has not been investigated prospectively to date.

For the purposes of this study, patients with intracranial teratomas should be registered in order to obtain better information regarding the epidemiology and biology of this rare disease. A complete diagnostic work-up according to the guidelines for malignant intracranial GCTs is recommended (tumour markers in serum and CSF, CSF cytology and complete radiographic assessment including imaging of the spinal axis). Central review by reference institutions, particularly pathology, will contribute important information on histological grading and appearance of malignant microfoci. The specific search for malignant microfoci constitutes a relatively novel approach. This evaluation requires the routine use of immunohistochemical analysis as part of the reference pathological review. Teratomas, in which macroscopic residual is present after surgical resection and in which malignant microfoci of yolk sac tumour have been detected, will be treated according to the guidelines for malignant non-germinomatous GCTs as will histologically pure teratomas with elevated tumour markers.

Surgery is the main treatment option for teratoma; additional treatment may be delivered according to histology and resection status. In this group of patients quality of survival data will be collected to describe for the first time the quality of survival at diagnosis (surgery), at the end of treatment and at follow-up. Treatment for mature and immature teratoma needs to be individualised, based on the age of the patient, clinical status, tumour stage and histology. Thus, no overall therapeutic strategy will be outlined in the protocol but recommendations will be given on an individual basis.

The goal for the future is to accrue sufficient data on incidence and epidemiology of teratoma, biological and histological behaviour, impact of surgery and of other treatments in order to develop standardised guidelines for diagnosis and treatment of this subgroup of patients. To this end, it is therefore also desirable to store CSF and fresh tissue samples and make them available to the national tissue banks.
2 AIMS OF THE STUDY

2.1 Primary objectives

2.1.1 Germinoma

- To maintain current high EFS rates using a risk adapted approach
  - In localised germinoma: to omit whole brain and spinal irradiation by using combined treatment with standard chemotherapy and ventricular irradiation (+/- boost)
  - In bifocal tumours (pineal + suprasellar): to treat as non-metastatic disease and to omit whole brain and spinal irradiation by using combined treatment with standard chemotherapy and ventricular irradiation (+/- boost)
  - In metastatic disease: to maintain current excellent EFS in metastatic germinoma with craniospinal irradiation

2.1.2 Malignant non-germinoma

- To improve EFS in high risk patients by intensifying treatment
  - by dose escalation of standard chemotherapy in patients identified as high risk at diagnosis
  - by standardising the surgical approach for residual disease after treatment

2.1.3 Teratoma

- To register patients and collect data regarding diagnostics, treatment and outcome in order to develop future treatment strategies

2.2 Secondary objectives

2.2.1 Germinoma

- To minimize long term effects of irradiation by sparing spinal and whole brain radiotherapy in non-metastatic disease

2.2.2 Malignant non-germinoma

- In standard risk, to maintain EFS with standard chemotherapy and local irradiation

2.2.3 Teratoma

- To evaluate the influence of surgery and treatment on outcome to assist in the development of a future treatment strategy

2.2.4 For all histological subtypes:

- To improve accuracy of diagnosis and staging in all registered patients
- To standardise neurosurgical intervention
- For all patients requiring biopsy or resection according to protocol guidelines, to store fresh tumour material, and CSF where possible, for use in future biological studies (see pathology appendix F.5 for details)
- To collect information on side effects on all registered patients (including follow-up patients), particularly relating to growth, endocrine status, neurological status and quality of survival (QOS)
3 STUDY DESIGN

3.1 Type of study and expected accrual

This is a prospective, non-randomised multicentre study stratified according to risk groups.

On the basis of recruitment to SIOP CNS GCT 96, an annual accrual in the region of 75 new cases per year is expected internationally.

3.2 Time schedule, study duration

The end of the study will be defined 2 years following recruitment of the last patient. The duration of recruitment is expected to last 5 years in order to include the required number of patients. Data on long term survival will be collected for at least 5 years from diagnosis.

3.3 Stratification of risk groups

Patients will be stratified according to results of imaging (MRI head and spine), tumour markers in serum and CSF, CSF cytology and/or histology (in case of negative markers).

For diagnostics and therapy please see chapters 5, 6 and 7

Figure 8: Risk stratification

<table>
<thead>
<tr>
<th>Diagnostic group (see chapter 5.2.3)</th>
<th>Specific risk</th>
<th>Staging* (see chapter 5.3.2)</th>
<th>Treatment group</th>
</tr>
</thead>
<tbody>
<tr>
<td>GERMINOMA</td>
<td></td>
<td>non-metastatic</td>
<td>NON-METASTATIC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>metastatic*</td>
<td>METASTATIC*</td>
</tr>
<tr>
<td>NON-GERMINOMA</td>
<td>age &gt; 6 years and AFP &lt; 1000 NG/ML</td>
<td>non-metastatic</td>
<td>STANDARD RISK irr. acc. to staging</td>
</tr>
<tr>
<td></td>
<td>age &lt; 6 years and/or AFP &gt; 1000 NG/ML</td>
<td>metastatic*</td>
<td>HIGH RISK irr. acc. to staging</td>
</tr>
<tr>
<td>TERATOMA</td>
<td></td>
<td>non-metastatic</td>
<td>INDIVIDUAL</td>
</tr>
</tbody>
</table>

* patients who are incompletely staged and in whom metastases can therefore not be excluded should be treated as metastatic and are not registered as study patients
4 PATIENT SELECTION CRITERIA AND STUDY ENTRY

4.1 Registration

Consent for the study must be obtained prior to treatment of patients according to protocol. Registration should be completed by fax or RDE (remote data entry by MARVIN) as soon as possible after consent is obtained and in any case must take place before treatment is started. The Fax sheet should be sent to the national coordinating/data centre. The national data centre should inform the international data centre of the registration.

In countries where trial insurance is required this will only cover study patients (at/after date of arrival of registration fax at coordination centre).

4.2 Inclusion and exclusion criteria for study patients

Inclusion criteria

- Primary diagnosis of an intracranial germ cell tumour
- Main residence in one of the participating countries
- Written consent for trial participation, diagnosis and treatment according to the protocol and consent for data transfer

There is no upper or lower age limit for inclusion in the study.

Note: For females of child-bearing potential, a negative pregnancy test prior to study treatment is required. Any patient who is of reproductive age should agree to use adequate contraception for the duration of treatment and until at least 6 months after end of therapy.

Exclusion criteria

- Primary diagnosis predating the opening of SIOP CNS GCT II
- Patients with CNS GCTs as second malignancies
- Patients in whom treatment according to CNS GCT II is not intended
- Patients with a medical, psychiatric or social condition incompatible with protocol treatment
- Participation within a different trial for treatment of germ cell tumours and/or concurrent treatment within any other clinical trial. The only exceptions to this are trials with different endpoints, involving aspects of supportive treatment which can run parallel to SIOP CNS GCT II without influencing the outcome of this trial e.g. trials on antiemetics, antimycotics, antibiotics, strategies for psychosocial support etc.
- Pregnancy and lactation
- Any treatment not given according to protocol prior to registration

Patients excluded from the trial based on presence of exclusion criteria maybe eligible for registration as follow-up patients.

4.2.1 Definition of patient status

Study patients are those patients who fulfill the inclusion criteria, and no exclusion criteria are given.
The accuracy of initial diagnosis and staging in intracranial GCTs has a significant impact on treatment decisions and thus outcome. Diagnosis of GCTs is based on clinical symptoms and signs, markers, neuroimaging, CSF cytology and histological confirmation (where indicated) (Table 15). All these aspects should be examined by a multidisciplinary team including neurosurgeon, oncologist, neuroradiologist, pathologist before treatment, preferably including any surgical intervention (Diez 1999, Rosemblum 2000, Packer 2000).

**Table 15: Diagnostic assessment procedures**

<table>
<thead>
<tr>
<th>Order of diagnostic procedures</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. MRI head and spine</td>
<td></td>
</tr>
<tr>
<td>2. tumour markers in serum and CSF</td>
<td></td>
</tr>
<tr>
<td>- AFP</td>
<td></td>
</tr>
<tr>
<td>- total HCG</td>
<td></td>
</tr>
<tr>
<td>3. exclusion of metastases</td>
<td></td>
</tr>
<tr>
<td>- CSF cytology</td>
<td></td>
</tr>
<tr>
<td>- MRI spinal if not done with head scan</td>
<td></td>
</tr>
<tr>
<td>4. biopsy* if indicated (i.e. marker negative)</td>
<td></td>
</tr>
<tr>
<td>5. final stage- and risk-stratification based on all the above</td>
<td></td>
</tr>
<tr>
<td>6. baseline pre-treatment investigations</td>
<td></td>
</tr>
<tr>
<td>- weight and height</td>
<td></td>
</tr>
<tr>
<td>- vision</td>
<td></td>
</tr>
<tr>
<td>- renal function</td>
<td></td>
</tr>
<tr>
<td>- hearing</td>
<td></td>
</tr>
<tr>
<td>- endocrine status (see appendix C for details)</td>
<td></td>
</tr>
<tr>
<td>- blood count and routine chemistry</td>
<td></td>
</tr>
<tr>
<td>- quality of life assessments, neuro-cognitive assessments <code>where performed</code></td>
<td></td>
</tr>
</tbody>
</table>

*or resection

The sequence of decisions between diagnosis and start of therapy may to some extent be determined by the patient’s clinical condition, which may dictate emergency action; the pathway for initial decision making, which allows for such eventualities, should therefore be followed (Figure 9).
5.1 Clinical presentation

The symptoms and signs at presentation of GCTs and their appearance are dependent on the site of involvement (suprasellar, pineal or both) and on histological tumour types that can determine hormonal activity. Duration of symptoms before diagnosis is related to velocity of tumour growth, being longer in germinoma (especially of the suprasellar site) in comparison to malignant NGGCTs. Median time from first symptom to diagnosis in suprasellar germinoma is reported to range from 3 to 36 months. Full medical history should be recorded including family history and past medical history with particular reference to previous malignancy or intracranial pathology such as lymphocytic pituitary infiltration, which has been reported to precede the development of germinoma.

Table 16: Typical presentation of CNS GCT

<table>
<thead>
<tr>
<th>pineal site</th>
<th>symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>cerebral aqueduct obstruction</td>
<td>raised intracranial pressure</td>
</tr>
<tr>
<td>compression/invasion of the tectal plate</td>
<td>upward gaze, convergence paralysis (Parinaud’s Syndrome)</td>
</tr>
<tr>
<td>suprasellar site</td>
<td>symptoms</td>
</tr>
<tr>
<td>invasion of chiasm</td>
<td>visual disturbance</td>
</tr>
<tr>
<td>disruption of hypothalamo-pituitary axis</td>
<td>endocrine dysfunction (DI, GHD)</td>
</tr>
<tr>
<td>direct production of selected oncoproteins (β-HCG)</td>
<td>testosterone increase (peripheral pubertas precox)</td>
</tr>
</tbody>
</table>

The most frequent endocrine disturbance seen at diagnosis in suprasellar tumours is diabetes insipidus (DI) (see also chapter 7.1.1.2), typically appearing as part of the classical triad with symptoms and signs of hypothalamo–pituitary dysfunction and visual disturbance. With tumours in the pineal region, raised intracranial pressure is more likely to occur whereas endocrine disturbances are rare, but their presence suggests infiltration of the hypothalamo-pituitary axis either by continuous tumour growth or by bifocal disease (Hoffman et al, 1995). Ectopic germinoma can involve rare sites such as basal nuclei; in such circumstances symptoms can be mental deterioration and hemiparesis. The presence of symptoms of DI in patients with pineal tumours is not regarded as sufficient evidence of bifocal disease.
for the purposes of treatment; they should only be treated as bifocal if there is radiological evidence of suprasellar involvement.

5.2 Diagnostic investigations

5.2.1 Markers

GCTs may secrete specific tumour markers including alpha-fetoprotein (AFP) and total HCG. AFP is a glycoprotein with a half-life of 5 days. Normal laboratory value (serum) is ≤ 25 ng/ml. Total HCG is produced by the placenta or similar structures. It is also seen if trophoblastic tissue (syncytiotrophoblastic cells) are present (slight elevation >5 IU/l but ≤ 50 IU/l). It describes the total HCG and various populations of total HCG (free and nicked). Half-life is 16 hours, normal laboratory value is < 5 IU/l (appendix F). Markers are elevated at diagnosis in the majority of patients with malignant NGGCTs (80% in the serum, >60% in CSF), and their presence, in conjunction with consistent MRI appearances, is sufficient for diagnosis, without the need for biopsy.

Assessment of tumour markers (AFP and total HCG) in both serum and CSF is mandatory in order to distinguish between germinoma and NGGCT. Tumour markers are to be repeated in serum and CSF if > 2 weeks has elapsed between diagnosis and the planned start of treatment in cases with raised markers at diagnosis.

Table 17: Conversion of AFP units

<table>
<thead>
<tr>
<th>unit</th>
<th>arithmetic operation</th>
<th>unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>ng/ml</td>
<td>x 1</td>
<td>= µg/l</td>
</tr>
<tr>
<td>µg/l</td>
<td>x 1</td>
<td>= ng/ml</td>
</tr>
<tr>
<td>ng/ml</td>
<td>x 0.83</td>
<td>= kU/l</td>
</tr>
<tr>
<td>kU/l</td>
<td>x 1.205</td>
<td>= ng/ml</td>
</tr>
<tr>
<td>µg/ml</td>
<td>x 830</td>
<td>= kU/l</td>
</tr>
<tr>
<td>kU/l</td>
<td>x 0.0012</td>
<td>= µg/ml</td>
</tr>
<tr>
<td>kU/l</td>
<td>x 1</td>
<td>= IU/ml</td>
</tr>
<tr>
<td>IU/ml</td>
<td>x 1</td>
<td>= kU/l</td>
</tr>
</tbody>
</table>

AFP 1000 ng/ml = 830 kU/l

5.2.2 Histological Classification of Intracranial Germ Cell Tumours

CNS GCTs are characterised by histological heterogeneity and are classified according to the WHO classification for intracranial germ cell tumours (see appendix F.5). As intra-tumour heterogeneity may be subtle, the initial diagnostic work-up should include evaluation by an experienced paediatric pathologist and central histological review is mandatory for patients in this study. If possible, CSF and fresh tumour tissue should be taken and stored according to guidelines of the national tumour banks for storage of material (see appendix I.1 – I.3).

5.2.3 Determination of Diagnostic group

If marker levels are ≤ 25 ng/ml (AFP) and ≤ 50 IU/l (total HCG), a biopsy should be performed. If any components of malignant NGGCT are present in a mixed tumour, then the tumour is classified as NGGCT, regardless of the presence of germinoma or teratoma in the biopsy (Figure 10).
Note:
- In the event of serum or CSF AFP > 1000 ng/ml at diagnosis, or age < 6 years, patients are stratified as high risk and are treated more intensively. In these patients a stem cell harvest according to institutional or national practice is mandatory.
- In the event of bifocal disease (pineal + suprasellar) and negative tumour markers in serum and CSF, a germinoma is suspected and no histological verification is required. Such cases must be confirmed by central review of MRI (head and spine).
- Teratoma combined with germinoma will be treated as germinoma but should proceed to complete resection of the residual tumour in case of stable disease, which should precede radiotherapy in all cases.
- Teratomas with malignant microfoci, verified by central histopathological review, are regarded as mixed malignant germ cell tumours for the purposes of treatment in this protocol and should therefore be treated accordingly (as non-germinoma).
- Teratoma with a marker increase of AFP > 25 ng/ml and/or total HCG > 50 IU/l in serum and/or CSF are treated like malignant non-germinomatous germ cell tumours.

Figure 10: Grouping for diagnosis

![Diagram of grouping for diagnosis]

Abbreviations:
- CHC = Chorio-Carcinoma
- YST = Yolk Sac Tumour
- EC = Embryonal Carcinoma

* only in case of bifocal disease (only pineal-suprasellar) diagnosis of germinoma is accepted without biopsy.
5.2.4 Neuroimaging

Only those patients with localised germinoma are eligible for ventricular irradiation without a boost that have a 100% response to chemotherapy before RT. All other patients will be treated with chemotherapy, ventricular irradiation and a boost. Careful attention to neuro-imaging and central review of scans after chemotherapy is therefore essential for the correct allocation of treatment.

MRI is the best imaging modality although CT can contribute information on tumour cellular density and calcification. MRI appearances in typical locations (suprasellar, bifocal, pineal), in conjunction with clinical signs, are strongly predictive of the presence of an intracranial GCT. A correct interpretation of imaging should take into account the MRI appearance of normal anatomy of pineal and suprasellar regions at different ages and of that of other benign or malignant lesions typical in these sites (Zimmermann 1982, Satoh 1995, Fujimaki 1994).

MRI should be performed before biopsy in all cases and within 48 hours following surgery if resection is performed (not required after biopsy only). Spinal MRI should ideally be performed before lumbar puncture and surgery and should include the full spine (C0 – S3; not only the medulla). Pre-contrast T1 sequences are mandatory, especially after surgery.

