

Management of Germ Cell Tumors in Children: Approaches to Cure

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Summary

The introduction of cisplatin chemotherapy and current advances in the surgical treatment have resulted in a dramatic improvement of the prognosis of children with malignant germ cell tumors (GCT). Cisplatin chemotherapy generally results in sufficient systemic tumor control, but local relapses may still occur in patients who did not receive adequate local treatment. Therefore, the therapeutic consideration must take into account age, primary site of the tumor, and its histology. In gonadal tumors, there is a high chance of primary complete resection since these tumors tend to be encapsulated, and particularly testicular GCT are often detected at a low tumor stage. In contrast, a primary complete resection may be impossible in large nongonadal tumors such as sacrococcygeal or mediastinal GCT. In these tumors, a neoadjuvant or preoperative chemotherapy after clinical diagnosis by imaging and evaluation of tumor markers significantly facilitates complete resection on delayed surgery. In addition, the impact of chemotherapy on local tumor control may be enhanced by locoregional hyperthermia. In most intracranial GCT complete resection is impossible and may be associated with significant morbidity. Nevertheless, biopsy is essential for diagnosis in nonsecreting tumors. In intracranial GCT, radiotherapy significantly contributes to local tumor control, and doses are stratified according to histology. These general considerations have been integrated into national and international cooperative treatment protocols. In most current protocols, treatment is stratified according to an initial risk assessment that includes the parameters age, site, histology, stage, completeness of resection and the tumor markers alpha₁-fetoprotein (AFP) and human chorionic gonadotropin (β-HCG). With such modern protocols overall cure rates above 80% can be achieved. Moreover, the previously high-risk groups may now expect a favorable prognosis with this risk-adapted treatment, whereas an increasing number of low-risk patients are treated expectantly or with significantly reduced chemotherapy. As current biologic studies reveal distinct genetic patterns in childhood GCT, it can be expected that further combined clinical and genetic studies will be valuable for risk assessment of childhood GCT.

Zusammenfassung

Mit der Einführung der cisplatinhaltigen Chemotherapie und der Optimierung der chirurgischen Behandlung hat sich die Prognose der malignen Keimzelltumoren (KZT) bei Kindern dramatisch verbessert. Die cisplatinhaltige Chemotherapie resultiert in der Regel in einer guten systemischen Tumorkontrolle. Jedoch können lokale Rezidive auftreten, wenn keine ausreichende lokale Behandlung erreicht wird. Daher müssen die Parameter Alter, primäre Tumorlokalisation und Histologie in den therapeutischen Überlegungen berücksichtigt werden. Bei den meisten gonadalen KZT kann eine komplette Tumorsektion erreicht werden, da diese oft eine Tumorkapsel haben und besonders Hodentumoren zumeist früh erkannt werden. Dagegen ist eine komplette primäre Resektion bei vielen extragonadalen KZT z.B. der Steißbeinregion oder des Mediastinums nicht möglich. Hier erleichtert eine präoperative oder neoadjuvante Chemotherapie nach klinischer Diagnosestellung anhand der radiologischen Befunde und der Tumormarker-Konstellation die komplette Tumorentfernung während der verzögerten Tumorsektion. In besonderen Fällen kann der Effekt der Chemotherapie auf die lokale Tumorkontrolle durch eine lokoregionale Tiefenhyperthermie-Behandlung potenziert werden. Bei intrakranialer Lokalisation ist die komplette Resektion oft unmöglich und teilweise mit schwerwiegenden Komplikationen behaftet. Daher ist bei nichtsezernierenden KZT eine Tumorbiopsie notwendig. Die Radiotherapie, deren Dosis entsprechend der Histologie stratifiziert wird, kann signifikant zur lokalen Tumorkontrolle der intrakranialen KZT beitragen, so dass in ausgewählten Fällen keine Resektion erforderlich ist. Diese allgemeinen Erwägungen werden in nationalen und internationalen kooperativen Therapiestudien berücksichtigt. In den meisten aktuellen Protokollen wird die Therapie risikostratifiziert anhand der Parameter Alter, Lokalisation, Histologie, Stadium, Resektionsstatus und der Tumormarker Alpha₁-Fetoprotein (AFP) und humanes Choriogonadotropin (β-HCG). Innerhalb dieser Studien werden für die Gesamtgruppe Heilungsraten über 80% erreicht. Darüber hinaus konnte die Prognose der früheren Hochrisiko-Gruppen deutlich gebessert werden, während eine zunehmende Zahl von Niedrigrisiko-Patienten nach der Operation ausschließlich nachbeobachtet oder mit deutlich reduzierter Chemotherapie behandelt wird. Da aktuelle molekularbiologische Studien differenzierte genetische Muster bei KZT im Kindes- und Jugendalter aufzeigen, die sich von denen bei KZT im Erwachsenenalter unterscheiden, ist zu erwarten, dass zukünftige kombinierte klinische und genetische Studien für die Risikobeurteilung bei KZT bei Kindern hilfreich sein werden.

