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Review

Germ-cell tumors in childhood and adolescence

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Summary

In mature and immature teratoma the treatment is surgical. The risk of recurrence can be estimated from the parameters primary site (with the coccygeal tumors being most at risk), histological grade of immaturity and completeness of the primary resection including the adjacent organ of origin (coccyx, ovary, testis etc.). In case of a microscopically complete tumor resection there is no role for adjuvant chemo- or radiotherapy irrespective of the histological grade of immaturity.

Malignant germ-cell tumors (GCT) account for 2.9% of all malignant tumors of children younger than 15 years of age. More than half of the tumors occur at extragonadal sites such as the ovaries (26%), the coccygeal region (24%), the testes (18%) and the brain (18%) represent then primary sites.

In patients with extensive tumor growth, metastatic disease or secreting intracranial tumors a delayed tumor resection after preoperative chemotherapy is preferable. In these patients malignant non-seminomatous GCT may be diagnosed clinically due to the increased serum or cerebrospinal fluid levels of the tumor markers AFP and/or β-HCG. Current risk adapted treatment protocols containing cisplatinum allow long-term remissions in about 80% including patients with bulky or metastatic tumors. In the cisplatinum era the prognostic factors like histology, primary site of the tumor and initial tumor stage have partly lost their former impressive significance in infants and children. On the other hand the completeness of the primary tumor resection according to oncological standards has been established as the most powerful prognostic parameter superior to tumor marker levels or primary site of the tumor.

Key words: children, diagnosis, germ-cell tumor, prognosis, review, therapy, tutorial

Introduction

Cooperative studies have greatly advanced both our clinical understanding and the therapeutic success in pediatric germ-cell tumors (GCT). Whereas the first protocols were strongly influenced by previous studies on testicular GCT in adults [1], the trials on pediatric GCT clearly revealed the specific diagnostic, therapeutic and prognostic characteristics of GCT in infancy and childhood [2–11]. Moreover, biological studies demonstrated that pediatric GCT show a distinct genetic profile [12, 13]. Therefore, due to the profound differences in their biology and their clinical presentation the data obtained in adult GCT cannot simply be transferred to pediatric patients without scrutiny, but the special clinical settings have to be considered carefully.

This article reviews the current knowledge on epidemiology, biology, diagnosis and therapy in both intra- and extracranial GCT in children and adolescents. With a view to the ongoing German protocols a risk adapted therapeutic strategy for pediatric GCT is presented, and the prognosis under this therapeutic strategy is illustrated.

Epidemiology

Malignant germ-cell tumors are rare tumors contributing 2.9% to the central Tumor Registry of the German Society for Pediatric Oncology and Hematology [14]. In Germany the incidence of malignant GCT is 0.6/100,000 children, varying significantly according to sex and age. Teratoma contribute additional 50% [14] so that from these data the overall incidence of GCT can be estimated as 0.9/100,000. In neonates mature and immature teratoma predominate (girls: 0.9/100,000, boys: 2.6/100,000). In the first years of life the overall incidence of GCT decreases (< 0.1/100,000 for both sexes at five years of age) [14]. Simultaneously, among toddlers the relative proportion of malignant entities, especially yolk sac tumors (YST) increases. The incidence of gonadal tumors, mainly seminomas and dysgerminomas, increases with the onset of puberty. In young men GCT represent the most common malignant tumor entity (yearly incidence: 7–8/100,000) [15]. In general, girls have a higher overall incidence of GCT, but boys are more at risk of malignant GCT [14].

Histological classification of germ-cell tumors

GCT are characterized by a high heterogeneity of their histological differentiation, but they show a similar histological pattern independent of their primary site or sex. They are classified according to the WHO-classification of testicular [16] and ovarian tumors [17], respectively. The histological evaluation of GCT is difficult because of the heterogeneous appearance of the tumors and because of conflicting terminology. Therefore, the initial diagnostic work-up should include the evaluation by an experienced pediatric pathologist and according to the guidelines of the German GCT protocols a central reference histology is mandatory in order to achieve a standardized and reliable histopathological diagnosis and grading.

According to the holistic concept of Teilum [18, 19] GCT arise from totipotent primordial germ cells which are capable of embryonic and extraembryonic differentiation. Yolk sac tumors (YST) and choriocarcinoma (CHC) follow an extraembryonic differentiation pattern and are characterized by a significant secretion of α1-fetoprotein (AFP) or human choriogonadotropin (HCG or β-HCG), respectively. Embryonal carcinoma (EC) represent tumors of immature totipotent cells. Teratoma display an embryonal differentiation mimicking organ structures of all germ layers. In teratoma the histological grade of immaturity is defined by the extent of immature (predominantly neuroepithelial) elements [20]. Finally, the germinomatous tumors [synonyms: seminoma (testis), dysgerminoma (ovary), germinoma (brain)] may be interpreted as tumors displaying morphological features of undifferentiated germ epithelium. Interestingly, in contrast to testicular GCT of adult patients pediatric GCT do not develop from intratubular *in situ* carcinoma[21].

The histological subentities show a highly heterogeneous biology and clinical course. In most patients the response to the different therapeutic modalities can be predicted from the histological appearance and the tumor marker profile (Table 1). Twenty-five percent of all pediatric GCT present as tumors with more than one histological type. In this situation therapy and prognosis depend on the tumor entity with the highest malignancy.