It is recommended that central review of radiology should be performed at diagnosis, at re-evaluation and at the end of treatment. Criteria and time-points for mandatory reviews are detailed in section 5.3.

All imaging data should be stored in DICOM-format for further reviews.

For optimum imaging of GCTs, MRI should be performed according to the following minimal requirements:

**BRAIN**

**Pre-contrast sequences:**
T1-weighted, axial
T2-weighted and FLAIR axial
T1-weighted, 3 mm thick through the midline structures

**Post-contrast sequences:**
T1-weighted, coronal
T1-weighted, axial (as the pre-contrast sequence)
T1-weighted, sagittal 3 mm thick as precontrast through the midline structures

These sequences should be supplemented by a 3D volumetric acquisition if necessary for surgery planning or for volumetric tumour measurement.

**SPINE**

T1-weighted, sagittal 3mm, post-contrast
If necessary, T1-weighted axial post-contrast, everywhere where prominent vessel or meningeal disease are visible. Do not perform fatsat sequences.

Assessment of neuro-imaging findings
A germ cell tumour usually appears as a solid mass that is similar to grey matter and shows prominent enhancement following the administration of contrast. The main distinguishing radiological features of pure germinomas relate to their typical sites of involvement, with 30% of cases bifocal and <10% metastatic, in which multifocal involvement is seen mainly within the ventricular system. The diagnosis
of germinoma may be suspected because of pituitary disturbance, when the lesion is still small; in these cases the MRI can show the lack of the bright spot of the neuro-hypophysis in T1 weighted images together with thickening of the hypothalamus and infundibular stalk; larger masses present a more homogeneous pattern compared with malignant NGGCTs; on CT they are hyperdense, with calcification sometimes present; on MRI they are hypo- or isointense on T1 and hyper-or isointense on T2 weighted images. The presence of fat and calcification or intratumoural cysts suggests the possibility of a mature teratomatous component (Tien1990, Fiyimaki 1994, Sumida1995).

Differential diagnoses
In the suprasellar sites the main differential diagnosis is Langerhans Cell Histiocytosis and in adolescents and young adults sarcoidosis for small lesions, and low grade gliomas for larger lesions; in the pineal location the differential diagnosis includes a large variety of tumours like PNETs, low grade astrocytomas and pinealocytomas, which are all seen less frequently at this site.

5.3 Response criteria

Each national reference radiologist can perform their assessment of response either by (1) calculation of the volume by volumetry or by (2) 3-dimensional measurement of the longest diameters and the approximation to the volume according to the formula of a rotational ellipsoid (a x b x c/2). Whichever method is employed should be applied consistently to every case to avoid variations due to the measurement procedure.

Note: review of response by the national reference radiologist is mandatory for

1. all cases with localised germinoma following chemotherapy including bifocal tumours
2. any case with residual disease after chemotherapy and/or radiotherapy

Those cases in which response is difficult to define by the national review radiologist will be circulated amongst the radiology panel.

The agreed response criteria for assessment of intracranial GCTs are as follows:

**Complete remission (CR)**
No evidence of disease based on clinical and radiographic assessment (e.g. MRI in three dimensions) and normal tumour markers. As the pituitary stalk is a structure that physiologically shows contrast enhancement any kind of abnormal thickening or enhancement has to be categorised as questionable and therefore as PR. Similarly, if anything more than physiological enhancement due to the internal cerebral veins is seen at the pineal gland the response has to be classified as PR for the purposes of the study and treatment. If tumour markers are elevated at diagnosis, they must return to age-related normal values

Please note: In situations where it is still unclear if a CR is achieved, it is possible to discuss this patient with the international reference centre in Würzburg.

**Partial response (PR)**
> 50% decrease in the sum of the volume of all measurable lesions (calculated from the maximum diameters on MRI in three dimensions); no evidence of progression of any lesion, no new lesions and no rise in tumour markers. Failure of tumour markers to decline according to age related normal values in the presence of radiological CR is defined as PR.

**Stable disease (SD)**
< 50% decrease in the sum of the product of the volume of all measurable lesions, no evidence of progression in any lesions, and no new lesions and no rise of tumour markers if elevated at diagnosis.
**Progressive disease (PD)**
> 25% increase in the size of any measurable lesion and/or appearance of new lesions; increasing tumour markers (except first week of chemotherapy).

**Growing teratoma syndrome (GTS)**
progression of any tumour lesion but decline of tumour markers during chemotherapy.
5.3.1 CSF cytology

Cytology should be obtained by lumbar puncture or by ventricular tap at diagnosis. In the event of raised intracranial pressure and the necessity for urgent surgical intervention, CSF can be collected intraoperatively and used for stratification, provided that CSF is obtained before any other intervention (eg biopsy, ventriculostomy, shunt insertion). If no cytology has been collected before operation a lumbar puncture should be done on day 10 (or later) after surgery.

5.3.2 Determination of tumour stage

In the presence of either positive CSF cytology and/or visible deposits in brain or spine on MRI, tumours are defined and treated as metastatic disease (Figure 11).

Figure 11: Definition of disseminated disease

**GROUPING FOR DISSEMINATION**

- cranial MRI: two or more foci?
  - yes* 
    - MRI spinal
    - CSF cytology
    - metastatic disease
  - no
- spinal MRI: positive?
  - yes 
    - CSF cytology
    - metastatic disease
  - no
- CSF-cytology: positive?
  - yes 
    - metastatic disease
  - no
- non-metastatic disease

* In case of bifocal tumor (only pineal-suprasellar) and negative spinal MRI and negative CSF-cytology, disease is classified as non-metastatic.

Note:

- Non-metastatic patients are those with negative CSF cytology and only one tumour site on imaging (except bifocal).
- Bifocal tumours are only tumours with synchronous appearance of a pineal and suprasellar lesion. They are also treated as localised disease. Tumour boost has to be adapted to both sites. If in bifocal tumours, markers in serum and CSF are negative, a germinoma is suspected and no
histological verification is required. Such cases must be confirmed by central review of MRI (head and spine).

- The presence of symptoms of DI in patients with pineal tumours is not regarded as sufficient evidence of bifocal disease for the purposes of treatment; they should only be treated as bifocal if there is radiological evidence of suprasellar involvement
- In the presence of more than one tumour site on MRI (head and spine, except bifocal) and/or postive CSF-cytology, patients are treated as metastatic disease.

### 5.4 Role of surgery at diagnosis

In patients with suspected GCT, the aim of the initial diagnostic assessment including MRI and markers is to establish whether or not histological diagnosis is necessary. Although there is a consensus that surgery is required for diagnosis in all patients with negative markers in serum and CSF or borderline secretion of markers, the value of initial extensive surgical resections, especially total or near-total, is unproven (Nam 1999) and should not be undertaken in patients in this study. Primary surgical resection only constitutes the treatment of choice if MRI indicates an unequivocally localised and circumscribed tumour, with radiological appearances strongly suggestive of mature teratoma. In the parasellar site, surgical intervention should not be attempted “with radical intent”, in order to preserve endocrine and neurological functioning.

In cases without raised markers, in which biopsy is required for diagnosis, the use of stereotactic biopsy has been the standard procedure in the past (Nam 1999). However, the efficacy of neuroendoscopic biopsy via third ventriculostomy in germ cell and non-germ cell tumours of the pineal and of the third ventricle is now well established (Pople 2001), and is particularly suitable when ventricular drainage is also required. In those patients with involvement of the anterior third ventricle, making third ventriculostomy impossible, ventriculoscopy is the procedure of choice to establish external or internal ventricular drainage. This can be used to obtain biopsies and CSF (see neurosurgery appendix G).

**Note:**
- CSF sampling within a surgical intervention is required to be prior to biopsy or ventriculostomy
- early neuropathology review is recommended, according to national arrangements
- for patients requiring biopsy or resection according to protocol guidelines, fresh tumour material should be stored, and CSF where possible, for use in future biological studies (see appendix I)

### 5.5 Additional pre-treatment investigations

- repeat tumour markers in serum and CSF if > 2 weeks between diagnosis and start of treatment if raised at diagnosis.
- if there is a long delay between surgery and start of treatment (> 4 weeks) patients should be restaged
- MRI should be repeated within 48 hours after any surgical resection but is not mandatory following biopsy only.
- full blood count, differential
- serum electrolytes (Na, K, Ca, P, Mg) and creatinine
- liver function tests and LDH
- GFR or creatinine clearance (in patients due to receive chemotherapy)
- urine osmolality (early morning), phosphate and creatinine
- viral serology (according to national practice)
- baseline endocrine evaluation (including height, weight and pubertal status)
- hearing assessment
- ophthalmological assessment
- Lansky-Kamowsky score (see Appendix D.4)
5.6 Investigations during treatment

Investigations relating to both monitoring of disease and of response to treatment are outlined in chapters 6 and 7 for germinoma and NGGCT respectively.

5.7 Investigations at the end of treatment

Assessment at the end of treatment is determined by the tumour subtype, treatment delivered and patient's condition (see appendix C.4-C.5).

5.8 Follow-up plan and monitoring of relapse risk

In general, it is recommended that patients should be followed up for a period of at least 5 years after the end of treatment to include imaging. Since recurrence of germinoma may occur later than this, clinical follow-up for at least 10 years is advised.

5.8.1 Malignant GCTs

Relapse is seen most frequently in the first 2 years off treatment. Other follow-up investigations will be determined by the site of primary tumour, clinical symptoms and deficits and treatment received. Recommendations can be found in appendix C.5.

5.8.2 Teratoma

Children with intracranial teratoma should be followed up every three months in the first year, including clinical assessment, markers and MRI. In the event of incomplete resection, clinical assessment and markers should be carried out more frequently as for malignant tumours (see appendix C.4).

5.9 Long term effects and follow-up

In intracranial GCTs, endocrine function is frequently compromised at diagnosis. Special attention to growth and other endocrine function in follow-up is therefore essential, and should be reviewed annually. Other organs or systems at risk following chemotherapy and radiotherapy include the kidneys and hearing. Therefore both should be evaluated at the end of treatment and, if necessary, during follow-up. Neuro-cognitive functioning may be affected by both tumour and treatment, particularly radiotherapy. It should therefore be monitored closely during follow-up in order to arrange appropriate support (see Appendix C).

5.10 Framework of Quality of Survival evaluation

5.10.1 What determines quality of survival?

QOS is important for all children treated for cancer, and particularly for those with primary intracranial tumours. Brain tumour survivors have poorer quality of survival than normal children and other survivors of childhood cancer. Both radiotherapy and chemotherapy have been implicated as contributing factors.
to adverse neurological, neuropsychological and endocrine outcomes following treatment for this condition. However, direct effects of the tumour itself, peri-operative complications, and family and psychosocial variables may also be important.

5.10.2 Value of a prospective study
The effect of cranial radiotherapy on cognition is thought to be dose dependent, but findings are limited by the cross-sectional nature of published studies, and there is very little on children treated for germ cell tumours where, in contrast to other primary intracranial tumours, surgery is not the primary treatment. Prospective longitudinal data is needed to confirm whether quality of survival can be preserved with lower doses of radiotherapy, and is integral to the design of the present study. The collected information will, for the first time, provide a brief but wide-ranging longitudinal data set for children and young adults with intracranial germ cell tumours.

5.10.2.1. The impact of localisation and intracranial pressure
It is a well known observation that patients with suprasellar tumors are more likely to develop endocrine function disorders, also raised intracranial pressure could have a lasting effect on neurocognitive functioning as well. These variables had to be taken into account, when morbidity of adjuvant treatment is evaluated.

5.10.3 Endocrine function
Between 60 and 95% of children with brain tumours experience hormonal deficits, particularly growth hormone insufficiency, within 2-5 years of treatment. Hormonal status may have detrimental effects on physical, cognitive and psychological aspects of QoS.

5.10.4 Central Hypopituitarism
Dose- and fractionation-dependent neurotoxic effects of cranial irradiation have been thought to be responsible for the evolving hierarchical loss of post-operatively intact anterior pituitary function. The few prospective and longitudinal studies of children with tumours in the posterior fossa, distant from the pituitary axis, have shown subtle neuroregulatory deficits in growth hormone (GH) secretion, which appear to be present prior to, and compounded by, irradiation. Chemotherapy may be additively toxic, progressively disrupting central GH release mechanisms and thereby confusing the interpretation dynamic pituitary function tests.

5.10.5 Peripheral target organ effects
The aetiology of short stature in children treated for brain tumours is further confounded by irradiation-induced skeletal spinal damage and an early puberty, limiting the time for growth despite GH replacement. With older spinal irradiation techniques, subfertility and hypothyroidism, potentially compromising future reproductive and skeletal health, affected approximately one-third of survivors. With the added toxicity of chemotherapy, this incidence increased to approximately two-thirds. These figures may underestimate subfertility, particularly in females, as more survivors achieve adulthood and/or their increasing longevity unmasks an increase in premature menopause.

5.10.6 Data to be collected
(see diagnostic and pre-treatment assessment CRF, Appendix D.4)
Height, sitting height, weight, pubertal stage and serum concentrations of thyrotropin (TSH), gonadotropins and sex steroids will be measured at the same four time points as other outcome data (see section 5.10.9). Adult height will also be measured (aged 20). Measurement of gonadotropins and sex steroids will be restricted to those children aged eight years or older. Age at onset of puberty (calculated retrospectively from annual examination) and menarche, as well as the use of supplemental hormone therapy will be recorded.
5.10.7 Audiology
Audiology will be documented according to CTC-criteria when it is performed during treatment and is included in the investigations at the end of treatment.

5.10.8 Hypotheses to be tested
According to the SIOP CNS GCT II protocol, three groups of patients are observed:
- teratoma
- germinoma
- malignant NGGCT

Teratoma will be treated by surgery as the main treatment option and additional treatment according to histology and resection status. In this group of patients QoS data will be collected to describe for the first time the QoS at diagnosis (surgery), end of treatment and follow-up.

For germinoma patients, QoS in those receiving ventricular irradiation (± boost) will be compared with patients receiving craniospinal irradiation. This study will test the hypotheses that allocation to one or other treatment arm will be associated with a difference in QoS.

For patients with NGGCT, QoS in those receiving local irradiation will be compared with those receiving craniospinal irradiation. The group of high risk patients will be observed separately. This study will test the hypotheses that allocation to one or other treatment arm will be associated with a difference in QoS.

Results for QoS assessment will be compared to population norms where available.

5.10.9 Evaluation time points of the Framework of Quality of Survival

Four evaluation time points are planned for indirect tests (questionnaire based assessment).
- Exam 1: at diagnosis (prior to treatment or up to 4 weeks after start of chemotherapy or 14 days after start of radiotherapy, if no chemo to be delivered).
- Exam 2: after end of radiotherapy (within 6 weeks post Rx),
- Exam 3: two years after diagnosis (± 4 weeks)
- Exam 4: five years after diagnosis (± 4 weeks).

The instruments to be used in this study are the same as used in other therapy optimisation studies for brain tumours (see PNET IV).

This set includes:

**HRQL:**
*PedsQL and PEDQOL:*
HRQL for patients aged 18 and under will be assessed using either the generic PedsQL 4.0 (Varni et al, 2002), or the PEDQOL questionnaire (Calaminus et al, 2000). Age appropriate child and parent reports should be used.

**EORTC QLQ-30 and MFI:**
For patients aged 16 and over, HRQL will be assessed using the generic EORTC QLQ-C30 questionnaire and brain tumour module (Aaronson et al, 1993; Fayers et al, 1995). The Multidimensional Fatigue Inventory (MFI) covering five dimensions of fatigue: general, physical, mental fatigue, reduced activity, and reduced motivation (Smets et al. 1995) has demonstrated good psychometric properties (Flechtner and Bottomley 2002) is recommended to use in addition.

**Health Status:**
Health Utilities Index (HUI)
The Health Utilities Index (HUI) allows comparison of global health status for the ‘attributes’ or
domains of vision, hearing, speech, dexterity, ambulation, cognition, emotion, and pain, as well as
providing an overall multi-attribute summary score. The HUI has been widely used to measure health
status in children with cancer, including brain tumours. The measurement of QoS of children in this
study forms one part of the Study of QoS of children with brain tumors enrolled in CCLG and

Behaviour and Psychological Status:
Child and parent report behaviour and psychological status will be measured using age appropriate
versions of the Strength and Difficulties Questionnaire (SDQ) (Goodman 1997; 1998).

Social and living environment (Germany only):
A parent’s questionnaire will be distributed together with the above described measures to obtain
information of social and education status.

All questionnaires are printed together in booklet form, which will be sent from the national data centre
after patient registration, during treatment and as specified above (see appendix L).

