ПРОТОКОЛ ЛЕЧЕНИЯ

ГЕРМИНАТИВНО-КЛЕТОЧНЫХ ОПУХОЛЕЙ

SIOP CNS GCT 96

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1. AIMS AND PLAN OF THE PROTOCOL 1.1 Introduction

This is an international study for malignant intracranial germ cell tumors of the national **pediatric** oncology groups of Great Britain, France and Germany and centres in Italy. It is also open to participation by other SIOP members.

For the purpose of this study the tumors will be divided into germinoma and secreting tumors.

1.2 Primary objectives

1.2.1 Germinoma

To evaluate and to compare in a non-randomized treatment protocol two different approaches, one option with craniospinal radiotherapy alone in a reduced dose of 24 Gy craniospinal and 16 Gy tumor boost and one option with the combination of chemotherapy and local irradiation.

In germinoma data on patients treated according to both options will be collected during the first 2 to 3 years of the study to evaluate whether a randomized study will be feasible.

1.2.2 Secreting tumors

To increase survival in a one-arm-treatment plan using a combination of 4 courses of cisplatin-based chemotherapy followed by focal radiotherapy in non-metastatic cases and craniospinal irradiation in children with metastases.

The results will be compared with those obtained in the previous study of the French and German groups.

2. CLASSIFICATION OF INTRACRANIAL GCTs 2.1 .

Incidence and site

Intracranial germ cell tumors are rare tumor entities in childhood and adolescence, they account for about 30% of all germ cell tumors. Extra- and intracranial GCTs are identical in their histologic pattern (21, 22, 30, 40, 50, 54, 62). Intracranial GCTs occur mainly in midline sites such as the pineal and the suprasellar region (7, 13, 25, 26, 27, 37, 45, 56). Germinomas are preferentially localized in the suprasellar region but may also occur in ^ the pineal region. Embryonal carcinomas, yolk sac tumors or choriocarcinomas mainly occur in the pineal region and can secrete the tumor markers alpha 1-fetoprotein (AFP) *4* and human chorionic gonadotropin (HCG), but usually it is the beta ,,fraction chain" which is elevated. Mature intracranial teratomas are histologically benign tumors while immature teratomas are potentially malignant according to their grade of immaturity.

2.2 Histological diagnosis of intracranial GCTs

In 1993, a detailed histological classification for CNS tumors was proposed by Kleihues and co-workers (30). Intracranial germ cell tumors were classified as follows:

1. germinoma
2. embryonal carcinoma
3. yolk sac tumor (endodermal sinus tumor)
4. choriocarcinoma
5. teratoma

5.1 immature teratoma

5.2 mature teratoma

5.3 teratoma with malignant transformation

6. . mixed germ cell tumor (At biopsy not all components actually present will be seen.)

In the majority of intracranial germ cell tumors mixed tumor entities are diagnosed.

1.3 Secondary objectives

To use the same diagnostic protocol for imaging and laboratory investigations before, during and after treatment.

To establish and use a common documentation system regarding general patient's data, including diagnostic tests, clinical evaluation, surgery, histology, radiotherapy, chemotherapy and toxicity.

To collect information about toxicity, prognostic factors and tumor markers.

To collect epidemiological data: this will include documentation of incidence and the site, also the histologic pattern of intracranial secreting and non-secreting GCTs in children and adolescents. Associated malformations in the patients as well as the epidemiology of tumors and malformations in

relatives will also be registered.

In order to achieve these objectives, it is necessary for any child suspected to have an intracranial germ cell tumor to be discussed as soon as possible with a participating pedia-tric oncology centre.

3. RATIONALE OF TREATMENT

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3.1 Background 3.1.1 Germinoma

The majority of intracranial GCTs are pure germinomas cured by radiotherapy alone in up to 90% of the cases (9, 18, 26, 27, 34. 49, 51, 57-59). Although multicentric origin of germinal tumor growth is rare and difficult to separate from metastatic spread (43), it should be emphazised, that pure germinoma can arise at different sites within the central neuroaxis (7, 30, 35, 50). Ways of spread are leptomeningeal or direct infiltration of the surrounding normal brain (7, 33). Cerebral seeding has been estimated to occur in some 7 to 12% of patients. The vast majority occur intracranially (33) mainly at the margins of the irradiated fields, if no chemotherapy has been additionally administered (4, 33, 36, 52). Leptomeningeal recurrences can be attributed to the restricted treatment volume and can be estimated to occur in 10% of patients who did not receive irradiation of the spinal canal and cranial meninges.

3.1.2 Secreting tumors

Secreting intracranial tumors such as yolk sac tumors, embryonal carcinoma and chorio-carcinoma are considered to have a poor prognosis (1, 2, 3, 4, 9, 10, 13, 15, 17, 26-29, 38, 43-46, 49, 52, 58); in order to improve the survival of patients affected by these tumors, different approaches adding chemotherapy to conventional surgery and radiotherapy have been initiated in recent years. Recently neo-adjuvant or pre-operative chemotherapy was employed in secreting tumors to increase the remission rate (3, 7, 17, 18, 19, 24, 44, 45);

at the time of delayed tumor resection the histology of these pretreated tumors has been mature teratoma (24, 44) in most cases.

3.1.3 Teratoma

Mature intracranial teratomas, although being benign tumors, have a worse prognosis in newborn infants because of tumor site and concomitant hydrocephalus which may produce lethal brain damage. When occurring at the end of the first decade they can be cured by surgery alone (12).

2.3 Secretion of tumor markers

Secreting tumors are defined as malignancies which produce substantial levels of tumor markers.

Intracranial yolk sac tumors and choriocarcinoma produce AFP and B-HCG respectively (1 7, 25, 28, 29, 58, 60). Low levels of secretion of AFP and B-HCG have also been observed respectively in germinoma and teratoma (5, 35, 41, 42). Therefore only substantial elevation of the tumor markers, choriogonadotropin (B-HCG) > 50 IU/1 and/or alpha 1-fetoprotein (AFP) > 25 ng/ml leads to the definition and clinical diagnosis of a secreting tumor. Half-life of AFP is 6 days, of B-HCG is 16 hours. The tumor markers AFP and B-HCG should be measured in serum and CSF. Embryonal carcinoma is also a malignant tumor entity but often without tumor marker expression. It is treated like a secreting GCT.

2.4 Final diagnosis

The final diagnosis will be made on both the histology of the tumor and evaluation of tumor markers. In patients with significant marker elevation: B-HCG > 50 IU/1, AFP > 25 ng/ml (serum/CSF) a histological evaluation is not necessary before starting therapy.

the late morbidity of irradiation. In MAKEI 89 the craniospinal irradiation was reduced to 30 Gy with an additional local tumor boost of 15 Gy (19).