Tumor markers

Depending on their histological differentiation (Table 1) GCT tend to secrete the tumor markers AFP and/or β-HCG which help to establish a clinical diagnosis in tumors presenting at a typical localization. It has to be considered that the AFP levels may be excessively elevated in neonates and infants (Figure 1). Therefore, in the first two years of life only AFP levels significantly above the age-related normal value can be regarded as diagnostic for a secreting germ-cell tumor [22]. In general, the tumor marker profile is highly specific for the histological differentiation of the tumors (Table 1). Nevertheless, there may be a secretion of β-chains of HCG in seminoma/germinoma (< 50 IU/l) which is often related to the histological presence of syncytiotrophoblast-like giant cells [23]. Some patients with immature teratoma show a moderate elevation of the AFP level (< 100 µg/l), sometimes associated with histologically detectable small foci of YST within the teratoma [23, 24].

Table 1. Biological characteristics of the histological germ-cell tumor subentities.

	Histological grading	Tumor marker		Sensitivity to	
		AFP	β-HCG	Chemo-therapy	Radio-therapy
Seminoma/germinoma	Malignant	–	(+)	+++	+++
Embryonal carcinoma	Malignant	–	–	+++	?
Yolk sac tumor	Malignant	+++	–	+++	?
Choriocarcinoma	Malignant	–	+++	+++	?
Teratoma, mature/immature	Benign/pot. malignant	–/(+)	–	?	?

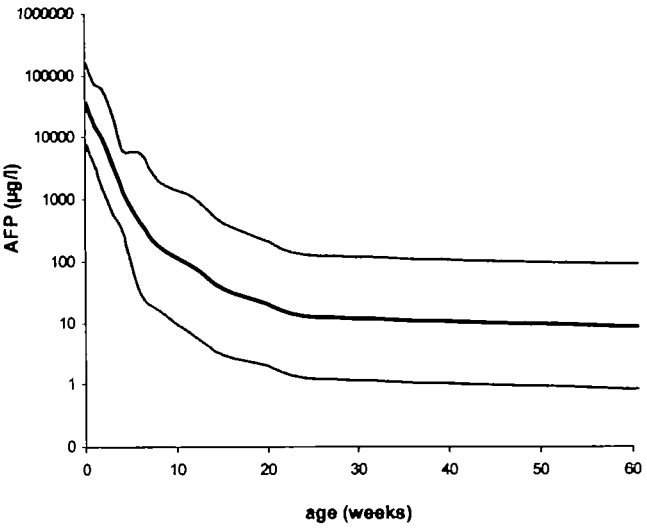

Figure 1. Serum AFP levels of term babies without additional factors associated with AFP-elevation (median and 95% interval) [22].

Genetics

Pediatric GCT show a pattern of cytogenetic aberrations which is different from their adult counterparts. More than 80% of adult malignant GCT display a distinct and specific chromosomal aberration, the isochromosome 12p [25]. The remaining isochromosome 12p-negative tumors frequently show an amplification of 12p (homogeneously staining regions or tandem repeats) [25]. These aberrations have been observed in both, testicular and ovarian tumors, and in extragonadal mediastinal GCT. In children younger than 10 years an isochromosome 12p has been found only in a vast minority of patients [12, 13], although interphase cytogenetic studies have demonstrated aberrations of the short arm of chromosome 12 in some YST [26]. On the other hand,

aberrations at both the short and the long arm of chromosome 1, at the long arm of chromosome 6 and the sex chromosomes have been found frequently, but no consistent correlation between cytogenetic aberrations, histology and primary site of the tumor has been established [12, 13].

Localization

In children younger than 15 years the most common primary sites are the ovary (26%), the coccyx (24%), the testis (18%) and the brain (18%). In infancy coccygeal tumors are by far most prevalent. Other extragonadal sites are the mediastinum (4%), the retroperitoneum (4%) and the vagina (2%).

The relative incidence of GCT with regard to the histological subentities and the primary site shows a characteristic age-dependent pattern. Teratomas of the coccyx are most commonly found in neonates, while ovarian teratomas occur between the 6th and the 14th year of age. Coccygeal tumors in children older than four years usually present as malignant YST [27], and half of the patients with relapsing teratoma present with a malignant histology, most common YST [4]. Among the ovarian tumors, dysgerminoma are most prevalent during puberty, whereas the other malignant entities develop at all ages. Germinomatous tumors can also appear at extragonadal sites like the brain (approx. 50% of all intracranial GCT [8]) or mediastinum but they have not been observed yet at the coccyx.

Tumor spread and relapse pattern

Malignant GCT are characterized by their infiltrative growth pattern and by lymphogenous and hematogenous spread. The testicular GCT spread into the retroperitoneal lymph nodes, while spread into inguinal lymph nodes occurs in stage pT4 tumors, only. In ovarian GCT lymphogenous spread can be observed in the lymph nodes at the renal hilus. In intraabdominal and intracranial GCT dissemination can occur via ascites or cerebrospinal fluid, respectively. The most common sites of distant metastases are the lungs and the liver. In a recent evaluation of 95 patients with sacrococcygeal YST registered in the German cooperative protocols 15% of the patients had lymph node metastases while 35% suffered from distant metastases at diagnosis. Compared to adults brain metastases of extracranial GCT are extremely rare. Relapses most commonly present as local recurrence at the primary site of the tumor.