5.10.10 Neurocognitive assessment

An ‘add-on layer’ of direct, face-to-face assessments will be used, when feasible, to measure
neurocognitive outcome. These may only be possible in some centres. The tests required to measure
certain domains of function, are defined in terms of the Cattell-Horn-Carroll theory of cognitive abilities
(Carroll, 1993). These domains include: fluid intelligence (Gf), crystallized intelligence (Gc), short-term
memory (Gsm), visual-constructive intelligence (Gv), cognitive speediness (Gs), psychomotor abilities
(Gpm), and reaction time/decision speed (Gt). The following tests are appropriate to measure the
capacity of these domains: progressive matrices (Gf), vocabulary (Gc), number recall (Gsm), visual-
motor abilities (Gv), continuous performance test (CPT - for attention) (Gs/Gsm), pegboard test (Gpm),
and tapping test (Gt).

Countries could either adopt part or all of this battery, or derive scores for the same underlying neuro-
cognitive factors using the WISC (preferably WISC IV) or the K-ABC (preferably K-ABC II) and the Wide
Ranging Assessment of Visuomotor Abilities (WRAVMA) plus additional attention testing.

Neurocognitive assessment should take place at time of diagnosis and approximately two years after
diagnosis. To estimate long-term effects an additional assessment approximately five years after
diagnosis is recommended. Administration of indirect and direct assessment should be simultaneous at
these time points. In Germany the patients will be tested if possible according to the agreement
achieved within the HIT-Network (Basisdiagnostikum) (see appendix A8).

5.10.11 Coordination of the Quality of Survival project

Data will be collected by the national data centres and pooled and evaluated at the international data
centre together with the clinical information. The project will be co-ordinated by the Quality of Life Group
in Bonn in cooperation with the international members of the Quality of Survival Group.

5.10.12 Patient Information and Declaration of Consent
All patients and/or their parents will be informed about the purpose of the Quality of Survival evaluation. A declaration of consent will be signed by the patients/parents prior to the Quality of Survival evaluation at time of consent for treatment (see appendix A).
6 TREATMENT OF GERMINOMA

This chapter describes treatment of histologically confirmed pure germinoma and germinoma ± teratoma, in the presence of AFP ≤ 25 ng/ml and total HCG ≤ 50 IU/l in both serum and CSF (see chapter 5).

Note: Histological confirmation is not recommended for bifocal germinoma (see chapter 5).

For conversion of AFP units from ng/ml to kU/l see chapter 5.2.1

\[
25 \, \text{ng/ml} = 20.75 \, \text{kU/l}
\]

Figure 12: Treatment of germinoma (± teratoma)

SIOP CNS GCT II: Therapy for intracranial germinoma
histologically proven germinoma (± teratoma), AFP ≤25 ng/ml and ßHCG ≤ 50 IU/l in serum and CSF

6.1 Non-metastatic germinoma (± teratoma) (uni- and bifocal)

- Fully staged, with no evidence of spinal dissemination based on both MRI scan and CSF cytology (see chapter 5).
- In bifocal tumours, with pineal and suprasellar components, histological confirmation is not required, and germinoma may be diagnosed on the basis of radiological appearance and markers within the defined limits.
- In case of a pineal tumour and symptoms of DI, treatment is planned according to the radiologically verified tumour site. The presence of symptoms of DI in patients with pineal tumours is not regarded as sufficient evidence of bifocal disease for the purposes of treatment; they should only be treated as bifocal if there is radiological evidence of suprasellar involvement.
- The tumour is reassessed following chemotherapy, to determine the need for resection of residual tumour prior to radiotherapy, which should be based on a multi-disciplinary team review of each case. It is not necessary for residuals to be resected in principle; only those with a poor radiological response to chemotherapy (stable disease), in which the presence of teratoma is more likely (see neurosurgical guidelines, Appendix G). Radiological review is mandatory for all patients after
chemotherapy to document response, only those with a CR will receive WVI alone after chemotherapy, those with PR will receive an additional tumour boost.

- Radiotherapy (section 6.1.6) should commence after haematological recovery from the fourth cycle of chemotherapy (about day 84), or as soon as possible after surgery for resection of residual.

6.1.1 Chemotherapy in non-metastatic fully staged germinoma

Chemotherapy consists of two courses of carboplatin/etoposide, alternating with two courses of ifosfamide/etoposide and should commence as soon as possible following diagnosis.

Courses 1 and 3

| Carboplatin | 600 mg/m²/day | day 1 |
| Etoposide   | 100 mg/m²/day | days 1, 2, 3 |

Courses 2 and 4

| Ifosfamide  | 1800 mg/m²/day | days 1, 2, 3, 4, 5 |
| Etoposide   | 100 mg/m²/day  | days 1, 2, 3 |

Please note:

- The maximum dose of carboplatin is 1200 mg (equivalent to BSA 2m²).
- It is also possible to use etoposide phosphate instead of etoposide in equivalent dose. 114 mg etoposide phosphate equals 100 mg etoposide.
- Ifosfamide dosing and administration differ from those used in treatment of non-germinoma.
- Courses should be given at 21 day intervals, subject to count recovery.
- **Metastatic and incompletely staged germinoma do not receive chemotherapy in this protocol**

6.1.1.1 Details of Chemotherapy Administration in germinoma (CCLG)

Carboplatin, Etoposide/Etoposide phosphate and Ifosfamide should be diluted prior to infusion according to locally validated practice and/or procedures for the aseptic preparation of chemotherapy agents, with particular reference to the preparation of chemotherapy agents that are to be administered as Investigational Medicinal Products (IMPs) in a clinical trial. The infusion fluids and volumes for infusion should be selected to permit the drug to be administered over the stated time. Such practice and/or procedures should also reflect the published data on the compatibility of the IMP with the intended container, the chemical stability of the IMP with the proposed diluent for infusion at the intended final concentrations of the prepared infusion and the appropriate storage conditions consequent on the choices made.

A central venous catheter is recommended for the delivery of this chemotherapy. Further guidance regarding delivery of chemotherapy can be found in Appendix E.

**Etoposide** (100 mg/m²)/ **Etoposide phosphate** (114 mg/m²) (on Days 1 - 3 of each cycle) should be given as an IV infusion over 1 - 4 hours, prior to carboplatin. If etoposide phosphate is used, 114 mg of etoposide phosphate is equivalent to 100 mg etoposide.
**Carboplatin** (600 mg/m² on Day 1, Cycles 1 and 3 (Maximum dose: 1200 mg)) should be given as an IV infusion over 1 hour.

**Ifosfamide** (1800 mg/m² on Days 1 - 5, Cycles 2 and 4) should be given as an IV infusion over 3 hours. Concurrent administration of hydration and MESNA is recommended to avoid urothelial toxicity. Other nephrotoxic drugs, including aminoglycoside antibiotics, should be used with caution with ifosfamide.

Please note: Ifosfamide dosing differs from that used in the treatment of NGGCT.

**MESNA** should be given at a dose of 2200 mg/m²/day (120% of the daily ifosfamide dose) and should be continued for about 24 hours following completion of the last dose of ifosfamide. It is recommended that this is given as a continuous infusion, infused either separately or added into the hydration fluid according to institutional practice. On Day 1 an additional **bolus infusion** of 360 mg/m² (20% of the daily ifosfamide dose) should be given prior to the ifosfamide infusion.

**Hydration** fluid should commence three hours before start of ifosfamide and run continuously until at least 24 hours following the completion of the last ifosfamide infusion.

**Note:** If the volume of the etoposide infusion on day 1 is used in place of the first three hours of hydration fluid, care must be taken, to ensure that the volume is sufficient to provide fluid at the specified rate. The hydration fluid used may be according to institutional practice and should be infused at a rate that provides, inclusive of the volumes of the chemotherapy and MESNA infusions, a total of at least 83 ml/m²/hour (2 l/m²/day). **Note:** depending on the volume used for drugs, the total fluid volume administered is likely to be significant. Consideration should be given to capping this at 3 l/m²/day. A suggested infusion regimen can be found in Appendix E.

In the rare event of haemorrhagic cystitis, MESNA or hydration should be increased and diuretics added, according to institutional practice. Particular attention must be paid to urine output and plasma electrolytes in patients with diabetes insipidus.

**Note:** If etoposide is used in place of hydration fluid, care must be taken to ensure that the volume is sufficient to provide fluid at the required rate.

### 6.1.1.2 Supportive care during chemotherapy

**Beware!** Diabetes Insipidus (DI) is a common complication encountered in the treatment of malignant CNS GCTs. DI should be controlled prior to starting chemotherapy, and particular attention should be paid to sodium and fluid balance throughout treatment in all cases. Detailed guidelines for the management of DI are given in Appendix E. Clinicians are advised to work closely with their colleagues in endocrinology.

Anti-emetic treatment should include a 5HT antagonist. Administration of steroids (e.g. dexamethasone) during chemotherapy should be avoided if at all possible, and only used for anti-emesis if other therapies fail. If symptoms of raised intracranial pressure develop during treatment, the cause (e.g. hydrocephalus) should be actively sought. Steroids should only be used as a short-term measure prior to definitive treatment of raised pressure. In patients with raised intracranial pressure at the time of the first chemotherapy course particular care should be taken about hyperhydration. In such cases therapy modifications should be discussed with the co-ordinator.

The prophylactic use of cotrimoxazole (sulfamethoxazole/trimethoprim) is optional and should be based on local practice, as no case of pneumocystis carinii infection has been reported in the SIOP CNS GCT 96 series. Prophylactic antibiotic/antifungal decontamination may be used if it is the normal practice in the treating hospital. The choice of antibiotics used during episodes of febrile neutropenia should be based on local guidelines.
Preservation of fertility
In adolescent males, the possibility of sperm cryopreservation should be discussed prior to the initiation of chemotherapy. In postpubertal females, gonadal protection may be considered, and should be based on local or national recommended practice.

6.1.2 Toxicity, dose modifications and delays

Please refer to Common Toxicity Criteria for documentation of toxicities (appendix F.3). Chemotherapy for patients less than one year of age or weighing less than 10 kg should be prescribed on the basis of weight (kg). The dose is calculated from the dose in m² using the formula: 1m² = 30kg

In children less than 4 months of age, ifosfamide should be omitted and substituted by cyclophosphamide in an equivalent dose after discussion with the national co-ordinator.

6.1.2.1 Haematological toxicity

Courses of chemotherapy should be delayed until haematological recovery from the previous course has taken place, defined by neutrophils ≥1.0 x 10⁹/l or WBC ≥ 2.0 x 10⁹/l and platelets 100 x 10⁹/l and rising. Significant delays should be discussed with the national chief investigator.

6.1.2.2 Ototoxicity

Audiometry should be performed prior to starting chemotherapy, and between courses if there are clinical concerns regarding hearing. Modifications in treatment are based on the Brock / CTC (SIOP) Grading (see also appendix F.6).


<table>
<thead>
<tr>
<th>Grade</th>
<th>Subjective hearing (CTCAE v. 3.0)</th>
<th>Audiometry (PTA) (Bilateral) (Brock classification (Brock et al., 1991))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Loss &lt;40 dB on all frequencies</td>
</tr>
<tr>
<td>0</td>
<td>None (no change)</td>
<td>Loss ≥ 40 dB at 8000 Hz</td>
</tr>
<tr>
<td>1</td>
<td>-</td>
<td>Loss ≥ 40 dB at 4000 Hz</td>
</tr>
<tr>
<td>2</td>
<td>Hearing loss not requiring hearing aid or intervention OR Tinnitus not interfering with activities of daily living (ADL)</td>
<td>Loss ≥ 40 dB at 4000 Hz</td>
</tr>
<tr>
<td>3</td>
<td>Hearing loss requiring hearing aid or intervention OR Tinnitus interfering with ADL</td>
<td>Loss ≥ 40 dB at 2000 Hz</td>
</tr>
<tr>
<td>4</td>
<td>Profound bilateral hearing loss (&gt; 90 dB) OR Disabling tinnitus</td>
<td>Loss ≥ 40 dB at 1000 Hz</td>
</tr>
</tbody>
</table>

Note: Grading for audiometry is based on loss in both ears – thus the grading (including that for modification of chemotherapy) is based on the lowest grading, i.e. the ‘best ear’.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Chemotherapy Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None – continue carboplatin</td>
</tr>
<tr>
<td>1</td>
<td>None – continue carboplatin</td>
</tr>
<tr>
<td>2</td>
<td>None – continue carboplatin</td>
</tr>
<tr>
<td>3</td>
<td>Omit carboplatin</td>
</tr>
<tr>
<td>4</td>
<td>Omit carboplatin</td>
</tr>
</tbody>
</table>
6.1.2.3 Nephrotoxicity

- Both glomerular and tubular toxicity must be monitored during treatment with carboplatin and ifosfamide.
- The estimation of GFR must be performed before the first and third course of chemotherapy.

Treatment should be modified as follows:
If GFR/creatinine clearance < 80 ml/min per 1.73 m$^2$ or serum creatinine > 1.2 mg/dl or > 1.5 x upper limit of normal:

- Delay chemotherapy for one week, and repeat GFR, by measurement of clearance of radioisotope.
- If repeated GFR still < 80 ml/min per 1.73 m$^2$: discuss with co-ordinator.

In case of nephrotoxicity CTC grade 2 reduce ifosfamide dose by 30%. In case of nephrotoxicity CTC grade 3 or 4 withhold ifosfamide and use cyclophosphamide instead (equivalent dose 1:4).

6.1.2.4 Neurotoxicity

If CTC grade 3 or 4 central neurotoxicity occurs, consider the use of Methylene Blue (methylthionin) 50 mg as i.v. infusion. Prolong ifosfamide to 4-8 hours with the next application, and infuse Methylene Blue 50 mg three times a day. In the next course, apply Methylene Blue one dose of 50 mg 24 hours prior to ifosfamide. During ifosfamide give three-times daily Methylene Blue as described above. If repeated grade 3 or 4 neurotoxicity occurs, consider withholding ifosfamide and substitute cyclophosphamide (see above).

6.1.3 Investigations before each course of chemotherapy.

- Clinical assessment including neurological examination
- Weight
- Full blood count
- Blood biochemistry – electrolytes, urea, creatinine, ALT/AST, alkaline phosphatase, bilirubin, albumin, magnesium, calcium, phosphate
- Note: GFR estimated by radioisotope clearance, or other locally approved method, or by direct measurement of urinary creatinine clearance before first and third course
- Pure tone audiometry (before first course, with additional assessments based on local practice and if any concern regarding hearing)

6.1.4 Tumour evaluation after four courses of chemotherapy

- Clinical assessment, including neurological examination
- MRI of the head with and without contrast
- Serum markers; CSF markers in all cases of doubt.
6.1.5 Surgical treatment of non-metastatic germinoma

Medical treatment is curative in most cases of germinoma. Decisions regarding definitive surgery can therefore be delayed until assessment of residual disease after chemotherapy. Pure germinomas usually disappear completely after few doses of RT or cycles of chemotherapy while germinomas with teratomatous components may have a more complex pattern of response with slow regression of residual tumours. Profound morphological regressive changes sometimes occur within the lesions (increased necrosis and cystic components, increased volume of mature residual teratomatous components).

Surgical excision should be attempted in cases of known germinoma plus teratoma, and cases of germinoma in which there is no apparent response to treatment. It should also be considered in cases of partial response, in which the radiological appearance at reassessment following chemotherapy is suggestive of teratoma.

The optimum timing of surgery is after the end of chemotherapy, but may also be considered following radiotherapy.

Small residual masses in cases of germinoma that have responded to chemotherapy and/or radiotherapy should not be resected but a watch and wait strategy should be adopted.

6.1.6 Radiotherapy in non-metastatic germinoma, completely staged

6.1.6.1 CR following primary chemotherapy

Patients with CR (response criteria see chapter 5.3) following primary chemotherapy receive whole ventricular irradiation ensuring that the original tumour bed (TB) is included in this target volume (Whole ventricular & tumour bed irradiation (WV&TB-RT)). In this group, no additional boost to the tumour bed area will be given. It is a study requirement that scans are reviewed by the national reference neuroradiologist to confirm CR prior to delivery of ventricular radiotherapy without boost.

<table>
<thead>
<tr>
<th>Volume</th>
<th>Total dose (Gy)</th>
<th>Dose per fraction (Gy)</th>
<th>Number of fractions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole Ventricle + Tumour bed</td>
<td>24</td>
<td>1.6</td>
<td>15</td>
</tr>
</tbody>
</table>

6.1.6.2 PR or SD following primary chemotherapy

Patients with PR or SD (response criteria see chapter 5.3) following primary chemotherapy +/- surgery receive whole ventricular irradiation ensuring that the original tumour bed and any residual disease is included in this target volume (WV&TB-RT) followed by a boost to the primary tumour bed.

