Management of Germ Cell Tumors in Pediatric Patients

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KEYWORDS

- Germ cell tumor • Pediatric • Adolescent • Teratoma • Surgery

KEY POINTS

- Optimal surgical treatment for germ cell tumors involves intact resection of the tumor without rupture or spillage while sparing vital structures whenever possible.
- If upfront surgical resection is not possible, would require resection of adjacent organs, and/or would result in unacceptable morbidity, biopsy and chemotherapy should be pursued as an initial strategy.
- Appropriate staging involves both radiographic and intraoperative assessment and is critical for determining needed treatment.
- Platinum-based chemotherapy is used for all malignant germ cell tumors, except for stage I ovarian or testicular germ cell tumors, for which a strategy of observation may be undertaken.
- Future efforts will focus on how to safely decrease the intensity of therapy for low-risk tumors and improving surveillance and treatment for relapsed or refractory disease.

INTRODUCTION

Germ cell tumors (GCT) arise from primordial germ cells and vary widely in their clinical behavior, histology, and locations. The majority of GCTs will develop in the gonads or along the midline structures of the body.[1] Genetic aberrations leading to disruption in the molecular signaling responsible for primordial germ cell migration early in development may provide rationale for why GCTs originate in extragonadal locations.[2]

Because GCTs are often managed by different specialists with outcomes heavily influenced by factors such as patient age and tumor location, variation in their management is common. Thus, establishing best practices for the treatment of pediatric GCTs remains an area of active investigation. Recent advances and current efforts have focused on limiting the toxicities of therapy, identifying new therapies for relapsed and refractory tumors, defining the best practices for surgical staging and

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resection, and developing novel methods to monitor for disease relapse. Owing to the rarity of pediatric GCTs, the establishment of multidisciplinary, multi-institutional, and multinational collaboratives has been vital for the study of such efforts.[3]

Herein we review the current concepts that are essential for the successful management of extracranial GCTs developing in children and young adults. Areas of controversy, treatments remaining under active investigation, and scenarios where treatment may vary for children and young adults are highlighted.

EPIDEMIOLOGY

Pediatric GCTs are rare, with an estimated incidence of 11.7 and 6.7 per million among boys and girls, respectively.[4] Although uncommon, GCTs account for approximately 3% of tumors occurring in children under the age of 15, and approximately 14% of tumors among children and young adults ages 15 to 19 years.[2,5] Benign, mature teratomas (MT) represent the most common histology, with the incidence of malignant GCTs varying based on age, sex, and location.

Although most individuals developing GCTs have no known predisposing risk, several conditions associated with an increased risk have been identified. Males with cryptorchidism or Klinefelter's syndrome are at an increased risk for the development of testicular and mediastinal GCTs.[6] Females with Turner's syndrome carry an increased risk for development of ovarian GCTs.[7] Individuals with gonadal dysgenesis syndromes are also at an increased risk for developing GCTs, particularly gonadoblastoma, in streak gonads.[8] An increased incidence of GCTs observed to occur among some families also points to the possibility of heritable genetic risk factors, and the identification of these risk factors remains a subject of ongoing research.[9]

CLASSIFICATION

GCTs arise from pluripotent primordial germ cells. The extent and mode of cellular differentiation that has occurred at the point of tumorigenesis serves as the basis for the categorization of the various histologic subtypes (**Fig. 1**). For clinical purposes, GCTs are commonly classified according to **Box 1**.

MTs are characterized by the presence of well-differentiated tissue derived from ectodermal, mesodermal, and/or endodermal germ layers. The clinical behavior of MTs is generally benign, such that surgical extirpation is the only treatment required. Rare cases of malignant degeneration of tissues within MTs have been described in adults. Immature teratomas (IT) contain immature neuroepithelium and are graded
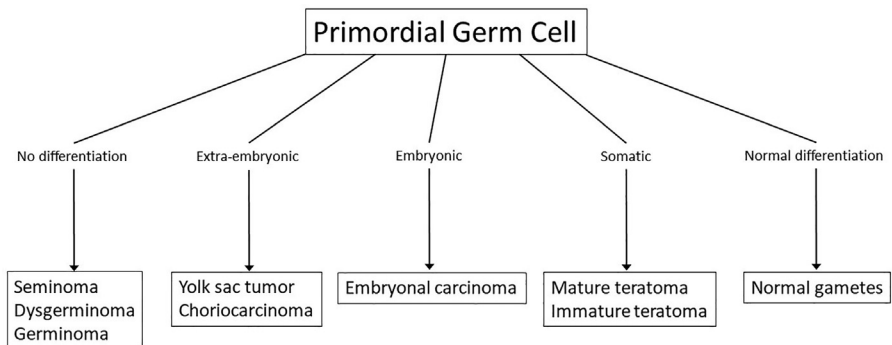

Fig. 1. Development of GCTs from the primordial germ cell.