Diagnosis

In most patients the diagnosis can be established with regard to the clinical picture, the typical localization, tumor imaging and the measurement of the tumor markers. In neonates and young infants the physiologically elevated AFP-levels have to be considered. In children older than two years an elevation of the AFP-levels of more than 100 μg/l is highly indicative for a malignant GCT with a component of YST. Nevertheless, an acute liver disease with an elevation of the AFP-levels due to hepatocellular regeneration, AFP secreting liver tumors like hepatoblastoma and hepatocellular carcinoma and some rare tumors (e.g., pancreaticoblastoma), rare cases of hereditary persistence of AFP or hereditary diseases associated with elevated AFP-levels (e.g., hereditary tyrosinemia, ataxia teleangiectatica) should be excluded [28]. In some teratoma with a higher degree of immaturity elevation of the AFP can be observed and correlates with the histological detection of small foci of YST [23, 24]. Nevertheless, in case of a complete tumor resection microfoci of YST would not urge to change the therapeutic strategy [4, 11].

The establishment of a clinical diagnosis is of high priority in intracranial non-germinomatous tumors at the pinealis or suprasellar region, as the chance of a complete tumor resection can be significantly improved by preoperative chemotherapy. Thus, by establishing a clinical diagnosis a second brain surgery can be avoided. Moreover, the diagnostic value of stereotactic biopsies is limited, since the relevant tumor component may not be included in the small tumor samples. Therefore, the finding of elevated tumor markers (AFP or β-HCG) in the serum or the CSF appear to be clinically more relevant than a confined stereotactic biopsy.

A primary resection of secreting tumors at all sites may be indicated only in those tumors, in which the diagnostic imaging suggests a high chance of a primary complete tumor resection. On the other hand, a (preferably open) tumor biopsy is mandatory in non-secreting tumors at all sites.

Treatment

Treatment of pediatric GCT is based on a multimodal strategy that includes surgery, chemo- and radiotherapy. Depending on their distinct biology the histological subentities differ significantly in their response to chemo- and radiotherapy. Germinomatous tumors are highly sensitive to both radio- and chemotherapy [8]. On the other hand, the therapeutic impact of radiotherapy has not yet been clearly defined in non-germinomatous malignant GCT. Treatment data show that EC, CHC and YST show a restricted sensitivity only to high doses (> 50 Gy) of irradiation [8]. Compared to their malignant counterparts, in immature teratoma the therapeutic role of chemo- or radiotherapy still has to be determined [4]. Therefore, in these tumors the complete surgery represents the mainstay of treatment [4, 11].

Historical reports of the 1980s discussed treatment regimen including vincristine, adriamycin, actinomycin D and cyclophosphamide combined with irradiation [29]. Radiotherapy was administered simultaneously to

chemotherapy up to a dose of 30 Gy. The entire chemotherapy was continued for 18–20 months. Thirty percent of the patients survived. Ten percent died of toxicity complication. Ablin et al. reported about 93 children with extracranial malignant germ-cell tumors treated between 1978–1984 [3]. Patients received a combination of vinblastine, bleomycin, cisplatinum, cyclophosphamide, actinomycin D and doxorubicin. The observed toxicity aside hematological effects was mainly cardiac due to doxorubicin and pulmonary as induced by bleomycin, but no toxic death was recorded. The achieved event-free survival rates were around 50%.

Data of the UKCCSG study on malignant germ-cell tumors registered between 1979 and 1987 described the results of several chemo-regimen [30]: Low-dose VAC treatment was seen to be ineffective (EFS 8%). The combination platinum, vinblastine and bleomycin (days 2, 9, 16) caused unacceptable pulmonary toxicity due to bleomycin whereas the combination of bleomycin (day 1 only), etoposide and cisplatinum showed superior results with no proven pulmonary complication (EFS 84%). Good results were also obtained with high-dose VAC with or without doxorubicin resulting in an EFS of 87%.

Cisplatinum has been demonstrated as the most effective single chemotherapeutic agent in both childhood and adult GCT. From the 1980s etoposide has been introduced as the first drug active in cisplatinum resistant GCT. Recently, there have been attempts to replace cisplatinum by carboplatinum in order to reduce the cumulative nephro- and ototoxicity (e.g. JEB, Table 2) [6, 9]. Some studies have shown the superior efficacy of carboplatinum regimen compared to non-platinum regimen previously applied in children [6, 7, 9]. On the other hand, an analysis of prognostic factors in non-seminomatous GCT revealed that even in localized tumors an intensive cisplatinum-based chemotherapy resulted in higher survival rates than carboplatinum therapy [31].

In summary, the regimens PEI, BEP, PVB, CarboPEI and JEB (Table 2) have a synergistic cytotoxic activity and can be regarded as standard regimens that are applied in currently open pediatric GCT protocols. Encouraged by the results of previous studies, attempts have been made to reduce the cumulative chemotherapy doses by introducing shorter but more intensive regimen.

Table 2. Standard chemotherapy regimen in pediatric GCT.