<table>
<thead>
<tr>
<th>Volume</th>
<th>Total dose (Gy)</th>
<th>Dose per fraction (Gy)</th>
<th>Number of fractions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole Ventricle + Tumour bed</td>
<td>24</td>
<td>1.6</td>
<td>15</td>
</tr>
<tr>
<td>Tumour bed boost</td>
<td>16</td>
<td>1.6</td>
<td>10</td>
</tr>
<tr>
<td>Tumour bed (total)</td>
<td>40</td>
<td>1.6</td>
<td>25</td>
</tr>
</tbody>
</table>

Table 19: Irradiation in non-metastatic germinoma in CR

Table 20: Irradiation in non-metastatic germinoma in PR / SD

In the rare situation of germinoma plus teratoma, resection should take place prior to radiotherapy. In the event of incomplete resection, increased radiotherapy dose should be administered. In this
occassion the local tumour boost should increase to a total dose of 54.4 Gy (see Table 21). Any cases of doubt should be discussed with a radiotherapy co-ordinator.

Table 21: Irradiation in non-metastatic germinoma plus teratoma and stable disease after chemotherapy (incompletely resected)

<table>
<thead>
<tr>
<th>Volume</th>
<th>Total dose (Gy)</th>
<th>Dose per fraction (Gy)</th>
<th>Number of fractions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole Ventricle + Tumour bed</td>
<td>24</td>
<td>1.6</td>
<td>15</td>
</tr>
<tr>
<td>Tumour bed boost</td>
<td>30.4</td>
<td>1.6</td>
<td>19</td>
</tr>
<tr>
<td>Tumour bed (total)</td>
<td>54.4</td>
<td>1.6</td>
<td>34</td>
</tr>
</tbody>
</table>

6.1.6.3 Dose modifications and delays (see appendix H)

6.1.7 Investigations at the end of treatment (following radiotherapy)

Tumour evaluation
- MRI head and spine, with and without contrast
- Serum markers (AFP and total HCG)

Treatment related investigations
- Blood biochemistry – electrolytes, urea, creatinine, ALT/AST, alkaline phosphatase, bilirubin, albumin, magnesium, calcium, phosphate
- Pure tone audiometry
- Glomerular filtration rate
- Urine osmolality (early morning) and phosphate, creatinine for calculation of tubular reabsorption of phosphate.
- Endocrinological assessment
- MRI angiography according to local practice

(Data were published from the childhood cancer survivor study also including SEER data showing a 59 fold higher risk for stroke in germinoma patients at five-years-survival treated between 1973 and 2003 (Acharya et al 2015). These observations could not be found in the European SIOP CNS GCT 96 trial (Calaminus et al 2013). Caution has to be given to this finding and in the follow-up procedures we recommend to do an MRI with angiography after the end of treatment and at 5 years after the end of treatment to better quantify the risks.

See also flow sheets for follow-up investigations appendix C.4
6.2 Metastatic germinoma (± teratoma)

Please note that metastatic and incompletely staged germinomas do not receive chemotherapy in this protocol.

6.2.1 Surgical treatment

Radiotherapy is curative in most cases of germinoma. Decisions regarding definitive surgery can therefore be delayed until assessment of residual disease after radiotherapy. Pure germinomas usually disappear after completion of RT while germinomas with teratomatous components may have a more complex pattern of response with slow regression of residual tumours. Profound morphological regressive changes sometimes occur within the lesions (increased necrosis and cystic components, increased volume of mature residual teratomatous components).

Surgical excision should be attempted in cases of known germinoma plus teratoma, and cases of germinoma in which there is no apparent response to treatment.

Small residual masses of the primary tumour in cases of germinoma that have responded to radiotherapy should not be resected but a watch and wait strategy should be adopted. Since no residual metastases have been described in the SIOP CNS GCT 96 trial, special recommendations for resection of metastases after RT are not given.

6.2.2 Radiotherapy in metastatic or incompletely staged germinoma

All patients receive radiotherapy to the craniospinal axis (CSA-RT) followed by a boost directed at the tumour bed and all sites of macroscopic metastatic disease.

**Table 22: Irradiation in metastatic or incompletely staged germinoma**

<table>
<thead>
<tr>
<th>Volume</th>
<th>Total dose (Gy)</th>
<th>Dose per fraction (Gy)</th>
<th>Number of fractions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Craniospinal axis</td>
<td>24</td>
<td>1.6</td>
<td>15</td>
</tr>
<tr>
<td>Tumour bed boost</td>
<td>16</td>
<td>1.6</td>
<td>10</td>
</tr>
<tr>
<td>Tumour bed (total)</td>
<td>40</td>
<td>1.6</td>
<td>25</td>
</tr>
<tr>
<td>Boost to intracranial metastases</td>
<td>16</td>
<td>1.6</td>
<td>10</td>
</tr>
<tr>
<td>Intracranial metastases (total)</td>
<td>40</td>
<td>1.6</td>
<td>25</td>
</tr>
<tr>
<td>Boost to spinal metastatic deposits</td>
<td>16</td>
<td>1.6</td>
<td>10</td>
</tr>
<tr>
<td>Spinal metastatic deposits (total)</td>
<td>40</td>
<td>1.6</td>
<td>25</td>
</tr>
</tbody>
</table>

In the rare situation of germinoma plus teratoma, resection should take place prior to radiotherapy. In the event of incomplete resection, increased radiotherapy dose should be administered (see table 23). Any cases of doubt should be discussed with the national radiotherapy co-ordinator.
Table 23: Irradiation in metastatic germinoma plus teratoma and stable disease (incompletely resected)

<table>
<thead>
<tr>
<th>Volume</th>
<th>Total dose (Gy)</th>
<th>Dose per fraction (Gy)</th>
<th>Number of fractions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Craniospinal axis</td>
<td>24</td>
<td>1.6</td>
<td>15</td>
</tr>
<tr>
<td>Boost to tumour bed</td>
<td>30.4</td>
<td>1.6</td>
<td>19</td>
</tr>
<tr>
<td>Tumour bed (total)</td>
<td>54.4</td>
<td>1.6</td>
<td>34</td>
</tr>
<tr>
<td>Boost to intracranial metastases</td>
<td>30.4</td>
<td>1.6</td>
<td>19</td>
</tr>
<tr>
<td>Intracranial metastases (total)</td>
<td>54.4</td>
<td>1.6</td>
<td>34</td>
</tr>
<tr>
<td>Boost to spinal metastatic deposits</td>
<td>25.6</td>
<td>1.6</td>
<td>16</td>
</tr>
<tr>
<td>Spinal metastatic deposits (total)</td>
<td>49.6</td>
<td>1.6</td>
<td>31</td>
</tr>
</tbody>
</table>

6.2.2.1 Dose modifications and delays (see appendix H)

6.2.3 Investigations at the end of treatment (following radiotherapy) see flow sheets Appendix C.4

Tumour evaluation
- MRI head and spine, with and without contrast
- Serum and CSF markers (AFP and total HCG)
- CSF cytology

Treatment related investigations
- Full blood count
- Pure tone audiometry
- Endocrinological assessment
- MRI angiography according to local practice (see chapter 6.1.7)
7 TREATMENT OF MALIGNANT NONGERMINOMATOUS GERM CELL TUMOURS

This chapter describes the treatment of cases with:

- raised markers (AFP > 25 ng/ml and/or total HCG > 50 IU/l) in serum or CSF

Conversion of AFP units from ng/ml to kU/l (see chapter 5.2.1)

<table>
<thead>
<tr>
<th>AFP 25 ng/ml</th>
<th>= 20.75 kU/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFP 1000 ng/ml</td>
<td>= 830 kU/l</td>
</tr>
</tbody>
</table>

- histological evidence of yolk sac tumour, choriocarcinoma or embryonal carcinoma, regardless of the presence of germinoma (see chapter 5)

Note: The presence of metastatic disease does not influence risk group allocation but determines the fields for radiotherapy.

Figure 13: Treatment in malignant non-germinoma (± Germinoma ± Teratoma)

7.1 Standard risk non-germinoma (± Germinoma ± Teratoma)

- AFP ≤ 1000 ng/ml
- age ≥ 6 years

7.1.1 Chemotherapy in malignant non-germinoma with standard risk

Chemotherapy is based on a combination of cisplatin, etoposide and ifosfamide (PEI) and should commence as soon as possible following diagnosis.
Each course of PEI consists of:

- **Cisplatin** 20 mg/m²/day days 1, 2, 3, 4, 5
- **Etoposide** 100 mg/m²/day days 1, 2, 3
- **Ifosfamide** 1500 mg/m²/day days 1, 2, 3, 4, 5

**Please note:**
- It is also possible to use etoposide phosphate instead of etoposide in equivalent dose. 114 mg etoposide phosphate equals 100 mg etoposide.
- Ifosfamide dosing and administration differ from those used in treatment of germinoma.
- Courses should be given at 21 day intervals, subject to count recovery.
- In case of replacement of Cisplatin by Carboplatin, the total equivalent dose of Carboplatin is 600 mg/m²! Given as one dose only on day 1! (see Appendix E).

A total of four courses is given. There is a tumour reassessment following the third course, and the fourth course is given after surgery in cases with resectable residuum. The fourth course of PEI is followed by radiotherapy (section 7.1.6) and, in the event that there is residual tumour after radiotherapy, which has become amenable to surgery, resection should be attempted at that stage.

**Note:** In case of malignant viable tumour cells in the resected residual tumour, one course HD-PEI with stem cell support (see appendix E for dosages and details of administration), instead of one course PEI, is administered prior to radiotherapy.

### 7.1.1.1 Details of Chemotherapy Administration (CCLG)

Cisplatin, Etoposide/ Etoposide phosphate and Ifosfamide should be diluted prior to infusion according to locally validated practice and/or procedures for the aseptic preparation of chemotherapy agents, with particular reference to the preparation of chemotherapy agents that are to be administered as Investigational Medicinal Products (IMPs) in a clinical trial. The infusion fluids and volumes for infusion should be selected to permit the drug to be administered over the stated time. Such practice and/or procedures should also reflect the published data on the compatibility of the IMP with the intended container, the chemical stability of the IMP with the proposed diluent for infusion at the intended final concentrations of the prepared infusion and the appropriate storage conditions consequent on the choices made.

A central venous catheter according to local practice is essential for the delivery of this chemotherapy. Further guidance regarding delivery of chemotherapy can be found in Appendix E.

**Etoposide** (100 mg/m²)/ **Etoposide phosphate** (114 mg/m²) (on Days 1 - 3 of each cycle) should be given as an IV infusion over 1 - 4 hours, prior to cisplatin and ifosfamide. If etoposide phosphate is used, 114 mg of etoposide phosphate is equivalent to 100 mg etoposide.

**Cisplatin** (20 mg/m² on days 1 - 5 of each cycle) should be given as an IV infusion over one hour. It must be accompanied by an adequate diuresis. In the absence of DI, this should be achieved with a forced mannitol diuresis, which should be administered as an infusion of Mannitol 15-20% according to national practice, 40ml/m² over 1 hour, concurrently with each cisplatin infusion and approximately 3-4 and 6-7 hours after the cisplatin infusion. For patients with significant diuresis secondary to DI, mannitol is unlikely to be needed, and it is suggested that it should be omitted if a urinary output of at least 400 ml/m² over 6 hours is maintained.
Please note: In case of replacement of Cisplatin by Carboplatin, the total equivalent dose of Carboplatin is 600 mg/m²! Given as one dose only on day 1 over one or two hours! (see Appendix E).

Ifosfamide (1500 mg/m² on Days 1 – 5 of each cycle) should be given as an IV infusion over 3 hours, following Cisplatin. Concurrent administration of hydration and MESNA is recommended to avoid urothelial toxicity. Other nephrotoxic drugs, including aminoglycoside antibiotics, should be used with caution with ifosfamide and cisplatin.

Please note: Ifosfamide dosing differs from that used in the treatment of germinoma.

It is suggested that MESNA should be given at a dose of 1800 mg/m²/24 hours (120% of the daily ifosfamide dose) and should be continued for about 24 hours following completion of the last dose of ifosfamide. It may be given according to institutional practice, either as a continuous infusion (alongside, or added to the hydration fluid), or as bolus infusions of 600 mg/m² at times +0 h, +4 h and +8 h, on Days 1 – 5 and as a continuous infusion on Day 6. On Day 1 an additional bolus infusion of 300 mg/m² (20% of the daily ifosfamide dose) should be given prior to the ifosfamide infusion.

Hydration should commence at least three hours before start of Cisplatin and run continuously until at least 24 hours following the completion of the last Cisplatin infusion.

Note: If the volume of the etoposide infusion on day 1 is used in place of the first three hours of hydration fluid, care must be taken, to ensure that the volume is sufficient to provide fluid at the specified rate.

Note: The hydration fluid used may be according to institutional practice and should be infused at a rate that provides, inclusive of the volumes of the chemotherapy and MESNA infusions, a total of at least 125 ml/m²/hour (3 l/m²/day). Depending on the volume used for drugs, the total fluid volume administered is likely to be significant. Consideration should be given to capping this at 3.5 l/m²/day or 4 l/m²/day. A suggested infusion regimen can be found in Appendix E.

In the rare event of haemorrhagic cystitis, MESNA or hydration should be increased and diuretics added, according to institutional practice. Particular attention must be paid to urine output and plasma electrolytes in patients with diabetes insipidus.

In the rare event of haemorrhagic cystitis, MESNA or hydration should be increased and diuretics added, according to institutional practice. Particular attention must be paid to urine output and plasma electrolytes in patients with diabetes insipidus.

A total of four courses is given. The fourth course of PEI is followed by radiotherapy (see section 7.1.6) but, if there is residual tumour after 3 courses, surgery should be considered (see appendix G) followed by a fourth course of chemotherapy prior to radiotherapy.

7.1.1.2 Supportive care during chemotherapy

Beware!

Diabetes Insipidus (DI) is a common complication encountered in the treatment of malignant CNS GCTs. DI should be controlled prior to starting chemotherapy, and particular attention should be paid to sodium and fluid balance throughout treatment in all cases. Detailed guidelines for the management of DI are given in Appendix E9. Clinicians are advised to work closely with their colleagues in endocrinology.

Anti-emetic treatment should include a 5HT antagonist. Administration of steroids (e.g. dexamethasone) during chemotherapy should be avoided if at all possible, and only used for anti-emesis if other therapies fail. If symptoms of raised intracranial pressure develop during treatment, the cause (e.g. hydrocephalus) should be actively sought. Steroids should only be used as a short-term measure prior to definitive treatment of raised pressure. In patients with raised intracranial pressure at the time of the first chemotherapy course particular care should be taken about hyperhydration. In such cases therapy modifications should be discussed with the co-ordinator.
The prophylactic use of cotrimoxazole (sulfamethoxazole/trimethoprim) is optional and should be based on local practice, as no case of pneumocystis carinii infection has been reported in the SIOP CNS GCT 96 series. Prophylactic antibiotic/antifungal decontamination may be used if it is the normal practice in the treating hospital. The choice of antibiotics used during episodes of febrile neutropenia should be based on local guidelines.

**Preservation of fertility**

In adolescent males, the possibility of sperm cryopreservation should be discussed prior to the initiation of chemotherapy. In postpubertal females, gonadal protection may be considered, and should be based on local or national recommended practice.

### 7.1.2 Toxicity, dose modifications and delays

Please refer to Common Toxicity Criteria for documentation of toxicities (appendix F.3).

Chemotherapy for patients less than one year of age or weighing less than 10 kg should be prescribed on the basis of weight (kg). The dose is calculated from the dose in m² using the formula: \(1 \text{m}^2 = 30 \text{kg}\)

In children less than 4 months of age, ifosfamide should be omitted and substituted by cyclophosphamide after discussion with the national co-ordinator.

#### 7.1.2.1 Haematological toxicity

Courses of chemotherapy should be delayed until haematological recovery from the previous course has taken place, defined by neutrophils ≥1.0 x 10⁹/l or WBC ≥ 2.0 x 10⁹/l and platelets 100 x 10⁹/l. Significant delays should be discussed with the national chief investigator.

#### 7.1.2.2 Ototoxicity

Audiometry should be performed prior to alternate courses of chemotherapy. Modifications in treatment are based on the Brock / CTC (SIOP) Grading (see appendix F.6). If any dose alterations are required on the basis of ototoxicity, audiological assessment should be performed before each subsequent course of chemotherapy.