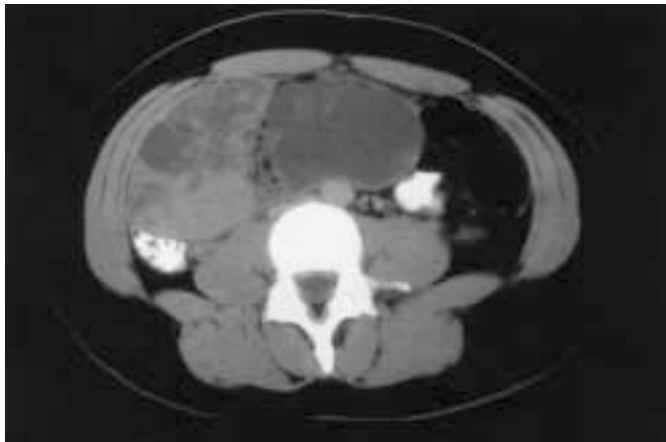


Fig. 1. Computerized tomography of a 16-year-old girl with an ovarian mixed malignant GCT with yolk sac tumor and immature teratoma components (with kind permission of the Institute for Diagnostic Radiology, Heinrich-Heine University, Düsseldorf).

Introduction

The past two decades have been characterized by a dramatic improvement of the prognosis of malignant germ cell tumors (GCT) both in the adult and in the pediatric population. This can mainly be attributed to national and international cooperative therapeutic protocols that utilized cisplatinum-based combination chemotherapy integrated into a multimodal therapeutic approach. Although the first pediatric trials have been designed in the light of the previous experience in malignant testicular GCT in adults, these studies have soon revealed the particular clinical and biological features of childhood GCT. Moreover, the early observations have allowed tailoring therapy more specifically to the pediatric setting and introducing stratification of chemotherapy according to distinct risk groups.

This review summarizes the rapid development during recent years, and describes what should be considered up-to-date therapy of pediatric GCT. Lastly, this article outlines possible future perspectives for treatment stratification that aim for lower short- and long-term toxicity but maintain high overall cure rates.

Epidemiology

In the pediatric age group, malignant GCT contribute 2.9% to the central Tumor Registry of the German Society for Pediatric Oncology and Hematology [1]. In Germany the incidence of malignant GCT is 0.6/100,000 children up to 15 years old. Since teratomas contribute additional 50%, the overall incidence of GCT can be estimated as 0.9/100,000. The distribution of GCT with regard to tumor site and histology varies significantly with age. In neonates mature and immature teratomas predominate. In the first years of life the overall inci-



Fig. 2. Local recurrence of a sacrococcygeal yolk sac tumor with pronounced gluteal swelling.

dence of GCT decreases, but among toddlers the relative proportion of malignant tumors such as 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 at all. Figures 1–5 show typical examples of gonadal and nongonadal GCT.

Histologic Classification of Germ Cell Tumors

GCT are characterized by a profound heterogeneity of their histologic differentiation. They are classified according to the WHO classifications of testicular, ovarian or intracranial tumors [2–4]. In our experience, these classifications constitute a more precise morphologic description than the British classification as they allow outlining all histologic components of mixed malignant GCT. As intratumor heterogeneity may be subtle, the initial diagnostic work-up should include the evaluation by an experienced pediatric pathologist. According to the guidelines of the German GCT protocols, a central histologic evaluation is mandatory in order to achieve a standardized and reliable histopathologic diagnosis and grading.