PEI (MAKEI 96, SIOP CNS GCT 96, MAHO 98)			
Cisplatinum[a]	20 mg/m^2	Over 1 h	Day 1, 2, 3, 4, 5
Etoposide	100 mg/m^2	Over 3 h	Day 1, 2, 3
Ifosfamide[b]	1500 mg/m^2	Over 20 h	Day 1, 2, 3, 4, 5
Two to four cycles			
PVB (MAHO 98)			
Cisplatinum[a]	20 mg/m^2	Over 1 h	Day 4, 5, 6, 7, 8
Vinblastin	3 mg/m^2 or 0.15 mg/kg	I.v. bolus	Day 1, 2
Bleomycin[c]	15 mg/m^2	Over 24 h	Day 1, 2, 3
Three cycles			
BEP (MAHO 98)			
Bleomycin[c]	15 mg/m^2	Over 24 h	Day 1, 2, 3
Etoposide	80 mg/m^2	Over 3 h	Day 1, 2, 3
Cisplatinum[a]	20 mg/m^2	Over 1 h	Day 4, 5, 6, 7, 8
Three cycles			
JEB (UKCCSG GCII)			
Carboplatinum	600 mg/m^2	Over 1 h	Day 2
Etoposide	120 mg/m^2	Over 1 h	Day 1, 2, 3
Bleomycin[c]	15 mg/m^2	Over 15 min	Day 3
Five cycles, or two cycles after complete remission			
CarboPEI (SIOP CNS GCT 96)			
Carboplatinum	600 mg/m^2	Over 1 h	Day 1
Etoposide	100 mg/m^2	Over 3 h	Day 1, 2, 3, 22, 23, 24
Ifosfamide[b]	1800 mg/m^2	Over 3 h	Day 22, 23, 24, 25, 26
Two cycles			

[a] Plus mannitol forced diuresis.
[b] Plus mesna uroprotection.
[c] Omitted in children < 1 year, 7.5 mg/m^2 in children < 2 years.

Side effects of chemotherapy

The problematic pulmonary toxicity of bleomycin which also had been reported as a problem in combination with reduced kidney function [32] or potentiated by anesthesia [33], lead to regimen without implementing this drug. On the other hand, the highly efficient combination of cisplatinum, etoposide and ifosfamide (PEI) is associated with a higher degree of myelosuppression and bears the risk of tubular nephropathy [34]. The risk of therapy-related secondary leukemia is dependent on the applied therapeutic modalities with an estimated cumulative risk of 1.0% (3 of 442 patients, Kaplan–Meier method at 10 years follow-up) for patients treated with chemotherapy only and 4.2% (3 of 174 patients) for patients treated with combined radio- and chemotherapy [35].

Therapeutic strategies of the international SIOP-CNS-GCT 96 protocol and the currently open German protocols for extracranial GCT

In general different strategies have been applied in pediatric GCT protocols. Some have stratified chemotherapy according to the response to treatment (e.g., one standard chemotherapy regimen to a total of two cycles after complete remission [6]). In other protocols therapy is stratified according to initial diagnostic parameters, and only in case of insufficient response to treatment therapy is further intensified. In the following chapters, the SIOP-CNS-GCT 96 protocol and the German protocols for extracranial GCT and their risk adapted therapeutic strategies are summarized.

In the current protocols the cumulative treatment

could be significantly reduced for most patients without jeopardizing the overall cure rates. It must be considered that a reduction of treatment may be harmful to those patients that are not diagnosed and treated according to the standards outlined in the previous chapters. Therefore, the German Cancer Society, the German Cancer Aid and the consulted ethical committees strongly recommend that a stratification of therapy according to the outlined criteria is appropriate for protocol patients, only.

SIOP-CNS-GCT 96 protocol on malignant intracranial GCT

The therapeutic strategy for malignant intracranial GCT is stratified according to the histological differentiation (i.e., germinoma vs. secreting GCT) and initial tumor stage. The ongoing SIOP-CNS-GCT protocol aims to evaluate the two different therapeutic options in intracranial germinoma with regard to both their therapeutic impact and their specific acute and long-term toxicities. For secreting intracranial tumors the effect of a combined treatment with PEI (Table 2) and risk adapted radiotherapy is examined.

In intracranial germinoma, which account for 50% of all intracranial GCT and do not secret significant amounts of β-HCG, a histological verification of the tumor is mandatory. According to the current SIOP-CNS-GCT 96 protocol patients can be treated either with craniospinal irradiation with 24 Gy and a tumor boost of 16 Gy or with a multimodal treatment including two cycles of chemotherapy (CarboPEI, Table 2) followed by a focal irradiation (40 Gy). As GCT may arise in neighborhood to sensitive structures like the chiasma opticum, it is recommended to consult a reference radiotherapist for detailed recommendation on optimal treatment techniques. It has been demonstrated that a five-year event-free survival of 91% and five-year overall survival of 94% can be achieved by radiotherapy only [36]. With the combined chemo- and radiotherapy approach a three-year relapse-free survival of 96% and an overall three-year survival of 98% has recently been reported, but it has to be considered that in this study two of the four observed relapses occurred after the evaluated three-year observation period [37].

The secreting intracranial GCT (YST, CHC, EC) show an inferior prognosis compared to germinoma. In these patients four cycles of cisplatinum based chemotherapy (PEI, Table 2) are applied, followed by a delayed tumor resection and radiotherapy. The radiotherapy is stratified according to the initial staging. Non-metastatic tumors receive focal irradiation (54 Gy), whereas patients with intracranial or spinal metastases or tumor cells in the CSF receive a craniospinal irradiation (30 Gy plus 24 Gy tumor boost). The summary of several cooperative protocols [8] and the preliminary data of the SIOP-CNS-GCT 96 protocol suggest that a long term remission can be obtained in about two thirds of patients.