> **Box 1**
> **Classification of GCTs**
>
> Teratomas
>   Mature
>   Immature
>
> Malignant GCTs
>   Germinomatous GCTs
>   Seminoma (testicle)
>   Dysgerminoma (ovary)
>   Germinoma (extragonadal)
>   Nongerminomatous GCTs
>   Yolk sac (endodermal sinus) tumor
>   Choriocarcinoma
>   Embryonal carcinoma
>   Gonadoblastoma
>
> Mixed GCTs
>   Different histologies present within the same tumor

as I, II, or III based on the degree of immaturity. Among adult practitioners, ITs are considered malignant owing to their propensity for local recurrence and local and distant spread.

Malignant GCTs are subdivided into germinomatous and nongerminomatous subtypes ("seminomatous" and "nonseminomatous" are synonymous). Germinomatous GCTs are rare in young children, but their incidence increase among teenagers and young adults. Nongerminomatous tumors, particularly yolk sac tumors, are the most common malignant GCTs occurring before puberty. Gonadoblastomas are rare and can transform to become GCTs of other histologies. They occur almost exclusively in the streak gonads of individuals with disorders of sexual development and such a disorder should be suspected when the diagnosis of gonadoblastoma is made.[8] It is common for tumors to exhibit mixed histologies, with more than 1 malignant GCT type present with or without the presence of a teratoma as well. Somatic malignancies can also develop from within a GCT and should be suspected when tumors are not responding to therapy as anticipated.

ROLE OF TUMOR MARKERS

GCTs secrete substances that are detectable in the systemic circulation, the 2 most relevant being alpha fetoprotein (AFP) and β-hCG (**Table 1**). AFP is elevated in the serum of an estimated 95% to 100% of patients with yolk sac tumors. The measurement of serum AFP is informative during the initial workup for a suspected GCT, for surveillance, and to assess the response to therapy.[10] One exception is in the context of a suspected GCT occurring in infants, for whom serum AFP levels are difficult to interpret because of the marked elevation from the time of birth until its eventual decrease to adult ranges throughout the first 2 to 3 years of life.[11] In addition to its role at diagnosis, the rate of AFP decline after the initiation of therapy is an important prognostic indicator and may provide guidance with respect to the need for therapeutic intensification.

β-hCG is a placental protein that can be elevated in the serum of patients with choriocarcinoma. It is more rarely, and less markedly, elevated in the context of embryonal and germinomatous tumors. It is also useful in the initial workup and surveillance of GCTs, and its rate of decline may hold prognostic value during the course

Table 1
Serum tumor marker levels for pediatric GCTs

GCT Type	AFP	β-hCG	LDH
MT	-	-	-
IT	+/−	-	+/−
Seminoma/dysgerminoma	-	-	+
Yolk sac tumor	+	-	-
Choriocarcinoma	-	+	-
Embryonal carcinoma	+	+	+/−

+ usually elevated; +/− may be elevated; - usually not elevated.

of treatment for germinomatous tumors in adults.[12] Last, lactate dehydrogenase, although less specific than either AFP or β-hCG, is also useful in the initial diagnosis and surveillance of GCTs, particularly germinomatous tumors.

STAGING AND RISK GROUPS

Pediatric GCTs are staged according to the Children's Oncology Group (COG) system (**Table 2**).[13] Distinct adult staging systems for gonadal GCTs also exist and include the International Federation of Gynecology and Obstetrics for ovarian malignancies, and the American Joint Committee on Cancer system for testicular malignancies.