Fifty-four patients **were** treated according to protocol guidelines. In the protocol patients 4 relapses occurred at 10, 11, 15 and 24 months after diagnosis. In one patient recurrence was spinal and in another patient one isolated bone metastasбis was observed. In 2 children relapses were detected intra-abdominally. All relapsing patients had a ventriculoperito-neal shunt. These relapses could be salvaged by second-line chemotherapy treatment. Event-free survival was 90%±3% in protocol patients, whereas survival was 100%.

An additional 29 patients were classified as follow-up patients because of deviations from the protocol (age > 15 years, late registration (more than 4 weeks after diagnosis), registration in relapse, non-protocol chemo- or radiotherapy).

3.2.3 French data for germinoma

In the national TC 88 pilot protocol of the SFOP (SocieteFrancaise d'Oncologie Pedia-trique) (47), a combination of 2 cycles of chemotherapy consisting of cisplatin or carbo-platin, vinblastine and bleomycin were administered with 30 **Gy** local irradiation. Because of 3 relapses (2 meningeal and 1 local) it was thought that vinblastine, bleomycin and perhaps carboplatin dosage were not adequate for cerebral tumors and 30 Gy were not 1 enough. So in the TC 90 (6) protocol, the agents carboplatin, etoposide and ifosfamide were used in addition to local irradiation of 40 Gy. Thirty-one patients were treated fol- (lowing the TC 90-protocol: 30 had focal irradiation, 1 patient received craniospinal ra-diotherapy after 2 cycles of chemotherapy. One local relapse occurred. The event-free survival was 93

±7%, whereas survival was 100%.

3.2.4 Conclusion and rationale of the SIOP study

Given the high cure rates achieved in both the German and the French studies an attempt will be made to reduce side effects and late sequelae of the treatment without compromising the high cure rates. It remains to be shown whether additional chemotherapy and restriction of irradiation to the primary tumor site (9, 16, 32) will reduce acute and late morbidity.

In teratoma the effectiveness of adjuvant radiotherapy (50 Gy) as proposed in MAKEI 86/89 is not proven. Out of 13 registered patients four patients died of tumor of whom two were neonates without chances of curative intervention (9).

Due to the rarity of these neoplasms only a very limited number of patients has been enrolled in national studies. Thus there is a need for international cooperation to share experience and expertise and to create an effective treatment regimen and follow-up strategy for children affected by these tumors.

3.2 Review of recent treatment data for intracranial germ cell tumors

3.2.1 Experience in USA and Japan

In the USA, the MSK-group (15) treated patients regardless of marker secretion using primary chemotherapy based on high dose carboplatin, bleomycin and vinblastine with radiotherapy reserved for inadequate response. Preliminary results revealed a high incidence of death due to toxicity and the final results of this protocol are awaited.

The group ofChang and coworkers, Taiwan, treated 13 children with malignant intracranial germ cell tumors including germinoma and non-germinoma. The chemotherapy used consisted of cisplatin, bleomycin, vinblastine and etoposide which was combined with focal irradiation and intrathecal injections as well as with craniospinal irradiation. Three children with germinoma and three with non-germinoma were treated with chemo- and radiotherapy. Four other children received chemotherapy alone of whom only one child achieved complete response, and all the children's tumours progressed and they died despite receiving irradiation. Complete response and long-term remission was achieved only in patients with combination therapy (chemo- and radiotherapy). Patients with focal irrradiation and intrathecal injections had the same outcome as children with craniospinal irradiation (11).

3.2.2 German data for germinoma

The National MAKEI (maligne Keimzelltumoren) 86/89 protocols followed previous radiotherapeutic practice; in MAKEI 86 (17) a total radiation dose of 36 Gy was administered to the whole CNS followed by a boost dose of 14 Gy to the tumor area. Because of its high efficacy, the daily fractions

were decreased from 1.8 Gy to 1.5 Gy, in order to reduce

Thus 25 patients were evaluated. Ten patients developed local recurrence. Nine of the 10 relapsing patients died of their disease, one patient is still alive with disease. Fifteen patients are alive without signs of tumor. The EFS is 66±6% with a median follow-up of 29 months (0-112 months).

An additional 21 patients were classified as follow-up patients because of deviations from the protocol (age > 15 years, late registration (more than 4 weeks after diagnosis), registration in relapse, non-protocol chemo- or radiotherapy).

In both, the protocol and follow-up patients, the results correlated directly with the cumulative cisplatinum dose given. Platinum administered at 400 mg/m^2 doubled the event-free survival from 3 8±17% to 74±5%.

3.3.3 French data for secreting tumors

In the French SFOP protocols the strategy was to cure patients by chemotherapy without radiotherapy as is done for extracranial germ cell tumors. There were 2 consecutive chemotherapy protocols. In the TC 88-protocol (47) the chemotherapy regimen consisted of alternating courses of vinblastine, bleomycin, carboplatin and etoposide, ifosfamide. In the TC 90-protocol (6), secreting tumors were treated with 6 cycles of chemotherapy (each cycle consisting of carboplatin (600 mg/m^2) day 0 and etoposide (150 mg/m^2) days 0-2 and then ifosfamide (1.8 g/m^2) days 21-25 and etoposide (150 mg/m^2) days 21-23 followed by complete tumor resection when there was tumor residue. In both protocols treatment was continued by 55 Gy local irradiation only when there was unresectable residual disease.

The results were as follows:

Twenty-seven patients were registered from January 88 to November 94. Twenty-four patients are evaluable, whereas 3/24 patients are still under treatment. Fifteen patients received chemotherapy alone. Nine patients were given radiotherapy to the primary tumor site after chemotherapy. Three of 9 received craniospinal irradiation. Fourteen of 15 patients with chemotherapy alone relapsed. Nine patients are in first remission. 6 patients are in second or third remission after radiotherapy and/or high dose chemotherapy. Eight patients died of their disease. The overall survival is about 63%. The conclusion was: Al thus 25 patients were evaluated. Ten patients developed local recurrence. Nine of the 10 relapsing patients died of their disease, one patient is still alive with disease. Fifteen patients are alive without signs of tumor. The EFS is 66±6% with a median follow-up of 29 months (0-112 months).

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In the combined chemotherapy/focal radiotherapy arm (option B) the dose of etoposide will be reduced. In patients with positive CSF-cytology or visible (MRI/CT) spinal meta-stases (53) craniospinal irradiation will also be given.