MAKEI and MAHO protocols on extracranial malignant GCT

Surgical treatment

Both gonadal and extragonadal GCT are treated according to a similar therapeutic concept: only in small, non-metastatic tumors in which the radiographic examinations shows no evidence of invasive growth beyond the organ of origin a primary resection is indicated. In patients with bulky, invasive or metastatic tumors a preoperative chemotherapy followed by a delayed tumor resection is preferred to avoid the risk of incomplete resection. A decline of the tumor markers according to their serum half-life indicates for a favorable response to chemotherapy [38].

Tumor resection is considered complete, if it is performed as en bloc resection of the tumor including the adjacent organ of origin. On microscopy the resection margins must be free of tumor cells. In testicular tumors a high inguinal orchidectomy is mandatory. Ovarian tumors must be resected including the ovary and the Fallopian tube. In coccygeal tumors the complete en toto resection including the whole coccyx is essential [27]. A recently published review summarizes the standard surgical procedures in gonadal and extragonadal pediatric GCT in detail [39].

In patients with tumor residues after an initial tumor resection a second-look surgery is essential to achieve a secondary complete resection. In general, there is no role for debulking surgery in pediatric GCT. Usually, surgery of metastases is not indicated [27] unless they show an insufficient response to chemotherapy.

Adjuvant treatment

According to the MAHO 98 protocol for testicular GCT patients with stage IA mature teratoma or YST are treated according to a watch-and-wait strategy. All other patients receive two to three cycles PVB ($\leqslant$ stage IIB; Table 2) or the more intensive BEP (stage IIC–IV; Table 2). PEI is reserved as salvage therapy in patients with relapsing or poorly responding tumors.

In the current MAKEI 96 protocol patients with completely resected stage T_1 tumors are treated according to a watch-and-wait strategy which includes frequent (weekly) controls of the relevant tumor markers. Completely resected stage T_2 tumors receive two to three cycles of a two agent regimen (PE, Table 2), whereas a three-agent combination is applied after incomplete resection (PEI, Table 2) [40, 41]. Guided by the observation of lethal or severe chronic bleomycin-associated pulmonary fibrosis bleomycin was omitted in the current MAKEI 96 protocol. Ovarian dysgerminoma are treated according to the same strategy. Irradiation is omitted to preserve fertility.

Teratoma

Teratoma represent a distinct histological entity that shows a significant diversity of the clinical course in dependence of the histological grade of immaturity [4, 20]. Mature teratoma are considered as benign tumors, whereas immature teratoma may show clinical features of malignancy. The surgical treatment should follow the same principles as outlined above for the malignant GCT.

The risk of recurrence can be estimated from the parameters primary site of the tumor, histological grade of immaturity and completeness of the tumor resection [4]. Nevertheless, the role of adjuvant chemotherapy has not yet been established, but recent reports have shown that chemotherapy is not indicated after complete tumor resection, even if there were small foci of malignant YST [4, 11].

Follow-up

A complete clinical remission is defined as normalization of the tumor-markers within the age-related normal range and the absence of suspective residual structures, even in patients with normalized tumor markers, as these structures may represent remaining mature teratoma. If any of these criteria is not fulfilled, a diagnostic reevaluation and – if necessary – change or intensification of treatment is highly indicated. Most relapses occur within the first two years after diagnosis, although in some patients late recurrences up to five years after diagnosis of an intracranial germinoma or sacrococcygeal teratoma have been observed. Therefore, the initial follow-up examinations after completion of chemotherapy must be performed in short intervals, including frequent (i.e., weekly) controls of the tumor markers AFP and β-HCG. In watch-and-wait patients the decline of the AFP values must be evaluated with regard to its serum half-life of approximately six to seven days. Especially in infants younger than two years in whom the interpretation of AFP may be difficult due to the physiologically elevated serum levels it has been proven helpful to compare the AFP decline with the graph given in Figure 1. A slower decline or a secondary rise of the AFP levels strongly indicate for an incomplete tumor resection or a recurrence of YST.

In addition, the follow-up examinations must include repeated imaging of the primary site of tumor. In case of residual structures after chemotherapy a resection of these residues is indicated, since mature teratoma may have remained which bears the risk of a later tumor progression [42]. Positron emission tomography examinations have not been proven useful in this situation, as these cannot distinguish between mature teratoma and residual necrosis or scars [43].

In intracranial tumors repeated endocrinological examinations at diagnosis and during follow-up are mandatory, since especially tumors of the suprasellar region can be associated with endocrinological symptoms like diabetes insipidus or panhypopituiarism. In children treated with cisplatinum-containing polychemotherapy (esp. plus ifosfamide) the renal function has to be monitored carefully for tubular nephropathy. In children a prolonged phosphaturia can lead to renal rachitism with consecutive growth retardation, while adolescents are at risk of renal osteomalacia [34]. These long-term sequelae can be avoided by supplementation of phosphate and vitamin D. Further attention should be drawn to the risk of therapy-related secondary leukemia that depends on treatment intensity and modality. In the German series the cumulative risk at 10 years follow-up was 1.0% for patients that received chemotherapy only and 4.2% for patients that were treated with both radio- and chemotherapy (Kaplan–Meier estimates) [35].

Relapse treatment

In patients with recurrent or refractory tumors who had previously been treated with a non-platinum or carboplatinum therapy, cisplatinum based regimens (preferably PEI) have been successfully applied [9, 41]. In this report on localized malignant GCT a complete remission (CR) could be achieved in 90% after cisplatinum chemotherapy (TGM 85 protocol). In the consecutive TGM 90 protocol cisplatinum was replaced by carboplatinum with the cumulative doses of the further agents remaining unchanged. In this protocol the CR rate was 58% after carboplatinum chemotherapy as first line treatment, but after introduction of cisplatinum as a second line treatment for the remaining patients with an insufficient response the overall CR rate could be raised to 90% [9].