<table>
<thead>
<tr>
<th>Grade</th>
<th>Subjective hearing (CTCAE v. 3.0)</th>
<th>Audiometry (PTA) (Bilateral) (Brock classification (Brock et al., 1991))</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None (no change)</td>
<td>Loss &lt;40 dB on all frequencies</td>
</tr>
<tr>
<td>1</td>
<td>-</td>
<td>Loss ≥ 40 dB at 8000 Hz</td>
</tr>
<tr>
<td>2</td>
<td>Hearing loss not requiring hearing aid or intervention OR Tinnitus not interfering with activities of daily living (ADL)</td>
<td>Loss ≥ 40 dB at 4000 Hz</td>
</tr>
<tr>
<td>3</td>
<td>Hearing loss requiring hearing aid or intervention OR Tinnitus interfering with ADL</td>
<td>Loss ≥ 40 dB at 2000 Hz</td>
</tr>
<tr>
<td>4</td>
<td>Profound bilateral hearing loss (&gt; 90 dB) OR Disabling tinnitus</td>
<td>Loss ≥ 40 dB at 1000 Hz</td>
</tr>
</tbody>
</table>

**Note:** Grading for audiometry is based on loss in both ears – thus the grading (including that for modification of chemotherapy) is based on the lowest grading i.e. the ‘best ear’.
<table>
<thead>
<tr>
<th>Grade</th>
<th>Chemotherapy Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>1</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>Substitute carboplatin 600 mg/m² for day one [in one dose] instead cisplatin for five days</td>
</tr>
<tr>
<td>3</td>
<td>Omit any platinum</td>
</tr>
<tr>
<td>4</td>
<td>Omit any platinum</td>
</tr>
</tbody>
</table>
7.1.2.3 Nephrotoxicity

- Both glomerular and tubular toxicity must be monitored during treatment with cisplatin and ifosfamide.
- The estimation of GFR must be performed before the first and third course.

Treatment should be modified as follows:
If GFR/creatinine clearance < 80 ml/min per 1.73 m² or serum creatinine > 1.5 x upper limit of normal:
- Delay chemotherapy for one week, and repeat GFR, by measurement of clearance of radioisotope.
- If repeated GFR still < 80 ml/min per 1.73 m²: discuss with co-ordinator.

In case of nephrotoxicity CTC grade 2 reduce ifosfamide dose by 30%. In case of nephrotoxicity CTC grade 3 or 4 withhold ifosfamide and use cyclophosphamide instead (equivalent dose 1:4).

7.1.2.4 Neurotoxicity

If CTC grade 3 or 4 central neurotoxicity occurs, consider the use of Methylene Blue (methylthionin) 50 mg as i.v. infusion. Prolong ifosfamide to 4-8 hours with the next application, and infuse Methylene Blue 50 mg three times a day. In the next course, apply Methylene Blue one dose of 50 mg 24 hours prior to ifosfamide. During ifosfamide give three-times daily Methylene Blue as described above. If repeated grade 3 or 4 neurotoxicity occurs, consider withholding ifosfamide and substitute cyclophosphamide (see above).

7.1.3 Investigations before each course of chemotherapy

- Clinical examination including neurological assessment
- Weight
- Full blood count
- Blood biochemistry – electrolytes, urea, creatinine, ALT/AST, alkaline phosphatase, bilirubin, albumin, magnesium, calcium, phosphate
- Serum markers (AFP and total HCG)
- Pure tone audiometry (before first and third course, with additional assessments based on local practice and if any concern regarding hearing)
- GFR estimated by radioisotope clearance, or other locally approved method, or by direct measurement of creatinine clearance (before first and third course)
7.1.4 Tumour evaluation after three courses of PEI chemotherapy

- Clinical assessment, including neurological examination
- Serum markers (AFP and total HCG)
- CSF markers (AFP and total HCG) – mandatory if raised at diagnosis
- CSF cytology - mandatory if positive at diagnosis
- MRI of the head with and without contrast
- MRI of spine - if involved at diagnosis

If there is residual tumour found by imaging after the third course of PEI chemotherapy, resection of the residue should be carried out, if possible, before radiotherapy, (see neurosurgical guidelines, appendix G). It is strongly recommended that scans of patients with residual tumour at this stage are reviewed by the national reference neuroradiologist. The presence of active malignancy in the resected specimen indicates poor response to treatment and it is recommended that such cases should receive subsequent treatment with High-dose-PEI and stem-cell rescue (bone marrow or PBSC if collected) according to the high risk strategy. Those patients in whom tumour markers fail to respond to chemotherapy at any stage or have not returned to normal by the end of the third course of PEI, should be discussed with the study co-ordinator with a view to intensifying treatment. Cases in which markers continue to rise despite chemotherapy will require individual treatment and must be discussed with the national chief investigator.

7.1.5 Surgical treatment of NGGCTs

Medical treatment is curative in most cases of NGGCT. Decisions regarding definitive surgery can therefore be delayed until assessment of residual after three courses of chemotherapy. Patients with resectable residual disease after 3 courses of chemotherapy should be considered for surgery at this time point. If not resectable at this time, resection of any persistent residual tumour which has become amenable to surgery should be attempted following radiotherapy. Tumours may disappear completely after a few cycles of chemotherapy or doses of RT but some cases, particularly those with teratoma components, have a more complex pattern of response with slow regression of residual tumours despite marker normalization. Profound morphological regressive changes sometimes occur within the lesions (increased necrosis and cystic components, increased volume of mature residual teratomatous components). However, if malignant viable cells are detected, and even if complete removal is obtained, this means that the tumour is chemoresistant and deserves intensification of chemotherapy.

It is recommended that cases in which there is doubt about the need for definitive surgery should be discussed with one of the surgeons of the study committee.
7.1.6 Radiotherapy for NGGCTs

Although NGGCTs are less radiosensitive than their germinoma counterparts, radiotherapy represents a crucial part in the management of this malignant intracranial germ cell tumour (see chapter 1). Radiotherapy according to dissemination is given only in patients older than or equal 6 years of age at time of radiotherapy. For details on administration see appendix H.

7.1.6.1 Non-metastatic disease in NGGCTs

Patients with localised disease at diagnosis receive focal irradiation.

Table 24: Irradiation in non-metastatic NGGCTs

<table>
<thead>
<tr>
<th>Volume</th>
<th>Total dose (Gy)</th>
<th>Dose per Fraction (Gy)</th>
<th>Number of fractions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumour site</td>
<td>54</td>
<td>1.8</td>
<td>30</td>
</tr>
</tbody>
</table>

7.1.6.2 Metastatic disease or incompletely staged

Table 25: Irradiation in metastatic or incompletely staged NGGCTs

<table>
<thead>
<tr>
<th>Volume</th>
<th>Total dose (Gy)</th>
<th>Dose per Fraction (Gy)</th>
<th>Number of fractions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebrum</td>
<td>30</td>
<td>1.5</td>
<td>20</td>
</tr>
<tr>
<td>Spinal axis</td>
<td>30</td>
<td>1.5</td>
<td>20</td>
</tr>
<tr>
<td>Tumour site</td>
<td>24</td>
<td>1.6</td>
<td>15</td>
</tr>
<tr>
<td>Intracranial metastatic deposits</td>
<td>24</td>
<td>1.6</td>
<td>15</td>
</tr>
<tr>
<td>Spinal metastatic deposits</td>
<td>20.8</td>
<td>1.6</td>
<td>13</td>
</tr>
<tr>
<td>Total tumour dose</td>
<td>54</td>
<td></td>
<td>35</td>
</tr>
<tr>
<td>Total dose to intracranial metastatic deposits</td>
<td>54</td>
<td></td>
<td>35</td>
</tr>
<tr>
<td>Total dose to spinal metastatic deposits</td>
<td>50.8</td>
<td></td>
<td>33</td>
</tr>
</tbody>
</table>

* If more than 2/3 of the spine is involved with macroscopic disease the total dose will be limited to 45 Gy (additional boost dose: 15 Gy in 10 daily fractions of 1.5 Gy).
7.1.7 Investigations at the end of treatment (following radiotherapy if age ≥ 6y or high dose therapy if age < 6y)

Tumour evaluation
- MRI head and spine, with and without contrast
- Serum markers (AFP and total HCG) (CSF markers only if not negative at last evaluation)
- CSF cytology if positive at time of diagnosis

Treatment related investigations
- Blood biochemistry – electrolytes, urea, creatinine, ALT/AST, alkaline phosphatase, bilirubin, albumin, magnesium, calcium, phosphate
- Pure tone audiometry
- Glomerular filtration rate
- Urine osmolality (early morning) and phosphate, creatinine for calculation of tubular reabsorption of phosphate.
- Endocrinological assessment

7.2 High risk non-germinoma (± Germinoma ± Teratoma)

- AFP > 1000 ng/ml
- or
- age < 6 years

7.2.1 Chemotherapy in malignant non-germinoma with high risk

Treatment of patients who fall into the high risk group will be based on a strategy employing high dose therapy and peripheral blood stem cell rescue (Schmoll et al, 2004) according to institutional practice (see appendix E.10), following induction chemotherapy with cisplatin, etoposide and ifosfamide (PEI).

Chemotherapy should commence as soon as possible following diagnosis.

Course of PEI consists of:

- **Cisplatin** 20 mg/m²/day days 1, 2, 3, 4, 5
- **Etoposide** 100 mg/m²/day days 1, 2, 3
- **Ifosfamide** 1500 mg/m²/day days 1, 2, 3, 4, 5

**Please note:**
- It is also possible to use etoposide phosphate instead of etoposide in equivalent dose. 114 mg etoposide phosphate equals 100 mg etoposide.
- Ifosfamide dosing and administration differ from those used in treatment of germinoma
- Courses should be given at 21 day intervals, subject to count recovery.
- In case of replacement of Cisplatin by Carboplatin, the total equivalent dose of Carboplatin is 600 mg/m²! Given as one dose only on day 1! (see Appendix E).

Peripheral blood stem cells should be harvested according to institutional practice following the first and/or second course of PEI (see appendix E.10).

A total of two courses of standard PEI is given. This is followed by two courses of high dose PEI (HD-PEI).
Each course of high dose PEI consists of:

- **Cisplatin** 20 mg/m²/day days 1, 2, 3, 4, 5
- **Etoposide** 300 mg/m²/day days 1, 2, 3, 4, 5
- **Ifosfamide** 2000 mg/m²/day days 1, 2, 3, 4, 5

See appendix E.3 for details of administration.

There is a tumour reassessment following the third course of chemotherapy, (first course of HD-PEI), for consistency of evaluation with standard risk treatment. All patients proceed to a second course of HD-PEI followed by a further reassessment for all patients with evidence of residual disease at the previous reassessment.

Patients with resectable residual disease after high dose therapies should be considered for surgery at this time point.

Radiotherapy is then delivered to all patients aged 6 years or more, according to stage at diagnosis. In children less than 6 years of age, close follow-up is mandatory and radiotherapy may be considered. All such patients should be discussed with the national co-ordinator.

Following radiotherapy, resection of any persistent residual tumour which is amenable to surgery should be attempted.

### 7.2.1.1 Details of Chemotherapy Administration

Cisplatin, Etoposide/Etoposide phosphate and Ifosfamide should be diluted prior to infusion according to locally validated practice and/or procedures for the aseptic preparation of chemotherapy agents, with particular reference to the preparation of chemotherapy agents that are to be administered as Investigational Medicinal Products (IMPs) in a clinical trial. The infusion fluids and volumes for infusion should be selected to permit the drug to be administered over the stated time.

Such practice and/or procedures should also reflect the published data on the compatibility of the IMP with the intended container, the chemical stability of the IMP with the proposed diluent for infusion at the intended final concentrations of the prepared infusion and the appropriate storage conditions consequent on the choices made.

A central venous line according to local practice is essential for the delivery of this chemotherapy. Further guidance regarding delivery of chemotherapy can be found in Appendix E.

### Stem Cell collection prior to HD-PEI

High dose chemotherapy and stem cell support should only be undertaken in centres with the necessary infrastructure and support in order to meet local and national standards (see appendix E.10). In case of an insufficient collection of stem cells or viable tumour cells at time of resection which than requires treatment intensification a bone marrow harvest has to be performed (requirements for stimulation and harvesting see appendix E.10).

### HD-PEI chemotherapy

Etoposide (300 mg/m²)/ Etoposide phosphate (342 mg/m²), (on days 1 - 5 of each cycle) should be given as an IV infusion over 1 - 4 hours, prior to cisplatin and ifosfamide. If etoposide phosphate is used, 342 mg of etoposide phosphate is equivalent to 300 mg etoposide.
Cisplatin (20 mg/m², on days 1 - 5 of each cycle) should be given as an IV infusion over one hour. It must be accompanied by an adequate diuresis. In the absence of DI, this should be achieved with a forced mannitol diuresis, which should be administered as an infusion of Mannitol 15-20 % according to national practice 40ml/m² over 1 hour, concurrently with each cisplatin infusion and approximately 3-4 and 6-7 hours after the cisplatin infusion. For patients with significant diuresis secondary to DI, mannitol is unlikely to be needed, and it is suggested that it should be omitted if a urinary output of at least 400 ml/m² over 6 hours is maintained.

Please note: In case of replacement of Cisplatin by Carboplatin, the total equivalent dose of Carboplatin is 600 mg/m² ! Given as one dose only on day 1 over one or two hours ! (see Appendix E).

Ifosfamide (2000 mg/m², on Days 1 – 5 of each cycle) should be given as an IV infusion over 3 hours, following cisplatin. Concurrent administration of hydration and MESNA is recommended to avoid urothelial toxicity. Other nephrotoxic drugs, including aminoglycoside antibiotics, should be used with caution with ifosfamide and cisplatin.

Please note: Ifosfamide dosing differs from that used in the treatment of germinoma.

It is suggested that MESNA should be given at a dose of 2400 mg/m²/24 hours (120% of the daily ifosfamide dose) and should be continued for about 48 hours following completion of the last dose of ifosfamide. It may be given according to institutional practice, either as a continuous infusion (alongside, or added to the hydration fluid), or as bolus infusions of 800 mg/m² at times +0 h, +4h and +8 h, on Days 1 – 5, and as a continuous infusion on Days 6 & 7. On Day 1 an additional bolus infusion of 400 mg/m² (20% of the daily ifosfamide dose) should be given prior to the ifosfamide infusion.

Hydration should commence at least three hours before cisplatin and run continuously until at least 48 hours following the completion of the last ifosfamide infusion.

Note: If the volume of the Etoposide infusion on day 1 is used in place of the first three hours of hydration fluid, care must be taken, to ensure that the volume is sufficient to provide fluid at the specified rate.

The hydration fluid used may be according to institutional practice and should be infused at a rate that provides, inclusive of the volumes of the chemotherapy and MESNA infusions, a total of at least 125ml/m²/hour (3l/m²/day). Note: Depending on the volume used for drugs, the total fluid volume administered is likely to be significant. Consideration should be given to capping this at 3.5 l/m²/day or 4 l/m²/day. A suggested infusion regimen can be found in Appendix E.

In the rare event of haemorrhagic cystitis, MESNA or hydration should be increased and diuretics added, according to institutional practice. Particular attention must be paid to urine output and plasma electrolytes in patients with diabetes insipidus.

The treatment schedule of HD-PEI should be modified only in exceptional cases, e.g. high fever or documented significant toxicity (please contact national investigator / co-ordinator).

Reinfusion of stem cells

Stem cell support will be administered on day 7 of HD-PEI therapy according to local guidelines.

Management following HD-PEI chemotherapy
There is a tumour reassessment following the third course of chemotherapy (first course of HD-PEI) for consistency of evaluation with standard risk treatment. All patients proceed to a second course of HD-PEI followed by a further reassessment for all patients with evidence of residual disease at the previous reassessment.

Patients with resectable residual disease after high dose therapy should be considered for surgery at this time point.

Radiotherapy is then delivered to all patients aged 6 years or more, according to stage at diagnosis. In children less than 6 years of age, close follow-up is mandatory and radiotherapy may be considered. All such patients should be discussed with the national co-ordinator.

Following radiotherapy, resection of any persistent residual tumour which is amenable to surgery should be attempted.

7.2.1.2 Supportive care during chemotherapy

**Beware!**

Diabetes Insipidus (DI) is a common complication encountered in the treatment of malignant CNS GCTs. DI should be controlled prior to starting chemotherapy, and particular attention should be paid to sodium and fluid balance throughout treatment in all cases. Detailed guidelines for the management of DI are given in Appendix E.9. Clinicians are advised to work closely with their colleagues in endocrinology.

Anti-emetic treatment should include a 5HT antagonist. Administration of steroids (e.g. dexamethasone) during chemotherapy should be avoided if at all possible, and only used for anti-emesis if other therapies fail. If symptoms of raised intracranial pressure develop during treatment, the cause (e.g. hydrocephalus) should be actively sought. Steroids should only be used as a short-term measure prior to definitive treatment of raised pressure. In patients with raised intracranial pressure at the time of the first chemotherapy course particular care should be taken about hyperhydration. In such cases therapy modifications should be discussed with the co-ordinator.

The prophylactic use of cotrimoxazole (sulfamethoxazole/trimethoprim) is optional and should be based on local practice, as no case of pneumocystis carinii infection has been reported in the SIOP CNS GCT 96 series. Prophylactic antibiotic/antifungal decontamination may be used if it is the normal practice in the treating hospital. The choice of antibiotics used during episodes of febrile neutropenia should be based on local guidelines.

**Preservation of fertility**

In adolescent males, the possibility of sperm cryopreservation should be discussed prior to the initiation of chemotherapy. In postpubertal females, gonadal protection may be considered, and should be based on local or national recommended practice.