3.3 Review of recent treatment data for secreting tumors

3.3.1 Introduction

Two recent treatment approaches are in use for secreting tumors. One is to give intensive and prolonged chemotherapy alone (15, 11, 6) with additional radiotherapy for inadequate response, which was necessary in most of the patients treated in this way, and the other is to give a combination of chemotherapy and radiotherapy (MAKEI) which has achieved good results.

3.3.2 German data for secreting tumors

In the MAKEI 86 protocol (18), 2 courses ofPVB (cisplatin 20 mg/m^2 day 1-5, vinblasti-ne 2 mg/m^2 day 1+2, bleomycin 15 mg/m^2 day 1-3 continuously infused) were given after clinical or histological diagnosis followed by 36 Gy craniospinal irradiation plus 14 Gy tumor boost. After radiotherapy, 2 courses of etoposide 150 mg/m^2 day 1-3 and ifosfami-de 1.5 g/m^2 day 1-5 (without cisplatin because of the risk ofototoxicity (20)) were given. In MAKEI 89 (19) (using the same dosages) 2 courses of PEB (cisplatin, etoposide, bleomycin) were administered followed by tumor resection and 2 courses of PIV (cisplatin, ifosfamide, vinblastine), and craniospinal irradiation of 30 Gy plus a tumor boost of 20 Gy.

In MAKEI 86/89 patients were registered between October 86 and October 94. Results were as follows: 27 patients were treated according to protocol guidelines, 2/27 patients died post-operatively.

4. INITIAL DIAGNOSTIC WORK UP 4.1 Confirmation of diagnosis

If an intracranial germ cell tumor is suspected, the following diagnostic steps should be undertaken immediately, if possible.

In patients with clinical and radiologic evidence for intracranial germ cell tumors tumor markers (AFP, C-HCG, HCG) should be measured in serum and CSF. Elevation is defined as > 25 ng/ml for AFP and > 50 IU/1 for J3-HCG in serum or CSF.

If tumor markers are elevated, a histologically verified diagnosis is not necessary. If markers are not elevated, a histologically verified diagnosis is mandatory (see neurosur-gical guidelines, pages 43-47).

4.2 Clinical staging

For clinical staging the following examinations are required:

- Radiological measurement of size and site of the primary tumor (or tumors, ifmultifo-cal) by CT or MRI
- Measurement of metastatic spread by spinal MRI or myelogram
- CSF-cytology

4.3 Other studies

Virus litres for CMV, hepatitis, HSV, HIV, varicella zoster, measles and rubella, complete endocrinological status, pure tone audiogram or BAER (brain stem auditory evoked response), ophthalmological examination and complete neurological evaluation. Endocrinological evaluation should also be done (see pages 40-43).

though biological remission was obtained in all cases, cure could not be achieved by chemotherapy alone and local radiotherapy was needed.

3.3.4 Conclusions and rationale of the SIOP study

The results of the French and German studies and studies elsewhere have demonstrated that secreting tumors must be treated with intensive chemotherapy and that radiotherapy is required for local tumor control.

Without combined therapy secreting intracranial germ cell tumors, after operation and irradiation, have had a two-year probability of survival of less than 6 % (17). Preoperative chemotherapy has been shown to be effective in facilitating complete resection of large or infiltrating tumors and in diminishing the risk of a primary operation (3, 7, 17, 18, 19, 24, 44, 46). The results of the recent French and German treatment protocols revealed that local tumor control is more important for treatment outcome than control of meningeal dissemination (9). Therefore, irradiation of the tumor site only is to be administered unless there is evidence for macroscopic meningeal dissemination or multiple site disease.

This study will examine the effect of intensive (preoperative) chemotherapy in order to increase survival and to avoid craniospinal irradiation in non-metastatic cases.

5. TREATMENT OF PURE CNS GERMINOMA

-the following tumors are included:

pure germinoma germinoma with mature and/or immature teratoma

5.1 Summary

In pure CNS germinoma after biopsy or surgical resection there will be 2 options for treatment to be decided by country or centre.

Option A will consist of craniospinal irradiation and option B will combine chemo- and radiotherapy. Please note that germinoma with elevated markers in serum and CSF (AFP > 25 ng/ml, fi-HCG > 50 IU/1) will be treated like secreting tumors. If other tumor components such as mature or immature teratoma are detected as the main histological diagnosis, please contact your co-ordinator for planning of treatment.

5.2 Option A: craniospinal irradiation 24 Gy + tumorboost 16 Gy

Part of	Number fractions	Dose per Fraction	Total dose	Duratio (weeks)
Cerebru	15	1.6 Gy	24.0 Gy	3
Spinal axis	15	1.6Gy	24.0 Gy	3
Tumor boost	+10	1.6Gy	16.0 Gy	+2
Total	25		40.0 Gy	5

Radiotherapy will take about 5 weeks. For the craniospinal axis 15 fractions with 1.6 Gy single

dose will be administered over 3 weeks. A boost to the tumor bed will be given afterwards over 2 weeks in 10 fractions of 1.6 Gy. In patients with multifocal and metasta-tic disease additional boosts have to be administered to these tumor sites,

4.4. Conclusion of initial work-up

At the end of these investigations the patient will be classified to havegerminoma or a secreting germ cell tumor, either non-metastatic or metastatic. Rarely a patient will be found to have 2 separate tumors in the suprasellar and pineal area without evidence of metastatic disease elsewhere. These patients are classified as patients with non-metastatic multifocal disease and will be treated according to the protocol for non-metastatic tumors (focal radiotherapy). Embryonal carcinoma even with normal markers will be treated like secreting tumors.

In mixed germ cell tumors the treatment decision has to be based on the most malignant component.

Pure immature and mature teratomas are not included in this protocol.

Administration of etoposide (100 mg/mVday):

Etoposide is given in 125 or 250 ml of a normal saline solution over 1 hour before or after carboplatin and ifosfamide. Administration of ifosfamide:

Ifosfamide is added to an infusion of 250 to 500 ml of normal saline solution after first being dissolved in the solvent or in 20 ml of normal saline solution and is given over 3 hours.

The intravenous hydration consisting of 2 l/mVday of glucose solution with electrolytes and MESNA begins at least 30 minutes prior to the start of ifosfamide.

The 3 hours infusion of ifosfamide must be accompanied by MESNA (over 24 hours, uromitexan) to prevent bladder toxicity. The 24 hours dose of MESNA is 2.2 g/m^2 and this dose is repeated on each day of the ifosfamide course. MESNA is added to the hydration fluidin continuous infusion. In the event of hemorrhagic cystitis, hydration may be increased and a diuretic may be added (furosemide 0,5 mg/kg) 2 and 6 hours after the injection.

Ifosfamide must not be used with aminoglycosides and other nephrotoxic drugs,

Particular attention must be paid to urine output and plasma electrolytes in patients with diabetes insipidus.