In conclusion, we prefer cisplatinum containing regimen in patients with relapsed tumors, if the organ toxicities related to the previous treatment allow further cisplatinum therapy. On the other hand patients suffering from severe cisplatinum-related toxicity may be treated with a combination of carboplatinum and high-dose etoposide (at 400–600 mg/m^2 on three days). In our experience high-dose chemotherapy with stem-cell support, as it has been applied in adult patients [41], has resulted in long-term remissions only in those patients in whom a clinical complete remission could be achieved prior to high-dose chemotherapy. Therefore, we regard high dose chemotherapy as indicated for consolidation treatment, only.

In our experience more than 90% of relapses occur at the primary site of the tumor. For example in the above mentioned series of 95 sacrococcygeal YST only one patient had a distant recurrence, whereas nine patients had a local and four patients a combined local and distant relapse. Therefore, relapse chemotherapy must be accompanied by an intensive local therapy, preferably complete resection of the recurrent tumor after tumor-reduction by preoperative chemotherapy. We could demonstrate that patients with local recur-

rences and poor response to conventional chemotherapy may profit from locoregional hyperthermia combined with platinum-based chemotherapy. This approach significantly enhanced local tumor control [31]. To our knowledge, newly developed drugs like paclitaxel or gemcitabine which have been recently applied in phase I and II studies in relapsed adult GCT have not yet been studied in children with relapsing or refractory GCT. In conclusion, as the insufficient local tumor control at the primary site of tumor represents the main problem in most patients, further significant advances in relapsing GCT may probably be based on a further improvement of local therapy.

Prognosis

In the pre-cisplatinum era the prognosis was determined by the parameters histology, primary site and tumor stage. The malignant non-germinomatous intracranial GCT showed the most unfavorable prognosis with an EFS of 5% [44] followed by the malignant sacrococcygeal GCT (5%–10%, own experience in non-protocol patients retrospectively reported during the MAKEI 83 period). The introduction of cisplatinum to GCT treatment led to a significant improvement of the prognosis with now more than 80% of all patients being cured. A recent study of prognostic factors in children with localized GCT introduced high AFP-levels as a distinct prognostic parameter for tumors treated with carboplatinum, but the authors still concluded that this prognostic factor may not be relevant in patients primarily treated with intensive cisplatinum chemotherapy [9].

The event-free survival rates of patients (enrolled in the German MAKEI trials) with non-testicular GCT with respect to the primary site of the tumor and the histological differentiation are summarized in the Figures 2 and 3. It has to be considered that a further differentiation between each site and histological subentity is mandatory, as a specific histology may bear a different prognosis dependent of the site. For example the non-germinomatous intracranial GCT remain to be high at risk, although by current protocols long-term remissions can be achieved in approx. Two-third of all patients, depending on the intensity (i.e., cumulative cisplatinum dose) of chemotherapy [8]. On the other hand intracranial germinoma have an excellent prognosis with an EFS of approximately 95%. Among the extracranial tumors the testicular GCT have the most favorable prognosis (EFS 97%) even despite malignant (e.g., YST) histology and irrespective of the initial tumor stage [5].

In conclusion, in the cisplatinum era the previous prognostic parameters like histology, primary site and tumor stage have partly lost their former impressive prognostic relevance, while the completeness of the tumor resection seems to establish as a new, highly relevant prognostic factor. In advanced and infiltrating tumors the rate of complete resections can be significantly increased by a preoperative chemotherapy. Moreover, preoperative chemotherapy helps to avoid extended surgery with the risk of severe mutilation. Therefore, this strategy appears to be most appropriate in advanced and infiltrating tumors.

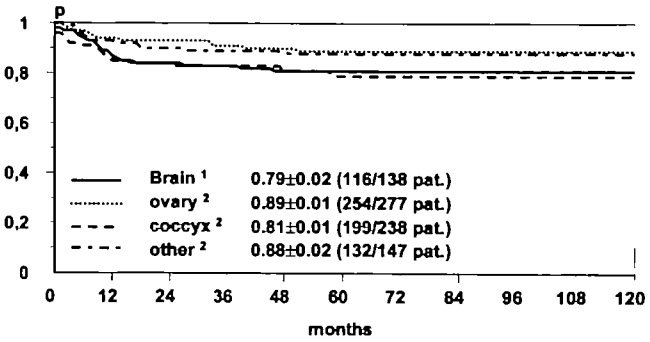

Figure 2. Event-free survival in correlation to the primary site of tumor (Kaplan–Meier estimate at 10 years) under risk adapted therapy according to the MAKEI 83-96 protocols for non-testicular germ-cell tumors. [1]The prognosis of the intracranial GCT was significantly influenced by the histological differentiation, with the secreting GCT and teratoma having an EFS of 0.65 each. [2]At the sacrococcygeal site the immature teratoma were higher at risk of recurrence (EFS 0.75) compared to secreting GCT (EFS 0.8) and mature teratoma (EFS 0.89), whereas at the ovarian or other extracranial sites an EFS of more than 0.9 could be achieved in both mature and immature teratoma.