According to the holistic concept of Teilum [5, 6], GCT arise from totipotent primordial germ cells which are capable of embryonic and extraembryonic differentiation. YST and choriocarcinoma (CHC) follow an extraembryonic differentiation pattern and are characterized by significant secretion of alpha₁-fetoprotein (AFP) and human choriogonadotropin (HCG or β-HCG), respectively (table 1) [7]. Embryonal carcinoma (EC) represent tumors of immature totipotent cells. Teratomas may mimic organ structures of all germ layers. The histologic grade of immaturity of teratoma is defined by the extent of immature (predominantly neuroepithelial) elements [8]. Finally, germinomatous tumors (synonyms: seminoma



Fig. 3. Sagittal magnetic nuclear resonance tomography of an 18-month-old-boy with a sacrococcygeal yolk sac tumor showing small extrapelvine and large intrapelvine tumor components and pronounced tumor extension into the spinal canal (with kind permission of Dr. May, Dr. Rausch, Diagnostic Radiologists, Düsseldorf).

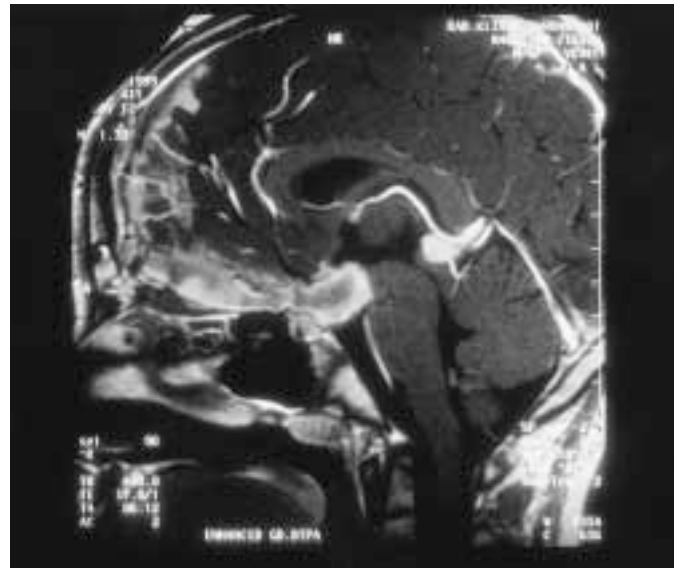


Fig. 5. Sagittal magnetic nuclear resonance tomography of an 12-year-old girl with an intracranial germinoma showing two tumor foci at the pineal and suprasellar region (with kind permission of the Institute for Diagnostic Radiology, Inner City Medical Center, Ludwig-Maximilians University, Munich).

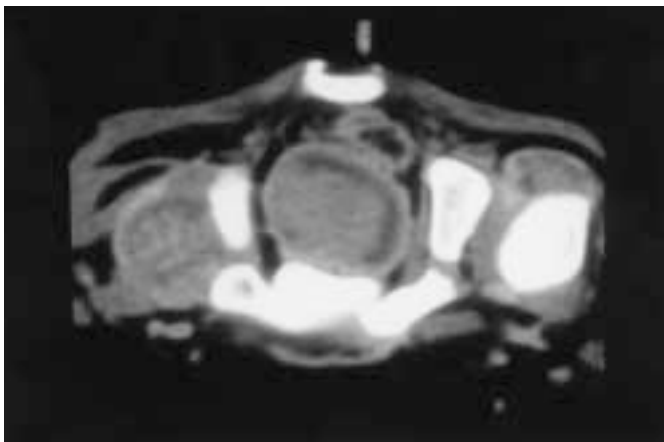


Fig. 4. Computerized tomography of a 4-month-old girl with a vaginal yolk sac tumor (with kind permission of the Institute for Diagnostic Radiology, Heinrich-Heine University, Düsseldorf).

(testis), dysgerminoma (ovary), germinoma (brain)) display morphological features of undifferentiated germ epithelium. In contrast to testicular GCT of adult patients, pediatric GCT do not develop from carcinoma in situ [9].