Before each sequence of chemotherapy blood count, creatinine and electrolytes must be done. 1.0)c 10^9/! neutrophils and 100 x 10^9/! platelets, normal creatinine and electrolytes are required before starting each sequence of chemotherapy.

5.3.2 Dose modifications

If white blood cells are < 2.000/ul (2 x 10^9/!) or neutrophils <1.000 (1 x 10^9/!) or platelets are

<100.000/^1 (100 x 10^9/!) the beginning of the next course of therapy wait until neutrophils >1.000/ul and platelets (PLTs) are >100.000/ul.

5.3 Option B: CarboPEl 2 x carboplatin / etoposide ifosfamide / etoposide + 40 Gy focal radiotherapy

In pure germinoma, if combination treatment is administered (option B) chemotherapy will consist of two cycles of carboplatin/etoposide, ifosfamide/etoposide after surgery followed by local radiotherapy according to'the tumor area.

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chemotherapy (1 cycle): day 1 Carboplatin 600 mg/m^2 days 1,2,3
Etoposide 100 mg/m^2 days 22,23,24,25,26
Ifosfamide 1800 mg/m^2 days 22, 23, 24
Etoposide 100 mg/m^2

The second cycle of chemotherapy should be started on day 43;

Radiotherapy:

Part of CNS	Number of fractions (weeks)	Dose per fractions	Total dose	Duration
Tumor	25	**1.6 Gy**	40 **Gy**	**, 5**

The radiotherapy should be started after hematological recovery from the second cycle of chemotherapy (about day 64). For patients with positive CSF-cytology or spinal metasta-ses at time of diagnosis craniospinal irradiation is mandatory as described in the radiotherapy protocol according to option A.

5.3.1 Administration of chemotherapy for germinoma

Administration of carboplatin (600 mg/m^day) :

Carboplatin is given in 125 **or** 250 ml of 5% normal saline solution over 1 hour.

5.

3

Option B:

CarboPEl

5.

2 x carboplatin / etoposide

ifosfamide / etoposide

+ 40 Gy focal radiotherapy

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chemotherapy (1 cycle):	day 1	Carboplatin	600 mg/m^2
	days 1,2,3	Etoposide	100 mg/m^2
	days 22, 23. 24, 25, 26	Ifosfamide	1800 mg/m^2
	days 22, 23, 24	Etoposide	100 mg/m^2

The second cycle of chemotherapy should be started on day 43:

Radiotherapy:

PartofCNS	Number of fractions	Dose per fraction	Total dose	Duration (weeks)
Tumor	25	1.6Gy	40 Gy	5

The radiotherapy should be started after hematological recovery from the second cycle of chemotherapy (about day 64). For patients with positive CSF-cytology or spinal metasta-ses at time of diagnosis craniospinal irradiation is mandatory as described in the radiotherapy protocol according to option A.

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Carboplatin is given in 125 or 250 ml of 5% normal saline solution over 1 hour.

6. TREATMENT OF SECRETING INTRACRANIAL GCTS AND EMBRYONAL

CARCINOMA

The following tumors are included:

- any tumor with secretion of markers AFP > 25 ng/ml and/or B-HCG > 50 IU/1 in serum and/or CSF

- any tumor including one of these components: yolk sac tumor, choriocarcinoma and embryonal carcinoma

6.1 Summary

There is only one protocol for treatment of secreting tumors. Chemotherapy is administered after clinical diagnosis by tumor marker elevation or by biopsy. After the second and fourth cycle of chemotherapy clinical evaluation and radiological imaging are necessary. If tumor growth is detected during treatment, surgery may be necessary. In this case please discuss further treatment with your co-ordinator. If there is tumor residue after the fourth course of chemotherapy, resection of the residue should be considered, if possible. before radiotherapy. Those patients in whom tumor markers have not returned to normal by the end of chemotherapy, are off protocol. Also in these cases further therapy should be discussed with the co-ordinator (national or international).

6.2 Chemotherapy (4 cycles):

days	1, 2, 3,4, 5	Cisplatin 20 mg/m^day
days	1,2,3	Etoposide 100 mg/mVday
days	I, 2, 3, 4, 5	Ifosfamide 1500 mg/m^day

Second cycle of chemotherapy will start on day 22 (therapy interval day 1 = day 22)

Please check glomelurular filtration rate (GFR) and serum calcium, potassium, phosphate and bicarbonate before the first and after each subsequent therapy course. If GFR is < 80 ml/min/1.73 m^2 cr serum creatinine is more than 1.2 mg/dl or serum electrolytes are abnormal before tht next course of therapy, discuss therapy with your national coordinator or with the international coordinator. Audiometry is mandatory every two courses of PEI chemotherapy. If hearing function is reduced by more than 50 dB at 2.000 hertz - no cis-platin should be asiministered.

In patients with rased intracranial pressure at the time of the first chemotherapy course particular care should be taken about hyperhydration. In such cases therapy modifications should be discussd with the coordinator.

In patients aged kss than one year or of weight less than 10 kg dose calculation must be done according to '<g: 30 kg == $1m^2$.

5.3.3 • Supportive care

Prophylactic use o cotrimoxazole (sulfamethoxazole/trimethoprim) over the whole period of treatment to ivoid pneumocystis carinii infection is recommended and also until 3 months after completion of all therapy (including radiotherapy).

Prophylactic antibr.tic/antifungal decontammation may be used if it is the normal practice in the trea'.ng hospital. The use of antibiotics in febrile episodes during therapy, after blood culture: ire taken, is mandatory. Be aware of possible mycotic infections (or. mycotic selection) inder antibiotics!

Growth factors sh'.uid not be given as some germ cell tumours have growth factor receptors.

Surgery

If after the second cycle of chemotherapy the tumor markers have fallen but the tumor is growing or if residual tumor is present at the end of chemotherapy, surgery may be required (see surgical guidelines, page 37).