7.2.2 Toxicity, dose modifications and delays

Please refer to Common Toxicity Criteria for documentation of toxicities (appendix F.3).

Chemotherapy for patients less than one year of age or weight less than 10 kg should be prescribed on the basis of weight (kg). The dose is calculated from the dose in m² using the formula: \[ 1 \text{m}^2 = 30 \text{kg} \]

In children less than 4 months of age, ifosfamide should be omitted and substituted by cyclophosphamide after discussion with the national co-ordinator.
7.2.2.1 Haematological toxicity

Courses of chemotherapy should be delayed until haematological recovery from the previous course has taken place, interpreted by neutrophils \( \geq 1.0 \times 10^9/l \) or WBC \( \geq 2.0 \times 10^9/l \) and platelets \( 100 \times 10^9/l \). Significant delays should be discussed with the national chief investigator.
7.2.2.2 Ototoxicity

Audiometry should be performed prior to alternate courses of chemotherapy. Modifications in treatment are based on the Brock / CTC (SIOP) Grading (see appendix F.6). If any dose alterations are required on the basis of ototoxicity, audiological assessment should be performed before each subsequent course of chemotherapy.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Subjective hearing (CTCAE v. 3.0)</th>
<th>Audiometry (PTA) (Bilateral) (Brock classification (Brock et al., 1991))</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None (no change)</td>
<td>Loss &lt;40 dB on all frequencies</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>Loss ≥ 40 dB at 8000 Hz</td>
</tr>
<tr>
<td>2</td>
<td>Hearing loss not requiring hearing aid or intervention OR Tinnitus not interfering with activities of daily living (ADL)</td>
<td>Loss ≥ 40 dB at 4000 Hz</td>
</tr>
<tr>
<td>3</td>
<td>Hearing loss requiring hearing aid or intervention OR Tinnitus interfering with ADL</td>
<td>Loss ≥ 40 dB at 2000 Hz</td>
</tr>
<tr>
<td>4</td>
<td>Profound bilateral hearing loss (&gt; 90 dB) OR Disabling tinnitus</td>
<td>Loss ≥ 40 dB at 1000 Hz</td>
</tr>
</tbody>
</table>

**Note:** grading for audiometry is based on loss in both ears – thus the grading (including that for modification of chemotherapy) is based on the lowest grading i.e. the ‘best ear’.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Chemotherapy Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>1</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>Substitute carboplatin 600 mg/m² for day one [in one dose] instead cisplatin for five days</td>
</tr>
<tr>
<td>3</td>
<td>Omit any platinum</td>
</tr>
<tr>
<td>4</td>
<td>Omit any platinum</td>
</tr>
</tbody>
</table>

7.2.2.3 Nephrotoxicity

- Both glomerular and tubular toxicity must be monitored during treatment with carboplatin and ifosfamide.
- The estimation of GFR must be performed before the first, third and fourth courses of chemotherapy.

Treatment should be modified as follows:
If GFR/creatinine clearance < 80 ml/min per 1.73 m² or serum creatinine > 1.2 mg/dl or > 1.5 x upper limit of normal:
- Delay chemotherapy for one week, and repeat GFR, by measurement of clearance of radioisotope
- If repeated GFR still < 80 ml/min per 1.73 m²: discuss with co-ordinator

In case of nephrotoxicity CTC grade 2 reduce ifosfamide dose by 30%. In case of nephrotoxicity CTC grade 3 or 4 withhold ifosfamide and use cyclophosphamide instead (equivalent dose 1:4).
7.2.2.4 Neurotoxicity

If CTC grade 3 or 4 central neurotoxicity occurs, consider the use of Methylene Blue (methylthionin) 50 mg as i.v. infusion. Prolong ifosfamide to 4-8 hours with the next application, and infuse Methylene Blue 50 mg three times a day. In the next course, apply Methylene Blue one dose of 50 mg 24 hours prior to ifosfamide. During ifosfamide give three-times daily Methylene Blue as described above. If repeated grade 3 or 4 neurotoxicity occurs, consider withholding ifosfamide and substitute cyclophosphamide (see above).

7.2.3 Investigations before each course of chemotherapy

- Clinical examination
- Weight
- Full blood count
- Blood biochemistry – electrolytes, urea, creatinine, ALT/AST, alkaline phosphatase, bilirubin, albumin, magnesium, calcium, phosphate
- Serum markers (AFP and total HCG)
- Pure tone audiometry (before first and third courses, with additional assessments based on local practice and if any concern regarding hearing)
- GFR estimated by radioisotope clearance, or other locally approved method, or by direct measurement of creatinine clearance (before first course, PEI, and before third and fourth courses, HD-PEI)

7.2.4 Tumour evaluation after three and four courses of chemotherapy

- Clinical assessment, including neurological examination
- Serum markers (AFP and total HCG)
- CSF markers (AFP and total HCG) – mandatory if raised at diagnosis
- CSF cytology - mandatory if positive at diagnosis
- MRI of the head with and without contrast
- MRI of spine - if involved at diagnosis

If there is residual tumour found by imaging after the third course of chemotherapy (2 x PEI, 1 x HD-PEI), resection of the residue should be carried out, if possible, before radiotherapy, (see neurosurgical guidelines, Appendix G). It is strongly recommended that scans of patients with residual tumour at this stage are reviewed by the national reference neurradiologist. The presence of active malignancy in the resected specimen indicates poor response to treatment and it is recommended that such cases should receive subsequent treatment according to the high risk strategy. Those patients in whom tumour markers fail to respond to chemotherapy at any stage or have not returned to normal by the end of the third course of chemotherapy, should be discussed with the study co-ordinator with a view to intensifying treatment. Cases in which markers continue to rise despite chemotherapy will require individual treatment and must be discussed with the national investigator / co-ordinator.
7.2.5 Surgical treatment of NGGCTs

Medical treatment is curative in most cases of NGGCT. Decisions regarding definitive surgery can therefore be delayed until assessment of residual after chemotherapy. Tumours may disappear completely after few cycles of chemotherapy or doses of RT but some cases, particularly those with teratoma components, have a more complex pattern of response with slow regression of residual tumours despite marker normalization. Profound morphological regressive changes sometimes occur within the lesions (increased necrosis and cystic components, increased volume of mature residual teratomatous components).

Patients with resectable residual disease after three courses of chemotherapy should be considered for surgery at this time point. If not resectable at this time, resection of any persistent residual tumour which is amenable to surgery should be attempted following radiotherapy. It is recommended that cases in which there is doubt about the need for definitive surgery should be discussed with one of the surgeons on the study committee.

7.2.6 Radiotherapy for non-germinomatous germ cell tumours

Although non-germinomatous germ cell tumours are less radiosensitive than their germinoma counterparts, radiotherapy represents a crucial part in the management of this malignant intracranial germ cell tumour (see chapter 1). Radiotherapy according to dissemination is given only in patients older than or equal 6 years of age at time of radiotherapy. For details on administration see appendix H.

7.2.6.1 Non-metastatic disease

Patients with localised disease at diagnosis receive focal irradiation.

Table 26: Irradiation in non-metastatic NGGCTs (+ germinoma, + teratoma)

<table>
<thead>
<tr>
<th>Volume</th>
<th>Total dose (Gy)</th>
<th>Dose per Fraction (Gy)</th>
<th>Number of fractions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumour site</td>
<td>54</td>
<td>1.8</td>
<td>30</td>
</tr>
</tbody>
</table>

7.2.6.2 Metastatic disease

Table 27: Irradiation in metastatic NGGCTs (+ germinoma, + teratoma)

<table>
<thead>
<tr>
<th>Volume</th>
<th>Total dose (Gy)</th>
<th>Dose per Fraction (Gy)</th>
<th>Number of fractions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebrum</td>
<td>30</td>
<td>1.5</td>
<td>20</td>
</tr>
<tr>
<td>Spinal axis</td>
<td>30</td>
<td>1.5</td>
<td>20</td>
</tr>
<tr>
<td>Tumour site</td>
<td>24</td>
<td>1.6</td>
<td>15</td>
</tr>
<tr>
<td>Intracranial metastatic deposits</td>
<td>24</td>
<td>1.6</td>
<td>15</td>
</tr>
<tr>
<td>Spinal metastatic deposits</td>
<td>20.8</td>
<td>1.6</td>
<td>13</td>
</tr>
<tr>
<td>Total tumour dose</td>
<td>54</td>
<td></td>
<td>35</td>
</tr>
<tr>
<td>Total dose to intracranial metastatic deposits</td>
<td>54</td>
<td></td>
<td>35</td>
</tr>
<tr>
<td>Total dose to spinal metastatic deposits</td>
<td>50.8</td>
<td></td>
<td>33</td>
</tr>
</tbody>
</table>

* If more than 2/3 of the spine is involved with macroscopic disease the total dose will be limited to 45 Gy (additional boost dose: 15 Gy in 10 daily fractions of 1.5 Gy).
7.2.6.3 Dose modifications and delays (see appendix H)

7.2.7 Investigations at the end of treatment (following radiotherapy if age > 6y or high dose therapy if age < 6y)

Tumour evaluation
- MRI head and spine, with and without contrast
- Serum markers (AFP and total HCG), CSF
- CSF cytology

Treatment related investigations
- Blood biochemistry – electrolytes, urea, creatinine, ALT/AST, Alkaline phosphatase, bilirubin, albumin, magnesium, calcium, phosphate
- Pure tone audiometry
- Glomerular filtration rate
- Urine osmolality (early morning) and phosphate, creatinine for calculation of tubular reabsorption of phosphate.
- Endocrinological assessment
8 TERATOMA

8.1 Investigations for diagnosis

AFP, total HCG in serum and CSF negative for markers
MRI of head and spine
Proven histology

8.2 Treatment

Teratoma will be treated by surgery as main treatment option and additional treatment according to histology and resection status. Treatment for mature and immature teratoma needs to be individualised, based on the age of the patient, clinical status, tumour stage and histology. Thus, no overall therapeutic strategy will be outlined in the protocol but recommendations will be given on an individual basis.

The goal for the future is to accrue sufficient data on incidence and epidemiology of teratoma, biological and histological behaviour, impact of surgery and of other treatments in order to develop standardized guidelines for diagnosis and treatment of this subgroup of patients. In this group of patients quality of survival data will be collected to describe for the first time the quality of survival at diagnosis (surgery), at the end of treatment and at follow-up.
To this end, it is therefore also desirable to store tissue samples and make them available to the national tissue banks.

8.3 Follow-up

Follow-up investigations are dependent on chosen treatment, and tumour- or treatment-related sequelae. Regular imaging, together with clinical examination should be performed during follow-up, as described in section 5.8 and appendix C.
9 DETERMINANTS OF SAFETY

9.1 Definition and explanation of terms

An **adverse event (AE)** is any untoward medical occurrence in a patient administered an investigational medicinal product (IMP) or receiving another treatment intervention in the protocol defined treatment and which does not necessarily have a causal relationship with this treatment. An AE can be any unfavourable and unintended sign including an abnormal laboratory finding, a symptom, or a disease temporally associated with the use of an IMP or another in the protocol defined treatment, whether or not considered related to the IMP or another treatment. ‘Another treatment intervention’ in the protocol defined treatment includes surgery or radiotherapy, including treatment for teratoma according to recommendations given on an individual basis.

An **adverse reaction (AR)** is any untoward and unintended response to an IMP, which is related to any dose administered. All AEs judged by either the reporting investigator or the sponsor's delegate as having a reasonable causal relationship to an IMP qualify as ARs. The term AR and toxicity are synonymous. The expression ‘reasonable causal relationship’ means to convey in general that there is evidence or argument to suggest a causal relationship.

A **serious adverse event (SAE) or serious adverse reaction (SAR)** is any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing inpatients’ hospitalisation, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect.

An **unexpected adverse reaction (UAR)** is an AR the nature or severity of which is not consistent with the applicable product information.

Examples of UARs:
- an expected /listed AR with an unexpected more severe clinical outcome (e.g. fatal)
- a more specific reaction than listed in the applicable product information (e.g. when “acute renal failure” is listed, “interstitial nephritis” is more specific and therefore unexpected)
- an increase in the rate of occurrence of an expected AR is considered as unexpected.

A **suspected unexpected serious adverse reaction (SUSAR)** is an SAE where a causal relationship to the IMP is suspected, i.e. SAR, and where the nature or severity is not consistent with the product information, i.e. SUSAR.

9.2 Serious Adverse Events Requiring Immediate Reporting on SAE Form (see appendix D.9)

Any of the following AEs occurring from first day of protocol defined treatment until end of the follow-up within the trial 2 years after treatment initiation must be reported, as long as no exception criterion for SAE reporting according to 9.3 is met.

From 3 months after end of trial treatment up to 2 years after treatment intiation, SAEs only have to be reported on the SAE form as long as the investigator suspects a causal relationship of the SAE to the protocol defined treatment.

- **AE which results in death**
  
  *Death* is an OUTCOME of an AE and must be reported together with the cause of death on the SAE form.

- **AE which is life-threatening**
  
  The term "life-threatening" refers to an AE in which the patient was at immediate risk of death at the time of the AE, i.e. required immediate intervention with life-saving intensive care treatment. It does not refer to an event which hypothetically might have caused death if it were more severe.

- **AE requiring hospitalisation**

  or

- **AE requiring prolongation of hospitalisation**
**Hospitalisation** is defined as at least one overnight admission. Only AEs which are considered unanticipated (clinically unexpected) by the investigator and SAEs which are clinically expected but unexpectedly severe (CTCAE°4-5) require immediate reporting on the SAE form. Hospitalisation without underlying AE is not an SAE. Examples are:

- Hospitalisation for protocol procedures e.g. chemotherapy, surgery, routine supportive treatment, biopsy or monitoring of the study.
- Elective hospitalisation for a pre-existing condition (i.e. a condition other than the indication for the chemotherapy) that has not worsened.
- Admission to a rehabilitation centre or hospice.
- Hospitalisation for social reasons (e.g. due to anxiety but otherwise treatable on an outpatient basis).

**AE or AR resulting in persistent or significant disability or incapacity**

Disability is defined as a substantial disruption in a person’s ability to conduct normal life functions e.g. persistent blindness, deafness.

**A congenital anomaly or birth defect**

Pregnancy and its outcome should be reported on an SAE form in order to identify and follow up on outcome of pregnancy and on any congenital abnormalities, also births from fathers under chemotherapy are to be reported on the appropriate SAE form. However, pregnancy itself is per definition not serious. Follow-up of a pregnancy will be done using specific additional questionnaires supplied by the Safety Desk.

**Other medically important conditions**

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are in the opinion of the investigator clinically unexpected and not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious and are reportable on an SAE form e.g. bronchospasm.

**Clinically relevant abnormal unanticipated biological or vital signs**

Abnormal biological or vital signs commonly occur under chemotherapy but when considered clinically relevant by the physician i.e. unexpected or with severity of CTCAE grade 4 (except for haematologic toxicities grade 4) require **immediate reporting on SAE form** e.g. nephrotoxicity (GFR ≤ 19ml/min/1.73 m²) or cardiac toxicity (FS<28%, LVEF < 40%).

**Cancer: Secondary malignancies**

Secondary malignancies e.g. skin cancer, myelodysplastic syndrome (MDS) usually occur later, but when they occur during protocol treatment, including 3 months from the last day of protocol defined chemotherapy, they should be reported immediately on SAE form as well as being documented on the Event Form. From 3 months after end of trial treatment up to 2 years after treatment initiation, secondary malignancies have to be reported on the SAE form as long as the investigator suspects a causal relationship to the protocol defined treatment.

### 9.3 Protocol-Specific Exceptions for SAE Reporting

**IMPORTANT NOTE:** The following do not require reporting on the SAE form:

- SAEs that occur after registration but prior to start of treatment
- Hospitalisation due to signs and symptoms of disease progression.
- Expected hospitalisation for procedures such as blood transfusion for haematological toxicity CTCAE°1-4, antibiotic treatment of neutropenic fever or CTCAE°1-3 infections, or controlled pain relief and nutritional support for gut toxicity CTCAE°1-3 or other expected toxicity CTCAE°1-3 is not to be reported on an SAE form.
- SAEs which occur later than 3 months after completion of protocol-defined treatment and up to the end of the follow-up within the trial 2 years after first day of protocol defined treatment, do not have
to be reported on the SAE form as long as the investigator does not suspect a causal relationship of the SAE to the protocol defined treatment.

**Be aware:**
Each fatal case has to be reported on an SAE form, irrespective of the cause of death, until 3 months after end of trial treatment. From then up to 2 years after treatment initiation, each treatment related fatal case has to be reported on an SAE form.

SAEs which do not require immediate reporting on an SAE form, even if hospitalisation is required, are to be reported by CRF (toxicity check list) (see Appendix D): these include:
- Haematological toxicity: e.g. haemoglobin, WBC, granulocytes/neutrophils, platelets (CTCAE°1-4).
- Infections and fever, incl. neutropenic fever (CTCAE °1-3).
- Gut toxicity (mucositis / stomatitis, vomiting, diarrhoea) (CTCAE°1-3).
- Other expected AEs CTCAE°1-3.