Risk groups for pediatric GCTs have been developed based on factors known to influence outcomes. The current system was developed with international collaboration between COG and the UK Children's Cancer and Leukemia Group as a part of the Malignant Germ Cell International Collaborative (MaGIC) (**Table 3**).[14] The MaGIC risk stratification schema identifies which pediatric patients with GCT may be appropriate to receive reduced therapy and who may require an intensification of therapy based on historical outcomes. In this regard, it is expected to inform treatment recommendations for future clinical trials.

MEDICAL THERAPY

Platinum-based chemotherapy serves as the backbone for the medical treatment of pediatric and adult GCTs.[15] Bleomycin, etoposide, and cisplatin are administered as the standard regimen for adult GCTs. The regimen has been adapted for the treatment of pediatric GCTs by including a reduced dose of bleomycin and is commonly referred to as "PEb."[16] Owing to the pulmonary toxicity of bleomycin and ototoxicity and other toxicities of cisplatin, both adult and pediatric studies have examined the role of alternative agents and dose reduction strategies.[17] Recent experience in children suggests, for instance, that carboplatin may be substituted for cisplatin leading to reduced toxicity while maintaining similar event-free survival rates and overall survival rates.[18,19]

A recognition that most children with GCTs experience excellent overall survival has led to a decrease in the amount of chemotherapy given.[14] Historically, chemotherapy was recommended for all malignant GCTs. Studies have shown, however, that stage I gonadal GCTs can be successfully treated with surgery and observation alone, with many patients requiring no further therapy, and those experiencing relapse nearly always being successfully salvaged with chemotherapy.[20,21] As such, observation alone after complete surgical staging and resection may be appropriate for children with

Table 2
COG staging system for pediatric GCTs

Stage	Testis	Ovary	Extragonadal
I	Complete resection via orchiectomy. Lymph nodes negative.	Limited to ovary (with negative evaluation of peritoneum), no evidence of extraovarian disease	Complete resection at any site with negative margins (including coccygectomy for sacrococcygeal teratomas)
II	Trans-scrotal biopsy performed, microscopic disease in scrotum or cord, failure of tumor markers to normalize	Microscopic residual disease, peritoneal evaluation negative, failure of tumor markers to normalize	Microscopic residual disease with negative lymph nodes, failure of tumor markers to normalize
III	Retroperitoneal lymph node involvement without visceral or extra-abdominal involvement	Lymph node involvement, metastatic nodule, gross residual disease, or biopsy only, contiguous visceral involvement (omentum, bladder, intestine), peritoneal evaluation positive	Lymph node involvement, gross residual disease, biopsy only
IV	Distant metastases	Distant metastases	Distant metastases

Data from Rescorla F, Billmire D, Stolar C, et al. The effect of cisplatin dose and surgical resection in children with malignant germ cell tumors at the sacrococcygeal region: a pediatric intergroup trial (POG 9049/CCG 8882). *J Pediatr Surg*. 2001;36(1):12-17.

stage I malignant gonadal GCTs. Otherwise, PEb is recommended for intermediate and poor risk GCTs (stage I extragonadal outside of a clinical trial and all stage II–IV disease).

Medical therapy for IT is controversial. Platinum-based chemotherapy was historically administered, with early adult studies noting higher rates of relapse among women with grades 2 and 3 ovarian ITs who did not receive chemotherapy.[22] As such, the administration of bleomycin, etoposide, and cisplatin chemotherapy for all grades 2 and 3 IT is commonly recommended by adult practitioners. For children, it has long been recognized that outcomes for IT are excellent without chemotherapy.[23] Among pediatric practitioners, it is now generally accepted that ITs are largely unresponsive to chemotherapy and its use has fallen out of favor.[23,24]

GENERAL PRINCIPLES IN THE SURGICAL MANAGEMENT OF PEDIATRIC GERM CELL TUMORS

Surgery is a key component in both the treatment and staging of pediatric GCTs. During the initial workup, ultrasound examination, computed tomography (CT) scans, or MRI may be useful for imaging the primary tumor. Both cystic and solid components may be appreciated. CT scans or MRI are then generally necessary to evaluate the primary tumor. The presence of fat and calcium, often present in MTs and mixed GCTs, may be appreciated on CT scans and MRIs. It must be emphasized that, although the presence of cystic components, calcium, and fat are frequently identified on diagnostic imaging for MTs, these features can frequently be seen in mixed and other malignant GCTs, so the diagnosis of MT must not be assumed given these findings (**Fig. 2**).