6.4Radiotherapy

This should start after the last course of chemotherapy and after surgery (if undertaken) as soon as there has been hematological recovery from the last course (usually 3 weeks). 4

- non-metastatic disease (neg. CSF-cytology, neg. Spinal MRI) -				
PartofCNS	Number of fractions	Dose per fraction	Total dose	Duration (weeks)
Tumor	30	1.8Gy	54.0Gy	6

- metastatic disease (pos. CSF-cytology/pos. spinal MRI) -				
PartofCNS	Number of Fractions	Dose per Fraction	Total dose	D (weeks)
Cerebrum	20	1.5Gy	30.0 Gy	4
Spinal axis	20	1.5Gy	30.0 Gy	4
Tumor boost	+15	1.6Gy	24.0 Gy	+ 3
Total	30		54.0 Gy	7

6.2.1Administration of cisplatin, ifosfamide, etoposide (PEI)

Etoposide will be given prior to cisplatin and ifosfamide as a one hour infusion; if the volume of the dilution results in a long infusion time, etoposide can instead be administered undiluted. Cisplatin is

given in a split dose of 20 mg/m^day combined with a forced mannitol diuresis: Cisplatin will be given as a one hour infusion. Mannitol in a dose of 40 ml/m^2 should be administered 3 hours and 30 minutes prior to cisplatin, and 30 minutes, 3 and 6 hours after cisplatin. The addition of magnesium during the time of cisplatin treatment (180 mg/m^2) days 1 to 21 is mandatory.

Ifosfamide is given after cisplatin over 22 hours continuously. Mesna (uromitexan) is administered as uroprotection in an equivalent dose. At day 1, 20% of the Mesna dose is given as a bolus at the beginning of therapy while 80% is given continuously over 22 hours with ifosfamide. Mesna will be administered on day 1 to day 7, that is for two days longer than Ifosfamide. Ifosfamide must not be used with aminoglycosides or other nephrotoxic drugs.

The addition of calcium, potassium, phosphate and magnesium according to serum levels, and a forced diuresis during the treatment are mandatory. The intravenous hydration should consist of 2 l/m^day as a glucose solution with electrolytes.

6.2.2 Dose modifications

These are the same as for germinoma treated using arm B (see 5.3.2).

Audiometry – if possible - is mandatory prior to every chemotherapy course. If hearing function is reduced by more than 50 Dz at 2000 Hertz, no cisplatin should be administered (please discuss with the co-ordinator).

6.2.3 Supportive care (see 5.3.3)

7. Investigations

7.1 During treatment

7.1.1 Monitoring of tumor

CT/MRI of The primary tumor must be done after the second and forth course of chemotherapy. CSF-cytology, if positive at the beginning, must be done after the second and forth course of chemotherapy.

7.1.2 Monitoring of markers

Monitoring of markers (serum/CSF) must be done before each course of chemotherapy and unitil normalization of values.

7.1.3 Spinal evaluation

Spinal CT/MRI should be done before chemotherapy and after the end of radiotherapy. If spinal metastases were detected at the beginning, spinal MRI should be done also after the second and forth course of chemotherapy.

7.1.4. Other studies

Laboratory studies should be done before every course of treatment to evaluate the influence of therapy on hematological and nephrological parameters. Endocrinological investigations, if pathological at the beginning, should be repeated after the end of chemotherapy and also during follow-up (see pages 40-43).

8. INVESTIGATIONS AT THE END OF TREATMENT

Four weeks after the end of treatment a complete check-up should be done in patients treated

either with radiotherapy (germinoma option A) or with combined chemo- and radiotherapy (germinoma option B and secreting tumors).

8.1 Tumor evaluation

This should include CT/MRI of the primary tumor site and a spinal MRI, particularly if metastases were present at the time of diagnosis. Ophthalmologic examination and an audiogram or BAER should also be done.

CSF-cytology should be done again, if positive at the last evaluation. AFP and B-HCG should be measured in serum and CSF.

8.2 Laboratory studies

Complete blood count (CBC), platelets, bilirubin, GPT, GOT, Gamma GT, alkaline phos-patase should be measured together with renal function and complete endocrine evaluation.

8.3 Other studies

A complete clinical and neurological evaluation of the patient is mandatory.

10. ELIGIBILITY AND REGISTRATION 10.1 General criteria for patient eligibility

-age < 18 years

-diagnosis confirmed by histology and/or tumor markers

-complete initial work-up

-no previous treatment except surgery

10.2 Additional patients

- age > 18 years

- late registration (more than 4 weeks after diagnosis)

- registration in relapse '

- non-protocol chemo- or radiotherapy

As long as no appropriate protocol exists for patients aged > 18 years, these patients will be treated using the same protocol as for younger patients and they will be analysed separately. Patients who died after diagnosis before therapy should be registered in the protocol for estimation of tumor incidence.

10.3 Patient registration

It has been agreed, that all patients will be registered through an international Registration and Coordination Centre. In countries with an existing national organisation for treatment of germ cell tumors

the patient's registration will be made through this organisation, which will be responsible for the treatment of the patients. If there is no established national organisation, the International Coordination Centre will take this responsibility. All eligible patients should immediately be notified to the International and the National Coordination Centre (if existing) by fax.

9. FOLLOW-UP

For follow-up please use pages 88-90 of the protocol.

12. ENDOCRINE INVESTIGATIONS AND MONITORING OF GROWTH

The majority of children with intracranial germ cell tumors present with neurological symptoms and signs. A significant number of patients present with features of anterior or posterior pituitary deficiency. They may show delayed growth and development and/or diabetes insipidus. Rarely, especially in children with pineal tumors, accelerated growth and precocious puberty may be present. Cranial radiotherapy may cause GH deficiency and may also advance the onset of puberty.

At diagnosis (before or after surgery but before radiotherapy and chemotherapy, and preferably the patient should not be receiving dexaniethasone) :

Standing height

Sitting height

Weight

Head circumference

Pubertal status (Tanner score for breast development, pubic hair and genital development.

Record date of menarche)

Bone age

GnRH and Synacthen test (measure serum LH, FSH, TSH, and cortisol at 0,30 and 60 minutes)

Serum free thyroxine and prolactin

Serum oestradiol (girls) or testosterone (boys)

Serum IGF1 and/or IGF-BP3

24 hour urinary GH

If the patient has thirst, polyuria (especially at night), persistent or recurrent hyperna-traemia or other symptoms suggestive of diabetes insipidus: Water deprivation test with measurement of urine and plasma osmolality.

At every out-patient visit (or 3 monthly for 5 years, then 6 monthly until growth is complete, but more often if clinically indicated).

11. RESPONSE CRITERIA

- complete response (CR)

No evidence of disease clinically and on diagnostic imaging studies, and normal tumor markers. Tumor markers, if present at diagnosis, must fall to normal values according to the appropriate half life of the marker (AFP = 6 days; HCG =16 hours).

- partial response (PR)

> 50 % decrease in the sum of the volume of all measurable lesions (calculated from the maximum diameters); no evidence of progression in any lesion, and no new lesions and/or declining tumor markers, if present at diagnosis (AFP must decline by 1-2 logs, HCG must decline by 2-4 logs).

- stable disease (SD)

< 50 % decrease in the sum of the products of the volume of all measurable lesions; no evidence of progression in any lesion, and no new lesions; tumor markers (AFP and HCG), if present at diagnosis, unchanged or declining by less than the criteria specified above.