In most patients, the response to the different therapeutic modalities can be predicted from the histologic appearance and the tumor marker profile (table 1). About 25% of all pediatric GCT present as tumors with more than one histologic type. In this situation therapy and prognosis depend on the component with the highest malignancy.

Tumor Markers

The tumor markers AFP and/or β -HCG are helpful for clinical diagnosis in tumors that present at a typical localization (table 1) [7]. However, it has to be considered that serum AFP may be excessively elevated in neonates and infants [10]. Therefore, in the first 2 years of life only AFP levels significantly above the age-related normal value can be regarded as diagnostic for a secreting GCT. In general, the tumor marker profile is highly specific for the histologic differentiation of the tumors (table 1). However, there may be a secretion of β -chains of HCG in seminoma/germinoma (<50 IU/l) related to syncytiotrophoblast-like giant cells. Some patients with immature teratoma may show a moderate elevation of the AFP level (<100 μ g/l), sometimes associated with histologically detectable small foci of YST within the teratoma [11].

Biology

Molecular studies of the imprinting status of GCT revealed that gonadal and nongonadal GCT share a common cellular origin, the primordial germ cell although at different stages of their development [12–14]. These data substantiate the hypothesis that nongonadal GCT develop from germ cells that have mislocated during their embryonic development.

Pediatric GCT show a pattern of cytogenetic aberrations different from their adult counterparts. More than 80% of adult malignant GCT display a distinct and specific chromosomal aberration, the isochromosome 12p [15]. The remaining

Table 1. Biological characteristics of the histologic germ cell tumor subentities

	Histological grading	Tumor markers		Sensitivity to	
		AFP	β -HCG	chemotherapy	radiotherapy
Seminoma/germinoma	malignant	–	(+)	+++	≥ 24 Gy
EC	malignant	–	–	+++	≥ 45 Gy
YST	malignant	+++	–	+++	≥ 45 Gy
CHC	malignant	–	+++	+++	≥ 45 Gy
Teratoma, mature/immature	benign/potentially malignant	–/(+)	–	?	?

isochromosome 12p-negative tumors frequently show amplification of 12p (homogeneously staining regions or tandem repeats). These aberrations have been observed in both testicular and ovarian tumors and in mediastinal GCT.

In children younger than 10 years an isochromosome 12p has been found only in a small minority of malignant GCT [16, 17]. On the other hand, aberrations at both the short and the long arm of chromosome 1, at the long arm of chromosome 6 and of the sex chromosomes have been found frequently [16]. Lastly, virtually all prepubertal teratomas are normal on conventional cytogenetic analysis or on comparative genomic hybridization [17–19].

Therapy

The Pre-Platinum Era

Until 1980, the prognosis of children with malignant GCT was poor, and outcome was determined by the parameters age, site, histology and stage. Only low-stage testicular YST in children younger than 2 years and ovarian dysgerminoma had a more favorable prognosis after radical resection [20–23].

The introduction of adjuvant chemotherapy with vincristin, actinomycin D, and cyclophosphamide (VAC) in the 1960s constituted a first and important step towards cure as for the first time lasting complete remissions were achieved in a significant proportion of patients [24–26]. However, the cure rates in nonseminomatous GCT were still unsatisfactory as a result of relapses during the first 2 years of follow-up.

Cisplatinum Chemotherapy

The modern era of GCT chemotherapy began in the mid 1970s with the identification of the efficacy of cisplatinum in testicular GCT. In 1977, Einhorn and Donohue [27] reported a complete response rate of 85% in patients with metastatic testicular GCT with a combination of cisplatinum, vinblastin, and bleomycin (PVB) after tumor resection. Most importantly, the overall good response was also translated into durable

remissions. Nevertheless, relapses or refractory cancers – although rare – established the need for second-line therapies, and etoposide soon emerged as an active drug with a single-agent efficacy superior to vinblastin [28]. In addition, the efficacy of ifosfamide in cisplatinum-refractory GCT has been documented. The combination of cisplatinum with etoposide and ifosfamide for recurrent testicular GCT results in a 30% durable remission rate and can now be considered standard relapse treatment [29].