### 9.4 Adverse Event Documentation

AEs, including serious adverse events, are to be collected and are documented on the case report forms (CRF) from the first day of protocol defined treatment (CRF form) until the end of follow-up within the trial 2 years after completion of protocol defined therapy (follow up form).

AEs are graded for severity according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0, see Appendix F.3 or [http://ctep.info.nih.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf](http://ctep.info.nih.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf)

AEs are collected using a checklist CRF covering all anticipated ARs graded according to CTCAE v.3.0. (see Appendix F.3) The check list has a free-text box for documenting other clinically relevant AEs. Documentation of the treatment given and associated side effects has to be carried out by the treating physician / the clinical investigator, with support by a documentation assistant if appropriate, in a timely fashion, i.e. prior to the start of the next therapy element. Therapy documentation forms according to the NCI criteria will be provided for each therapeutic element. AEs occuring during follow up are documented on follow up forms. Both therapy documentation and follow up forms are included in Appendix D.

The CRF represents the period from the start of the respective therapy element to the start of the next element. For documentation the highest grade of toxicity observed during this period will be listed.

### 9.5 Serious Adverse Event Reporting

SAEs as defined by the protocol in Section 9.1 – 9.3 are reportable on an SAE form to the SIOP CNS GCT II Safety Desk within 24 hours. This applies for SAEs from first day of protocol defined treatment until end of the follow-up within the trial 2 years after treatment initiation. The patient identification must be replaced by the international patient trial number before forwarding the SAE form or any other information.

**Address:**

<table>
<thead>
<tr>
<th>SIOP CNS GCT II Safety Desk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zentrum für Klinische Studien (ZKS)</td>
</tr>
<tr>
<td>Universitätsklinikum Münster</td>
</tr>
<tr>
<td>Von-Esmarch-Str. 62</td>
</tr>
<tr>
<td>48149 Münster</td>
</tr>
<tr>
<td>Germany</td>
</tr>
</tbody>
</table>

The investigator is responsible for the assessment of seriousness, severity (CTCAE v. 3.0) and relatedness of the SAE. The SAE form should be completed with as much information as possible.
Where possible, a diagnosis rather than a list of symptoms should be given. The investigator should not wait for full details before making the initial report. SAEs must be followed up until the condition resolves or stabilises. The investigator must fax any relevant follow-up information to the safety desk as soon as possible. In case of fatal or life-threatening SAEs, the investigator must fax as much follow-up information as possible within 8 days of the initial SAE report. In case of death a copy of an autopsy protocol should be provided, if any.

In case of death, the investigator has to supply the competent authority and Ethics Committees with all details which may be additionally requested by them.

9.6 Serious Adverse Event Collection, Assessment and Distribution

The SIOP CNS GCT II Safety Desk will document each SAE, check it and query additionally required information.

The International chief investigator who is placed in Germany reviews each SAE again for seriousness and relatedness and assesses each SAR for expectedness according to the relevant product information.

The SIOP CNS GCT II Safety Desk transfers all relevant safety information to the National Coordinator of each country. Information about SAEs including SUSARs will be forwarded by the end of 3 business days after knowledge of the case at the Safety Desk. The National Coordinator of each country is responsible for ensuring that competent authorities, ethics committees and investigators participating within his/her country are informed of all SUSARs and that all other relevant safety information including Annual Safety Reports are submitted in accordance with national legal requirements.

According to Directive 2001/20/EC,

- fatal or life-threatening SUSARs have to be submitted no later than 7 calendar days from first knowledge at the Safety Desk,
- other SUSARs have to be submitted no later than 15 calendar days from first knowledge at the SIOP CNS GCT II Safety Desk.

The Safety Desk will provide a CIOMS 1 form for any SUSAR report and inform the National Coordinators about the relevant time limit.

The International chief investigator is responsible for the ongoing safety evaluation of the trial. The SIOP CNS GCT II Safety Desk informs the international chief investigator based in Germany immediately about any safety relevant information coming to its knowledge as do the National chief investigator inform the SIOP CNS GCT II Safety Desk. In case of safety relevant issues (besides SUSARs) which require expedited reporting, the SIOP CNS GCT II Safety Desk will support the International chief investigators in preparing an appropriate report in due time and will distribute the report to the National chief investigator of each country.

Submission of such reports has to take place not later than 15 calendar days from knowledge of the reportable information. Reportable safety relevant issues may be e.g. an increase in the rate of occurrence or a qualitative change of an expected serious adverse reaction, which is judged to be clinically important, new events related to the conduct of the trial and likely to affect the safety of the subjects, or recommendations of the Data Monitoring and Safety Committee where relevant for the safety of the subjects.

Regarding the Annual Safety Reports, the International chief investigator based in Germany is responsible for providing the updated risk-benefit assessment of the trial (Part 1 of the report). The SIOP CNS GCT II Safety Desk is responsible for preparing all other parts of the Annual Safety Report, finalising it and distributing it to the National Coordinators for submission in a timely manner.

Annual Safety Reports have to be submitted within 60 days of each anniversary of the date of first authorisation of the trial by a competent authority.
More details of the shared reporting obligations between National Coordinator and Safety Desk are laid down in the contractual agreement between the sponsor and the National Coordinator.

The statistician of the trial will provide information for the Data Monitoring and Safety Committee (for detailed information see chapter 11). The SIOP CNS GCT II Safety Desk will supply additional information if requested by the Committee.

Relevant Product Information for the assessment of expectedness is for:

- Cisplatin: Manufacturer's Product Information, see Appendix E.5
- Carboplatin: Manufacturer's Product Information, see Appendix E.6
- Etoposide: Manufacturer's Product Information, see Appendix E.7
- Ifosfamide: Manufacturer's Product Information, see Appendix E.8

### 9.7 Late Effects of Chemotherapy

The main focus of late effect evaluation is on:

- Cardiac toxicity,
- Renal toxicity,
- Ototoxicity,
- Infertility.

For investigation flow charts please see Appendix C.

### 9.8 Timepoints

The study will be open to recruitment for 5 years, assuming that accrual of patients is as expected. At the end of these 5 years the expected number of patients was not reached, therefore the recruitment is prolonged for two years (end of recruitment will be 01.07.2018). A further follow-up period of two years will be required in order to capture the vast majority of events, which are expected to occur within 18 months of diagnosis. Data on long term survival, side effects of treatment and quality of survival will be collected for at least a further 5 years from end of treatment. Since recurrence of germinoma may occur later than this, clinical follow-up for at least 10 years is advised. Recommendations can be found in appendix C (Follow-up investigations) and chapter 5.8.

Stopping rules are discussed in chapter 10 (statistics).

### 9.9 Toxicity checks

The toxicity checks may follow national guidelines or recommendations of late effects trials.

These are outlined in Chapter 5 investigation and treatment of germinoma and NGGCT (chapters 6 and 7 respectively).
10 STATISTICAL CONSIDERATIONS

10.1 Study questions

The aim of the study is to demonstrate that equivalent or better event free survival (EFS) can be achieved in study patients with CNS GCT, with reductions in therapy where appropriate. Patients of the study SIOP CNS GCT 96 will be evaluated as control groups. The potential bias of historical comparisons will be considered in the interpretation of results. Study questions in the diagnostic subgroups are:

1. Can the pEFS be increased in patients with localized Germinoma by better staging (lower proportion of misclassified patients) and modified radiotherapy?
2. Can the pEFS be increased in patients with non-Germinoma by intensification of chemotherapy in high-risk patients and resection of the tumour in patients with residual tumour after chemotherapy?

Patients with non-metastatic Germinoma and CR after 2 x CarboPEI (defined as low-risk Germinoma) will receive modified radiotherapy (ventricular irradiation alone) as compared to previous studies. A group of patients with these features can be defined from historical data and the survival outcomes for this low risk group are very good (pEFS above 90%) but, because of differences in diagnostic criteria the precise size of this is uncertain. Since this therapy modification may increase the risk of relapse, this group of patients will be monitored closely (see chapter 10.9).

The treatment of patients with metastatic germinoma will be the same as in previous studies but due to refined staging and thus possible adjustments to the patient population these patients will be included in the analysis of outcome, but will also be looked at separately with a descriptive analysis comparing the results with historical data of SIOP CNS GCT 96.

In patients with Non-germinoma two groups of patients are likely to profit from the new stratification:
Patients with AFP ≥ 1000 ng/ml: these patients will receive a dose intensified schedule with the aim to increase survival which was poor in the historical group with standard treatment (EFS 35 % )
Patients with residual disease after chemotherapy: in these patients it is strongly recommended to resect the residual in an attempt to improve survival, as the EFS in the group with residual is only 44% in the historical controls.
Patients with teratoma will be registered but no therapeutic question will be asked, but an evaluation of QoS will be performed.

10.2 Main end point

The main end point is the event free survival (EFS), defined as time from the date of diagnosis to the first of:
- Death from any cause,
- Relapse,
- Progressive disease on therapy (for patients who never responded to therapy, the date of event will be the date of the beginning of the treatment),
- Or second malignancy.

Probability of EFS will be estimated using the Kaplan-Meier method.

10.3 Secondary end points

- Overall survival, defined as time to death from any cause, measured from the date of diagnosis
- Short and long term toxicity.
10.4 Analysis

The test for the null hypothesis (no difference) for question 1 and 2 will be carried out according to the “intention to treat” principle for all study patients of the respective diagnostic groups (Germinoma and Non-Germinoma) in order to minimize the bias in the estimation of the treatment effect. The EFS in the two groups (study patients and historical control) will be compared with the log-rank test stratified by participating group and risk group.

For both groups (germinoma and non-germinoma) an analysis will also be performed on a per-protocol basis in addition to the main intent-to-treat analysis. Patients for the per-protocol analysis are all patients with complete diagnostic procedures, administration of all blocks of chemotherapy required by the protocol and radiotherapy delivered according to the protocol with dosage deviations less than 10%. Patients, who died during treatment will be analysed in the per protocol analysis. If there are conflicting results for the per-protocol and the intent-to-treat analysis, the steering committee and the data monitoring committee will have to decide about the implication on conclusions from the main analysis.

Confidence intervals for all estimates will be calculated and reported.

10.5 Sample size

Participating countries include Denmark, France, Germany, Italy, The Netherlands, Norway, Sweden, Spain and the United Kingdom. Other countries such as Austria and Switzerland are likely to participate. Based on the known incidence in each country expected to participate in the trial, the expected annual accrual is around 50 for all germinoma and 30 for patients with secreting GCT (non-germinoma). With a study duration of 5 years the total patient accrual will be 250 for all germinoma and 150 for pooled patients with non-Germinoma.

The probability of a type I error is set to 0.05 for the tests of the main study questions. All other tests conducted for the analysis of further results and subgroup analysis will be descriptive and explorative. Assuming a pEFS of 85% for Germinoma in the historical control group the power will be 0.8 to detect a difference of 8% between the controls and the experimental group (pEFS=0.93). The power will be 80% to detect a difference of 8% for the subgroup of patients with non-metastatic germinoma (baseline 84%, about 200 patients per group).

Assuming a pEFS of 60% for Non-Germinoma in the historical control group the power will be 0.8 to detect a difference of 16% to the experimental group (pEFS=0.76).

Based on previous studies, the expected percentage of cases lost to follow-up is negligible (less than 5%), and therefore not included in the sample size calculation; calculations were done according to Freedman (Freedman, 1982).

10.6 Interim analysis of Event Free Survival

Two interim analyses are planned for each of the diagnostic groups. The O’Brien and Fleming rules will be followed. The boundary proposed in such rules requires very strong evidence of an effect to terminate at the first interim test, whereas the criteria at the final test are rather close to those for a single sample design (that is a design with no interim testing). At the discretion of the study chairmen and the DMSC other timepoints and frequencies of interim analysis may be chosen. The p-values will then be based on a Lan-DeMets spending function approach with O’Brien-Fleming type spending function. If any of the boundaries are reached, patient recruitment will be stopped by the DMSC, the study chairmen will be informed and a study committee meeting will be held to discuss further continuation or modification of the trial.
Final analysis will be performed three years after recruitment of the last patient.

Two interim analyses are planned:

<table>
<thead>
<tr>
<th></th>
<th>p value *</th>
<th>Approximate timing of the analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>First analysis</td>
<td>0.0005</td>
<td>3 years after the beginning of recruitment</td>
</tr>
<tr>
<td>Second analysis</td>
<td>0.014</td>
<td>End of inclusion</td>
</tr>
<tr>
<td>Final analysis</td>
<td>0.045</td>
<td>3 years after the end of recruitment</td>
</tr>
</tbody>
</table>

p value *: Nominal p values for overall type I error of 0.05 O'Brien-Fleming boundaries

10.7 Stopping rule (monitoring toxicity)

Interim analysis on severe toxicity will take place twice a year (toxicity grade 3 and 4, of which monitored toxicities are nephrotoxicity, ototoxicity, neurotoxicity and toxic deaths). The information will be forwarded to the DMSC who will look at the data confidentially and if there is a safety issue, recommend to the TSC whether and how the study should proceed.

The rate of toxic deaths observed in each diagnostic subgroup (Germinoma and Non-Germinoma) will be compared to a reference rate in order to detect an absolute excess of toxic deaths with a Wald sequential plan.

In the SIOP CNS GCT 96 study, 2 toxic deaths were observed among 172 patients in the Germinoma diagnostic group and 2 among 118 patients with non-germinoma.

Based on this previous experience, we choose the following parameters: $p_0 = 1\%$ and $p_1 = 5\%$, with $\alpha = 5\%$ and $\beta = 1\%$. This means that the risk to wrongly conclude that there is an excess of toxic deaths (whereas the real rate is equal to $p_0 \leq 1\%$) is equal to $\alpha = 5\%$. On the other hand, the power to detect an excess of toxic deaths (if the real rate is equal to $p_1 = 5\%$) is equal to $1-\beta = 99\%$.

Using the Wald’s test with these parameters, the boundaries are:

<table>
<thead>
<tr>
<th>No. of patients With at least 30 weeks follow up or toxic death</th>
<th>No. of toxic deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-7</td>
<td>2</td>
</tr>
<tr>
<td>8-47</td>
<td>3</td>
</tr>
<tr>
<td>48-87</td>
<td>4</td>
</tr>
<tr>
<td>88-127</td>
<td>5</td>
</tr>
<tr>
<td>128-167</td>
<td>6</td>
</tr>
</tbody>
</table>

If the number of toxic deaths observed in Germinoma and/or Non-Germinoma reaches the boundary defined in this sequential plan (for example a third death occurs amongst the first 30 patients), then a full analysis will be considered.

10.8 Stopping rules for severe toxicity

Serious Adverse Events (section 9) should be reported to the SIOP Safety Desk, which will transmit the information to the National Coordinators. Transmission of this information will be done to the Data Monitoring and Safety Committee (DMSC) when appropriate. Stopping rule analysis will occur every 6 months. The information will be forwarded to the DMSC who will decide whether and how the study will proceed.
Subgroup Analysis of non-metastatic low risk Germinoma

At the time of the final analysis a test for non-inferiority will be done comparing the pEFS at three years of patients with non-metastatic low-risk Germinoma with a historical control group. If the upper limit of a one sided 95% confidence interval of the estimate for the difference (control – experimental group) is below 15% non-inferiority will be concluded. If the test is not significant, this group cannot be included in the test of the main study question for Germinoma.

With a pEFS of 95% in the control group, a non-inferiority range of 15% and a type 1 error of 5% there will be a power of 80% to prove non-inferiority with a sample size of n=45 (Rodary et al. 1989). With a baseline of 90% 67 patients are needed to have a power of 80%. When 50 patients with Germinoma are enrolled in the study, an interim analysis will be performed to estimate the proportion of patients with non-metastatic Germinoma and CR after 2 x CarboPEI (low risk Germinoma). From this estimate the DMSC and the study committee will decide whether the sample size is achievable for proof of non-inferiority.

Three interim analyses are planned to monitor the possibility of higher risk of relapse in patients with non-metastatic low-risk Germinoma when 25, 50 and 75% of the patients have a potential follow up of 6 months. Type I error is set to 10% for each analysis. The overall error of about 30% is acceptable for safety reasons. If the upper limit of a one sided confidence interval for the one-year cumulative incidence of relapse is above 5%, the DMSC and the study committee will decide upon further treatment strategy for this group.

10.9 Analysis of non-germinoma who are considered high risk or who have residuals after chemotherapy

Two descriptive subgroup analyses will be done:

1. The EFS of patients with non-germinoma and high AFP at diagnosis will be compared with the historical control group (n=16). Given a pEFS of 35% for in the historical control group and about the same number of patients in the study group the power will be 0.7 to detect a difference of 47% between the controls and the experimental group (alpha=5%, one-sided).