- progressive disease (PD)

- 25 % increase in the size of any measurable lesion and/or the appearance of new lesions; increasing tumor markers.

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At every out-patient visit (or 3 monthly for 5 years, then 6 monthly until growth is complete, but more often if clinically indicated).

Standing height

Sitting height

Weight

Head circumference

Pubertal status •

These results should be plotted on standard growth charts. **One year after completion of cranial radiotherapy :**

GnRH, TRH, and Synacthen test

(measure serum LH, FSH, TSH, and cortisol at 0,30 and 60 minutes)

Serum free thyroxine and prolactin Serum oestradiol (girls) or testosterone (boys) Serum IGF1 and/or IGF-BP3 Bone age

Annually (all patients)

The important clinical aspects which should be monitored include assessment of growth, puberty and gonadal dysfunction.

Bone age

Serum free thyroxine, TSH, cortisol, oestradiol (girls), testosterone (boys), prolactin,

IGF1 and/or IGF-BP3

Urinary GH

If growth velocity is poor

Discuss with your endocrinologist. •

If IGF1, IGF-BP3 and urinary GH suggest GH deficiency, then refer to a pediatric endocrinologist. If these results are equivocal, do another test for GH deficiency e.g. argini-**ne or** glucagon stimulation.

If growth velocity is excessive or if there are signs of precocious puberty, then refer to

a pediatric endocrinologist.

Measure serum oestradiol (girls), testosterone (boys), LH and FSH.

Consider treatment to delay puberty.

If symptoms suggestive of diabetes insipidus occur, then refer to a pediatric endocrinologist. Undertake a water deprivation test.

Endocrinological advice

It is essential that an experienced paediatric endocrinologist is involved in the care of these patients. These guidelines are intended to help the oncologist but the endocrinologist will be needed to advise appropriate tests and their interpretation, and on treatment.

Glossary

GH growth hormone

GnRH (LHRH) gonadotrophin releasing hormone

TRH (TH) thyrotrophin releasing hormone

LH luteinising releasing hormone

FSH . follicle stimulating hormone

TSH - thyroid stimulating hormone (thyrotrophin)

ACTH corticotrophin

IGFI insulin-like growth factor 1

IGFI-BP3 insulin-like growth factor binding protein 3

Note: It may be neccessary to centralize some assays e.g. urinary GH

13. NEUROSURGICAL GUIDELINES

As CNS germ cell tumors are very rare, management will be difficult, especially in those patients in whom chemotherapy is used as the primary treatment in the presence of raised intracranial pressure. Coordination and cooperation between the neurosurgeon and the pediatric oncologist is essential for success. Furthermore it is possible that the surgical techniques involved (24, 38, 55) will not universally

be available to those well-versed in pediatric neurosurgical practice. It is therefore recommended that these cases are referred to expert specialist pediatric oncologic centres.

13.1 Anticipated flow-chart

clinical presentation CT or MRI = lesion in pineal region or supra-sellar region or both of the above or diffuse or multicentric

13.1.1 Germ cell marker studies on blood/CSF

markers positive chemotherapy markers negative or borderline operation

13.2 Control of elevated intracranial pressure

In the majority of cases in which there are symptoms of raised intracranial pressure (ICP) there will be obstructive hydrocephalus. It should, however, be possible to control the raised ICP in the short-term, pending results of marker studies on blood and full neuroradio-logical evaluation, by administration of dexamethasone which should be accompanied by an antacid and/or a H2 antagonist.

However in those children in whom there is severely raised ICP or in whom a delay in completing evaluation or commencing chemotherapy is anticipated, the hydrocephalus will need to be controlled by establishment of a formal CSF diversion; in these children a ventriculo-peritoneal shunt is recommended. In experienced institutions the possibility of an endoscopic third ventriculostomy should be considered.

The precise technique of insertion of the shunt is left to the choice of the individual neu-rosurgeon but an impeccable technique is emphasized in order to minimize complications that might delay definitive treatment. The insertion of anti-tumor filters is unneccessary. At the time of shunt insertion, the opportunity should be taken to obtain CSF for exfolia-tive cytology and for marker studies (AFP, B-HCG) as well as routine microbiology and biochemistry: the importance of placing CSF specimens for cytology in plastic containers rather than glass (to avoid cell-adherence to the wall of the container) and of immediate transfer to the cytology laboratory is emphasized.

13.2.1 CSF sampling

It is essential to obtain CSF for marker studies and for cytology. Clearly the presence of **an** intracranial mass will raise concern about the safety of CSF sampling. Therefore the patient's clinical condition will determine how the CSF can be obtained.

13.3 Direct tumor surgery

In those children in whom markers are positive at a significant level either in blood or CSF then direct tumor surgery will be required only in those cases in which there is residual disease after 2-4

courses of chemotherapy; surgery will not be needed for diagnosis or for primary treatment as the former will be provided by the positive markers and the latter will be addressed by the chemotherapy. The neurosurgeon must therefore be prepared to stay his hand! Direct tumor surgery (24,38,55) will only be required under the following circumstances

13.3.1 Marker negative single site disease This will either be in the pineal region or in the suprasellar region. Open operation is recommended with a view to achieving a maximal surgical excision and obtaining tissue for histological diagnosis: it is very important to submit the greatest possible amount of tumor tissue to the neuropathologists, especially in the case of pineal region lesions in view of the well-recognized tendency for these tumors to be heterogeneous. Open biopsy or if not possible stereotactic biopsy is therefore recommended. Obviously in some cases the pathology will be other than germ cell tumor: for example in the pineal region one may expect primitive neuroectodermal tumor, pineocytoma, ependymoma or glioma. In the suprasellar region, these and also craniopharyngioma or even metastatic lesions or inflammatory pathology may be found (4, 13, 39, 51, 58, 59).

13.3.2 Marker negative multiple site disease

In those cases in which there is disease in the pineal region and at other sites in the neu-raxis (suprasellar, spinal, subarachnoid space, brain parenchyma etc. (40)) surgery is only required to establish a definite diagnosis. The differential diagnosis includes germ cell tumor, primitive neuroectodermal tumor, lymphoma, glioblastoma and rarely others.

13.3.3 Marker positive single site disease

In those cases, in which there has been an incomplete response (see page 34) to chemotherapy, open operation is required to excise the residuum.

13.4 Classification of surgical procedures

It is very important that a uniform description is used and the following is recommended:

-Biopsy

When no attempt is made to excise tumor more than is needed to obtain tissue for the pathologist. Either open or stereotactic method should be specified.