In relapsing and refractory GCT, the therapeutic value of high-dose chemotherapy with autologous stem cell transplantation has been investigated. These analyses have shown only limited efficacy in prognostically unfavorable tumors such as cisplatinum-resistant, mediastinal GCT with high β -HCG or multiple relapses [30]. Nevertheless, in some patients introduction of high-dose chemotherapy into first-line treatment of high-risk tumors may be beneficial [31]. Lastly, ‘modern’ drugs such as paclitaxel and gemcitabine are currently under investigation.

Development of Cooperative Protocols for Pediatric GCT

Encouraged by the data discussed above, prospective pediatric protocols for gonadal and nongonadal GCT were initiated. The first published trial was conducted by the US Children’s Cancer Group (CCG) and included 54 children with malignant nonseminomatous GCT. Patients underwent initial resection followed by VAC + PVB chemotherapy over a 2-year period [32]. 15 of 20 evaluable patients with ovarian nonseminomatous GCT achieved complete remission. The prognosis of children with nongonadal GCT was worse (complete remission in 10/18 patients) but still encouraging compared to all other previous studies.

The consecutive CCG protocol included 93 children and confirmed the previous observation that gonadal GCT were more favorable than nongonadal GCT (4-year event-free survival (EFS) rates 63% vs. 42%) [33]. This difference was mainly attributed to a higher rate of complete resections in gonadal tumors.

In the consecutive US Intergroup protocol, the therapeutic impact of cisplatin dose intensification at 200 mg/m²/cycle was evaluated. The interim analysis and the analysis of sacro-coccygeal GCT reveal that cisplatin escalation may increase the therapeutic efficacy, however at an apparently higher renal and auditory toxicity [34, 35].

The analysis of the UKCCSG (United Kingdom Children's Cancer Study Group) study on malignant germ cell tumors registered between 1979 and 1987 [36] included several chemotherapy regimens: Low-dose VAC treatment was seen to be ineffective (EFS rate 8%). The PVB combination (days 2, 9, 16) caused unacceptable pulmonary toxicity due to bleomycin, whereas the combination of bleomycin (day 1 only), etoposide and cisplatin (BEP) showed superior results with no proven pulmonary complication (EFS rate 84%). Further analysis and comparison of different regimens of the UKCCG GC I and GC II protocols also demonstrated the high efficacy of platinum-based regimens such as BEP and JEB (carboplatinum (600 mg/m²/cycle), etoposide, bleomycin) that resulted in a 5-year EFS rate of 57% and 87% in nongonadal GCT, respectively [37]. The recent analysis of the UKCCG GC II study underscores the high efficacy of the JEB regimen that resulted in a 5-year EFS rate of 88% [38].

The French study group first reported 35 children with ovarian and nongonadal advanced-stage GCT treated with a VAC + PB regimen (2-year survival rate 63%) [39]. In the consecutive TGM 90 protocol, cisplatin was replaced by carboplatinum (400 mg/m²/cycle) [40, 41]. This regimen produced less favorable results than the British JEB regimen that used higher single and cumulative doses of carboplatinum. In the current French protocol, alternating combinations of cisplatin with etoposide or ifosfamide are administered, resulting in superior response compared to the previous carboplatinum-based strategy.

In both the French TGM 90 and the British GC II studies, the analysis of prognostic factors revealed the impact of high AFP serum levels at diagnosis, a finding that could not be confirmed by other studies that used a cisplatin-based regimen [42, 43] as well as the ongoing French protocol.

From 1982 on, the German protocols for testicular (MAHO) and nontesticular (MAKEI) GCT included cisplatin- and etoposide-based regimens integrated into a multimodal approach that included delayed resection after preoperative or neoadjuvant chemotherapy for advanced tumors [42–47]. As a consequence of the excellent EFS rates above 80% achieved with the first protocols, cumulative chemotherapy was stepwise reduced from 8 cycles to 6 and currently to 4–5 cycles. This reduction of cumulative chemotherapy did not affect outcome [42, 43].