As a part of the staging process for ovarian, testicular, sacrococcygeal, and retroperitoneal GCTs, abdominal and retroperitoneal imaging via CT scan or MRI is

Table 3
Proposed MaGIC pediatric GCT risk stratification system

Risk Group	Age (y)	Location	COG Stage	Survival (%)
Low	Any age	Testis	I	100
	Any age	Ovary	I	96
	Any age	Extragonadal	I	93
Standard	<11	Testis	II/III	99
	<11	Testis	IV	96
	≥11	Testis	II/III	93
	≥11	Testis	IV	83
	<11	Ovary	II/III	97
	<11	Ovary	IV	92
	≥11	Ovary	II/III	85
	<11	Extragonadal	II/III	91
	<11	Extragonadal	IV	79
Poor	≥11	Testis	IV	83
	≥11	Extragonadal	III	61
	≥11	Ovary	IV	60
	≥11	Extragonadal	IV	40

Adapted from Frazier AL, Hale JP, Rodriguez-Galindo C, et al. Revised risk classification for pediatric extracranial germ cell tumors based on 25 years of clinical trial data from the United Kingdom and United States. J Clin Oncol. 2015;33(2):195-201.

necessary to evaluate for signs of intraperitoneal spread and/or retroperitoneal lymphadenopathy. Chest imaging is indicated to rule out pulmonary metastases. When feasible and when the expected morbidity is minimal, upfront surgical resection for all GCTs is preferable. If a tumor is deemed unresectable or resection would be associated with unacceptable morbidity, a preoperative biopsy and the establishment of venous access for chemotherapy is most appropriate, followed by definitive surgical resection when appropriate.

SURGICAL MANAGEMENT OF PEDIATRIC OVARIAN GERM CELL TUMORS

The optimal operation for ovarian GCTs involves a complete resection of the tumor without rupture or spillage and performance of complete peritoneal staging.[20] Rupture or spillage will result in upstaging and may necessitate the addition of chemotherapy that might have otherwise been avoided. If complete resection of the tumor would require en bloc removal of any organ other than the ipsilateral ovary and fallopian tube, a biopsy should be performed and resection should be postponed until after the administration of neoadjuvant chemotherapy.

For suspected malignant GCTs, resection via ipsilateral oophorectomy is the operation of choice. If uninvolved, the fallopian tube can be preserved. If an MT is suspected in the setting of negative serum tumor markers, an ovarian-sparing approach should be pursued whenever possible. This factor is especially relevant, considering that the development of metachronous lesions on the contralateral ovary can occur in an estimated 8% to 10% of patients.[25] If an ovarian-sparing operation is performed and the diagnosis of IT is ultimately rendered, completion oophorectomy has traditionally been recommended, although some investigators would advocate instead for close surveillance.

The performance of complete intraperitoneal staging is of vital importance. Failure to do so may result in an inability to assign stage I and the need for chemotherapy
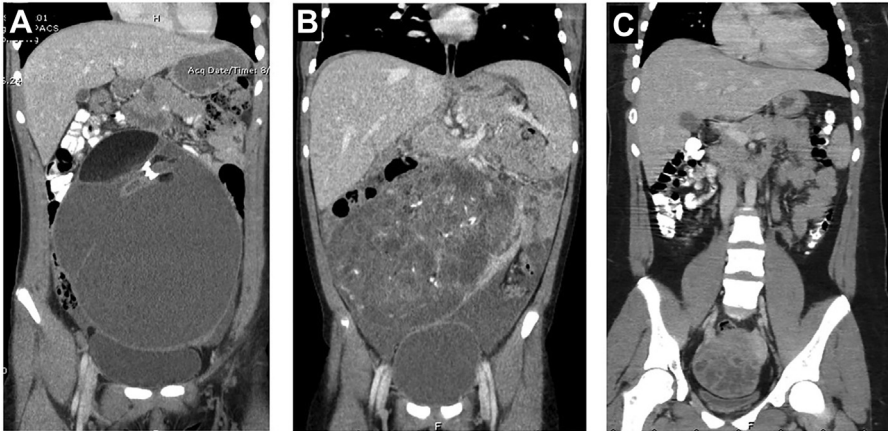
Fig. 2. Coronal CT images of ovarian GCTs. (*A*) Left ovarian MT in a 14-year-old girl. The tumor is mostly cystic with solid elements including calcium and fat noted in the most cephalad portion. (*B*) Left ovarian grade 3 IT in a 7-year-old girl. The tumor is complex with cystic and solid components including internal fat and calcifications noted. The fluid in the pelvis is worrisome for preoperative rupture. Rupture and diffuse nodularity of the peritoneal cavity was confirmed at laparotomy. Microscopic foci of yolk sac tumor were present throughout the mass on final pathology. (*C*) Right ovarian yolk sac tumor in a 15-year-old girl. The tumor is complex, also with cystic and solid components.