-Partial resection

When there is visible tumor at the end of an attempted resection. If there is any doubt cavity biopsies should be taken and examined separately wherever possible.

-Extensive resection

When there is no visible residual tumor at the end of an attemped resection. When possible this should be

supported by cavity biopsies examined separately by the pathologist. In all cases of partial or extensive resection there should be post-operative imaging to confirm or refute the impression gained by the neurosurgeon at operation.

14. PATHOLOGY GUIDELINES

Intracranial germ cell tumors do not differ histologically from those of gonadal or other sites (21, 22, 30, 40, 50, 54, 62). Thus, the same diagnostic criteria can be applied, and the tumors should be classified according to the WHO classification. It is essential that all tumor components are mentioned, since the biological behaviour is determined by the most malignant component. In most cases, the diagnosis can be made by conventional light microscopy. However, in some cases it is necessary to perform additional investigations including immunohistochemistry and electron microscopy. In situ hybridization has not been established as a routine method in most laboratories, but it may serve as a highly useful tool in the diagnostic work-up of intracranial germ cell tumors. This method can **now be** performed on paraffin sections using non-radioactive agents to detect structural and numerical chromosomal abnormalities as well as areas of gene amplification. The most specific and consistent chromosomal marker of germ cell tumors is the isochromo-some 12p or i (12p).

The following investigations are considered minimal requirements to establish the diagnosis and to correlate serological findings with the results of the morphological examinations:

ROUTINE HISTOLOGY on paraffin sections which are stained with hematoxylin and **eosin** (H&E), periodic acid Schiffs (PAS) reagent and reticulin stain.

Immunohistochemistry using antibodies against AFP, HCG and placental alkaline phos-phatase. For differential diagnosis from non-germ cell tumors it may be neccessary to include antibodies against different types of intermediate filaments (vimentin, cytokeratins, desmin, glial fibrillary acid protein (GFAP), neurofilaments). Epithelial membrane antigen (EMA) may also be helpful in this respect. Staining for MIB (Ki 67) is recommended to determine the proliferative activity of the tumor.

Using these methods it should be possible to obtain a definite diagnosis in most cases and to exclude other primary tumors and metastatic lesions from the differential diagnosis.

15. NEUROPATHOLOGY GUIDELINES IN STEREOTACTIC BIOPSIES OF INTRACEREBRAL GCTs (only to be used in cases where an open operation or excisional biopsy is not advisable - see neurosurgical guidelines (pages 37-40))

Intraoperative requirements: microtiter plate; fixatives (formalin, 2,5% buffered glutaral-dehyde); slides, cover slips and mounting medium; 50 ml tubes filled with fluids for rapid H&E staining.

Two persons are usually necessary for histological handling, written documentation and microscopy.

1. The stereotactic coordinates of the CT-defmed aiming point are determined by the neurosurgeon and the distance to this aiming point is noted for each specimen collected.

2. Each successively obtained specimen (usually 1 mm or less in diameter) is transferred to the tip of a disposable needle by the neurosurgeon. The needle is carefully grasped with forceps by the neuropathologist.

3. Intraoperative touch or partial teasing preparations using needle tips are made from the first and then every second or third specimen.

4. Each of these slides is H&E stained, mounted and immediately examined by the neuropathologist. The correct position of the needle can thus be verified, and a preliminary tumor diagnosis may be made.

5. The remaining tissue from smears and all other specimens are immediately immersed into the microtiter plate wells that were filled in advance with fixative. It is essential to prevent drying of the tissue.

6. One specimen may be snap frozen for cryostat sectioning, DNA extraction or other special procedures.

7. The microtiter plate is tightly covered and transferred to the neuropathology laboratory

8. Paraffin blocks (or plastic blocks in case of glutaraldehyde fixation) are made from **each** specimen separately. Sections are stained by H&E.

9. Following the first evaluation, appropriate special stains are made from selected blocks.

10.A schematic drawing from the complete sequence of specimens over the entire length of the needle tract is made by successive plotting of the histological findings, e.g.

edema/capsule . **tumor** necrosis tumor tumor/hemorrhage

-10 -8 -6 -4-2 - +2 +4 +6 +8

Note: The small amount of tumor tissue available from the tiny specimens requires close cooperation by the neurosurgeon, neuroradiologist, neuropediatrician and neuropatholo-**gist** if an accurate assessment is to be reached. Therefore, each case should be discussed in a clinico-pathological conference before making the final diagnosis.

16. SPECIFIC AND TECHNICAL OUTLINES FOR RADIOTHERAPY 16.1 Neuroaxis irradiation

- *Pure CNS Germinoma (Option A)*

- *Secreting Intracranial Germ Cell Tumors (metastatic)*

Radiotherapy should be started if possible within 3 weeks from diagnosis in patients having option A for pure germinoma. In all other patients radiotherapy should begin after surgery or, if no

surgery is required, as soon as there is hematological recovery from the chemotherapy (usually 3 weeks after the last course).

16.1.1 Whole brain or "helmet" -Held

Target volume

The cranial volume should include the whole skull, the cribriform fossa, the temporal fossae, the posterior fossa and the spinal cord to, or below, the C3 - C4 interspace where it will junction with the spinal volume.

Radiotherapy fields

The whole brain is treated using two parallel opposed lateral portals (34, 51). The central ray is stationary 3 cm posterior to the eyelid markers at the level of the block margin inferior to the middle cranial fossa. The distance to the eyelid surface has to be respected to protect the contralateral lens from the divergent beam. Collimator rotation helps to adapt the helmet portals to the divergent beam of the adjacent spine field. The patient's eye lenses, face and pharynx are shielded by customised blocks. Blocks are shaped so that the portals include the cribriform plate and the middle cranial fossa down to the 3rd / 4th or 4th / 5th vertebral interspace. '

Dose specification

The cranial dose must be specified on the central axis in the midplane of the opposed fields.

16.1.2 Spine field

Treatment volume

The spinal volume should cover the spinal dural sac from the junction with the cranial volume down to the level of S2. The width of the vertebrae should be covered with an allowance for scoliosis or rotation of the vertebral column, but a spade should not be used to cover the spinal nerve roots.

Radiotherapy fields

The spinal canal receives irradiation by a single, direct, dorsal portal. The spinal portal should be 5-6 cm wide (without additional enlargement in the sacral region). In children younger than 7-8 years 4,0 cm may be sufficient. It should extend inferiorly to the second sacral segment.