2. The EFS of patients with non-germinoma and residue after chemotherapy will be compared with the historical control group (n=43). Given a pEFS of 44% in the historical control group and about the same number of patients in the study group the power will be 0.8 to detect a difference of 28% between the controls and the experimental group (alpha=5%, one-sided).
11 DATA MONITORING AND SAFETY COMMITTEE (DMSC)

An independent DMSC composed of 3 international experts will monitor the progress of the trial on ethical and scientific backgrounds. The role of the DMSC is described in Attachment 1
12 ORGANIZATIONAL ASPECTS OF THE WORK-FLOW TO THE NATIONAL COORDINATION CENTRE

12.1 Registration

Registration of a new patient with intracranial germ cell tumour should be completed by fax or RDE (remote data entry by MARVIN) as soon as possible after diagnosis is clear and as soon as consent is obtained (registration fax see appendix D.2). Treatment on the study cannot be commenced until written consent has been obtained. The national coordination centre will give back a confirmation of registration by the end of the following business day including the patient’s trial number for further identification and the hospital code.

12.2 Risk stratification

To enable the national chief investigator to perform the risk stratification centrally, the registration should be as complete as possible at the time point of sending. If results of staging are pending at time point of registration, the primary inquiry should be sent as soon as possible after all results are present.

In most instances, the study registration (fax see appendix D.2), which includes information regarding tumour site, metastatic stage and tumour markers, is sufficient to recommend treatment according to protocol. In patients, who have undergone initial tumour resection, a copy of the surgical report and the histopathological report (local pathologist and reference pathologist) are additionally required.

For definite risk stratification tumour markers, imaging before surgery, surgical report and a local as well as a central histological report are mandatory. Preferably, imaging in 3 dimensions should be done for diagnosis and as well as a postoperative imaging to define resection status. Information according to tumour dissemination is also mandatory.

The information provided on registration and evaluation (diagnostic and pre-treatment assessment CRF) will be checked at the national coordination centre. The histological diagnosis is supported by the information regarding tumour markers and reference histopathological evaluation. In case of significantly elevated tumour markers (AFP and/or total HCG) a mixed malignant GCT is diagnosed, irrespective of pure teratomatous histology in the histopathological reports of the local and/or central pathologist.

The final assignment to the specific risk group will be made at the national coordination centre.

Additionally, the national chief investigator can be asked for therapy recommendation. For this purpose, the required information must be forwarded to the national coordination centre in written form. A written therapy recommendation will not be provided on the basis of oral information.

12.3 Distribution of the evaluation forms

Registration fax and all event forms should be printed from the protocol at the treating institution (see appendix D.2) in order to minimise delays in submission to the national coordination centre. In case of RDE the data entry should be done as soon as possible. In case of a serious adverse event, the SAE form must be sent to the SIOP CNS GCT II Safety Desk immediately (in practice by the end of the following business day).

In general, all CRFs (documentation forms) can be copied from protocol or requested from the national data manager. Please see appendix D for national circumstances. In case of RDE the documentation files are stored electronically.
12.4 Follow-up

The follow-up clinic has to take care that the follow-up intervals follow the outlined time schedule. In every patient, a follow-up status form will be sent to the clinic once a year until at least 5 years after diagnosis or five years after the last relapse, respectively, in order to document long-term survival. A late-event and quality-of-life documentation form will therefore be distributed to the clinic at the following time points: at diagnosis, after radiotherapy, 1, and 5 years after diagnosis.

If the patient discontinues follow-up in the treating centre, the clinic should either provide the follow-up information in conjunction with the new physician that will take care of the patient, or should provide the national coordination centre with the name and full address of the new physician, depending on national practice.

A patient is considered lost to follow-up, if the contact between the follow-up physician and the patient is lost during the planned follow-up period of ten years and cannot be restored (e.g., because of new unknown address, refusal of the patient to attend the follow-up examinations or withdrawal of the consent to electronic data documentation).
13 DOCUMENTATION AND DATA MANAGEMENT

13.1 Documentation at the participating hospital

13.1.1 Guidance for documentation

For quality assurance it is necessary for the national coordination centre to have all necessary information (documentation forms or electronic forms via RDE) at the right time point (table 28).

Table. 28: Time frame for documentation in Germany

<table>
<thead>
<tr>
<th>time point</th>
<th>documentation</th>
<th>time frame for posting</th>
</tr>
</thead>
<tbody>
<tr>
<td>diagnosis</td>
<td>obtain consent</td>
<td>immediately</td>
</tr>
<tr>
<td></td>
<td>registration</td>
<td>as soon as possible after obtaining consent and preferably before start of chemotherapy</td>
</tr>
<tr>
<td></td>
<td>operation note</td>
<td>as soon as possible, preferably before start of chemotherapy</td>
</tr>
<tr>
<td></td>
<td>local histopathology</td>
<td></td>
</tr>
<tr>
<td></td>
<td>reference histopathology</td>
<td>as soon as possible</td>
</tr>
<tr>
<td></td>
<td>patient’s evaluation (diagnostic and pre-treatment assessment)</td>
<td>as soon as possible</td>
</tr>
<tr>
<td></td>
<td>QoL CRFs</td>
<td>as soon as possible</td>
</tr>
<tr>
<td></td>
<td>Social and living inveromt</td>
<td>as soon as possible</td>
</tr>
<tr>
<td></td>
<td>neurocognitive assessment</td>
<td>as soon as possible</td>
</tr>
<tr>
<td>therapy</td>
<td>chemotherapy</td>
<td>after reevaluation</td>
</tr>
<tr>
<td></td>
<td>documentation including toxicity and response</td>
<td></td>
</tr>
<tr>
<td></td>
<td>irradiation documentation</td>
<td>as soon as possible after irradiation</td>
</tr>
<tr>
<td>serious adverse event</td>
<td>SAE-form</td>
<td>immediately (by the end of the next working day) via fax to safety desk</td>
</tr>
<tr>
<td>end of therapy</td>
<td>medical letter</td>
<td>as soon as possible</td>
</tr>
<tr>
<td></td>
<td>QoL CRFs</td>
<td>as soon as possible</td>
</tr>
<tr>
<td>diagnosis of relapse</td>
<td>event documentation</td>
<td>as soon as possible, preferably before start of second line treatment</td>
</tr>
<tr>
<td>follow-up</td>
<td>follow-up form</td>
<td>once a year</td>
</tr>
<tr>
<td></td>
<td>QoL CRFs</td>
<td>2 years and 5 years after diagnosis</td>
</tr>
<tr>
<td></td>
<td>neurocognitive assessment</td>
<td>2 years and 5 years after diagnosis</td>
</tr>
<tr>
<td>end of hospital follow-up</td>
<td>letter with address of the paediatrician/general practitioner</td>
<td>as soon as possible</td>
</tr>
</tbody>
</table>

Please use the detailed check list for documentation (appendix D.1) and keep it in the patient's file folder.

Registration fax and all event forms have to be copied from the protocol. In case of RDE forms can be filled in electronically by MARVIN.
Please take care that all documentation forms are filled in complete and legible in printed characters. Because this is an international study, plain text fields and comments have to be completed in the English language.
13.1.2 Corrections of entries, doubtful or missing data

Corrections of entries should be made by initialling/signing and dating the correction adding a short statement justifying the change. The incorrect entry should be crossed through with a single line (correction fluid must not be used) and should still be legible. If the paper form has already been sent to the national coordination centre, the amended page must be send (by fax) again.

In case of unclear or doubtful data found in the patient’s file, the investigator has to check them with the responsible physician in charge before sending the form to the coordination centre or entering the data in MARVIN. If the data cannot be clarified, a comment is necessary. If the doubtful data concerns arguable or missing results of examinations according to risk stratification (e.g. dissemination) or response, the national coordination centre has to be consulted and a comment on the form or in MARVIN should be made.

If questions cannot be answered because no corresponding data can be found in the patient’s file, the missing values should be marked with “not done” (n.d.). Exception: if examinations are already done or planned but the results are still outstanding. In this case please comment “will follow” and send the corresponding page again when the missing results are available.

Not documented variables are entered as not done.

Please ensure that all mandatory examinations for risk stratification and response evaluation are performed and results are available as soon as possible.

If you are not sure how to fill in any of the questions, do not hesitate to contact the data manager of the national coordination centre.

13.1.3 Authority to fill in and sign

Only the responsible physicians who are identified as investigators are authorised to fill in and sign the documentation. Additionally, data managers or research nurses who are also mentioned in the collaboration agreement or delegation log are allowed to fill in the documentation and sign them (national responsibilities).

13.1.4 Storing of the study patients’ files

The participating trial centre has to store
- the trial protocol including the national appendix and possible amendments
- all trial documents including the CRFs and correspondence with the national coordination centre for each study patient as long as required by national laws and regulations but not less than 5 years after closure of the study. For example, national law in Germany requires that trial documents are stored for at least 10 years.

13.2 Data management in the international coordination centre

When each patient is registered, they will be assigned a unique trial number by the international coordinating centre. The data will be stored in the international database when all information required for risk stratification is available.

Only on the registration fax, the full name of the patient is asked for to allow a consulting service with the national coordination centre. The name of the patient is stored separately from the data base on a
confidential patient identification list and is not mentioned on all further CRFs. In MARVIN the patients’ personal data are stored in a separate database.

The international datacentre does not receive the patients’ names. The patients are identified by birthdate and international trial number.

13.2.1 Completeness and source data verification

In the case of missing documentation, reminders will be sent by the national coordination centre.

Every incoming documentation will be checked for accuracy, legibility and completeness and will be compared with information already received before transmission to the international coordination centre and final entry into the database. If values are missing or arguable and cannot be clarified with other available documents, a query will be sent; in some cases, additional source data (eg MRI) will be requested. A copy of the operation note and histology report is required for quality assurance of risk stratification. Missing documentation or values concerning risk stratification will be requested at regular intervals until receipt. If information for risk stratification is not available for a long time and after repeated reminders, the study committee reserves the right to remove the patient from the study. Other values that remain missing are stated as “not done”.

If an entry has to be corrected (after review or additional query), it will be crossed out with a single line on the form and furnished with date, initials and short statement. In MARVIN these corrections will be done electronically. Furthermore the wrong data will be replaced with the right one in the database.

Additionally to the completeness and plausibility controls by reading, there will be plausibility controls inside the database and statistical program.

13.2.2 Hard- and software, programs for analysis and backup

Microsoft Office professional, SAS, MARVIN

13.2.3 Archiving

The international coordination centre will store
- the Trial Master File with all appertaining documents
- the study patient’s files
- the data base, defined interim and finishing analysis
as long as required by national laws and regulations.

The national coordination centre will store
- the Trial Master File
- the study patient’s files
- the national data base
as long as required by national laws and regulations.
14 QUALITY ASSURANCE

Monitoring will be carried out centrally on the national level with source data verification and mandatory reference histology. Furthermore, all documenting persons will be trained. Further standardization of internal actions within the national coordination centre and its reference institutions will be achieved.
15 INTERNATIONAL COOPERATION

The SIOP CNS GCT II protocol is primarily conceived for the application at European paediatric oncology centres. Cooperation of additional countries will be welcomed by the study committee in order to enlarge the number of patients to be recruited. For this purpose, the SIOP CNS GCT II protocol has been written in English and can thus be distributed to officially cooperating national study groups.

According to the GCP guidelines, each cooperating national study group is required to determine a National Chief Investigator, who chairs a national study committee and is a corresponding member of the international SIOP CNS GCT II study committee. The Chief Investigator must be qualified for this position as required by the national laws and regulations of the respective country. The National Chief Investigator is required to comply with European and national legal regulations. This includes the certification of all cooperating hospitals and may include patient insurance. For each country, the patient information leaflets should be translated into the native language.

Every 3 months, data will be sent from the national to the international coordination centre. Regulations on detail regarding international cooperation and data exchange are determined in a cooperation agreement.
16 ETHICAL ASPECTS

The SIOP CNS GCT II protocol, the patient information leaflets and consent forms have been submitted for review to the responsible Ethics committees of the international and national coordination centre (see appendix K).

The SIOP CNS GCT II study will not be open for recruitment until approval has been obtained. The Ethics committee will be informed about any changes and amendments to the protocol. The study coordinators will inform the committee about the (scheduled or premature) closure of the study.

In addition, the protocol is distributed according to national requirements to the responsible Ethics committees at all participating institutions (see Appendix J) prior to patient recruitment. The local investigators are responsible for the certification of his/her hospital as a study centre of the SIOP CNS GCT II protocol, based on the approval of the local Ethics committee and the notification to the competent local legal authority.

Prior to enrollment onto the SIOP CNS GCT II protocol, patients and their legal guardians must be informed about the nature of their disease, the therapy according to the SIOP CNS GCT II protocol and potential therapeutic alternatives. For this purpose, the protocol includes information leaflets appropriate for different age groups as well as guidelines for patient information (see appendix A). In addition, patients have to give their consent to participation in associated scientific projects including collection of tumour tissue and blood for molecular genetic analysis.

Patient data will be stored at the SIOP CNS GCT II international data centre and will not be distributed outside. Paper copies will be stored at the national coordination centres, including copies of original documents such as surgical notes, histopathological reports, medical reports and correspondence. Consequently, these paper files will necessarily include patient identifiers (full name, date of birth). However, international electronic data storage will be performed by unique trial number only. Only the patient’s personal data of German participants will be stored in a separate data base.

Patients have the right to be informed about the data stored. Consent for data management, storage and transmission will be required from the patient or their legal guardian in addition to the consent into study participation. At any time, the patients or their legal guardians may withdraw from their trial participation by revoking their informed consent and patients data will be deleted.
17 LEGAL AND ADMINISTRATIVE ASPECTS

The SIOP CNS GCT II study constitutes a therapy optimization trial that aims for an international epidemiological registration and an optimized diagnosis and treatment of children and adolescents with teratomas and malignant germ cell tumours. The SIOP CNS GCT II protocol has been designed according to the International Committee of Harmonization guidelines for Good Clinical Practice (ICH-GCP guidelines) and the respective European Union directive. Accordingly, the SIOP CNS GCT II protocol fully complies with the World Medical Association's Declaration of Helsinki (1964) as well as its updates and notes of clarification (for details see: http://www.wma.net/e/policy/b3.htm).

The national legal regulations (see appendix K) have been considered wherever appropriate. The national chief investigators have more than two years of experience in clinical studies.

According to the legal requirements, the protocol has been submitted for approval of the responsible national regulatory authorities and the responsible Ethic's committee of the national and international coordination centres and at the cooperating hospitals. After opening of the protocol and prior to the enrolment of the first patient, each participating clinical centre has to announce the study participation to the responsible local authority as required by national regulations.
18 REPORTS AND PUBLICATION POLICY

Interim reports:
Formal interim analyses will be performed at yearly intervals and the data will be reviewed by a data monitoring committee that is independent of the study co-ordinators and shall ensure both data quality and patient safety. The data monitoring committee will advise whether the data generated during the trial or data generated in other relevant trials allow further patient recruitment. Assuming that further patient recruitment is indicated, the data monitoring committee will also determine the frequency of future reviews based on the patient accrual and event rates.

Stopping rules will be adopted for the SIOP CNS GCT II trial according to the calculations presented in chapter 10.

Final report:
After the closure of the clinical trial and the evaluation of the biometric data, the study co-ordinators will summarize all relevant information in a final report that will include the clinical data, the statistical evaluation, evaluation of specific subgroups and the conclusions based on these data.

Publications:
Irrespective of the specific results of the SIOP CNS GCT II trial, the data will be published in international peer-reviewed journals. Publications will be submitted on behalf of the SIOP CNS GCT II study group, and in an attachment to the manuscript, the participating institutions will be listed. Prior to publication, the Chief Investigators will have to give their consent. Interim results will not be published, other than in abstract form. Additional publications, such as those regarding specific aspects of the SIOP CNS GCT II study will require the consent of the study co-ordinators.
19 REFERENCES


Baranzelli MC, Patte C, Bouffet E, Potras M, Merchant-Lacroix F, Sariban E, Roche H, Kalifa C: An attempt to treat paediatric intracranial AFP and ßHCG secreting germ cell tumours with chemotherapy alone. SFOP experience with 18 cases. Journal of Neuro-Oncology 37; 1998: 229-238


Hu J, Schuster AE, Fritsch MK, Schneider DT, Perlman EJ: Deletion mapping of 6q21-26 and frequency of 1p36 deletion in childhood endodermal sinus tumours by microsatellite analysis. Oncogene 2001; 20: 8042-8044


Matsutani, -M; Sano,-K; Takakura,-K; Fujimaki,-T; Nakamura,-O; Funata,-N; Seto,-T: Primary intracranial germ cell tumours: a clinical analysis of 153 histologically verified cases. J-Neurosurg. 1997 Mar; 86(3): 446-55


APPENDICES

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H. Irradiation
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J. Participating hospitals
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ATTACHMENT

Data monitoring and safety committee (DMSC)