when it otherwise may have been omitted. Pelvic ascites and/or peritoneal washings should be sent for cytology. The uterus and contralateral adnexa should be examined with suspicious lesions biopsied. Biopsy of a normal-appearing ovary is not indicated. For bilateral tumors, resection can be pursued if ovarian parenchyma can be spared and the tumors fully resected. Otherwise, biopsy and neoadjuvant chemotherapy are recommended. The omentum should be examined with suspicious lesions biopsied or resected via omentectomy. Peritoneal surfaces should be inspected and masses or nodules resected or biopsied.[26] Finally, retroperitoneal lymph nodes should be visualized and palpated. Abnormal-appearing, firm, or enlarged nodes should be removed. Sampling of normal-appearing nodes is not indicated, a practice that differs from traditional Federation of Gynecology and Obstetrics guidelines, where routine pelvic and retroperitoneal lymph node dissection is recommended.[16]

With modern therapy, the overall survival for pediatric malignant ovarian GCTs is generally excellent. The initial COG experience with observation only for stage I GCTs revealed an event-free survival of just 52%, but nearly all patients who experienced relapse were later salvaged with chemotherapy for an overall survival of 96%.[27] For advanced stage ovarian malignant GCTs, the overall survival after surgery and platinum-based chemotherapy remains high, especially for prepubertal girls, with rates expected to be between 85% and 100%.[14] Stage IV ovarian GCTs, particularly girls older than age 11 who have an estimated overall survival of 60%, represent a more challenging scenario where better treatments are needed. Studies have also shown that fertility and ovarian function can be preserved successfully for most patients treated for ovarian GCTs and efforts to improve on this outcome continue.[28,29]

SURGICAL MANAGEMENT OF PEDIATRIC TESTICULAR GERM CELL TUMORS

Surgical treatment of malignant testicular GCTs involves radical orchiectomy with high ligation of the spermatic cord at the level of the internal inguinal ring via an

inguinal incision. If an MT is suspected in a young child, a testicular sparing approach can be considered, but orchiectomy is still recommended for peripubertal and post-pubertal males. A scrotal approach to biopsy or resection is discouraged. Scrotal or-chiectomy, provided that intact resection of the tumor and testicle are accomplished, will not result in upstaging if the remainder of the spermatic cord is resected to the level of the internal inguinal ring during a subsequent procedure.[30] If there is tumor present in the latter specimen, the patient is upstaged to at least stage II. If a trans-scrotal biopsy is performed, the patient will be upstaged to at least stage II, and completion inguinal orchiectomy is recommended, although hemiscro-tectomy is not needed.

A CT scan or MRI of the abdomen and pelvis should be obtained to assess for retroperitoneal adenopathy and chest imaging obtained to assess for metastatic dis-ease. Nodes less than 1 cm in maximal diameter are considered negative. Nodes that are 2 cm or more are considered positive for metastatic disease, designating the patient as having at least stage III disease. Nodes that measure 1 cm to less than 2 cm are considered indeterminate and for a patient who would otherwise be classified as stage I, follow-up imaging in approximately 4 to 6 weeks is required. If these nodes are unchanged or enlarging, a biopsy is recommended. If the biopsies are negative, the patient can remain as stage I. If they are positive or a biopsy is not pursued, the patient is upstaged to stage III and should receive chemotherapy accordingly.