In summary, the regimens PEI (cisplatin, etoposide and ifosfamide), BEP, CarboPEI (carboplatinum, etoposide and ifosfamide), and JEB have a synergistic cytotoxic activity and can be regarded as standard regimens with comparable efficacy that are applied in currently open pediatric GCT protocols.

Side Effects of Chemotherapy

Pulmonary toxicity of bleomycin appears to be particularly problematic in combination with impaired kidney function [48] or under anesthesia [49]. As a consequence, regimens such as PEI that excluded bleomycin were evaluated. The highly efficient combination PEI is associated with higher myelosuppression and bears the risk of tubular nephropathy [50]. In our experience with this regimen, we observed clinically apparent hearing impairment in approximately 20% of patients. Although auditory and renal toxicity of the carboplatin regimen are smaller, carboplatin at effective doses (600 mg/m²/cycle) bears a substantial myelotoxicity [38]. The risk of therapy-related secondary leukemia is dependent on the applied therapeutic modalities with an estimated cumulative risk of 1.0% (3/442 patients, Kaplan-Meier method at 10-year follow-up) for children treated with surgery and chemotherapy only and 4.2% (3/174 patients) for children treated with combined radio- and chemotherapy [51]. Nevertheless, the risk-benefit analysis still favors the use of etoposide in first-line treatment because of its excellent cytostatic effect in childhood GCT.

Therapeutic Strategies of the International SIOP CNS GCT 96 Protocol and the Currently Open German Protocols for Extracranial Germ Cell Tumors

The general therapeutic strategy may vary between different protocols. Some protocols stratify the cumulative chemotherapy according to the response to treatment (e.g. one standard chemotherapy regimen to a total of 2 cycles after complete remission [37, 38]). In other protocols, therapy is stratified according to initial diagnostic parameters. In the following sections, the SIOP CNS GCT 96 protocol and the German protocols for extracranial GCT and their risk-adapted therapeutic strategies are summarized.

SIOP CNS GCT 96 Protocol on Malignant Intracranial GCT

Therapy for malignant intracranial GCT is stratified according to the histologic differentiation (i.e. germinoma vs. malignant nongerminomatous GCT) and stage. The ongoing SIOP CNS GCT protocol evaluates two therapeutic options in intracranial germinoma with regard to both their therapeutic impact and their specific acute and long-term toxicity. For malignant nongerminomatous intracranial tumors, the effect of combined treatment with PEI and risk-adapted radiotherapy is examined.

In germinoma (fig. 5), which account for 50% of all intracranial GCT and do not secrete significant amounts of β -HCG, histologic sampling is mandatory. According to the current SIOP CNS GCT 96 protocol, patients can be treated either

with craniospinal irradiation with 24 Gy and tumor boost of 16 Gy or with a multimodal treatment including two cycles of chemotherapy (CarboPEI) followed by focal irradiation (40 Gy). With radiotherapy only, a 5-year EFS rate of 91% and 5-year overall survival rate of 94% can be achieved [52]. With the combined chemo- and radiotherapy approach, a 3-year relapse-free survival rate of 96% and an overall 3-year survival rate of 98% have been reported. However, it should be considered that in this study 2 of the 4 observed events occurred after the evaluated 3-year observation period [53]. Lastly, strategies that excluded radiotherapy have not resulted in sufficient tumor control [54].

Malignant nongerminomatous intracranial GCT (YST, CHC, EC) have an inferior prognosis compared to germinoma. In these patients 4 cycles of PEI are applied, followed by delayed resection and radiotherapy. Radiotherapy is stratified according to initial staging. Nonmetastatic tumors receive focal irradiation (54 Gy), whereas patients with intracranial or spinal metastases or tumor cells in the cerebrospinal fluid receive craniospinal irradiation (30 Gy plus 24 Gy tumor boost). The meta-analysis of several cooperative protocols suggests that a long-term remission can be obtained in about two thirds of patients [55]. Again, strategies that exclude radiotherapy yield inferior results [54].