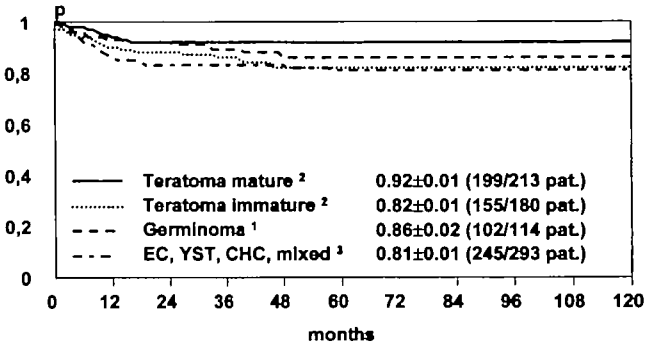

Figure 3. Event-free survival in correlation to the histological differentiation (Kaplan–Meier estimate at 10 years) under risk adapted therapy according to the MAKEI 83-96 protocols for non-testicular germ-cell tumors. [1]Compared to germinoma at other sites (EFS 0.93) the ovarian dysgerminoma had a comparably low EFS of 0.79, as some patients with localized tumors who were treated according to a watch-and-wait strategy relapsed during the follow-up. But all these patients were successfully treated with a cisplatinum chemotherapy. [2]Both mature and immature teratoma had higher relapse rates at the intracranial and sacrococcygeal sites. [3]The prognosis of extracranial secreting tumors was independent of the primary site.

Future perspectives

Central documentation and evaluation of children with GCT has allowed to introduce risk adapted therapy protocols stratified according to a standardized diagnostic work-up including tumor markers, tumor stage and histology. As the complete tumor resection has been established as a valuable prognostic parameter, site-specific surgical standards must be defined. Furthermore,

it has to be determined in how far biological parameters (e.g., specific genetic aberrations) may help to further define distinct risk groups.