For most pediatric patients with testicular GCTs, lymph node metastases are effectively treated with standard chemotherapy.[31] For prepubertal boys (age <11) who have completed chemotherapy in whom (1) persistently elevated tumor markers with a residual mass, or (2) negative tumor markers and a mass 2 cm or more, or one that is growing 6 to 8 weeks after completing therapy is encountered, resection of the mass should be pursued. Formal retroperitoneal lymph node dissection is not needed.[30] It is recommended, however, that peripubertal or postpubertal males (≥11 years of age) with a residual mass in the retroperitoneum at the completion of chemotherapy, with or without persistently elevated tumor markers, undergo retroperitoneal lymph node dissection using a nerve-sparing template. These rec-ommendations differ from adult guidelines, where either prechemotherapy or postchemotherapy retroperitoneal lymph node dissection is more commonly performed.[32]

Outcomes for pediatric patients treated for malignant testicular GCTs are generally excellent. Observation alone after appropriate surgical resection of stage I testicular GCTs has been well-studied in the context of multiple trials, with event-free survival rates ranging from 48% to 95%.[21,30,33] Importantly, the overall survival after an initial period of postsurgical observation approaches 100%, indicating, as with ovarian GCTs, that patients experiencing relapse of their disease after surgery are highly salvageable with addition of platinum-based chemotherapy. Patients presenting with more advanced stage testicular GCT continue to have a quite good survival, with the overall survival raging between 83% and nearly 100%, depending on the stage and age of the patient.[16,17,31]

SURGICAL MANAGEMENT OF PEDIATRIC EXTRAGONADAL GERM CELL TUMORS
Sacrococcygeal Germ Cell Tumors

Sacrococcygeal GCTs presenting in the neonatal period are more likely to be tera-tomas and predominately external in location. Those occurring later in childhood are more likely to be intrapelvic and malignant. The optimal surgical treatment for

neonatal sacrococcygeal GCTs involves intact removal of the tumor en bloc with the coccyx while avoiding injury or resection of adjacent organs, including pelvic floor musculature, so that future bowel, bladder, and reproductive functions are preserved and optimized.[34]

For suspected malignant sacrococcygeal GCTs, the primary tumor should be assessed with a CT scan or MRI to determine the feasibility of resection and the optimal operative approach. Should a peritoneal approach be used for resection, fluid and/or pelvic washings should be sent, and peritoneal surfaces and retroperitoneal lymph nodes assessed to evaluate for disease spread.[13] Preoperative imaging should be reviewed, and involvement of the tumor with surrounding structures, including the neural foramina, rectum, and/or genitourinary structures, assessed. Any suggestion that the tumor cannot be safely separated from vital structures should prompt a biopsy followed by the administration of neoadjuvant chemotherapy in lieu of upfront resection.[35] This point is particularly important in light of the fact that patients undergoing treatment for sacrococcygeal GCTs exhibit high rates of long-term bowel and bladder dysfunction.[36] The provision of neoadjuvant chemotherapy can facilitate eventual, less morbid surgical resection, with the expectation for similar overall survival compared with upfront resection.[13,35]

Mediastinal Germ Cell Tumors

Primary mediastinal GCTs are commonly large and involve critical structures. As with GCTs at other sites, the optimal surgical treatment involves complete resection of the tumor without rupture or spillage while preserving vital structures. The thymus is often involved and should be removed en bloc with the tumor. Large lesions with negative tumor markers and features consistent with an MT should be resected primarily. In asymptomatic or minimally symptomatic patients, this procedure can usually be done safely under general anesthesia via lateral thoracotomy or sternotomy. Lesions with elevated tumor markers that seem to be unresectable should be biopsied with chemotherapy administered if malignancy is confirmed.[37] An image-guided, percutaneous core needle biopsy is preferred. General anesthesia may be contraindicated in patients exhibiting findings of greater than 35 to 50% tracheal compression on CT scan or MRI, a peak expiratory flow rates of less than 50% predicted, or those with orthopnea.[38] These patients may require anesthetic strategies to allow for biopsy that do not risk airway collapse.