Dose specification

It is necessary to calculate the minimum and maximum depth of the target volume at the posterior edge of the vertebral bodies. The points of maximum depth are usually at C7 and L5. The spinal dose must be recorded as a maximum and minimum according to the maximum and minimum depths of the posterior vertebral bodies and the doses should be prescribed to the minimum. These doses, and whether or not a compensator is used, are to be recorded on the RADIOTHERAPY DATA sheet. If the calculated dose to these points varies by more than 10%, then a compensator must be designed to improve the uniformity of dose in this region. In the case of fast electrons, the energy should be chosen such that the 90% isodose line encompasses the deepest part of the target volume; the dose specification is made at the

90% isodose.

16.1.3 Field matching

Dependent on the divergence of treatment beams of the upper spinal field, collimator rotation is used for optimal matching of adjacent portals of the lateral helmet fields and the spinal field. To smooth our hot and cold spots beneath the surface, the junctions of the whole brain and spinal portals are shifted. The adjacent two spinal fields are matched on the depth of the dose specification (the dorsal border of the vertebral bodies).

16.2 Radiation treatment of the tumor region ^involved-field") 16.2.1 Boost to tumor bed (germinoma option A, secreting tumors)

Target volume

It seems that irradiation of the fci aniospinal axis can control subclinical disease of areas at risk in proximity to the primary tumor site. Therefore, the planning target volume of the boost - field can be restricted lo the primary tumor site defined at diagnosis. With ideal head fixation, the safety margins of the planning target volume should be 2 cm outside the tumor border as seen on pre<”perative CT or MRI scans.

Treatment technique

If possible computer assisted treatment planning should be performed. In the case of an ectopic, supra- or parasellar primary, the pineal region should be closely monitored during whole brain irradiation. S^ans should be repeated when 24.0 to 30.0 Gy have been given to the craniospinal axis. Any major changes, especially decrease of tissue volume of the pineal gland are likely to ideate malignancy in the pineal region itself. There also is a likelihood that the assumed tropic primary tumor may actually represent a metastasis previously undiscovered pineaj neoplasm and that there may be other (micro-) metasta-ses. Both tumor regions and ti.o ventricular system should be included in the treatment fields.

Exception:

If in pure germinoma the mul^ie tumor sites visible on MR cannot be encompassed by the treatment field or if there *i* macroscopic spinal seeding it is mandatory to contact the national reference centre. Und*/ these conditions the administration of chemotherapy has to be considered before irradi<i;.,n The dose prescription and definition of the target volume must be determined ind.. anally in cooperation with the national radiotherapeutic reference centre.

Dose specification

Radiation dose specification li/ irradiation of the tumor region is done according to the ICRU rules. Dose inhomogenb.../ within the target volume should not exceed the tolerance limits of 95 % and 107 %.

16.2.2 Irradiation of the tumor bed

(secreting intracranial germ cell tumors -non-metastatic disease)

Target volume / treatment technique

With ideal head fixation, the safety margins of the planning target volume should be 2 cm outside the tumor border as seen on preoperative CT or MRI scans. **If** possible computer assisted treatment planning should be performed.

Dose specification ' . -

Radiation dose specification for irradiation of the tumor region is done according to the ICRU rules. Dose inhomogeneity within the target volume should not exceed the tolerance limits of 95 % and 107 %.

16.3 Combined modality treatment

Radiation therapy alone in pure germinoma is recommended in Germany. If in other countries a combined modality treatment is performed (option B: irradiation of the primary tumor site only) the definition of the planning target volume is done according to the guidelines described in chapter 16. Additionally, the dose specification and documentation of radiotherapy chould be done according to the guidelines described in chapter 16.5.

16.4 Patient positioning

Neuroaxis irradiation

The patient is to be treated in an immobilisation device in the prone position to provide a stable and reproducible treatment delivery. The spine should be made as straight as possible. The immobilisation device should consist of a complete head shell, but a whole body **cast is** recommended. Alternatively vacuum pillows can be used.

Irradiation of the tumor region ("involved-field")

The patient is treated in the supine position. It is recommended that an individualized face mask is used to guarantee the reproducibility of head positioning. Head rests should be chosen in order to provide sufficient head inclination so that anterior-posterior beams will not traverse the lenses of the eyes.

16.5 Documentation

It is mandatory to document the field alignment using simulator films and polaroid photographs. At the start of radiotherapy verification films should be obtained of each irradiated field.

Portal films should be repeated once a week. Precise application of radiotherapy is essential for both tumor control and reduction of side-effects.

To give recommendations for optimal treatment techniques it is necessary to analyse the radiation protocols, the prescription of target volumes/doses and the accuracy of treatment delivery.

Therefore, it is requested that the following data (copies) be sent to the national coordination

centre or - if not established - to the international coordinator.

-imaging of the tumor region that was used for treatment planning

-radiation protocols

-simulation films

-portal films .

-computer assisted treatment plans

-Polaroid pictures of patient positioning and field alignment

-evaluation forms

- patient data . ,

- toxicity

- treatment technique / dose prescription

16.5.1 Acute treatment toxicity

Especially in patients who have previously received chemotherapy, neuraxis irradiation may lead to severe suppression of hemopoiesis as it covers a large volume of hemopoietic bone marrow. Steroid prophylaxis of cerebral edema may be required during whole brain irradiation. If acute brain edema occurs, steroids should be given i. v., radiation esophagi-tis may require analgesics and antifungal medication. The acute maximal toxicity and myelotoxicity during irradiation should be documented on the evaluation sheets.

16.5.2 Routine laboratory studies during radiotherapy

2 x weekly: red and white blood cell counts, platelet counts. If the patient is receiving steroid medication: blood glucose Ix weekly. Before and at the end of radiotherapy: sodium, potassium, calcium. GOT, GPT, Gamma-GT, LDH, creatinine. BUN, AFP, B-HCG, hormones of the pituitary axis (TSH, growth hormone, ACTH, FSH/LH - see endocrine guide lines pages 40-43).

Radiotherapy may need to be interrupted if the platelet count falls below 100 x 10 /I or the neutrophil count below 1.0 x 10^9/!.

Name:

SIOPCNSGCT96

FOLLOW-UP-PROGRAM FOR CHILDREN WITH CNS-GERM-CELL-TUMORS

	First and second year after primary surgery	**> 2 years after primary surgery**
Body measurements:	every 6 months	once a year
MRI or CT with contrast:	every 4 months	once a year

MRI spinal (if metastasis):	every 6 months	once a year
Ophthalmological evaluation:	every 6 months	once a year
Audiogram (BAER) (if abnormal at therapy):	once a year	once a year
Neurological examination:	every 6 months	once a year
Endocrinological testing:	once a year	once a year
Laboratory studies (Mg, P04, GFR):	every 6 months	once a year
Tumor markers: (AFP, HCG)	1 st year: every 4 weeks 2nd year: every 4 months	once a year