MAHO and MAKEI Protocols on Extracranial Malignant GCT

Surgical Treatment

Both gonadal and extragonadal GCT are treated according to a similar therapeutic concept: Only in small tumors with no evidence of invasive growth beyond the organ of origin or of metastases, primary resection is recommended. In patients with bulky, invasive or metastatic tumors, a preoperative chemotherapy followed by delayed resection is preferred to avoid incomplete resection. The decline of the tumor markers according to their serum half-lives indicates for a favorable response to chemotherapy [7, 10, 56].

Resection is considered complete if performed as en-bloc resection of the tumor including the adjacent organ of origin. The resection margins must be histologically free of tumor cells. In testicular tumors, a high inguinal orchidectomy is mandatory, and tumor biopsy is obsolete. Ovarian tumors (fig. 1) must be resected including ovary and Fallopian tube. In coccygeal tumors (fig. 2, 3) the complete en toto resection including the whole coccyx is essential [42, 57]. Additional attention should be paid to potential extension of the tumor into the spinal canal, which can be recognized on nuclear magnetic resonance tomography (fig. 3). In this situation, preoperative chemotherapy is advisable. A recently published review summarizes the standard surgical procedures in gonadal and extragonadal GCT in detail [58]. The rare vaginal YST of infancy (fig. 4) constitute the only exception as these very

chemosensitive tumors may also be cured without – according to oncologic standards – radical resection [59].

In patients with residues after initial tumor resection, second-look surgery is essential. Second-look surgery may at least partly overcome the otherwise unfavorable prognostic impact of incomplete resection [42, 43]. In general, there is no role for debulking surgery in pediatric GCT. Usually, surgery of metastases is not indicated unless they show insufficient response to chemotherapy [42, 46, 60].

Adjuvant Treatment

According to the MAHO 98 protocol for testicular GCT, patients with stage IA mature teratoma or YST are treated expectantly. All other patients receive 2–3 cycles PVB (\leq stage IIB) or the more intensive BEP (stages IIC–IV). PEI is reserved to salvage therapy in patients with relapsing or poorly responding tumors.

In the current MAKEI 96 protocol, patients with completely resected stage T1 tumors are treated according to a watch-and-wait strategy which includes frequent (weekly) controls of the relevant tumor markers. Completely resected stage T2 tumors receive 2–3 cycles of a two-agent regimen (PE). A three-agent combination is applied after incomplete resection (PEI) [61]. Ovarian dysgerminoma are treated according to the same strategy. Irradiation is omitted to preserve fertility.

Teratoma

Teratomas represent a distinct histologic entity that shows a significant diversity of the clinical course in dependence of the histologic grade of immaturity [8, 57]. Mature teratomas are considered benign tumors, whereas immature teratomas may show clinical features of malignancy. Surgical treatment should follow the same principles as outlined above for malignant GCT.

The risk of recurrence can be estimated from the following parameters: primary site of the tumor, histologic grade of immaturity, and completeness of the tumor resection [57].

The role of adjuvant chemotherapy has not yet been established. However, recent reports have shown that chemotherapy may not be indicated after complete resection, even in the presence of small foci of YST [57, 62]. Incompletely resected tumors have a 10% risk of relapse in mature and a 20% risk in immature teratomas [57]. Half of the recurrent tumors may display YST or EC histology. Adjuvant chemotherapy did not reduce the risk of recurrence. However, no malignant relapses have been seen after previous chemotherapy.

Follow-Up

Complete clinical remission is defined as normalization of tumor markers within the age-related normal range and the absence of suspicious residual structures. If any of these criteria are not fulfilled, a diagnostic re-evaluation and – if neces-

sary – change or intensification of treatment is urgently indicated. Most relapses occur within the first 2 years after diagnosis. However, in some patients late recurrences 5 years or later after diagnosis have been observed. 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 early during follow-up. In watch-and-wait patients, the decline of the AFP values must be evaluated with regard to its serum half-life of approximately 6–7 days. Especially in infants younger than 2 years, the interpretation of AFP may be difficult due to the physiologically elevated serum levels. In this context, it has been proven helpful to compare the AFP decline to the age-related reference values in neonates and infants [10]. A retarded decline or a secondary rise of the AFP levels strongly indicates for incomplete tumor resection or a recurrence of YST [7].