Germ Cell Tumors at Other Sites

Extracranial GCTs may also arise from the retroperitoneum, vagina, head and neck, and other sites. Cervical GCTs occurring in the neonatal period are often teratomas and require surgical resection for definitive management. Airway compromise is a critical concern and may require immediate postnatal securement of a safe airway and, in some cases, may necessitate in utero or extrapartum interventions. Malignant retroperitoneal GCTs may involve vital structures requiring an initial biopsy and the administration of neoadjuvant chemotherapy. At the time of eventual resection, intraperitoneal fluid and/or washings should be sent for cytology. Retroperitoneal lymph nodes and evidence of peritoneal spread should be assessed, and abnormal-appearing nodes or peritoneal implants should be removed or biopsied. Vaginal GCTs should be managed with the intent for vaginal preservation with neoadjuvant chemotherapy most commonly being given to facilitate a more limited, vagina-preserving resection.[39]

SURGICAL MANAGEMENT OF METASTATIC, REFRACTORY, AND RECURRENT DISEASE

Chemotherapy is administered when metastatic disease is diagnosed initially. Surgical resection should then be considered for the remaining residual masses that are more than 1 cm in size and/or when tumor markers remain elevated. Even in the context of metastatic disease, the administration of proper multimodality therapy, including surgical resection of distant metastases, is associated with long-term survival and is encouraged.[27]

Surgical resection must also be considered in the presence of recurrent or refractory disease.[40] Recurrent malignant GCTs may require salvage chemotherapy with consideration given to surgical resection of any residual mass.[41] Multiple regimens, including high-dose chemotherapy with stem cell rescue, have been used.[42] Biopsies revealing transformation to a somatic malignancy should be treated with therapy appropriate for that histology.[43] A teratoma without a malignant component is unlikely to respond to chemotherapy, and surgical resection for growing and/or symptomatic disease is warranted.

Growing teratoma syndrome describes a scenario in which local or distant metastases from a GCT continue to grow despite normalization of tumor markers with or without prior chemotherapy.[44] Given the lack of response to other therapies, surgical resection is warranted for lesions that are growing and/or causing symptoms. For cases where diffuse peritoneal studding is encountered, aggressive cytoreductive operations involving the stripping of peritoneal surfaces and the incorporation of hyperthermic intraperitoneal chemotherapy have been attempted and are commonly performed for adult ovarian carcinomatosis. The precise role of these treatments for pediatric GCTs is less clear.[45] There is little published information regarding outcomes for pediatric growing teratoma syndrome, although reports among adult patients indicate that, with surgical resection, outcomes are good with the majority of patients achieving long-term survival.[46,47]

FUTURE DIRECTIONS

Despite overall excellent outcomes associated with the majority of pediatric GCTs, several challenges remain. These issues include a need to identify areas where adult and pediatric providers can collaborate to study treatments and outcomes, fostering international collaborations to enroll more patients into clinical trials, improving outcomes for patients with stage III and IV disease, and decreasing the late effects associated with therapy. To this end, the ongoing COG AGCT 1531 trial will enroll children and young adults treated at both pediatric and adult centers and, in addition to North America, will enroll participants from multiple international centers. A commitment to international collaboration has been further established via the MaGIC consortium.

Additionally, targeted therapies have been evaluated for the treatment of otherwise medically refractory GCTs, with some success being reported for the tyrosine kinase inhibitor, sunitinib, and the cyclin-dependent kinase inhibitor, palbociclib.[48,49] Finally, given the limitations associated with the use of tumor markers, promising new methods including measurement of serum microRNA are being studied for the purposes of better monitoring disease burden, response to therapy and relapse.[50]

SUMMARY

Because they take their origin from migrating primordial germ cells, pediatric GCTs represent a vast array of histologies and occur in multiple locations. Overall, GCTs

are quite responsive to treatment, including surgery and chemotherapy. Proper technique for surgical resection and staging is critical to ensure favorable outcomes and to ensure that patients can receive appropriate therapy without being exposed to the risks associated with overtreatment or undertreatment. International collaborations and collaboration with adult centers will be critical in the support of current and future efforts focused on safely reducing the toxicities and the late effects associated with therapy and improving outcomes for high-risk patients.

CLINICS CARE POINTS

- Serum alpha fetoprotein, beta human gonadotropin and lactate dehydrogenase levels can be elevated and should be measured prior to treatment whenever a germ cell tumor is suspected.
- Rupture of germ cell tumors results in upstaging and must be avoided during operative resection.
- Intraoperative staging at the time of ovarian germ cell tumor resection is critical to ensure that an appropriate stage is assigned to ensure the patient is not over- or under-treated.
- Orchiectomy with high ligation of the spermatic cord via an inguinal incision is the preferred surgical approach to testicular germ cell tumor resection. A transscrotal approach should be avoided.

DISCLOSURE

The authors have nothing to disclose.

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