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References

1. Göbel U, Haas RJ, Jürgens H. Malignant non-testicular germ-cell tumors. Monogr Paediatr 1999; 18: 327–41.
2. Göbel U, Gutjahr P, Jürgens H et al. Die kooperative Therapiestudie für nichttestikuläre Keimzelltumoen MAKEI83 der GPO: Analyse nach 3 Jahren. Klin Pädiatr 1999; 198: 237–44.
3. Ablin AR, Krailo MD, Ramsay NK et al. Results of treatment of malignant germ-cell tumors in 93 children: A report from the Childrens Cancer Study Group. J Clin Oncol 1991; 9: 1782–92.
4. Göbel U, Calaminus G, Engert J et al. Teratomas in infancy and childhood. Med Pediatr Oncol 1998; 31: 8–15.
5. Haas RJ, Schmidt P, Göbel U et al. Treatment of malignant testicular tumors in childhood: results of the German National Study 1982–1992. Med Pediatr Oncol 1994; 23: 400–5.
6. Mann JR, Raafat F, Robinson K et al. UKCCSG's germ-cell tumour (GCT) studies: Improving outcome for children with malignant extracranial non-gonadal tumours – carboplatin, etoposide, and bleomycin are effective and less toxic than previous regimens. United Kingdom Children's Cancer Study Group. Med Pediatr Oncol 1998; 30: 217–27.
7. Mann JR, Pearson D, Barrett A et al. Results of the United Kingdom Children's Cancer Study Group's malignant germ-cell tumor studies. Cancer 1989; 63: 1657–67.
8. Calaminus G, Bamberg M, Baranzelli MC et al. Intracranial germ-cell tumors: A comprehensive update of the European data. Neuropediatrics 1994; 25: 26–32.
9. Baranzelli MC, Kramar A, Bouffet E et al. Prognostic factors in children with localized malignant nonseminomatous germ-cell tumors. J Clin Oncol 1999; 17 (4): 1212–8.
10. Kapoor G, Advani SH, Nair CN et al. Pediatric germ-cell tumor. An experience with BEP. J Pediatr Hematol Oncol 1995; 17: 318–24.
11. Marina NM, Cushing B, Giller R et al. Complete surgical excision is effective treatment for children with immature teratomas with or without malignant elements: A pediatric oncology group/children's cancer group intergroup study. J Clin Oncol 1999; 17: 2137.
12. Perlman EJ, Cushing B, Hawkins E et al. Cytogenetic analysis of childhood endodermal sinus tumors: A Pediatric Oncology Group study. Pediatr Pathol 1994; 14: 695–708.
13. Bussey KJ, Lawce HJ, Olson SB et al. Chromosome abnormalities of eighty-one pediatric germ-cell tumors: sex-, age-, site-, and histopathology-related differences – a Children's Cancer Group study. Genes Chromosomes Cancer 1999; 25: 134–46.
14. Kaatsch P, Kaletsch U, Michaelis J. Annual Report 1997; German Childhood Cancer Registry. Mainz, Germany: Deutsches Kinderkrebsregister 1998.
15. Heidenreich A, Kuczyk M, Albers P. Molecular pathogenesis and prognostic factors in testicular tumors. Urologe A 1998; 37: 593–608.
16. Mostofi FK, Sobin LH. Histopathological Typing of Testis Tumors. Geneva: World Health Organization 1993.
17. Serov SF, Scully RE. Histological Typing of Ovarian Tumors. Geneva: World Health Organization 1973.
18. Teilum G. Classification of endodermal sinus tumour (mesoblastoma vitellinum) and so-called 'embryonal carcinoma' of the ovary. Acta Pathol Microbiol Scand 1965; 64: 407–29.
19. Gonzalez-Crussi F. Extragonadal Teratomas. Atlas of Tumor Pathology, second series, fascicle 18. Washington, DC: AFIP 1970.
20. Gonzalez-Crussi F, Winkler RF, Mirkin DL. Sacrococcygeal teratomas in infants and children: Relationship of histology and prognosis in 40 cases. Arch Pathol Lab Med 1978; 102: 420–5.
21. Hawkins E, Heifetz SA, Giller R et al. The prepubertal testis (prenatal and postnatal): Its relationship to intratubular germ-cell neoplasia: A combined Pediatric Oncology Group and Children's Cancer Study Group. Hum Pathol 1997; 28: 404–10.
22. Blohm ME, Vesterling-Hörner D, Calaminus G et al. Alpha 1-fetoprotein (AFP) reference values in infants up to two years of age. Pediatr Hematol Oncol 1998; 15: 135–42.
23. Harms D, Jänig U. Germ-cell tumours of childhood. Report of 170 cases including 59 pure and partial yolk-sac tumours. Virchows Arch A Pathol Anat Histopathol 1986; 409: 223–39.
24. Heifetz SA, Cushing B, Giller R et al. Immature teratomas in children: pathologic considerations: A report from the combined Pediatric Oncology Group/Children's Cancer Group. Am J Surg Pathol 1998, 22: 1115–24.
25. Chaganti RS, Houldsworth J. The cytogenetic theory of the pathogenesis of human adult male germ-cell tumors. APMIS 1998; 106: 80–3 (discussion 83–4).
26. Jenderny J, Koster E, Borchers O et al. Interphase cytogenetics on paraffin sections of paediatric extragonadal yolk sac tumours. Virchows Arch 1996; 428: 53–7.
27. Göbel U, Calaminus G, Teske C et al. BEP/VIP in children and adolescents with malignant non-testicular germ-cell tumors. A comparison of the results of treatment of therapy studies MAKEI 83/86 and 89P/89. Klin Pädiatr 1993; 205: 231–40.
28. Schneider DT, Göbel U. Diagnostic value of elevated α_1-fetoprotein and human chorionic gonadotropic hormone in childhood. Tumordiagn Ther 1998; 19: 101–7.
29. Wollner N, Exelby PR, Woodruff JM et al. Malignant ovarian tumors in childhood: Prognosis in relation to initial therapy. Cancer 1976; 37: 1953–64.
30. Mann JR, Pearson D, Barrett A et al. Results of the United Kingdom Children's Cancer Study Group's malignant germ-cell tumor studies. Cancer 1989; 63: 1657–67.
31. Wessalowski R, Kruck H, Pape H et al. Hyperthermia for the treatment of patients with malignant germ-cell tumors: A phase I–II study in 10 children and adolescents with recurrent or refractory tumors. Cancer 1998; 82: 793–800.
32. Dalgleish AG, Woods RL, Levi JA. Bleomycin pulmonary toxicity: Its relationship to renal dysfunction. Med Pediatr Oncol 1984; 12: 313–7.
33. Goldiner PL, Schweizer O. The hazards of anesthesia and surgery in bleomycin-treated patients. Semin Oncol 1979; 6: 121–4.
34. Pratt CB, Meyer WH, Jenkins JJ et al. Ifosfamide, Fanconi's syndrome, and rickets. J Clin Oncol 1991; 9: 1495–9.
35. Schneider DT, Hilgenfeld E, Schwabe D et al. Acute myelogenous leukemia after treatment for malignant germ-cell tumors in children. J Clin Oncol 1999; 17: 3226–33.
36. Bamberg M, Kortmann RD, Calaminus G et al. Radiation therapy of intracranial pure germinoma: Results of the german cooperative prospective trials MAKEI 83, 86, 89. J Clin Oncol 1999; 17: 2585–92.
37. Bouffet E, Baranzelli MC, Patte C et al. Combined treatment modality for intracranial germinomas: Results of a multicentre SFOP experience. Société Française d'Oncologie Pediatrique. Br J Cancer 1999; 79: 1199–204.

38. Calaminus G, Vesterling-Hörner D, Bökkerink JP et al. The prognostic significance of serum alpha 1-fetoprotein in children and adolescents with malignant extracranial non-testicular germ-cell tumors. Klin Pädiatr 1991; 203: 246–50.
39. Rescorla F. Pediatric germ-cell tumors. Semin Surg Oncol 1999; 16: 144–58.
40. Xiao H, Mazumdar M, Bajorin DF et al. Long-term follow-up of patients with good-risk germ-cell tumors treated with etoposide and cisplatin. J Clin Oncol 1999; 15: 2553–8.
41. Bosl GJ. Germ-cell tumor clinical trials in North America. Semin Surg Oncol 1999; 17: 257–62.
42. Stenning SP, Parkinson MC, Fisher C et al. Postchemotherapy residual masses in germ-cell tumor patients: Content, clinical features, and prognosis. Medical Research Council Testicular Tumour Working Party. Cancer 1998; 83: 1409–19.
43. Stephens AW, Gonin R, Hutchins GD et al. Positron emission tomography evaluation of residual radiographic abnormalities in postchemotherapy germ-cell tumor patients. J Clin Oncol 1996; 14: 1637–41.
44. Jennings MT, Gelman R, Hochberg F. Intracranial germ-cell tumors: Natural history and pathogenesis. J Neurosurg 1985; 63: 155–67.

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