In addition, follow-up must include repeated imaging of the primary site of tumor. In case of residual structures after chemotherapy of extracranial GCT, resection is indicated since mature teratoma may have remained and bear the risk of tumor progression [63]. In our experience, positron emission tomography examinations have not been proven useful in this situation as these cannot distinguish between mature teratoma and residual necrosis or scars [64].

In intracranial tumors, repeated endocrinologic examinations at diagnosis and during follow-up are mandatory since especially tumors of the suprasellar region can be associated with diabetes insipidus or panhypopituitarism. In children treated with cisplatin and/or ifosfamide, the renal function has to be monitored carefully for tubular nephropathy. In children, a prolonged phosphaturia may lead to renal rickets with consecutive growth retardation while adolescents are at risk of renal osteomalacia [50]. These long-term sequelae can be avoided by supplementation of phosphate. Further attention should be drawn to the risk of therapy-related secondary leukemia that depends on treatment intensity and modality.

Relapse Treatment

In patients with recurrent or refractory tumors who had previously been treated with a non-platinum or carboplatin therapy, cisplatin-based regimens (preferably PEI) have been applied successfully [40, 61]. Therefore, we prefer cisplatin-containing regimens in patients with relapsed tumors if the organ toxicity related to the previous treatment allows further cisplatin therapy. On the other hand, patients with severe cisplatin-related toxicity may be treated with a combination of carboplatin and high-dose etoposide (at 400–600 mg/m² on 3 days). In our experience, high-dose chemotherapy with stem cell support, as it has been applied in adult patients [61], resulted in long-term remissions only in

those patients in whom a clinical complete remission could be achieved prior to high-dose chemotherapy [60]. Therefore, we would tend to reserve high-dose chemotherapy to consolidation treatment.

In our experience, more than 90% of relapses occur at the primary site of the tumor. For example, in our series of 104 sacrococcygeal YST only 2 patients had distant recurrences, whereas 17 patients had local and 3 patients combined local and distant relapses [60]. 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 recurrences and poor response to conventional chemotherapy may benefit from locoregional hyperthermia combined with platinum-based chemotherapy. This approach significantly enhanced local tumor control [60, 65, 66]. However, the analysis of recurrent sacrococcygeal GCT underscored the need to implement hyperthermia early as in late relapse situations hyperthermia showed no beneficial effect, probably as a result of cisplatin resistance or delayed chemotherapy due to myelotoxicity of the previous treatment [60]. Lastly, high-dose local irradiation at doses above 45 Gy has shown some beneficial effects after incomplete resection of the tumor recurrence, whereas irradiation at lower doses was ineffective [60].

As 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 further improvement of local therapy.

Future Perspectives

A multimodal approach that utilizes cisplatin/etoposide chemotherapy as well as tumor resection is highly effective for the treatment of pediatric GCT. In the light of the high cure rates achieved by current protocols, research must now focus on new aims. First, treatment must be further intensified in those patients with cisplatin-refractory or poorly responding tumors. The US study group evaluates a further dose escalation of cisplatin under protection with amifostine as a 200 mg/m²/cycle cisplatin dose yielded a small but significant survival advantage compared to a 100 mg/m²/cycle dose. However, results regarding toxicity are still pending. Furthermore, results of alternative high-dose chemotherapy studies in recurrent GCT have to be awaited. Locoregional hyperthermia constitutes an attractive alternative as cisplatin represents a very good thermosensitizer and hyperthermia may therefore overcome cisplatin resistance [60, 65, 66]. In addition, locoregional hyperthermia should hopefully result in less systemic side effects than cisplatin dose escalation.

On the other hand, patients should be identified that are only at a low risk of relapse and in whom adjuvant chemotherapy can either be withheld or significantly reduced, thus allowing

to minimize the impact on short- and long-term quality of life and treatment toxicity.

In this context, molecular genetic studies may also reveal some important information that may be utilized for risk stratification. For example, in mediastinal GCT, genetic analysis distinguishes two distinct genetic profiles by age that may correlate with a poor (adults) or favorable (infants) prognosis [19].

In conclusion, in the future clinical and molecular biologic information may allow distinguishing low-risk from high-risk patients accurately and thereby allow designing a multimodal approach to the individual patient.

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